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Investigating the IFN-α-induced neurobehavioural syndrome in Hepatitis C patients:
A Qualitative and Quantitative comparative study.

by

Kimberley Jane Smith

A thesis submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College Dublin, Dublin 2, Ireland.

This research was conducted in the Department of Psychology.

January 2010.
Declaration

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Abbreviations

ACTH: Adreno-Corticotrophin Releasing Hormone
ALT: Alanine Aminotransferase
ANOVA: Analysis of Variance
APOE: Apolipoprotein E
AVLT: Auditory Verbal Learning Task
BBB: Blood Brain Barrier
BDI: Beck Depression Inventory
BDNF: Brain Derived Neurotrophic Factor
CANTAB: Cambridge Neuropsychological Test Automated Battery
CCL5: CC-Chemokine Ligand 5
CD4: Cluster of Differentiation 4
CNS: Central Nervous System
CORT: Cortisol
CRF: Corticotrophin-Releasing Hormone
CSF: Cerebrospinal fluid
DEX: Dysexecutive
DSM-IV: Diagnostic and Statistical Manual for the Diagnosis of Psychiatric Disorders
ECT: Electroconvulsive Therapy
EGF: Epidermal Growth Factor
ELISA: Enzyme-Linked Immunosorbent Assay
EMQ: Everyday Memory Questionnaire
FDA: Federal Drug Authority
fMRI: Functional Magnetic Resonance Imaging
FNP: Face-name Pairs Task
GABA: Gamma-Aminobutyric Acid
GM-CSF: Granulocyte Macrophage Colony-Stimulating Factor
HADS: Hospital Anxiety and Depression Scale
HADS-A: Hospital Anxiety and Depression Scale-Anxiety score
HADS-D: Hospital Anxiety and Depression Scale-Depression score
HAM-A: Hamilton Anxiety Rating Scale
HAM-D: Hamilton Depression Rating Scale
HCV: Hepatitis C Virus
HPA-axis: Hypothalamic Pituitary Adrenal Axis
HRQOL: Health-Related Quality of Life
IDO: Indolamine 2,3-dioxygenase
IFN-α: Interferon-Alpha
IFN-γ: Interferon-Gamma
IFNRA1: Interferon Receptor gene-1
IL-1, 2, 4, 6, 8, 10: Interleukin-1, 2, 4, 6, 8, 10
IP-10: Human Interferon-Inducible Protein
IVDU: Intra-Venous Drug Use
Kyn: Kynurenine
M: Mean
MADRS: Montgomery-Asberg Depression Rating Scale
MCP-1: Monocyte Chemotactic Protein-1
MDD: Major Depressive Disorder
MHC: Major Histocompatibility Complex
MIF: Macrophage Migration Inhibitory Factor
MINI: Mini-International Neuropsychiatric Interview
MIP-1α: Macrophage Inflammatory Protein-1-Alpha
µg: Micrograms
ms: Milliseconds
n: Number
N/R: Non-responder
NMDA: N-Methyl-D-Aspartic Acid
OVLT: Organum Vasculosum of the Lamina Terminalis
PAE: Psychiatric Adverse Event
PEG-IFN-α: Pegylated Interferon-Alpha
PFC: Prefrontal Cortex
PSQI: Pittsburgh Sleep Quality Index
RNA: Ribonucleic Acid
SART: Sustained Attention to Response Task
SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Psychiatric Disorders
SCL-90: Symptom Checklist-90 item
SEM: Standard Error of the Mean
SF-36: Short Form-36 Health Survey
sIL-2r: Soluble IL-2 Receptor
SSRI: Selective Serotonin Reuptake Inhibitors
STAXI-2: State-trait Anger Expression Inventory
STAI-Y: State-trait Anxiety Questionnaire
SVR: Sustained Viral Response
TMT: Trail Making Test
TNF-α: Tumour Necrosis Factor-Alpaha
VCAM-1: Vascular Cell Adhesion Molecule-1
VEGF: Vascular Endothelial Growth Factor
WHOQOL-HIV BREF: World Health Organisation Quality of Life for HIV
5-HIAA: 5-Hydroxyindoleacetic Acid
5-HT: Serotonin
5-HTP: Tryptophan
5-HTTLPR: Serotonin Transporter Linked Promoter Region
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Summary

The aim of this thesis was to characterise the neurobehavioural change that accompanies treatment with the pro-inflammatory cytokine Interferon-alpha (IFN-α) in Hepatitis C patients (HCV) by using both qualitative and quantitative analysis to assess the impact this treatment had on patients and how this neurobehavioural change compared to patients with a primary depression.

Chapter 3 comprised a series of case-studies that analysed the psychiatric adverse events that occurred for five patients during treatment. The case-studies demonstrated the extent to which these adverse events impacted on the individual and which symptoms constituted their diagnoses.

The next two Chapters sought to validate and then administer an interview where patients were assessed on the impact that treatment had on their health, mood, cognition and overall perception of the treatment. In Chapter 4 the interview was administered to healthy Control participants and also patients who presented with HCV in order to validate the interview, and assess the impact of HCV on the individual minus the treatment. In Chapter 5 the interview was then administered to patients who were due to start treatment (prospective interview), or had completed treatment (retrospective interview). Results from Chapters 3 and 5 indicated that IFN-α induces a variety of social, occupational and psychological disturbances; we then sought to examine the effects that patients claimed IFN-α had on their memory and mood by using qualitative analyses, and also conducting these analyses in patients with a primary depression.

In Chapter 6 a short neuropsychological battery was administered to HCV patients, depressed patients, control participants and patients taking IFN-α. Results indicated that HCV had a deleterious effect on attention and verbal recall, and that patients with a primary depression had a recall specific impairment on the face-name pairs task that did not encompass recognition. However when patients taking IFN-α were administered the same short battery that was no effect on any of the tests that could not be explained by the general impairment caused by HCV.

Chapter 7 of the thesis concentrated on assessing the mood changes that occurred for patients when taking IFN-α, with those patients who developed the psychiatric adverse events of depression and hypomania being examined in further detail. Mood scores were broken down into their component domains, with total scores for the Hamilton-Depression and Hamilton-Anxiety rating scales being split up into
mood, behaviour, cognition and somatic symptom domains. Once split into these components the respective contribution of each of these domains to the overall score was assessed. It was found that there was a general behavioural syndrome that accompanied treatment with IFN-α, consisting of somatic and mood symptoms, which occurred for all patients. When we then examined treatment-induced depression we found this led to significantly more depressed mood symptoms, and where hypomania was experienced patients experienced significantly more anxious and negative cognitions. In order to explore IFN-α-induced depression in more detail, it was then compared to a primary depression, with results indicating that IFN-α-induced depression is mainly a disorder of mood, and primary depression is principally a disorder of negative cognitions, with both groups showing similar levels of somatic symptoms.

A theory of the psychological changes that accompany treatment with IFN-α is presented, with the focus of the thesis being on the general IFN-α-induced behavioural syndrome and also describing the IFN-α-induced depression. A proposal for behavioural change being due to baseline symptoms being magnified by IFN-α, a reduction in the threshold to cope with stressful stimuli and cytokine-induced sickness behaviours is presented.
CHAPTER 1

Literature Review
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1.1 Hepatitis C

1.1.1 Overview of Hepatitis C

The Hepatitis C virus (HCV) is a blood-borne virus which is a major cause of liver disease and death and affects approximately 170 million people worldwide (WHO, 2000). It is transmitted mainly through contact with contaminated blood and blood products as a result of blood transfusions prior to 1992 (when screening procedures were put in place) and the sharing of non-sterilised needles and syringes in the intravenous drug-using population (see Table 1.1) (Poynard et al., 2003).

### Table 1.1: Clinical features of HCV

<table>
<thead>
<tr>
<th>Means of Infection</th>
<th>Infection type</th>
<th>Pathogen</th>
<th>Genotype and disease progression</th>
<th>Clinical Features: Acute</th>
<th>Clinical Features: Chronic (&gt;6 months)</th>
<th>Summary of features of Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use non-sterilised needles/syringe and sharing of razors.</td>
<td>Virus mutates frequently as it replicates. Replicates preferentially in hepatocytes.</td>
<td>Genotypes 2 and 3 account for 19-22% of infections and are more responsive to interferon therapy.</td>
<td>Symptoms subside after several weeks as levels of serum alanine aminotransferase (ALT) decline.</td>
<td>Cirrhosis develops in 10-20% over 20 years (1-4% risk of these patients developing hepatocellular carcinoma)</td>
<td>Mortality in 5-15%.</td>
<td></td>
</tr>
</tbody>
</table>

Acute infection with HCV develops into a chronic infection in up to 80% of people (Heathcote and Main, 2005), with length of time infected being one of the most important factors for developing illness-related complications (see Table 1.1).
Many of the symptoms associated with chronic HCV infection are non-specific (e.g., fatigue) and the majority of patients can be mostly asymptomatic for a number of years with only 25-30% of patients seeking medical attention for those symptoms that can be attributed to the virus (Herrine, 2002). Over time, complications from infection such as cirrhosis and cancer increase, with rates of Hepatitis C associated mortality being as high as 15% (Heathcote and Main, 2002). As time is such an important factor in the development of the more serious side effects of HCV complications from viral acquisition in the 1960’s and 1970’s are anticipated to increase over the next 10 years (Patel et al, 2003) and estimates indicate that the prevalence of cirrhosis will double and liver-related deaths will triple within this time-frame (Davis et al, 2003).

1.1.2 Quality of life and HCV

As well of the physical costs of the disease (see Table 1.1), there are a number of psychological and social issues associated with this illness which impact upon the patient’s health-related quality of life (HRQOL) shown in Figure 1.1.

The most important HRQOL issues for patients with HCV are said to be fatigue, depression, stigma and neurocognitive effects (Foster, 2009; Gutteling et al, 2007; Hauser et al, 2004). Fatigue is often listed as the most important factor influencing HRQOL in patients with HCV (Kallman et al, 2007) and is one of the most commonly reported disease-related side-effects (Seaman et al, 2009). Depression has a higher lifetime prevalence in HCV than either Hepatitis B or healthy controls (Carta et al, 2007), and is reported to be present up to 40% of patients with HCV (Yovtcheva et al, 2001). Stigma affects up to 85% of patients with HCV (Moore et al, 2009), often due to the negative views that people hold about intra-venous drug abuse (Paterson et al, 2007) and lack of understanding (Zickmund et al, 2003). Also patients with HCV often report that they have what the literature calls “brain fog” (Perry et al, 2008; Reimer et al, 2005), a term which broadly describes a series of impairments in executive functions such as attention, concentration working memory and mental flexibility (Forton et al, 2001; Kramer et al, 2002; Hilsabeck et al, 2002; Weissenborn et al, 2004). Thus HRQOL is affected more by psychiatric and medical co-morbidities than the effect of the disease itself (Hauser et al,
Chapter I: Literature Review

2004), meaning that the proper assessment of the psychological and social effects of this disease are of particular importance.

Figure 1.1: Issues associated with quality of life in HCV


1.2 Interferon-alpha

1.2.1 Overview of IFN-α

There is currently no vaccine for HCV, so the need for effective treatment is important, and at this time the main Federal Drug Authority (FDA)-approved treatment for HCV is the pro-inflammatory cytokine pegylated-Interferon-α (PEG-IFN-α), a multi-functional pleiotropic protein with anti-proliferative, anti-viral and immunoregulatory functions (Stark et al, 1998). The action of IFN-α in HCV patients is characterised by the treatment ‘interfering’ with replication of the HCV virus, slowing down the rate at which viral cells proliferate and inducing a general increase in immune system functioning (Dafny and Yang, 2005); the sum of all these actions is a reduction in the viral load of HCV and oftentimes complete elimination of the virus. The ultimate aim of treatment is to sustain
this elimination of the virus post-treatment as measured by the sustained virological response (SVR). SVR is defined as 6 months of sustained HCV-RNA negative status following cessation of treatment and this response has been shown to be maintained in over 95% of patients (Lau et al., 1998; Marcellin et al., 1997).

The currently preferred method of treatment PEG-IFN-α plus Ribavirin offers a 2-3-fold improvement in response rate over standard monotherapy (Bacon, 2004; see Table 1.2), this increase in treatment efficacy is due to two factors; pegylation of the IFN molecule and co-administration with Ribavirin.

Table 1.2: Combinations of IFN-α used for HCV and response rates

<table>
<thead>
<tr>
<th>Type of IFN</th>
<th>Response rate (SVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α alone</td>
<td>6% (12 weeks)</td>
</tr>
<tr>
<td></td>
<td>16% (42 weeks)</td>
</tr>
<tr>
<td>IFN-α plus Ribavirin</td>
<td>34% (24 weeks)</td>
</tr>
<tr>
<td></td>
<td>41% (48 weeks)</td>
</tr>
<tr>
<td>PEG-IFN-α</td>
<td>25% (12 weeks)</td>
</tr>
<tr>
<td></td>
<td>39% (42 weeks)</td>
</tr>
<tr>
<td>PEG-IFN-α plus Ribavirin</td>
<td>54% (24 weeks)</td>
</tr>
<tr>
<td></td>
<td>61% (48 weeks)</td>
</tr>
</tbody>
</table>

Table showing various IFN preparations and examples of SVR rates taken from Bacon (2004). Pegylated Interferon (PEG-IFN). These rates do not take factors such as genotype and BMI into account which also impact on responsiveness (Hartwell and Shepherd, 2009).

Pegylation of the IFN molecule involves the attachment of polyethylene glycerol to the molecule which prolongs the half life of the protein meaning that the IFN is administered less often as well as increasing the SVR (see Table 1.2) (Lindsay, 2002), especially when used in combination with Ribavirin. There are two forms of PEG-IFN available (α-2a and α-2b). The second way that treatment efficacy is improved is through the co-administration of a daily weight-based dose of the synthetic nucleoside analogue Ribavirin; when used in isolation Ribavirin was shown to reduce serum alanine aminotransferase levels, but had no direct impact on HCV-RNA levels (Di Bisceglie et al., 1992; Dusheiko et al., 1996; Bodenheimer et al., 1997). However, when used in combination with IFN-α it has been shown that the broad spectrum viral actions of the Ribavirin (Bacon, 2004), and the specific viral actions of the IFN-α (Dafny and Yang, 2004; Feld and Hoofnagle, 2005) increase the sustainability of HCV elimination post-
treatment (Brillanti et al, 1994; Reichard et al, 1998; see Table 1.2). There is as of yet no agreed consensus as to how Ribavirin increases treatment efficacy with proposed mechanisms including immunomodulation of \( \text{T}_1 \) cells over \( \text{T}_2 \) (Tam et al, 1999), general reduction in synthesis of RNA (Feld and Hoofnagle, 2005), direct inhibition of HCV-RNA (Maag et al, 2001) and via action as a viral mutagen (Crotty et al, 2000; 2001).

There are a number of factors influencing treatment response rates, the first and most influential is the presenting genotype of HCV; with around 50% of patients with genotype 1 achieving SVR and around 80% with genotype 3 (Bacon 2004; Davis et al, 1998). Other factors that have a lesser impact but can still adversely affect treatment outcome include higher baseline levels of HCV-RNA (Elefsiniotis et al, 2008; Reddy et al, 2009); being of African-American race as opposed to Caucasian race (Muir et al, 2004) and degree of hepatic cirrhosis (Elefsiniotis et al, 2008; Reddy et al, 2009). As well as those issues associated with treatment efficacy, there is a substantial side effect profile associated with this compound.

1.2.2 Adverse events associated with IFN-\( \alpha \)

IFN-\( \alpha \) has a well-documented profile of adverse side-effects, which can be split into physical, behavioural and psychiatric symptoms, all of which can impact upon compliance (see Table 1.3). In most cases, there appears to be two distinct time periods during treatment where side-effects are observed. In the first period, up to 98% of patients experience an influenza-like side effect profile (Lindsay et al, 1996; McHutchison et al, 1998), which occurs around 8 hours after the initial injection, and consists of fever, chills, malaise, tachycardia and myalgias. This syndrome usually dissipates within the first 2 weeks of treatment (Wichers and Maes, 2002). The second distinct period occurs from week 4 onwards, and is where the more serious physical and psychiatric side effects of treatment (see Table 1.3) will often occur (Dieperink et al, 2000). The single most commonly reported and limiting side effect of treatment is fatigue (Cotler et al, 2000; Khalili et al, 2000), which can be explained by the hematologic effects that often accompany treatment (Kowdley, 2005). However, it is the psychiatric side effects of treatment that are the most common adverse events associated with treatment discontinuation (McHutchison et al, 1998).
Table 1.3: Adverse events associated with IFN-α

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Common</th>
<th>Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>• Flu-like symptoms</td>
<td>• Thyroid Dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Fatigue</td>
<td>• Haematological Disturbance</td>
</tr>
<tr>
<td></td>
<td>• Anorexia</td>
<td>• Auto-immune Dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulmonary Problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ocular Problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dermatologic Problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cardiovascular Problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infections</td>
</tr>
<tr>
<td>Behavioural</td>
<td>• Insomnia</td>
<td>• Psychomotor slowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Social Withdrawal</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>• Depressed Mood</td>
<td>• Major Depressive Episode</td>
</tr>
<tr>
<td></td>
<td>• Irritability</td>
<td>• Psychotic Symptoms</td>
</tr>
<tr>
<td></td>
<td>• Cognitive Disturbances</td>
<td>• Panic Attacks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypomanic Mood</td>
</tr>
</tbody>
</table>

Table showing potential side effects of IFN-α, with the table split into those symptoms that are more commonly observed, and those that are less common based on Cotler et al (2000), Davis et al (1998); Foster and Mathurin (2008); Kowdley (2005); Ong et al (2004)

1.2.3 Neuropsychiatric effects of IFN-α

A plethora of literature has reviewed the effects that IFN-α has on neuropsychiatric functioning (see Table 1.4). Of all the side effects, depression has emerged as the most investigated and most commonly reported side effect due to treatment with IFN-α. Other psychiatric side effects include an increase in anxiety and irritability, and a decrease in cognitive functioning. However, findings regarding anxiety have been mixed with some studies reporting a significant increase (Amodio et al, 2005; Bonaccorso et al, 2001), some a significant decrease (Hunt et al, 1997) and others no significant change (Kamei et al, 2002; Khalili et al, 2000). This is possibly explained by the fact that most studies use anxiety scales to assess anxiety symptoms rather than use a formal diagnostic interview with there also appearing to be little consistency between studies as regards the instruments used (see Table 1.4). Results for cognitive dysfunction have also been mixed with the most replicable result being in those studies that used the Auditory Verbal learning task (AVLT), (Juengling et al, 2000; Lieb et al, 2006; Tanaka et al, 2006), with 12 weeks of treatment having a deleterious effect on performance.

However, these deleterious effects are also mixed with some studies finding only immediate recall significantly affected (Lieb et al, 2006), and others finding a more global
impairment in this task (Tanaka et al, 2006). Other cognitive assessment batteries often find the only significant results are for reaction time rather than performance on the test itself (Kraus et al, 2005a; Majer et al, 2008).

Irritability is another neuropsychiatric side effect which when investigated has been shown to increase during treatment (see Table 1.4). While rates vary from 3.3% (Maddock et al, 2004) to 35% (Manns et al, 2001), it has consistently been shown that this is a side-effect that does occur during treatment with IFN-α. This is a side-effect that needs to be looked at in more detail using a carefully designed neuropsychological battery, which focuses on areas of the brain that are potentially affected by treatment.

In those cases where rarer side-effects can be attributed to IFN-α therapy case studies have been carried out and some of these rare events have included attempted suicide (Fukinishi et al, 1998; Janssen et al, 1994) and psychosis (Onyike et al, 2004; Robaeys et al, 2007a).

However, of all the neuropsychiatric side-effects that can occur during treatment, the most frequently reported and thoroughly investigated is depression, which can occur in up to 42% of patients (Schaefer et al, 2003b), leading to interest in what factors may lead some individuals to be more at risk of developing an IFN-α-induced depression.
### Table 1.4: Neuropsychiatric side-effects of IFN-α

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Author</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Amodio et al (2005)</td>
<td>↑ Significant increase in HAM-A, but no need for medication.</td>
</tr>
<tr>
<td></td>
<td>Bonaccorso et al (2001)</td>
<td>↑ Significant increase in HAM-A</td>
</tr>
<tr>
<td></td>
<td>Gohier et al (2003)</td>
<td>↑ 3% of patients presented with anxiety/irritability assessed using the HAM-A.</td>
</tr>
<tr>
<td></td>
<td>Hunt et al (1997)</td>
<td>● After 1 month anxiety decreased significantly, assessed using the HADS</td>
</tr>
<tr>
<td></td>
<td>Kamei et al (2002)</td>
<td>↔ No significant difference in anxiety scores after 4 weeks, assessed using the HAM-A.</td>
</tr>
<tr>
<td></td>
<td>Khalili et al (2000)</td>
<td>↔ Combination IFN and Ribavirin therapy did not result in any significant anxiety, unknown assessment.</td>
</tr>
<tr>
<td></td>
<td>Kraus et al (2003)</td>
<td>↑ During treatment the proportion of patients reaching the clinically relevant cut-off point for anxiety rose from 13% to a maximum of 24.5%, assessed using the HADS.</td>
</tr>
<tr>
<td></td>
<td>Lieb et al (2006)</td>
<td>↓ Anxiety scores decreased significantly during treatment assessed using the HADS.</td>
</tr>
<tr>
<td></td>
<td>Lotrich et al (2007)</td>
<td>↑ Anxiety scores increased significantly during treatment, and were associated with hostility scores, assessed using the HADS</td>
</tr>
<tr>
<td></td>
<td>Maddock et al (2005)</td>
<td>↑ Anxiety scores increased linearly with time, assessed using the STAI-Y.</td>
</tr>
<tr>
<td></td>
<td>Maes et al (2001)</td>
<td>↑ HAM-A scores increased significantly on treatment, reaching a maximum around weeks 2-6.</td>
</tr>
<tr>
<td></td>
<td>McHutchinson et al (1998)</td>
<td>↑ 5% of patients developed anxiety on treatment, unknown assessment.</td>
</tr>
<tr>
<td>Cognition</td>
<td>Quarantini et al (2007)</td>
<td>↑ 3.3% of patients developed panic attacks during treatment, assessed using the MINI</td>
</tr>
<tr>
<td></td>
<td>Amodio et al (2005)</td>
<td>↔ No change in neuropsychological functioning</td>
</tr>
<tr>
<td></td>
<td>Capuron et al (2005)</td>
<td>↔ There was no significant difference in performance in the visuospatial attention task between patients taking IFN and Hepatitis C patients not taking IFN, however, IFN was associated with an increased activation of the frontal lobe in this task assessed using fMRI.</td>
</tr>
<tr>
<td></td>
<td>Fontana et al (2007)</td>
<td>↑ 18% of patients met criteria for cognitive impairment at week 24.</td>
</tr>
<tr>
<td></td>
<td>Hilsabeck et al (2005)</td>
<td>↓ Only part B of the trail making test impaired, patients were significantly slower at week 24.</td>
</tr>
<tr>
<td></td>
<td>Juengling et al (2000)</td>
<td>↓ AVL T significantly affected by 12 weeks of treatment, verbal fluency test and trail making test were not affected. fMRI analysis showed significant hypometabolism after 3 months in the PFC</td>
</tr>
<tr>
<td></td>
<td>Kraus et al (2005a)</td>
<td>↔ AVL T immediate recall (not total recall) was significantly affected by 12 weeks of treatment, there was also a significant decrease in verbal fluency.</td>
</tr>
<tr>
<td></td>
<td>Lieb et al (2006)</td>
<td>↓ AVL T immediate recall (not total recall) was significantly affected by 12 weeks of treatment, there was also a significant decrease in verbal fluency.</td>
</tr>
<tr>
<td></td>
<td>Majer et al (2008)</td>
<td>↔ There was no main effect of IFN treatment on performance in the CANTAB test battery. Only reaction time was significantly slower 12 weeks into treatment compared to baseline</td>
</tr>
<tr>
<td></td>
<td>Manns et al (2001)</td>
<td>↓ Concentration impairment was reported in 16-21% of patients taking various combinations of IFN and Ribavirin, unknown assessment.</td>
</tr>
<tr>
<td></td>
<td>McHutchinson et al (1998)</td>
<td>↓ 5% of patients developed impaired concentration on treatment, unknown assessment</td>
</tr>
<tr>
<td>Depression</td>
<td>Tanaka et al (2006)</td>
<td>↓ There was a significant decrease in performance in the AVLT, both immediate and delayed recall with IFN treatment.</td>
</tr>
<tr>
<td></td>
<td>Amodio et al (2005)</td>
<td>↑ Significant increase in HAM-D, but no episodes of major depression</td>
</tr>
<tr>
<td></td>
<td>Bonaccorso et al (2001)</td>
<td>↑ Significant increase in MADRS which was correlated with a change in IL-6</td>
</tr>
<tr>
<td></td>
<td>Bonaccorso et al (2002)</td>
<td>↑ Significant increase in MADRS score at week 12, with 40.7% being diagnosed with depression using DSM-IV</td>
</tr>
<tr>
<td></td>
<td>Castelli et al (2009)</td>
<td>↑ 42% of patients taking developed depression, measured using the SCID.</td>
</tr>
<tr>
<td></td>
<td>Castera et al (2002)</td>
<td>↑ Significant increase in MADRS at week 12, with 4% developing MDD</td>
</tr>
<tr>
<td>Side effect</td>
<td>Author</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Depression</td>
<td>Castera <em>et al.</em> (2006)</td>
<td>39% of patients developed psychiatric side effects, with 4% being diagnosed with MDD</td>
</tr>
<tr>
<td>Depression</td>
<td>Cotler <em>et al.</em> (2000)</td>
<td>2% were diagnosed as being depressed based on Doctor consultation.</td>
</tr>
<tr>
<td>Depression</td>
<td>Dan <em>et al.</em> (2006)</td>
<td>Depression scores increased within the first half of treatment</td>
</tr>
<tr>
<td>Depression</td>
<td>Davis <em>et al.</em> (1998)</td>
<td>Depression occurred in 16% of patients taking IFN plus Ribavirin and 11% of patients taking IFN plus placebo (unknown diagnosis).</td>
</tr>
<tr>
<td>Depression</td>
<td>Dell’Osso <em>et al.</em> (2007)</td>
<td>12% of patients were diagnosed with depression during treatment using DSM-IV.</td>
</tr>
<tr>
<td>Depression</td>
<td>DeJterkink <em>et al.</em> (2003)</td>
<td>Up to 47% of patients developed depression during treatment, diagnosed using BDI.</td>
</tr>
<tr>
<td>Depression</td>
<td>Fattovich <em>et al.</em> (1996)</td>
<td>0.02% of patients tried to commit suicide due to depression on treatment, assessed using a retrospective questionnaire</td>
</tr>
<tr>
<td>Depression</td>
<td>Fried <em>et al.</em> (2002)</td>
<td>20-30% of patients (IFN without and with Ribavirin) developed depression (unknown diagnosis)</td>
</tr>
<tr>
<td>Depression</td>
<td>Gehier <em>et al.</em> (2003)</td>
<td>22% of patients developed depression, plus 5% presented with depression with suicidal ideation and 1 patient presented with suicidal ideation minus depression, assessed using the MADRS.</td>
</tr>
<tr>
<td>Depression</td>
<td>Hauser <em>et al.</em> (2002)</td>
<td>33% of patients met criteria for MDD, assessed using DSM-IV</td>
</tr>
<tr>
<td>Depression</td>
<td>Horioka <em>et al.</em> (2003)</td>
<td>23.2% of patients were diagnosed as having depression at least once during treatment by psychiatrist interview.</td>
</tr>
<tr>
<td>Depression</td>
<td>Hunt <em>et al.</em> (1997)</td>
<td>Depression was diagnosed in 4% of patients, assessed using the BDI.</td>
</tr>
<tr>
<td>Depression</td>
<td>Jinu <em>et al.</em> (1993)</td>
<td>8.7% of patients were diagnosed with depression, unknown assessment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Juernig <em>et al.</em> (2000)</td>
<td>After 12 weeks of treatment there was a significant increase in BDI score.</td>
</tr>
<tr>
<td>Depression</td>
<td>Kamei <em>et al.</em> (2002)</td>
<td>No significant difference in BDI scores after 4 weeks, assessed using the HAM-D</td>
</tr>
<tr>
<td>Depression</td>
<td>Khalili <em>et al.</em> (2000)</td>
<td>Combination IFN and Ribavirin therapy did not result in any significant depression, unknown assessment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Kraus <em>et al.</em> (2003)</td>
<td>IFN therapy resulted in 35% of patients reaching the relevant cut-off point for depression (15% reached this at baseline), assessed using the HADS.</td>
</tr>
<tr>
<td>Depression</td>
<td>Kraus <em>et al.</em> (2005a)</td>
<td>HADS depression scores rose significantly during treatment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Kraus <em>et al.</em> (2005b)</td>
<td>Depression scores increased significantly in patients taking IFN, reaching their highest scores at weeks 12-16, assessed using the HADS.</td>
</tr>
<tr>
<td>Depression</td>
<td>Kraus <em>et al.</em> (2007)</td>
<td>HADS depression scores increased significantly during treatment, with 31% of patients needing antidepressant therapy.</td>
</tr>
<tr>
<td>Depression</td>
<td>Lieb <em>et al.</em> (2006)</td>
<td>After 12 weeks of IFN therapy, 20% of patients met the criteria for mild-moderate depression, assessed using the BDI.</td>
</tr>
<tr>
<td>Depression</td>
<td>Lofitis <em>et al.</em> (2004)</td>
<td>33% of patients developed MDD, assessed using the SCID at some point during treatment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Lotrich <em>et al.</em> (2007)</td>
<td>39% of patients developed MDD within 12 weeks, depressive symptoms also increased significantly, assessed using the SCID, BDI and HADS.</td>
</tr>
<tr>
<td>Depression</td>
<td>Maddock <em>et al.</em> (2004)</td>
<td>20% of patients developed an organic mood disorder with depressive features, assessed using DSM-III criteria.</td>
</tr>
<tr>
<td>Depression</td>
<td>Maddock <em>et al.</em> (2005)</td>
<td>Depression scores increased linearly with time on treatment, assessed using the BDI.</td>
</tr>
<tr>
<td>Depression</td>
<td>Maes <em>et al.</em> (2001)</td>
<td>MADRS scores increased significantly during treatment, reaching a maximum at weeks 2-6. The MADRS score was significantly correlated with a decrease in serum DPP-IV activity, and increases in the kynurenic acid ratio and serum IL-8.</td>
</tr>
<tr>
<td>Depression</td>
<td>Majer <em>et al.</em> (2008)</td>
<td>MADRS scores increased significantly after 12 weeks of treatment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Manns <em>et al.</em> (2001)</td>
<td>Depression was diagnosed in 29-34% of patients taking various combinations of IFN and Ribavirin, unknown assessment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Martin-Santos <em>et al.</em> (2008)</td>
<td>There was a significant increase in HADS depression scores in those patients only who had no baseline anxiety or depressive symptoms</td>
</tr>
<tr>
<td>Depression</td>
<td>McHutchinson <em>et al.</em> (1998)</td>
<td>Depression was the main reason for treatment discontinuation, with 13% of patients developing this side effect on treatment, unknown assessment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Miyaoaka <em>et al.</em> (1999)</td>
<td>The rate of major depressive disorder increased from 4.5% at week 0 to a maximum of 38.3% at week 12, assessed using DSM-III. 12.1% of patients were discontinued due to depression.</td>
</tr>
<tr>
<td>Depression</td>
<td>Mulder <em>et al.</em> (2000)</td>
<td>No change in depression scores, assessed using the SCL-90, however, 16.7% of patients showed an increase in depressive symptoms during treatment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Okonoue <em>et al.</em> (1996)</td>
<td>0.9% of patients were diagnosed with depression during a study looking at high dose IFN, unknown assessment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Pariante <em>et al.</em> (1999)</td>
<td>20% of patients developed a major depressive disorder, assessed using DSM-II-R.</td>
</tr>
<tr>
<td>Depression</td>
<td>Pariante <em>et al.</em> (2002)</td>
<td>Treatment caused a significant increase in HAM-D scores in both patients with a pre-existing psychiatric disorder and those without.</td>
</tr>
<tr>
<td>Side effect</td>
<td>Author</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Quarantini et al (2007)</td>
<td>↑ Major depression occurred in 10% of patients, assessed using the MINI.</td>
</tr>
<tr>
<td></td>
<td>Raison et al (2005a)</td>
<td>↑ Over the course of treatment 38.9% of patients exhibited moderate to severe depression symptoms, assessed using the Zung self-rating depression scale</td>
</tr>
<tr>
<td></td>
<td>Raison et al (2007)</td>
<td>↑ 28% of patients not treated with a prophylactic dose of paroxetine developed a moderate or severe depression, assessed using the SCID</td>
</tr>
<tr>
<td></td>
<td>Robaeyns et al (2007b)</td>
<td>↑ 38% of patients became depressed on treatment, assessed using the Zung self-assessment scale</td>
</tr>
<tr>
<td></td>
<td>Russo et al (2005)</td>
<td>↑ 16.7% of patients developed major depression, assessed using the SCID.</td>
</tr>
<tr>
<td></td>
<td>Schaefer et al (2003a)</td>
<td>↑ 16% of all patients developed major depression, assessed using DSM-IV.</td>
</tr>
<tr>
<td></td>
<td>Schaefer et al (2003b)</td>
<td>↑ 42% of patients developed major depression, assessed using DSM-IV, with a significant difference in MADRS scores being seen after 4 months.</td>
</tr>
<tr>
<td></td>
<td>Yates and Gleason (1998)</td>
<td>↑ 37.7% of patients developed depression, unspecified diagnosis.</td>
</tr>
<tr>
<td>Irritability</td>
<td>Constant et al (2005)</td>
<td>↑ Irritable hypomania occurred in 50% of patients, assessed using the MINI</td>
</tr>
<tr>
<td></td>
<td>Khalili et al (2000)</td>
<td>↑ Irritability occurred in 28% of patients, unknown diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Kraus et al (2003)</td>
<td>↑ 24.5% of patients reached a clinically relevant score for the anger/hostility dimension of the SCL-90-R (this level was at 11% at baseline).</td>
</tr>
<tr>
<td></td>
<td>Kraus et al (2005a)</td>
<td>↑ Anger/hostility scores rose significantly with treatment, assessed using the SCL-90-R.</td>
</tr>
<tr>
<td></td>
<td>Lotrich et al (2007)</td>
<td>↑ Hostility scores rose significantly on treatment, and were associated with anxiety scores, assessed using the SCL-90-R.</td>
</tr>
<tr>
<td></td>
<td>Maddock et al (2004)</td>
<td>↑ 3.3% of patients developed an organic mood disorder with predominant irritability, assessed using DSM-III criteria.</td>
</tr>
<tr>
<td></td>
<td>Manns et al (2001)</td>
<td>↑ 34-35% of patients taking various combinations of IFN and Ribavirin showed irritability, unknown assessment.</td>
</tr>
<tr>
<td></td>
<td>McHutchinson et al (1998)</td>
<td>↑ 10% of patients developed irritability on treatment, unknown assessment.</td>
</tr>
<tr>
<td></td>
<td>Preau et al (2008)</td>
<td>↑ Control of anger was significantly lower in patients taking IFN, and this is turn was correlated with the psychological and social relationships dimensions of quality of life, assessed using the STAXI-2 and WHOQOL-HIV BREF.</td>
</tr>
<tr>
<td></td>
<td>Russo et al (2005)</td>
<td>↑ 16.7% of patients developed increased irritability, assessed using the SCID.</td>
</tr>
</tbody>
</table>

Table showing various neuropsychiatric side effects of Interferon-alpha, and how these side effects were assessed. Depression scores given in bold represent the percentages of patients that could be diagnosed with a major depressive disorder using an official diagnostic test, other rates given are based on depression rating scales. Arrows indicate which direction the change in mood or cognition is occurring in, with an increase indicated by an upwards arrow, a decrease indicated by a downwards arrow and no change indicated by two arrows pointing sideways. General questionnaires (in order of appearance): DSM (Diagnostic and Statistical manual for psychological disorders); MINI (Mini-International neuropsychiatric interview); SCID (Structured clinical diagnostic interview for DSM); SCL-90 (Symptom checklist-90); WHOQOL-HIV BREF (World Health Organisation quality of life for HIV). Anxiety questionnaires (in order of appearance): HAM-A (Hamilton anxiety rating scale); HADS (Hospital anxiety and depression scale); STAI-Y (State-Trait anxiety inventory). Cognitive tests (in order of appearance): AVLT (Auditory verbal learning test); CANTAB (Cambridge neuropsychological test automated battery). Depression questionnaires (in order of appearance): HAM-D (Hamilton depression rating scale); MADRS (Montgomery-Asberg depression rating scale); BDI (Beck depression inventory); HADS (Hospital anxiety and depression scale). Irritability questionnaires (in order of appearance): STAXI-2 (State-trait anger expression inventory).
1.2.4 IFN-α and depression

Those risk-factors that have been shown to impact on rates of depression in patients taking IFN-α can be split into 3 main categories, Biological; Genetic and Psychiatric. Biological risk-factors that have been identified and shown to affect rates of depression involve the serotonin system, the HPA axis and levels of circulating cytokines.

Serotonin

The neurotransmitter serotonin has long been believed to play a role in depression (Elhwuegi, 2004; Owens and Nemeroff, 1994); however, more recent research has linked the observed decrease in serotonin with a cytokine-mediated pathway (Maletic et al, 2007; Miura et al, 2008). When IFN-α is administered it has been shown that there is an upregulation of the enzyme indolamine 2,3-dioxygenase (IDO) which metabolizes tryptophan, the precursor to serotonin (Konsman et al, 2002). Thus, when IDO is overstimulated there is potentially a reduction in plasma tryptophan, and serotonin in the brain (Capuron et al, 2003a; Loftis et al, 2004; Schaefer et al, 2002; see Figure 1.2) which may lead to depression (Miura et al, 2008).

Figure 1.2: Tyrptophan-Kynurenine pathway

![Diagram showing the alteration of tryptophan metabolism by IFN-α. Tryptophan is normally converted in 5-hydroxy tryptophan (5-HTTP) and 5-HT. However, this metabolism is switched to the kynurenine (Kyn) pathway by IDO, which is induced by immune stimuli such as IFN-α, and it is this pathway that produced the neurotoxin quinolinic acid. Based on Konsman et al (2002).](image)

Clinical research in this area has found that this system is affected to a more substantial degree in cancer patients taking IFN-α that are depressed (Capuron et al, 2003a). Studies in
Hepatitis C patients have provided mixed results with some studies supporting a correlation between lower tryptophan levels and scores on a depression scale (Bonaccorso et al, 2002) and others not finding this correlation (Bannink et al, 2007; Maes et al, 2001).

The most convincing support for the involvement of this system is the observation that depressive symptoms in this cohort are effectively ameliorated by the use of SSRI's (Gleason et al, 2007; Kraus et al, 2005c, 2008; Morasco et al, 2007; Raison et al, 2007) implicating some role for serotonin in the relief of IFN-α-induced depression.

**Hypothalamic-Pituitary Adrenal (HPA) axis**

Interferons are acknowledged to activate the HPA axis (Dafny and Yang, 2005), which could in part be linked to the development of depression (Asnis et al, 2006; Raison et al, 2005b; Raison et al, 2008). Recent research has identified a pathway where stress can increases glucocorticoids and corticotrophin-releasing hormones (CRH) which act in tandem with an increase in cytokines to disrupt levels of serotonin, norepinephrine, and dopamine (Maletic et al, 2007, Anisman, 2009; Raison et al, 2006). Vulnerability in this pathway could mean a stress-related response to cytokines is in part responsible for IFN-induced depression.

IFN-α is also used as treatment for certain cancers such as malignant melanoma (Capuron et al, 2003a; Capuron et al, 2003b). Following the first injection of IFN-α, cancer patients with an enhanced response to the stress hormones cortisol and adreno-corticotrophin releasing hormone (ACTH) were significantly more likely to develop depression than patients who exhibited a lower response to these hormones (Capuron et al, 2003b).

**Circulating cytokines**

As IFN-α is a cytokine designed to affect immune system functioning, some researchers have chosen to look at baseline immune system functioning, and the relative increase in cytokines induced by treatment to see if that had any effect on the subsequent development of depression. It was found that a higher Interleukin-6 (IL-6) response at weeks 2-4 was predictive of a higher MADRS score 4-6 months later (Bonaccorso et al, 2001). Another study found that pre-treatment levels of circulating IL-6 predicted the incidence of developing a major depressive disorder (MDD), and using regression analyses the authors were able to predict the following month’s BDI score using the previous month’s IL-6 levels (Prather et al, 2009). Other studies
have also found that a significantly increased baseline concentration of IL-6 can be a predictor for subsequent depression (Wichers et al, 2006). As well as IL-6, other peripheral cytokines shown to correlate with an increase in depressive symptoms include the soluble IL-2 receptor (sIL-2r) and Tumor Necrosis Factor-α (TNF-α) (Wichers et al, 2007), with baseline levels of sIL-2r and IL-10 being significantly increased in those patients who went on to develop depression (Wichers et al, 2006). However, when central levels of cytokines were assessed by examining cerebrospinal fluid (CSF) it was found that while IFN-α induced a significant increase in the cytokines IL-6 and Monocyte Chemotactant Protein-1 (MCP-1), that only CSF concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) predicted depressive symptoms (Raison et al, 2009).

One of the main questions regarding biological risk factors for development of an IFN-α induced depression is how the immune system, which is a peripheral system, can exert effects on mood and behaviour via the central nervous system (CNS). There are two main theories regarding this question; the first supposes that cytokines may enter the brain. There are a number of ways in which cytokines may enter the brain. The first is via circumventricular regions where the blood-brain barrier (BBB) is more permeable (Maier et al, 1998) such as the organum vasculosum of the lamina terminalis (OVLT), with uptake mechanisms for cytokines such as IL-1 being demonstrated at the surface of the BBB (Begley, 1992; Ermisch et al, 1993). Active transport mechanisms for transportation into the brain have also being identified for cytokines, including IL-1 (Dunn, 1992a) and TNF-α (Gutierrez et al, 1993). Another hypothesis concerns the induction of adhesion molecules such as Vascular Endothelial Growth Factor-1 (VCAM-1) in the brain endothelium, which increases the potential for circulating T-lymphocytes the cross the BBB (Brown, 2001).

However, the second theory suggests that the immune system influences secondary factors that in turn interact with the CNS (Dantzer et al, 1998). In the second scenario, there is a complex interplay between stressors, the IDO-Kyn pathway (see Figure 1.2) and factors that influence neuroplasticity in the development of cytokine induced depression (Anisman, 2009; Anisman et al, 2005; Hayley et al, 2005; see Figure 1.3).
Chapter 1: Literature Review

Figure 1.3: Cytokine-mediated pathways that influence CNS

Diagram showing how cytokines affects factors that the CNS through a complex relationship the relationship with monoamines, growth factors and stress based on Anisman (2009) and Hayley et al., (2005). Stressors and cytokines both increase the amount of CRH, both in the CNS and peripherally, which in turn activates ACTH and cortisol (CORT) levels. CRH also has a bi-directional relationship with serotonin (5-HT) levels, and Gamma aminobutyric acid (GABA) acts as a mediator for this process. 5-HT levels are also influenced by the production of IDO, which favours the production of the neurotoxin kynurene (Kyn) over 5-HT. This stressor system (in red) and IDO-Kyn pathway (in green) both lead to a reduction in 5-HT. Cytokines also influence oxidative and apoptotic mechanisms, leading to a reduction in growth factors such as BDNF, which in turn leads to impaired neuroplastic processes and decreased neurogenesis (neuroplastic pathway in purple), as well as cytokines having an indirect effect on growth factor levels, stress has also been shown to have a direct effect. The culmination of these three pathways can lead to the development of major depression.

Genetic risk-factors

There is a variation in HCV patient’s susceptibility to developing depression, despite uniform pharmacotherapy. This is suggestive of some underlying biological vulnerability, which in turn could be caused by genetic risk-factors. The 5-HT transporter gene (5-HTT) has been shown to have a role in the development of depression (Bull et al., 2008), in addition to polymorphisms in the IFNRA1 gene (Yoshida et al., 2005), the Apolipoprotein E (APOE) ε4 allele (Gochee et al., 2004) and the IL-6 gene (Bull et al., 2008) in patients taking IFN-α. A recent finding by Lotrich et al (2008) shows that the short version of the 5-HTT linked promoter region (5-HTTLPR) is also a risk-factor for development of depression in patients taking IFN-α, suggesting that this
allele is of particular importance for assessing depression vulnerability as it is also a gene which has repeatedly been suggested to be involved in the occurrence of a primary depression in otherwise healthy individuals in response to a major life event (Caspi et al, 2003; Brown and Harris, 2008) or in general (Hoefgen et al, 2005; Pezawas et al, 2005).

Psychiatric risk-factors
Risk-factors implicating a psychiatric vulnerability as being a predictor of subsequent depression have been arguably the most researched in this field as simple reasoning would suggest that if a drug induces psychiatric side-effects, that a pre-existing vulnerability to developing a psychiatric disorder (be that a history, a current diagnosis or higher than normal rating on a psychiatric scale), should lead such patients to be more 'at risk' than others. Following an early observation that higher pre-treatment scores on a depressive rating scale led to cancer patients having a higher risk of becoming depressed (Capuron and Ravund, 1999), several studies have explored this observation in more detail, with an emerging consensus that this risk-factor results in patients being significantly more likely to develop depression when taking IFN-α (see Table 1.5).

1.2.5 Treatment of IFN-α induced mood changes
When depression occurs in patients taking IFN-α, it is traditionally ameliorated with the use of anti-depressant medication (Kraus et al, 2007). Some studies have investigated the prophylactic use of anti-depressants and found it to reduce the occurrence of depression in vulnerable individuals (Gleason et al, 2007; Morasco et al, 2007) Where a comparison between patients who did and did not take a prophylactic dose of paroxetine was undertaken, depression rates were 9% and 28% respectively (Raison et al, 2007).

Where psychopharmacological treatment of mood changes is not undertaken, it is found that patients have a more severe neuropsychiatric reaction to treatment (Maddock et al, 2004).
Table 1.5: Psychiatric risk-factors for development of IFN-a induced depression

<table>
<thead>
<tr>
<th>Risk-factor</th>
<th>Evidence For</th>
<th>Evidence Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric History</td>
<td>Patients in this study who became depressed were significantly more likely to have a history of psychiatric disorders (58%) than those who did not (30%). Raison et al. 2005a. When controlling for baseline Zung scores using logistic stepwise regression, it was found that a history of MDD was a significant predictor of moderate or severe depression. Ho et al. 2001. Veterans with a prior psychiatric diagnosis had a greater incidence of neuropsychiatric adverse events (32% of whom 26% had depression) during interferon treatment than those who did not (14%), however this result was not significant. Castellvi et al. 2009. Having a history of mood disorders was a significant predictor of developing major depression in the 42% of patients who developed depression.</td>
<td>Horikawa et al. 2003. No evidence prior history of psychiatric disorders was a risk-factor. Hauser et al. 2002. No difference in past psychiatric history between those who did and did not become depressed. Martín-Santos et al. 2008. A past history of depressive or anxiety disorders did not impact significantly on the likelihood to develop a new depression (patients with depression at baseline were excluded from this analysis). Lotrich et al. 2007. Of the 9 (39%) of patients that developed Major Depression only 3 of these (33%) had a past history of a major depressive episode, whereas 36% of the group that did not become depressed also had a history of psychiatric illness. Mulder et al. 2000. Despite the fact that having had a lifetime history of major depression meant higher mean depression scores throughout treatment that this did not predict the onset or worsening of these symptoms. Pariante et al. 1999. Patients with a pre-existing psychiatric disorder were not significantly more likely to develop psychiatric adverse events (24%) when compared to case controls (19%). Renault et al. 1987. Those patients with a past history of an affective disorder were not significantly more likely to develop an 'affective syndrome', as 57% of people who developed depression had this history whereas 47% of people who did not develop any psychiatric side effects also had Schaeler et al. 2003. More psychiatric patients had a higher baseline depression; however, there was no significant increase in depression in the psychiatric group (6%) compared with the methadone group (14%), former addiction group (29%) and the control group (12%) in the development of a new depression. In total 16% of all patients developed a new depression. However, those patients who were in the psychiatric group were more likely to develop severe depressive side effects. Castora et al. 2002. None of the 12% of patients who developed a depressive disorder had a psychiatric history. Diaperink et al. 2003. Of those patients receiving psychiatric care at baseline 45% met criteria for MDD, which rose to 56% (11% incidence of new depression); however of the patients not receiving psychiatric care at baseline there was a 23% increase in new depression during treatment. However, despite this a history of two or more psychiatric diagnoses was identified as a risk-factor for the having to start antidepressant treatment during IFN, despite not being significant (p=0.08), as well as a family history of mood disorders, which was significant. Yet, none of these factors were identified as being important for the development of depressive symptoms.</td>
</tr>
<tr>
<td>Risk-factor</td>
<td>Evidence For</td>
<td>Evidence Against</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Baseline personality/other mood scores.</td>
<td>Dell'Ossio et al. 2007 &lt;br&gt;Patients who went on to develop depression had significantly higher state (but not trait) scores on the STAI-Y. Of the 6 (12%) of patients who did develop depression, 33.3% presented with sub threshold manic-hypomanic symptoms compared with 7.5% of patients who did not develop depression. &lt;br&gt;Catellvi et al. 2009 &lt;br&gt;Low self directedness was a significant predictor of developing a major depressive disorder.</td>
<td>Hauser et al. 2002 &lt;br&gt;Martin-Santos et al. 2008 &lt;br&gt;In this study a past history of alcohol or opioid dependence did not make people more likely to develop depression. Raison et al. 2005a &lt;br&gt;No evidence that past substance use impacts on rates of depression. Renaud et al. 1987 &lt;br&gt;None of the patients in the drug abuse group developed the ‘affective syndrome’ though 67% of them developed delirium.</td>
</tr>
<tr>
<td>Substance use</td>
<td>Castera et al. 2006 &lt;br&gt;45% of those patients that became depressed had a history of IV drug use, only 15% of the patients who did not become depressed were from this same population. Schaefer et al. 2003 &lt;br&gt;43% of patients who dropped out of study had former drug addiction (compared with 18% in psychiatric group, 14% methadone group, and 13% control group). These patients also tended to have more often, but milder episodes of depression.</td>
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<tr>
<td>Higher baseline depressive symptom score</td>
<td>Castera et al. 2006 &lt;br&gt;There was a significant difference in baseline MADRS scores between those who did (baseline score 10.7) and those who did not (baseline score 4.2) become depressed. Miyaoaka et al. 1999 &lt;br&gt;Those patients that subsequently became depressed had a significantly higher score at baseline on the HAM-D (3.5) than those who did not become depressed (2.0). Martin-Santos et al. 2008 &lt;br&gt;A higher baseline HADS depression score led to a significantly increased risk of developing a depressive or anxiety disorder during treatment with IFN. Raison et al. 2005a &lt;br&gt;Elevated baseline SDS scores significantly predicted the severity of depressive symptoms (however, the authors note that increased depressive symptoms were related to a history of depression). Lotrich et al. 2007 &lt;br&gt;A higher BDI at baseline was predictive of higher BDI scores at month 1. Castera et al. 2002 &lt;br&gt;None of patients with normal MADRS baseline score (&lt;3) developed depression. 42% of patients with higher MADRS baseline scores developed depressive symptoms. Depernik et al. 2003 &lt;br&gt;The only identified risk-factor for the development of depressive symptoms was an elevated BDI score at baseline. Catellvi et al. 2009 &lt;br&gt;Baseline subclinical depression levels were a significant predictor of developing a major depression.</td>
<td>Of the 19 (49%) of patients that became depressed, most of these had significantly higher scores on vegetative-depressive scales of the Zung self rating scale at week 4, however, there was no difference at baseline. Dell'Ossio et al. 2007 &lt;br&gt;Score’s on the depressive component of MOODS-SR at baseline did not differ at baseline between those who subsequently did and did not become depressed.</td>
</tr>
</tbody>
</table>

Studies investigating the role of psychiatric risk-factors on the development of depression during IFN-α treatment for HCV.
### 1.2.6 Critical analysis of IFN-α research into depression

There are some limitations with studies that look into the occurrence of depression in patients taking IFN-α. The first of these is that many studies focus from the outset on the side-effect of depression and will often find higher rates of depression, as they are ‘on the look-out’ for this specific side effect. Where studies of general side-effects rather than the specific side-effects are undertaken lower rates of depression in the region of 0.02-16% are found (Cotier et al, 2000; Davis et al, 1998; Fattovich et al, 1996) as opposed to the rates of up to 42% seen in the more depression-specific type of study (Schaefer et al, 2003b).

Another problem is that many of these studies employ scales to examine depressive symptoms, rather than diagnose depression formally with DSM-IV. A problem with basing depression levels purely on these scales is that they are often high in somatic items and as IFN-α is a drug that induces ‘sickness behaviour’, many patients taking this drug will score highly on these items simply because they are sick, rather than been depressed per se (Trask et al, 2000).

It has been shown that those people who become depressed on treatment are more likely to have an increased baseline score on a depression scale (see Table 1.5). Raison et al (2005b) propose that all people prescribed IFN-α develop a side-effect profile, comprised of neuro-vegetative symptoms (those somatic aspects of sickness behaviour), or depressive-specific symptoms, (those symptoms specific to the behavioural parts of sickness behaviour). Both of these side-effect profiles are measured by depression rating scales. Thus if a person scores highly at baseline on one of these scales it would stand to reason that these scores would remain present throughout the course of the treatment, and that some additional-treatment related factors would also come into play. The additive effect would mean that this subset of patients would be more at risk of being diagnosed with a depressive disorder due to elevated scores on a depression rating scale. Should this be the case, then all patients would experience an increase in scores on a depression rating scale relative to time, which is something that much of the literature seems to support (Bonnacorso et al, 2005; Dan et al, 2006; Dieperink et al, 2003; Fontana et al, 2002, 2007; Fried et al, 2002; Hunt et al, 1997; Kraus et al, 2003, 2005a, 2005b, 2008; Lotrich et al, 2007; Maddock et al, 2004; Majer et al, 2008; Manns et al, 2001). In fact, some researchers have pinpointed a relative increase in somatic components of depressive rating scales as being primarily responsible for the increase in scores seen in many patients (Trask et al, 2000). However, many recent studies have become aware of the potential confounds associated with using only depression rating
scales and so diagnose MDD using DSM-IV-TR criteria. In order to meet criteria for diagnosis of MDD patients are required to show depressed mood for most of the day nearly every day, and/or demonstrate a direct loss in interest in activities every day for 2 weeks. Neither of these factors are somatic in nature, although it could be said that they may result from a primarily somatic complaint.

It will be important in future studies to determine the subscale loads of those items that are somatic or affective. A recent study by Capuron et al (2009) conducted in patients with malignant melanoma taking IFN-α looked in more detail at these subscales within the 17-item HAM-D, and compared the relative loadings of each symptom in patients who were diagnosed with an IFN-α-induced depression, and those patients with a primary depression. This study found that both sets of patients loaded onto similar items, with the only difference being depressed patients were more likely to feel guilty. However, a similar study that concentrated only on negative cognitions, found that depressed patients taking IFN-α presented with a different pattern of symptoms to patients who had a primary depression. They found that IFN depressed patients were significantly less likely to experience feelings of guilt, failure, dissatisfaction and self-dislike and suggested that cytokines induced an atypical form of depression that had yet to be defined (Pasquini et al, 2008). There is further evidence that depression in those people who are also medically-ill is characterized by the core symptoms of anhedonia, low positive affect and somatic symptoms, whereas depression in a primary depressed in-patient population is caused specifically by negative cognition symptoms (Clark et al, 1998). These three studies highlight the need for comparative studies between primary depression and the IFN-α-induced depression, in order to gain a better appreciation of the type of depression that patients taking IFN-α exhibit.

Another problem is that many studies will base their experiment purely on previous research. When an area like this is saturated with research it is often a good idea to both look at the research that has done before to see where gaps need to be filled, and also use qualitative measures based on patient’s self-report so that a more informed decision about what side-effects should be concentrated on can be made.

As well as issues relating to experimental design there is the simple, yet often ignored issue that many patients who have HCV are more depressed than a healthy population, in fact rates of depression in HCV patients can be as high as 40% (Yovtcheva et al, 2001). With studies that look at the occurrence of depression in patients taking IFN-α, many will report the total occurrence of depression including those people who were diagnosed with
depression at baseline rather than those incidences of a ‘new’ depression, and will report a high level of depression on treatment, but when the study is investigated in detail it will transpire that the level of depression occurring due to IFN is significantly lower (Hosoda et al., 2000). Some studies will report both the total occurrence and new occurrence (Dieperink et al., 2003) or exclude people at baseline who are suffering from any psychiatric disorder (Fontana et al., 2007).

Yates and Gleason (1998) found that in a study of 78 patients who were HCV positive, the main reasons for being referred for psychiatric consultation were showing psychiatric symptoms, consultations for liver transplantation and consultation for therapy with IFN-α, with the lowest number of patients referred for therapy being those patients receiving IFN-α who had developed depressive symptoms. Furthermore populations acquiring HCV tend to be from backgrounds that can lead them to have a higher level of depression regardless of treatment with IFN-α (Johnson et al., 1998). This evidence demonstrates that the HCV population are a vulnerable group generally, and that focusing on only treatment associated problems may lead clinicians and researchers alike to underestimate those problems associated with HCV itself.

1.3 Depression

1.3.1 Overview of depression

Depression is a disorder that currently affects approximately 121 million people worldwide, and is among one of the leading causes of disability in the world (WHO, 2009). Unipolar MDD is diagnosed by one or both of the two core symptoms of depressed mood and loss of interest and enjoyment in previously pleasurable activities (anhedonia) as well as ancillary symptoms (see Table 1.6), and is distinguished from a low mood by the duration and severity of symptoms that people present with.

Even though depression is characterised as an episodic illness, it has been found that up to 75% of patients who present with depression will relapse at some point in the future (Hollon et al., 2006), with each episode increasing the probability of a subsequent episode occurring (Solomon et al., 2008). As such, there has been a shift in thinking, and rather than depression being viewed as an episodic condition, many people instead view it as a chronic condition (Judd, 1997).

For some people depression is an understandable reaction to some external stressor, a so-called reactive depression (Paykel, 2003), however, in other cases there can be no apparent
reason for the depression to occur (endogenous depression). Both types of depression appear
to involve an underlying vulnerability, which could be due to genetics, cognitive distortions
or a biological difference (Beevers, 2005; El Hage et al, 2009).

Table 1.6: Clinical features of depression

<table>
<thead>
<tr>
<th>Mood</th>
<th>Depressed Mood; Irritable mood; Anxiety and apprehension; Distinct quality of depressed mood; Anhedonia; Loss of emotional reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td>Psychomotor retardation or agitation; Depressive stupor</td>
</tr>
<tr>
<td>Relationships</td>
<td>Deterioration in family relationships; Withdrawal from peer relationships; Poor work or educational performance.</td>
</tr>
<tr>
<td>Somatic State</td>
<td>Fatigue; Diminished activity; Loss of appetite or overeating; Aches and pains; Early morning waking; Diurnal variation of mood; Change in weight; Loss of interest in sex</td>
</tr>
<tr>
<td>Cognition</td>
<td>Negative view of self, world and future; Over-general memory; Cognitive distortions; Inability to concentrate; Indecision; Suicidal ideation; Excessive guilt; Mood-congruent delusions</td>
</tr>
<tr>
<td>Perception</td>
<td>Perceptual bias toward negative events; Mood-congruent hallucinations.</td>
</tr>
</tbody>
</table>

Table showing the clinical features of depression in adults taken from Carr and McNulty (2006)

1.3.2 Diagnostic issues in depression

There are a number of different sub-types of depression (see Table 1.7), which can be
distinguished by the symptoms individuals present with, and their reactivity to different types
of treatment (Parker et al, 2001a).

The first of these, atypical depression, is characterised by mood reactivity; the second
is melancholic depression, a neurovegetative depression characterised by anhedonia and lack
of mood reactivity. Finally, psychotic depression is a severe form of depression where
delusions and/or hallucinations accompany the depressed mood (DSM-IV-TR, 2000).

However, there have been calls to change the categorization of depression, with some
researchers arguing that depression is a disorder which can be viewed as lying on a
continuum from subthreshold depression to full threshold depression (Flett et al, 1997), as
even subthreshold depressive symptoms have been shown to have significant psychosocial
impairment (Lewinsohn et al, 2000). People who subscribe to the continuum theory of depression believe that rather than symptoms differentiating subtypes of depression, it would instead be better to categorise the disorder in terms of severity and chronicity (Klein, 2008).

Table 1.7: Subtypes of depression

<table>
<thead>
<tr>
<th>Subtype of depression</th>
<th>Core features</th>
<th>Ancillary symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical</td>
<td>Mood reactivity</td>
<td>Significant weight gain or increase in appetite; Hypersomnia; Leaden paralysis; Long standing pattern of interpersonal rejection.</td>
</tr>
<tr>
<td>Melancholic</td>
<td>Loss of pleasure in almost all activities; Lack of reactivity to usually pleasurable stimuli</td>
<td>Distinct quality of depressed mood; Depression regularly worse in morning; Early morning awakening; Marked psychomotor agitation/retardation; Significant anorexia or weight loss; Excessive or inappropriate guilt</td>
</tr>
<tr>
<td>Psychotic</td>
<td>Hallucinations; Delusions</td>
<td>As major depression</td>
</tr>
</tbody>
</table>

Table showing the subtypes of Major Depressive Disorder, based on criteria from DSM-IV-TR (2000).

Other researchers currently choose to categorise depression into melancholic and non-melancholic, as these two types of depression respond differently to treatment, with melancholic patients showing increased responsiveness to antidepressants and electroconvulsive therapy (ECT) and a decreased responsiveness to psychotherapy and placebo drugs when compared to non-melancholic patients (Brown, 2007). Melancholic depression is also differentiated from non-melancholic depression by poorer treatment outcome (McGrath et al, 2008), personality differences (Boyce et al, 1990), older age (Parker et al, 2001b), being less likely to have experienced a number of negative life events (Kohn et al, 2001), slower movement times (Pier et al, 2004), increased HPA activation (Antonijevic, 2006), and increased immune activation (Rothermundt et al, 2001).

1.3.3 Cognitive theories of depression

Modern cognitive theories of depression originated with the work of Aaron Beck (1963), who proposed that cognitive distortions in the perception of everyday events led depressed patients to automatically perceive the world they lived in and themselves in over-generalised and negative ways. He proposed a negative cognitive triad where the symptoms of depression
could be explained by a bias in the perception of events that are the result of negative views of the self, the personal world and the future (Beck, 1967, 1987). The other main cognitive theory of depression developed by Abramson et al. (1989) was the hopelessness theory. This theory proposed that depressogenic thinkers attributed negative life-events to stable (likely to persist over time) and global (likely to affect many things) causes, and infer that they are flawed and worthless due to their tendency to over-generalise and magnify events (Alloy et al., 2002; Abramson et al., 1989). The common features of these two theories is that negative inferential styles, schemas and dysfunctional attitudes lead to an increased risk of depression and also that stress interacts with this cognitive vulnerability to produce the depressive episode (Alloy et al., 1999; Carr and McNulty, 2006: see Figure 1.4).

Rumination has been identified as an additional possible cognitive factor which leads to the exacerbation of a depressive episode (Nolen-Hoeksema, 1991, 2000). This rumination would mean that the depressed patients continued focus on negative self-aspects and dysphoric symptoms would lead to the amplification and prolonging of depressed mood by interfering with attention and problem-solving (Nolen-Hoeksema, 1991, 2000). However, a recent theory of cognitive vulnerability to depression states that cognitive vulnerability to depression is the result of the inability to use rumination to correct negative thoughts (Beevers, 2005).

This idea of a cognitive vulnerability has been examined in prospective studies that claim that those participants with a high-risk cognitive style (defined as those people who displayed the most negative cognitions) were more likely to be diagnosed with a depression than those with a low-risk cognitive style (Alloy et al., 2006). However, those studies that investigate the impact of cognitive-vulnerability in recovered patients do not necessarily find this effect (Just et al., 2001).

Support for this theory comes from the success of cognitive therapies, which are one of the most effective treatments for mild to moderate MDD (Gaudiano, 2006; Butler et al., 2006), especially when used in conjunction with pharmacological therapies (Torpey and Klein, 2008). These therapies target cognitive distortions by having patients monitor and re-appraise their evaluation of negative cognition-activating events (Carr and McNulty, 2006). The most popular sub-type of cognitive therapy is Cognitive Behavioural Therapy (CBT) (Beck, 2005), a therapy which focuses on engaging patients in therapy using behavioural therapies such as scheduling activities, and then shifting the focus to a more cognitive therapy.
One of the main problems with this theory is the different cause and clinical presentation of the various sub-types of depression (see Table 1.7 and Section 1.3.2). Those people who have an endogenous depression (melancholia) have been identified as having the core symptom of anhedonia, whereas those people more susceptible to a reactive depression have the core symptom of hopelessness (Abramson et al., 1989). Anhedonia is primarily the result of an underlying depressed mood, whereas hopelessness, over-generalisation and the other negative cognitions would result primarily from cognitive distortions (Alloy et al., 2006). These two types of depression respond differently to treatments with non-melancholic depression responding better to cognitive therapies, and melancholia responding better to biological therapies (Brown, 2007).

Figure 1.4: Interaction between vulnerability, stress and factors that maintain depression

The likelihood is that the underlying cognitive vulnerabilities seen in depression are linked in with some biological difference in this population (Garcia-Torro and Aguirre, 2007), especially as CBT has been shown to have a similar effect on the brain to SSRI’s
(Linden, 2006, 2008). A possible way in which cognitive vulnerability could interact with these other systems to develop and maintain a depression is presented in Figure 1.4.

As the biological vulnerability interacts with the cognitive vulnerability, potential biological mechanisms for this vulnerability shall be discussed below.

1.3.4 Biological theories of depression

For many years the main biological theory of depression was the monoamine theory of depression, which posited that a deficit in the monoamine neurotransmitters noradrenaline and serotonin underlied depression (Elheweigi, 2004; Owens and Nemeroff, 2004). The main support for this hypothesis was that antidepressant drugs that targeted this system were able to ameliorate the symptoms of depression. Classically, these antidepressant drugs were (SSRls, that worked by increasing the amount of serotonin available in the post-synaptic cleft (Anderson, 2004). This observation coupled with evidence that tryptophan depletion led to depressive symptoms in people who had recovered from depression (Bell et al, 2001; Smith et al, 1997) seemed to support the monoamine theory of depression.

However, one of the largest studies conducted on treatment outcome in depression, the STAR*D study, has found that remission is only achieved in 50% of patients who take the SSRI citalopram (Trivedi et al, 2006), with those patients who have a melancholic depression significantly less likely to achieve remission (McGrath et al, 2008). Other studies have shown that antidepressant therapy is a better therapy for those people that have a mild to moderate depression (Casacalenda et al, 2002), and that the best treatment response is seen when combined with psychotherapy (Carr and McNulty, 2006; Torpey and Klein, 2008).

Additional support against the monoamine hypothesis comes from evidence that tryptophan depletion only causes a change in mood in those people who have previously experienced depression, in those people with no psychiatric history tryptophan depletion has no effect (Ruhe et al, 2007). This suggests that the serotonin system acts in conjunction with some other vulnerability factors in order to produce depression, and many researchers now question the validity of the monoamine theory of depression (Cowen, 2008), and are looking at alternative systems that interact with serotonin, thus explaining the delayed action of antidepressants.

Stress is acknowledged to be one the main precipitants of a major depressive episode (Kendler et al, 1999; Paykel, 2001), and vulnerability in this system has been proposed as a possible risk-factor for developing depression (El Hage et al, 2009; Holsboer, 2000).
Increased HPA activity is a replicable finding in many studies that investigate depression (Pariante and Lightman, 2008). This can be observed peripherally by increases in urinary cortisol (Maes et al, 1998), decreased corticosteroid receptor functioning (Modell et al, 1997), increased adrenal gland size (Rubin et al, 1996), enlarged pituitary gland volume (Krishnan et al, 1991), increased ACTH secretion (Carroll et al, 2007), increased vasopressin levels (Scott and Dinan, 1998) as well as evidence of hyperactive CRH function in the CNS (Holsboer, 2000; Raadsheer et al, 1994, 1995). Evidence for this theory is also supported by data that shows when patients who have had depression achieve remission, be that spontaneously or through treatment, HPA-axis functioning returns to normal (Nemeroff, 1996).

As depression also involves structural changes in the brain, notably in areas involved in mood regulation and learning and memory, such as the prefrontal cortex (PFC), hippocampus, cingulate and amygdala, there is also a focus on what factors in the brain could lead to these changes. One of the factors currently being explored is brain derived neurotrophic factor (BDNF), a protein involved in cell maintenance, plasticity, growth and death which is distributed widely through the brain (Murer et al, 1999). Depressed patients show significantly lower levels of serum BDNF, compared to treated depressed patients and controls (Shimizu et al, 2003). This observation has led to the neurotrophic hypothesis, which posits that stress and genetic vulnerability elevate glucocorticoids and alters cellular plasticity via the downregulation of growth factors and receptor sensitivity, leading to structural changes in the brain, especially the hippocampus (Duman and Monteggia, 2006).

Another biological theory of depression increasing in popularity is the cytokine theory of depression, which states that an alteration in immune system activation could, in part, be responsible for the symptoms of depression. This theory is gaining in popularity as cytokines, especially IL-1, IL-6 and TNF-α, have been shown to interact with serotonin (Capuron and Miller, 2004; Maes, 1995; Zhu et al, 2006), CRH (Anisman et al, 2008; Dantzer et al, 2008; Tilders and Schmidt, 1998) and BDNF and other growth factors (Khairova et al, 2009; Schulte-Herbruggen et al, 2005), all of which are implicated in the pathophysiology of depression (see Figure 1.3).
1.4 Cytokine theory of depression

1.4.1 Overview of the cytokine theory of depression

Cytokines are low molecular weight regulatory proteins that are produced during all phases of an immune response that modulate the immune response by regulating the movement, proliferation and differentiation of leukocytes (Wilson and Warise, 2008). Humans or animals administered a cytokine develop a behavioural syndrome and set of somatic effects termed ‘sickness behaviour’; these behaviours result in an alteration the motivational state of an organism so that it can preferentially respond to infections (Dantzer et al, 1998, 2008; Konsman et al, 2002). In other words, the organism will have depressed functioning of mood, activity and metabolism so that all of its energy is put into fighting illness. The observation that sickness behaviour and depression share common features (Dunn, 1992b; Dunn et al, 2005; see Table 1.8) has led many researchers to implicate raised levels of cytokines in the pathology of depression giving rise to the cytokine theory of depression.

**Table 1.8: Similarities between MDD and sickness behaviour**

<table>
<thead>
<tr>
<th>Somatic effects</th>
<th>Depression</th>
<th>Sickness Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatigue/ Loss of energy</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Weight loss/ Weight gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Appetite Loss/ Appetite Increase</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Insomnia/ Hypersomnia</td>
<td>Sleep Disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased body temperature</td>
</tr>
<tr>
<td>Behavioural effects</td>
<td>Depressed mood</td>
<td>Depressed mood</td>
</tr>
<tr>
<td></td>
<td>Feelings of worthlessness/ Guilt</td>
<td>Behavioural despair</td>
</tr>
<tr>
<td></td>
<td>Loss of interest in activities</td>
<td>Social withdrawal</td>
</tr>
<tr>
<td></td>
<td>Anhedonia</td>
<td>Anhedonia</td>
</tr>
<tr>
<td></td>
<td>Inability to concentrate</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Psychomotor agitation/ retardation</td>
<td>Suppression motor behaviour</td>
</tr>
<tr>
<td></td>
<td>Recurrent thoughts of death</td>
<td></td>
</tr>
</tbody>
</table>


Charlton (2000) argues that it is the somatic features of depression that form the core symptoms of the illness, and that the core emotion of depression is malaise. He characterises depression as an illness, where the mood changes are a consequence of the underlying physical state of the individual, and that it is this physical pathology that defines the depression, rather than the mood (as would traditionally be the case when diagnosing depression using DSM-IV).
Further evidence for the cytokine theory of depression comes from the observation that depression is more commonly observed in those people who have a co-morbid medical condition than those who are otherwise healthy, with rates of depression being as high as 50% in this population (Yates et al, 2004). Additional support for this theory comes from the observation that those patients whose diseases have an immunological component are especially vulnerable (Kronfol, 2002), such as multiple sclerosis where more than half of patients have some sort of mood disturbance or depression (Gold and Irwin, 2009; Lebrun and Cohen, 2009).

Depressed patients show elevated levels of pro-inflammatory cytokines including IL-1, IL-6 and TNF-α (Anisman, 2009; Kim et al, 2008; Schiepers et al, 2005), with a recent study that looked at a broad range of cytokines finding significantly elevated levels of MCP-1, Macrophage Inflammatory Protein-1α (MIP-1α), IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-12p70, IL-15, Eotaxin, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) and IFN-γ (Simon et al, 2008). Further to this it has been shown that peripheral cytokine levels are higher in people when in a depressive state than when in remission (Hernandez et al, 2008; Kim et al, 2007), and that treatment for depression with ECT or antidepressants can result in a reduction in cytokine levels (Hestad et al, 2003; Kenis and Maes, 2002; Kim et al, 2007; Kubera et al, 2001; Leonard, 2001). Further support for the cytokine theory of depression comes from evidence that giving patients the anti-inflammatory drug celecoxib plus fluoxetine leads to better treatment outcome using the 17-item HAM-D, than just using fluoxetine alone (Akhondzadeh et al, 2009).

1.4.2 Problems with the cytokine theory of depression

Cytokine levels can be directly correlated with the severity (Maes, 1999) and chronicity (Anisman et al, 1999) of a depression. However, while the cytokine theory of depression continues to grow in popularity there is still debate concerning the extent to which these peripheral cytokines are involved in MDD. One of the main problems with the cytokine theory of depression is that depressive states can occur without any increase of peripheral cytokines (Weizman et al, 1994) and tryptophan depletion can affect mood without having a correlated effect on cytokines (Ravindran et al, 1999). While many researchers find a significantly higher level of cytokines in people when depressed than when in remission (Hernandez et al, 2008; Kim et al, 2007), this finding is not always replicated with a significant decrease in depressed mood not always being correlated with a decrease in
peripheral cytokines (Kubera et al, 2000), and pivotal cytokines such as IL-6 not always yielding significant differences when compared to healthy controls (Carpenter et al, 2003).

It is possible that cytokines are involved in certain aspects of the depressive syndrome, such as sleep and appetite changes, rather than being the central neurobiological cause of depression (Dunn et al, 2005). It has been shown that a co-morbid medical condition and depression leads to more symptoms of anhedonia and negative affect, whereas a pure depression is characterised primarily by negative cognitions (Clark et al, 1998). This raises questions as to how much of a primary depression is caused by the symptoms of sickness behaviour, and how much cytokine-induced sickness behaviour may have in common with a primary depression.

In order to assess the effect that cytokines have on mood, we shall assess patients administered a cytokine for medical reasons (IFN-α), and ascertain the impact that this cytokine has on mood. We shall also conduct a detailed analysis of any psychiatric adverse events (PAEs) that may occur, in particular depression, and conduct a quantitative assessment of how this IFN-α-induced depression may compare to a primary depression in terms of neuropsychological functioning and mood.

1.5 Thesis aims

- Conduct a series of case-studies of psychiatric adverse events associated with treatment
- Develop a better understanding of the side effects of IFN-α by developing and administering a semi-structured interview both retrospectively and prospectively in order to ask them about how they found their experience of treatment.
- Use results from the interview and a critical analysis of literature on research done on depression in patients taking IFN-α to develop a psychiatric and neuropsychological test battery to deliver to patients before and during IFN-α treatment.
- Compare the results of patients taking IFN-α to patients with a primary depression in terms of mood and neuropsychological functioning.
CHAPTER 2

Methods and Materials
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2.1 Experimental Design

In order to gain a comprehensive appreciation of the nature of the IFN-α induced neurobehavioural syndrome, and how this could be distinguished from symptoms that may accompany infection with HCV or a primary depression it was decided to design a series of experiments where both qualitative and quantitative data would be gathered and analysed in detail.

The aim of the qualitative research was to provide an insight into the experience of taking IFN-α from the patient’s perspective, and also further detail those psychiatric adverse events (PAEs) that can occur on treatment. This was achieved through the designing and administration of a semi-structured interview, and conducting detailed case-studies into those patients who developed a PAE on treatment.

The aim of the qualitative research was to compare across groups using measures commonly used in the assessment of mood with this population, and also through the designing of a novel neuropsychological test battery. The groups to be compared included HCV patients who were treatment-naive and taking IFN-α, those patients taking IFN-α who did and did not become depressed and also those patients who developed a depression while taking IFN-α and patients with a primary depression.

For the mood battery IFN-α participants were assessed at Baseline prior to commencing treatment (Week 0), and then at Weeks 8 and 20, for the neuropsychological test battery patients were assessed at Weeks 0 and 8 only. This is because previous studies suggest that the main psychiatric side-effects of treatment occur in the first half of treatment (Dan et al, 2006) around week 8 to 12 (Lieb et al, 2006; Wichers et al, 2005) and also 16 to 20 (Schaefer et al, 2003b).

More information on the types of assessments used is contained within the introductions at the start of each individual chapter, however specifics regarding the design, administration and analysis of each test is contained within this chapter.
2.2 Quantitative tests

2.2.1 Psychiatric Rating scales (Self-rating)

2.2.1.1 Hospital Anxiety and Depression rating Scale (HADS)

This 14-item questionnaire was developed by Zigmond and Snaith (1983) with a reduced number of somatic items for use in a medically-ill population (see Appendix I). It contains seven depression (HADS-D) and seven anxiety (HADS-A) items, where participants read a statement about mood and then decide between four answers which vary regarding how much that statement may or may not apply to themselves. The short administration time for test completion, make this an ideal test to screen for potential anxiety and depression problems.

Procedure and scoring

Participants were handed the questionnaire and instructed to read through the 14 statements on the sheet and for each statement they were asked to circle the response below each statement which they felt most accurately represented how they had been feeling in the last week. There was a choice of four responses, which were worded with differing levels of symptom disability. Each response was scored on a scale of 0-3, with higher scores indicating that they were more affected by that particular symptom. Once all responses were made, the items were split respectively into the depression and anxiety components, with a different score obtained for both syndromes. Scores on the scale were interpreted as follows; 0-7 no significant anxiety or depression; 8-10 doubtful or mild cases and 11-21 likely to be definite cases.

2.2.2 Psychiatric Rating scales (Experimenter-rated)

2.2.2.1 Structured Clinical Interview for Diagnostic Criteria (SCID)

The first step in analysis of mood was to determine whether a formal diagnosis of a psychiatric disorder could be made. In order to do this the mood disorders section of the structured clinical interview for DSM-IV (SCID; Spitzer et al, 1992). This interview follows a highly standardised format, which allows for greater validity and reliability between researchers. This interview was developed to be used in conjunction with DSM-IV-TR (see Appendix I).
### 2.2.2.1.1 Major Depressive Episode (MDE)

In order to obtain a diagnosis of depression, patients were required to score 3 on one or both of the core symptoms of depression, which comprise of depressed mood most of the day nearly every day and/or anhedonia. These symptoms were required to have occurred for at least 2 weeks in the preceding month, with a positive response for either of these domains that did not meet the time requirement or a sub-syndromal experiencing of these symptoms being scored as ‘2’ (subthreshold response), and when symptoms were absent or false a score of ‘1’ being given. If patients did not score 3 on either of these symptoms they could not be diagnosed with depression and so the interview was terminated. Should patient’s score ‘3’ on either or both of the two core symptoms they would be asked additional questions about a significant weight loss or gain (with significance being defined as 5% of previous weight) and appetite reduction or increase, whether either insomnia or hypersomnia was present, psychomotor agitation or retardation, feelings of worthlessness and inappropriate guilt, diminished ability to think or concentrate, recurrent thoughts of death and dying and/or recurrent suicidal ideation. In order to be diagnosed with a current MDE at least 5 of the 9 items investigated had to be coded ‘3’. Subthreshold depression was defined as meeting full criteria for four items plus sub-threshold criteria for at least an additional two items.

Where a diagnosis of depression with melancholic features was made this was when additional criteria were met including the core symptoms of anhedonia and lack of mood reactivity. Additional symptoms included a distinct quality of depressed mood, depression regularly being worse in the morning, early morning awakenings, marked psychomotor agitation or retardation, significant anorexia or weight loss and excessive or inappropriate guilt.

### 2.2.2.1.2 Hypomanic Episode

In order to attain a diagnosis of hypomania patients were required to firstly meet the core symptoms for this disorder; a distinct period of elevated, expansive or irritable mood which lasted for at least 4 days, which is clearly different from normal mood. They were then required to meet criteria for an additional three items (or four if mood was only irritated). In line with the depression section, a rating of 3 was given if the symptom was met, 2 if it was subthreshold in intensity or duration and 1 if the criteria was not met.
Further criteria for the diagnosis of hypomanic mood included inflated self-esteem or grandiosity, a decreased need for sleep, being more talkative than usual, experiencing racing thoughts and flight of ideas, being easily distracted by irrelevant or unimportant external stimuli, showing an increase in goal-directed activity or psychomotor agitation and finally excessive involvement in pleasurable activities that have a high potential for painful consequences.

2.2.2.2 Hamilton Depression rating scale 24-item (HAM-D)
Following assessment of whether depression presents in a patient, the second step in determining the nature and severity of the depressive symptoms by using a scale for the individual symptoms of depression, and rating these symptoms on a scale, with a higher score being indicative of a higher rate of disability. The Hamilton Depression Rating Scale employed was based on the original 21-item Hamilton Rating Scale for Depression (Hamilton, 1960) which looks at depressed mood, guilt, libido, suicidal tendencies, insomnia (early, middle and late), work and interests, energy level, anxiety and irritability, somatic symptoms of anxiety, hypochondriasis, appetite, loss of weight, insight, retardation, agitation, diurnal variation, depersonalisation, paranoid and obsessional symptoms, with an additional 3 questions focusing on helplessness, hopelessness and worthlessness included taken from Guy (1976). The interview was administered in a highly standardised format (Williams 1988), and was developed and validated by members of the Neurobiology of Depression Research Group at St. Patrick’s Hospital headed by Professor Declan McLoughlin.

Procedure and scoring
The standardised nature of the interview meant that a set series of questions were laid out for interviewers to ask, with positive responses being followed on by additional questions, with responses to questions either being marked on a scale from 0-4 or 0-2 (see appendix I), with a higher mark indicating more dysfunction in that specific domain. For each question, the summary of what constituted meeting criteria for each score was provided next to each score, so that a reliable and reproducible score was obtained. Some questions were reliant on interviewer observation rather than direct questioning (insight, psychomotor retardation and agitation), and there were clear indices within the interview for what constituted each score. The diurnal variation question was only asked if patient’s had a diagnosis of depression made through the
SCID, as this question was only to be asked if the patient was depressed. When all questions had been asked the total score was summed and reported. A significant depressive episode was defined as one where the total score was higher than 21.

2.2.2.3 Hamilton Anxiety rating scale 14-item (HAM-A)

The 14-item HAM-A was used in order to assess the presence of the psychic and somatic side-effects of anxiety (Hamilton, 1959). The scale looks at anxious mood, tension, fears, insomnia, intellectual problems, depressed mood, somatic: muscular complaints, somatic: sensory complaints, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms and behaviour at interview.

Procedure and Scoring

The questions for this interview were standardised in a format similar to the HAM-D by the experimenter (see Appendix I), so that internal reliability for that experimenter could be achieved. Participants were asked a question for each of the symptoms, with a positive initial response to a question followed by further inquiry into the extent that issue was affecting the individual. Each symptom was marked on a 5 point scale from 0 (symptom not present) to 4 (symptom causing severe impairment). For those items where somatic side-effects were present, but it was more likely that treatment side-effects were causing the symptom rather than anxiety, a rating of 1 (doubtful/slight problems) was given. The final question was reliant on interviewer observation and marked according to criteria set out in the questionnaire according to how anxious the patient reported themselves to be in the previous questions, and how they behaved during the course of the interview, with a score of 4 being given if the participant was in a clear state of anxiety characterised by shaking, trembling etc. Participants could score between 0 and 56, with a score of <17 indicating mild or no anxiety, 18-24 indicating mild to moderate severity of symptoms, 25-30 indicating a moderate to severe symptomatology, and 30 plus meaning the anxiety is severe.
2.2.3 Neuropsychological tests

2.2.3.1 Materials for test-battery
All computer tests were run on a Dell Latitude D600 laptop with a 15.5 inch screen. Participants were instructed to place the laptop at a distance where they could see clearly and easily and comfortably reach the spacebar on the computer (as this was the button where most responses were made). When using the Cedrus RB-420 response pad patients were told to place the laptop at a distance where they could see and the response pad in a position on the table where they could comfortably reach and respond. All tests were programmed using the E-Prime 1.1 stimulus presentation package [Psychology Software Tools (PST), Pittsburgh, PA].

2.2.3.2 Neuropsychological tests for functioning of the hippocampus

2.2.3.2.1 Face-Name Pairs task (FNP)

Materials and Stimuli
This face-name task is a modified version of the design described by Zeineh et al, (2003). In order to avoid potential problems with ‘floor’ results, due to the older age of the population studied within this chapter (a variable shown to affect face-name recall, lab observation; see Appendix II), the number of faces to be remembered was reduced from eight to six. The six faces presented were all female (selected from a college yearbook, all presented in black and white and with all their hair removed). During both the encoding and retrieval phases these faces were presented on the right half of the screen. In the encoding phase the left side of the screen would contain the corresponding name, and in the retrieval phase the name was replaced by the prompt “Name?” (see Figures 2.1 and 2.2).

Procedure
Prior to the start of the experiment, participants read through on-screen instructions which instructed them to try and remember which name went with which face. The experimenter then read through these instructions to the participants to clarify understanding before asking them to press the spacebar which began the test.

This task comprised four blocks of immediate recall, and following a half hour break one block of delayed recall with face and name recognition components (see Figure 2.2).
Face-Name Encoding
During the encoding blocks (see Figure 2.1 and 2.2), participants viewed 6 face-name pairs, which were presented serially at a rate of 3.5 seconds per pair, with an inter-stimulus interval of 500ms. The presentation order was constant across each of the encoding blocks.

Distracter Task
Between each encoding and retrieval block, a distracter task was presented to participants for 35 seconds (see Figures 2.1 and 2.2). During this task participants saw a fixation cross (20mm) presented in the centre of the screen, and at pseudo-random intervals of between 2 to 4 seconds the circle would turn black for 500ms. Participants were instructed to press the space-bar whenever the circle “flashed” black as quickly and accurately as they could. A total of 10 targets was presented to the participants.

Figures 2.1 and 2.2: Diagrams of FNP

![Diagram of FNP](image)

**Figure 2.1:** FNP running order. The Face-Name task comprises 4 blocks of encoding, distraction and immediate retrieval followed by a block of delayed retrieval, which also involved name recall and face and name recognition components.

![Diagram of FNP](image)

**Figure 2.2:** FNP; Encoding, distracter and retrieval components. Participants first encoded the six faces and name for 3500ms each, following this they carried out a distracter task where they were required to press the spacebar every time the fixation cross turned black. Each block ended with the retrieval component where they were asked to call out the name they believed belonged to each face.
Immediate Face-Name Retrieval

Following the distracter task participants viewed the six faces, which were presented in a randomised order, this time without the accompanying names (see Figures 2.1 and 2.2). Each face was presented for 3.5 seconds, with an inter-stimulus interval of 500ms, upon presentation of each face, participants were asked to vocally recall the name that they believed to correspond to each face. The experimenter recorded correct and incorrect responses, with a non-response being recorded as incorrect (see Appendix I).

Delayed Face-Name Retrieval

After a 30 minute delay, where participants were completing other tasks, participants were required to complete the recall as many correct face-name pairs as possible.

Delayed Name Recall

Following the 30 minute delay, participants were asked to vocally recall as many names as they could remember from the experiment, the total names correctly recalled was summed and reported.

Delayed Face and Name Recognition

Following the delayed Name Recall and Delayed Face Name Retrieval, participants were instructed that they would be see fourteen faces on the screen, presented centrally. Each face remained on the screen until the participant chose to press the spacebar to move onto the next face. Six of the faces were those that had been seen in the experiment and the other eight were faces that had not previously been seen. For each face participants were instructed to circle ‘yes’ or ‘no’ on their response sheet (see Figure 2.3), and then rate their certainty of their response by circling a number between 1 and 6, where 1 was representative of them being highly confident of their response, and 6 being very unconfident of their response (see Appendix I). They were then required to complete the same process for names. The total accuracy for this part of the experiment was the number of faces which were part of the experiment which were correctly identified as being part of the experiment. Misses were calculated as those faces which were part of the experiment, but were not identified by the participant. Correct foils were calculated as the total number of faces which were correctly identified as not being part of the experiment. False positives were calculated as those faces which were incorrectly identified as being part of the experiment.
The total certainty of responses was summed by calculating the percentage certainty for each response, and then adding together each of the fourteen percentages together to create a total score.

**Figure 2.3: Diagram of FNP recognition components**

Face and Name Recognition components of the Face-Name task. For the face recognition component of the test participants were shown the faces they saw during the task interspersed pseudo-randomly with faces they did not see. For each face participants were required to circle on a separate sheet whether they saw the face ‘yes’ or ‘no’, and then how certain they were of their response on a scale of 1 to 6, with 1 being 100% confident and 6 being not confident at all. Participants were also required to do this with names.

### 2.2.3.2.2 Everyday Memory Questionnaire (EMQ)

**Materials and Stimuli**

This self-rating questionnaire developed by Sunderland, Harris and Gleave (1984), consists of twenty-eight questions which measure how often within the last 3 months participants believe they have had problems with aspects of memory which people should encounter on an everyday basis (see Appendix I). The relative frequency of perceived memory problems are rated on a nine-point scale which ranges from ‘Not at all in the last three months’ to ‘More than once a day’, with higher scores indicative of more perceived problems with memory.

**Procedure and Scoring**

Participants were given the EMQ, and the experimenter read the instructions out to the participant and clarified understanding. Once participants understood the task, they were
asked to read through the individual questions and circle the appropriate response at their own pace (there was no time limit for this task). Once finished, the total score was obtained by summing the individual scores (from 0 to 8 per question). The square root of the total score was then calculated (as in Sunderland et al, 1984), and is the score reported in this thesis.

2.2.3.3 Neuropsychological tests for functioning of the PFC

2.2.3.3.1 N-back Tasks (0-Back, 1-Back and 2-Back)

Materials and Stimuli

A short version of the working memory task developed by Meyer-Lindenberg et al, (2001) was administered due to fatigability of the target patient groups. The stimuli used consisted of grey diamond shapes (16.9° x 16.9°) which were either blank, or contained the numbers “1” in the top corner (1.2cm x 0.8 cm), “2” in the left corner (1.2cm x 0.8 cm), “3” in the right corner (1.2cm x 0.8 cm) or the number “4” in the bottom corner (1.2cm x 0.3 cm). All diamonds were contained within a 0.75 pt outline against a white screen (see Figure 2.4).

Responses were recorded on a Cedrus RB-530 response pad, which participants positioned according to where they felt comfortable. The response keys were positioned in the same spatial arrangement as seen on the screen.

Procedure

Each diamond was presented for 1800ms, and was followed by a blank screen for 200ms. Stimuli were presented in a pseudo-random sequence, where appropriate in a sequence of nine.

O-Back

Participants were instructed to view the screen and press the number on the keypad which corresponded to the number currently on screen as accurately and quickly as they could. A total of 45 stimuli were presented (see Figure 2.4)

1-Back

For this section of the task participants were instructed to press the keypad which corresponded to the number viewed one trial previously (i.e., the trial that was 1-Back). For this part of the experiment participants were required to hold the previous number they saw on-line while also attending to the current number on screen, meaning that they were required to constantly be updating the number they were responding to (see Figure
2.4). In order to break this section of the experiment up, the stimuli were broken up into sequences of nine, with a blank diamond presented after every nine numbers. This meant that participants were still required to respond on the blank diamond, but as the next trial started they had to withhold their response until the second number.

For both this and the 2-Back participants performed a short (44 s) practice run, which ran through two blocks of nine numbers. Participants continued through to the test itself once they and the experimenter were happy that they understood the task. The test itself comprised of five blocks of stimuli organised in a pseudo-random sequence.

2-Back

This section of the task was organised in a similar way to the 1-Back, except participants were required to respond to the number that was two trials back instead of one. This meant that after every block of nine there were two blank diamonds presented instead of one, and that participants were required to withhold their response for 2 trials at the start of each block until the third stimulus (see Figure 2.4).

For all sections of the N-Back total percentage correct (accuracy) and reaction time were automatically recorded by E-prime, and means were calculated using this package.
Diagram showing how participants should respond for each part of the N-back. For the 0-back they are required to press the number currently on screen, for the 1-back they are required to press the number they viewed one trial previously, and for the 2-back they are required to press the number viewed two trials previously. The stop sign indicates where participants should withhold their response.
2.2.3.3.2 Sustained Attention to Response Task (SART)

Materials and Stimuli

The numerical stimuli 1, 2, 3, 4, 5, 6, 7, 8, and 9 were presented centrally in black on a white screen. Each stimulus was 20mm in size and followed by a 20mm black diagonal response cross, contained within a circle.

Procedure

The digits 1 to 9 were presented sequentially for 500ms and were followed by a response cross for 500ms. Participants were instructed to press the spacebar on the response cross after every digit, except for the number “3” (see Figure 2.5). Therefore, every time the number 3 appeared, participants were required to withhold their response. This test comprised a single block, where there were 25 trials (i.e., the digits 1 to 9 were presented 25 times).

Figure 2.5: Diagram of the SART

Accuracy was calculated as the total percentage where the target number 3 was correctly ignored. Also calculated were errors of omission (percentage of stimuli 1, 2, 4, 5, 6, 7, 8, and 9, where a response was not made appropriately, indicating a pre-emptive or missed response by the participant). The final measure was errors of commission.
(percentage of target stimulus “3” that was incorrectly responded to). Also measured was task reaction time in ms.

2.2.3.3.3 Stroop Task

Materials and Stimuli

The words red, yellow, blue and green were presented in a coloured font that was congruent in 75% of trials (colour and word matched), and incongruent for 25% of trials (colour and word different). The words were presented centrally on a white background in Tahoma size 48 font. Participants made their responses on the Cedrus RB-530 response pad, where each of the four response keys corresponded to the four colours used in this experiment.

Procedure

It was explained to participants that they were required to press the keypad that corresponded to the colour that the word was written in rather than what the word itself was (see Figure 2.6), once they understood the task they pressed the spacebar to start.

Each word was presented centrally on the screen for 1300ms, with a blank screen presented for 300ms between each word. One block of 102 words was run, of which 7 of the trials were incongruent. Once completed, mean accuracy and reaction times for both the congruent and incongruent trials was calculated.

Figure 2.6: Diagram of the Stroop Task

A schematic showing how the stroop task was run. Each word was presented for 1300ms and participants asked to press the keypad that corresponded to the colour that the word was written in, rather than what the word itself was. Each word was followed by a 300ms break where a blank screen was shown.
2.2.3.3.4 Items from the Behavioural Assessment of Dysexecutive Syndrome (BADS)

The BADS was developed by Wilson et al. (1996), in order to assess impairments specific to the PFC utilising six tests and two questionnaires that are high in ecological validity. Due to time constraints and the fatigueability of the population to be tested, two of the tests and one of the questionnaires were chosen to administer to patients.

Zoo-Map Test

Materials and Stimuli

This test measures ability to formulate and implement a plan in a high demand (version 1) and low demand (version 2) condition. Instructions for the test were contained at the top of a sheet which also contained the zoo map in a black box (17cm x 14.5 cm; see Appendix I).

Procedure

Participants were read aloud the instructions at the top of the page. For version 1 they were instructed to plan a route in order to visit the specified animals in the order which allowed them to obey the specified rules. Participants were timed in how long it took them to plan out their route, and then the total time it took them to complete the test. For version 2 they were instructed to visit animals in the order indicated at the top of the page while obeying the same rules, and again were timed in how long it took them to plan and carry out the task.

Once both tests were completed they were marked according the scheme in the BADS handbook (page 3), with each animal visited in the correct order scoring ‘1’, and each incorrect animal visited, occasion path used more than once, deviation from the path or failure to make a continuous line meaning they had a point deducted. They could score a maximum of 8 for each version of the task, with a total possible score of 16.

Key-search Test

Materials and Stimuli

This test assessed ability to plan a strategy in order to solve a problem. The test was presented on a white A4 sheet of paper, with a square box (10 x 10cm) drawn in a black outline, under which there was a small back dot (see Appendix I).
Chapter 2: Materials and Methods

Procedure
Participants were instructed according to instructions in the BADS handbook (page 9), briefly they were asked to imagine that the square box in front of them was a field, and that somewhere in that field they had lost their keys, then starting from the black dot bellow the box, enter the field and draw out the route they felt would be most effective for them to find the keys, stopping only when they were 100% sure they had found the keys. They were handed a pen and timed while they carried out this task. Once completed, they were marked according to the scheme in the BADS handbook (page 20), with marks given for where they entered the field (0-3), finishing the search (0-3), whether a continuous line was drawn (0-1), whether the line was parallel (0-1) or vertical/horizontal (0-1), attempting to cover all ground (0-1), whether they found the keys (0-1), and the efficiency of the search pattern employed (0-5; demonstrated on page 21 of the BADS handbook). Participants could score a maximum of 16.

DEX questionnaire

Materials and Stimuli
This 20-item questionnaire was designed in order to quantify the various behaviours associated with dysexecutive syndrome. The ratings of the following behaviours (abstract thinking problems, impulsivity, confabulation, planning problems, euphoria, temporal sequencing problems, lack of insight and social awareness, apathy and lack of drive, disinhibition, disturbed impulse control, shallowing of affective responses, aggression, lack of concern, perseveration, restlessness/hyperkinesis, inability to inhibit, knowledge-response dissociation, distractability, loss of decision making ability, unconcern for social rules) are made on a Likert-scale, with participants reporting the frequency of each event from the questionnaire from never to very often (see Appendix I).

Procedure
Participants were instructed to read each of the statements and then mark down how often those things happened to them. Once complete the questionnaire was marked according to the following scale: never (0), occasionally (1), sometimes (2), fairly often (3), and very often (4). The score was then summed across each of the domains, with higher scores indicating more dysexecutive problems.
2.2.4 Statistical tests

Results from quantitative tests were analysed using parametric and non-parametric tests depending on data normality. Where data normality could not be established using the Shapiro-Wilk's test of normality a non-parametric test was run; in order to ascertain within-group variance a one-sample Kolmogorov-Smirnov analysis was run. Furthermore when data necessitated the formal comparison of two independent groups the Mann-Whitney U test was used, and where a within-groups design had been employed the Wilcoxon Signed-Rank test was used.

However, when normality was established parametric tests were used. T-tests were used when statistics necessitated the comparison of two groups; independent-samples t-tests were used to compare between two groups, repeated-measures t-tests were used to compare within groups. Where any violation of normal variation was seen, modified t-values and degrees of freedom were reported.

Where there were more than two groups ANOVA tests were used. A one-way ANOVA was used to analyse between-groups and a repeated-measures ANOVA was used to compare within-groups. Where there was mixed-methodology and both within and between-groups data needed to be analysed simultaneously a mixed-methods ANOVA was employed. When significance was detected post-hoc tests were employed in order to detect where significance lay; for the most part it was decided to use Bonferroni comparisons due to the more conservative nature of this test. All data were checked for homogeneity of variance and where appropriate, if this assumption was violated, modified degrees of freedom were used. For the repeated-measures ANOVA where assumptions of sphericity were violated as indicated by the epsilon value (i.e., a value of 1 indicates normal sphericity), modified degrees of freedom were used based upon either the Greenhouse-Geisser correction (when the value of the epsilon fell below 0.75 as this test was more conservative) or the Huynh-Feldt correction (when the epsilon value was above 0.75).
2.3 Qualitative tests

2.3.1 Development of Interview

This interview was designed based on the literature review conducted in Chapter 1 of this thesis, and through consultation with healthcare professionals who work closely with people who take IFN-α in St. James’s Hepatology Centre, Dublin. When a literature search was conducted in Pubmed using the terms “Interferon alpha and Hepatitis C and side-effects”, there was 2560 results. Of these results the side-effects of both treatment and HCV could be broadly broken down into effects on; health, psychological functioning (depression, anxiety and irritability), sleep and fatigue and finally cognition (see Chapter 1; Sections 1.2.2 and 1.2.3 for discussion of these side-effects).

It was therefore decided to develop an interview that would examine each of these domains in detail using both quantitative questions where participants would be asked to rate functioning in each of these areas on a Likert-scale and qualitative questions where they would be asked to explain their answers in more detail. Questions were developed based on the SF-36 health survey, the Pittsburgh Sleep Quality Index (PSQI) and other basic Likert scale questions that covered all the other domains (see Appendix III for a copy of all the interviews used in Chapters 2 and 3). The interview was developed and conducted with approval from the St. James’s Hospital Ethics Committee and the School of Psychology Trinity College Dublin Ethical Committee (see Appendix IV).

2.3.2 Administering the interview

Procedure

Each participant was sat perpendicularly to the interviewer, and was explained to that the interviewer would be recording the session so that they could transcribe the interview at a later date, and that once the interview was complete the interview would be transferred to a secure computer, and deleted from the recorder.

Once participants were comfortable, the interviewer read out the following short statement informing participants about the nature of the interview:

“This interview is designed so that I may try and understand how your illness makes you feel. In general anything you tell me will be in complete confidence, however if during the course of this interview something is said which may be a cause for concern and means that you own health and wellbeing or that of some-one else may be at risk I will advise you on how you can get help concerning
this with the help of your treatment nurse or the consultant hepatologist. However the results from this interview shall be in an anonymous format and your name will never be used in relation to the data gathered from this interview. Some questions may seem fairly personal and if you really don’t want to answer them then please just let me know. I would appreciate it if you could answer all questions as truthfully as possible.”

Due to the sensitive nature of some of the questions that were asked, there was a chance that patients could reveal sensitive information, and should this happen, clinicians involved in the care of that patient would be informed and henceforth the best course of action for that patient decided upon (for a discussion on this and other ethical issues please see Appendix V).

Once patients had given their verbal consent to the statement read out by the interviewer, the digital voice recorder was switched on and the interview began. The interviewer followed the transcript set out for themselves, unless anything was said which was of particular interest or more information was required for a certain question. If this was the case patients would be prompted by the interviewer asking “Can you tell me more about that?” Once the interview was complete the interviewer would ask if there was anything else that the patient thought it important to talk about, and following that the interview was terminated and the digital voice recorder switched off.

The experimenter then transferred the interview from the digital voice recorder onto the computer, following which it would be deleted from the voice recorder. Once transferred, the interview would be transcribed into a word document, where after it would be analysed.

Scoring

All quantitative data were rated on a five point scale, and was scored from 0-4, with 0 being the least impaired and 4 being the most impaired. The only exceptions to this were the bodily pain question, rated on a six point scale, in line with the question it was based on from the SF-36, and the difficulty sleeping question rated on a scale from 0-3 depending on the number of nights per week where difficulty was had sleeping. The question based on the PSQI was rated in a more complicated way in line with that questionnaire. In order to obtain a score for sleep quality, responses from questions 12a to 12d (see Appendix VI for formal analysis) were analysed, and a total score for sleep quality was obtained from 0 to 9, with 0 meaning sleep quality was excellent, and 9 meaning sleep quality was very poor. Where appropriate any qualitative data were coded using the principles of thematic analysis.
2.3.3 Choice of qualitative analysis

Qualitative interview analysis is based on observer impression, with the researcher breaking down data into core components which explain the content of most patient’s interviews. There are a number of analyses potentially employed by researchers; thematic analysis (where emergent themes are discussed), content analysis (where data is coded and categories determined), narrative analysis (where interviewers describe and explain a narrative of findings) and discourse analysis (where speech patterns and metaphors are analysed).

Qualitative analysis is a more involved form of analysis than quantitative, with the researcher and their interpretation of presenting issues being of paramount importance for the themes or categories that emerge from the data. This subjectivity has been used by some researchers as grounds for criticism and questions regarding reliability of results (Madill et al, 2000). However, this issue can in part be remedied by using a grounded theory framework (Glaser, 1992), where rather than inferring conclusions based on feelings and metaphors, there are systematic steps that a researcher must go through in order to code and breakdown material. In order to conduct a grounded-theory type analysis it is necessary for the researcher to become familiar with the data by immersing themselves somehow within it, the most time-consuming but effective way to achieve this is through transcription of each individual interview. After this a systematic coding of material takes place, and categories are defined and checked throughout text, discussion of findings takes place in order to justify findings. This type of realist framework can easily be applied when conducting either a content, narrative or thematic type analysis.

When deciding which type of analysis to conduct for this dataset thematic analysis was chosen due to its flexibility, pure qualitative nature (unlike the more quantitative form of content analysis; Ryan and Bernard, 2000) and the fact that it is better suited to the larger number of interviews to be studied (unlike narrative theory which is better suited to individual interviews), this also appeared to be the type of analysis favoured by other researchers within the field of qualitative HCV research (Butt et al, 2008; Conrad et al, 2009; Janke et al, 2008; Lally et al, 2008; Zickmund et al, 2003). There are two main types of thematic analysis that can be used; inductive analysis uses a top-down approach where the data drives the themes that are determined (Patton, 1990), whereas theoretical analysis is driven more by the researchers interest in
the area, and so is driven more-so by certain areas of interest (Boyzatis, 1998). As we wished to look at specific areas of interest, driven by research findings on the effects of IFN-α we decided that a theoretical thematic analysis would be the most appropriate for this dataset.

2.3.4 Principles of thematic analysis

For the qualitative data a thematic analysis was run within responses made in each category that was examined within the interview. The principle of thematic analysis is to extract the main themes that sum up best the content of patient’s interviews via a series of structured steps (see Table 2.1).

Table 2.1: Phases of thematic analysis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description of the process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Becoming familiar with data</td>
<td>Transcribing data; reading and re-reading data and noting down initial ideas</td>
</tr>
<tr>
<td>2. Generating initial codes</td>
<td>Coding interesting features of data in a systematic fashion across the entire data set, collecting data relevant to each code</td>
</tr>
<tr>
<td>3. Searching for themes</td>
<td>Collecting codes into potential themes, gathering all data relevant to each potential theme</td>
</tr>
<tr>
<td>4. Reviewing themes</td>
<td>Checking if the themes work in relation to the coded extracts and then the entire data set; generating a thematic 'map' of the analysis</td>
</tr>
<tr>
<td>5. Defining and naming themes</td>
<td>Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme</td>
</tr>
<tr>
<td>6. Producing the report</td>
<td>Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back to the analysis to the research question and literature; producing a scholarly report of the analysis</td>
</tr>
</tbody>
</table>

Phases of thematic analysis; taken from Braun and Clarke (2006)

Firstly the data is transcribed by ear in order to get more familiar with the data. Once this is done each interview is broken down into the categories that have been explored by the researcher (in the case of this interview that is health, sleep, fatigue, mood, personality and cognition). These identified patterns are then further broken down into sub-themes which are derived from recurring conversation topics, vocabulary, meanings and feelings (Taylor and Bogdam, 1989). By identifying themes the researcher is able to bring together individuals feelings and ideas in order to form what could be viewed as a collective experience of people studied in that particular
group. Once this was achieved, the rationale for creating each theme is discussed in detail within the results section. Categorical variables were examined during the thematic analysis, as these were the questions that acted as prompts for participants to speak at length about the various domains.

2.4 Recruitment and criteria for participants

2.4.1 Control participants

Control participants were recruited from the Trinity College Dublin electronic notice-board and an advert in the Irish Times newspaper. Once recruited, participants were informed that they would receive 20 Euros in return for completing the interview and neuropsychological tests or 10 Euros in return for completing the mood tests and blood sample. Inclusion criteria included being between 18 and 60 years of age; exclusion criteria included having any significant medical co-morbidities, being pregnant, having a poor grasp of the English language, having engaged in any potential risk factors for HCV infection, being pregnant, being on any drugs which could adversely affect results or current psychiatric morbidity.

2.4.2 HCV participants

Patients with HCV were recruited from St. James’s Hospital Hepatology Centre, via a poster in the waiting room of the clinic, posters sent out to the support groups ‘Positive Action’ and ‘Irish Haemophilia Society’ and, finally, through identifying suitable patients with nursing staff at the hospital and approaching them to see whether they would be willing to take part. For those people with HCV, inclusion criteria included being HCV positive and treatment-naive. Patients were required to be between 18 and 60 years old, and have a good grasp of the English language. Exclusion criteria included having any other significant medical co-morbidities which could influence results, being pregnant, current drug or alcohol abuse or any other current psychiatric diagnosis.

2.4.3 IFN-α participants

Patients were recruited from St. James’s Hospital Hepatology Centre, via the same procedures used to recruit the HCV patients, which included a poster in the waiting room for the out-patient clinic, posters being sent out to HCV support groups and
finally identifying suitable patients with the help of nursing staff and directly approaching patients.

For the interview chapter patients were required to be between 18 and 60 years old, and have a good grasp of the English language. Exclusion criteria included having any other significant medical co-morbidities which could influence results such as being pregnant, current drug or alcohol abuse or any other current psychiatric diagnosis.

For both the neuropsychological testing (Chapter 6) and mood (Chapter 7) chapters inclusion criteria included being between the ages of 18-65, having HCV, and due to start treatment with IFN-α. Exclusion criteria included being currently diagnosed with major depression or any other active psychiatric disorder, having actively abused substances (alcohol or drugs) within the previous six months, having any other significant medical co-morbidity which could influence results (e.g., HIV, heart disease, autoimmune condition).

2.4.4 Depressed participants
All Depressed patients were recruited from St. Patricks Hospital, Dublin. Prior to research commencing all consultants within the hospital were approached with information on the study, and signed off if agreeable to their patients being approached to take part in the study. Suitable patients were identified with the help of nursing staff, and by assessing patient charts, and then were approached directly to ask whether they were willing to take part. Inclusion criteria included being between the ages of 18 to 65, having MDD of mild to moderate severity. Exclusion criteria included any other significant medical or psychiatric co-morbidity, or being on any medication which could adversely influence results.
CHAPTER 3

Case-studies of IFN-α-induced psychiatric adverse events
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3.1 Introduction

Case-studies provide psychologists with an opportunity to examine rare adverse events in more detail. As IFN-α can be associated with psychiatric adverse events (PAEs), a number of studies have sought to describe the more extreme of these adverse events in more detail (see Table 3.1). Among the extreme PAEs described in literature are attempted suicide (Fukinishi et al., 1998; Janssen et al., 1994) and psychosis (Onyike et al., 2004; Robaeys et al., 2007).

**Table 3.1: Case studies of rare PAEs**

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient</th>
<th>PAE</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukinishi et al (1998)</td>
<td>50 year old woman with HCV. No psychiatric or medical history. Prescribed natural type IFN-α 9 MU (everyday for 14 days then reduced three times per week).</td>
<td>21 days after dose-reduction she became nervous about her illness and developed anxiety, irritability, insomnia and mild depression. After 5 weeks of treatment she attempted suicide by pouring lamp oil on herself and setting herself on fire</td>
<td>She was hospitalised and treated with anxiolytic and hypnotic drugs, and was discharged after 2 months.</td>
</tr>
<tr>
<td>Goldman (1994)</td>
<td>30 year old woman depressed prior to treatment. Prescribed 3 MU three times per week.</td>
<td>After 1 month of therapy she became irritable, and was crying with little or no provocation. She lost interest in socialising and reported diminished appetite, sleep, energy and concentration. She displayed suicidal ideation without a plan.</td>
<td>After 2-3 weeks of nortyptyline treatment her mood improved.</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td><strong>Patient</strong></td>
<td><strong>PAE</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td>Oniyke <em>et al</em> (2004)</td>
<td>39 year old male with history of IVDU. Prescribed 180μg weekly PEG-IFN and Ribavirin 1200mg.</td>
<td>After 3 weeks of treatment the patient presented with mania. He denied having hallucinations or delusions despite presenting with euphoric and grandiose symptoms. Showed poor insight and judgement.</td>
<td>Assessment of history revealed he had suffered a previous manic episode unrelated to IFN-α treatment. After treatment with Haloperidol and Lithium the mania remitted.</td>
</tr>
<tr>
<td>Robaeys <em>et al</em> (2007a)</td>
<td>49 year old female with no medical history. Prescribed 120μg IFN-α-2a weekly with 1000mg Ribavirin daily.</td>
<td>She developed an influenza-like syndrome with a loss of appetite, myalgia, arthralgia, fever and weight loss, and also developed delusional parasitosis.</td>
<td>Treatment had to be discontinued.</td>
</tr>
<tr>
<td>Schafer <em>et al</em> (2000)</td>
<td>33 year old male with history of substance abuse and Depression.</td>
<td>The patient initially developed an influenza-like syndrome. After 5 months he became paranoid and anxious. After 6 months he lost his appetite and weight. He became fatigued, anxious, depressed and irritable. After 8 months he became delusional, suspicious, paranoid, emotionally labile, socially withdrawn and developed suicidal ideation.</td>
<td>Treatment discontinued, but symptoms were only reduced when receiving antipsychotic medication.</td>
</tr>
<tr>
<td>Yokoyama <em>et al</em> (1996)</td>
<td>Patient 1: 38 year old female. Treated with 9 MU IFN-α-2a (everyday for 14 days then reduced three times per week). Patient 2: 57 year old female. Treated with 9 MU IFN-α-2a (everyday for 14 days then reduced three times per week).</td>
<td>Patient 1: After 2 weeks she developed an influenza-like syndrome and anxiety. After 1 month she became depressed and was displaying fatigue, insomnia, appetite loss, psychomotor retardation and self-accusation. Patient 2: She developed an influenza-like side-effect profile after a few weeks. Within a month she developed insomnia and became agitated and restless, becoming confused and delirious.</td>
<td>Patient 1: After 3 weeks of antidepressant therapy symptoms improved. Patient 2: She commenced neuroleptic therapy which improved symptoms within a month.</td>
</tr>
</tbody>
</table>

Table showing rare PAEs associated with IFN-α treatment

The aim of this Chapter was to examine the PAEs that can occur during therapy with IFN-α, by conducting case-studies with patients who were diagnosed with a psychiatric disorder using the Structured Clinical Interview for DSM-IV (SCID).
3.2 Methods and Materials

3.2.1 Psychiatric rating scales

A short mood battery was administered to patients due to start treatment with IFN-α at baseline, 8 weeks into treatment and 20 weeks into treatment. The test battery comprised the HADS, HAM-D, HAM-A, DEX questionnaire and SCID, all of which are described in further detail in Chapter 2 of this thesis (sections 2.2.1, 2.2.2 and 2.2.3.3.4).

3.2.2 Participants

39 patients due to start treatment with IFN-α were recruited from the Hepatology Unit at St. James’s Hospital Dublin. Of those patients recruited 5 developed a serious PAE on treatment (see Table 3.2). All patients were taking 180μg PEG-IFN-2b subcutaneously once per week, with a weight-based dose of Ribavirin (800-1200mg) once per day.

Participants were recruited via procedures laid out in Chapter 2 of this thesis (section 2.4.3).

Table 3.2: Demographic information for case-studies

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age ± SEM</th>
<th>Gender</th>
<th>Genotype</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomania</td>
<td>2</td>
<td>33.5 ± 2.5</td>
<td>M: 2 (100%)</td>
<td>3: 2 (100%)</td>
<td>IVDU: 2 (100%)</td>
</tr>
<tr>
<td>MDD</td>
<td>3</td>
<td>38.67 ± 3.5</td>
<td>M: 3 (100%)</td>
<td>1: 1 (33%)</td>
<td>IVDU: 3 (100%)</td>
</tr>
</tbody>
</table>

Table showing the demographic data for the 5 patients who developed a serious PAE on treatment (IVDU: patient infected through intra-venous drug use).
3.3 Case-studies

3.3.1 Case-studies of those patients who experienced severe psychiatric adverse effects on treatment.

Of those 5 patients who developed severe PAEs, four did so at Week 8 and one did so by Week 20. Their cases are described in more detail below.

3.3.1.1 Hypomanic Mood

Patient 402

**Background:** A 36 year old married male presenting with genotype 1 of HCV. The patient had a history of substance abuse and anti-social behaviour. He was prescribed 180µg PEG-IFN weekly with 1200mg Ribavirin daily, he was also taking with Nexium for acid reflux.

**Baseline Assessment:** The patient was very quiet and fairly uncommunicative; he reported having no problems with mood, yet did admit to having problems with stress. He did not readily elaborate of any of his answers and would often have to be prompted to give more detail for an answer. His Baseline mood scores were 10 for the HAM-D, 13 for the HAM-A, 11 for the DEX and 9 for the HADS-A and 5 for the HADS-D. His SCID showed no significant problems with any psychological disorder.

**Week 8 Assessment:** By week 6 of treatment this patient was reported to have developed some psychological side effects by his treatment nurse. At the Week 8 assessment they had been referred to a psychiatrist and prescribed Lithium and Olanzapine for a highly irritated mood. When administered the mood test battery he reported having low mood, but appeared elated and was displaying significant psychomotor agitation. Where at baseline the patient had been uncommunicative, he now appeared disinhibited and spoke at length about issues he was having without having to be prompted.

When the interview for the SCID commenced he reported displaying no interest in activities that had previously interested him, and was actively isolating himself from his family and friends. When asked about weight, he mentioned a significantly increased appetite and weight gain. His sleep was disturbed, with insomnia resulting from severe nightmares experienced for the last 2 weeks. He reported having no difficulty with falling asleep; however, he would wake frequently during the night and...
experienced early morning awakenings at 1-2am. Despite the observed agitation, the patient reported that he was suffering from severe fatigue to the point of leaden paralysis. When asked about how he felt about himself, he spoke of feeling worthless, and that the medication he was on did not help with this, but had helped with the anxiety and anger he had been experiencing previously. His ability to concentrate was very low, and finally when asked about suicidal ideation he did admit to thinking a lot about his own death and having fleeting thoughts of killing himself, however, he had not done anything about this.

In addition to the items explored in the MDE section of the SCID additional questions were asked about hypomanic mood as previous answers given indicated that this could have been the issue that was affecting the patient. He met the criteria for hypomanic mood as he displayed an abnormally elevated and irritable mood that had lasted for 3 weeks prior to the assessment. He was sleeping less than usual and while this seemed to distress him, it appeared that the treatment itself was responsible for any fatigue he was displaying rather than the reduced sleep. He was much more talkative than usual and reported racing thoughts, many of which were related to paranoid ideation, he kept referring to the fact that he had done some “bad things” and knew some “bad people”, and he believed that these bad people were going to come to his door and shoot him. He also displayed increased distractibility within the testing session as during the interview he would often start a new conversation in the middle of an answer for the previous question.

**Week 8 Summary:** Met diagnostic criteria for hypomanic episode (distinct period of persistently elevated mood, decreased need for sleep, more talkative than usual, racing thoughts, distractibility and excessive involvement in pleasurable activities that have a high potential for painful consequences). His mood scores increased to 28 for the HAM-D, 31 for the HAM-A, 31 for the DEX and 17 for the HADS-A and 12 for the HADS-D.

**Follow-up:** Following the assessment the patient encountered problems at home which led to him being thrown out of his home. He went on a drugs binge and ended up in the Accident and Emergency Department following an overdose; this involvement in an activity the patient found pleasurable that had highly painful consequences both for him and his family confirmed the diagnosis of hypomanic episode. Following this
incident he was discontinued from treatment at week 9 and referred to a psychiatrist for follow up sessions.
Patient 411

**Background:** A 31 year old single male with a history of substance abuse. He had genotype 1 of Hepatitis C and was prescribed 180μg of PEG-IFN weekly with 1200mg/day of Ribavirin. He was also taking Nexium for acid reflux.

**Baseline Assessment:** At Baseline the patient appeared open and talkative, he talked at length and unprompted about the support he received from the Narcotics Anonymous group that he was a part of. When administered the SCID, he reported a sub-threshold reduction in mood and enjoyment of previously enjoyable activities. His Baseline mood scores were 6 for the HAM-D, 6 for the HAM-A, 24 for the DEX and 6 for the HADS-A and 2 for the HADS-D.

**Week 8 Assessment:** Due to a reported low mood at week 4 the patient had been prescribed the anti-depressant Cipramil by his treatment nurse. When the patient came to the assessment he appeared to be more agitated and nervous than he had done at baseline. When administered the SCID he reported having depressed mood for most of the day nearly every day which had lasted for 3 weeks, with him feeling particularly bad over Christmas. He also spoke of a mild depersonalisation, and was isolating himself from other people. Where previously he had enjoyed going to the gym for 3-5 hours a week, he now did not go at all, and believed that this was not due to a loss of energy but a loss of motivation. His weight had decreased slightly although his appetite was normal. His sleep was reduced to 4 or 5 hours per night and he mentioned a severe problem with falling asleep as this often did not happen until 4am or 5am most mornings. When he did sleep he spoke of experiencing lucid dreams, which was something that he seemed to be enjoying. When asked why he believed his sleep to be affected, he referred to experiencing racing thoughts regarding his relationships with other people. Despite this reduction in sleep, he did not have any issues with fatigue, reporting that he had more energy than usual. When asked about how he felt about himself he talked about feeling rejected by people such as his father, and that he generalised this fear to other people. His memory was subsyndromally-impaired, and finally he experienced no suicidal ideation. When the HAM-D was administered, and the question about libido asked, the patient admitted to taking Viagra so that he could continue having sex, despite the fact he was not in a relationship with anybody. It was at this point that he admitted to engaging in risky sexual activity with an individual he
knew to be HIV positive, and at this point it was decided to administer the SCID for a hypomanic episode. Despite feeling depressed, his mood had been elevated for the last few days, and he reported feeling anxious and irritable and at times depersonalised. His sleep was reduced, yet he believed it was not a problem, and that he felt rested after this sleep. He also displayed psychomotor agitation, and an increase in goal-directed activity (specific to sexual gratification), and was involved in sexual indiscretions that had a high potential for adverse consequences. The patient was also more talkative than usual, and seemed more disinhibited than he had done in the previous session, as indicated by the fact he openly talked about his sex life, something he had not done previously. He also admitted to racing thoughts regarding relationships, both sexual and social.

**Week 8 Summary:** Met criteria for hypomanic episode (distinct period of expansive mood, decreased need for sleep, more talkative than usual, racing thoughts, increase in goal-directed activity and excessive involvement in pleasurable activities that have a high potential for harmful consequences). His mood scores increased to 20 for the HAM-D, 16 for the HAM-A, his DEX score actually decreased to 29, however both his HADS-A and HADS-D scores increased to 15 and 8 respectively.

**Follow-up:** At the Week 20 follow-up the patient reported that the 8 week session had been a “wake-up call” for him, and that he had previously assumed that nothing was wrong with him, but had been forced to admit that something was wrong, and so had been seeking help from both his treatment nurse and people at his narcotics anonymous treatment group. When administered the SCID at follow up, he reported that his mood had improved significantly, and that he was choosing to discontinue antidepressant treatment, however, his interest in previously enjoyable activities had not returned to normal. He reported a normal appetite, no problems with sleep, fatigue, feelings of worthlessness, no impaired concentration or memory and no suicidal ideation, however he still displayed psychomotor agitation. His HAM-D score increased to 24, however his HAM-A score decreased to 11, and his DEX score increased slightly to 35, his HADS-A score increased to 16 and HADS-D to 13. Despite this increase in most mood scores, his SCID interview indicated a subsyndromally depressed mood. Following his 5 month follow-up, the patient successfully completed a 48 week course of treatment with no further psychological issues.
3.3.3.2 Major Depression

Patient 417

Background: A 44 year old married male with a history of substance abuse. He presented with genotype 1 of Hepatitis C and was prescribed 180µg of PEG-IFN weekly with 1200mg/day of Ribavirin.

Baseline Assessment: At Baseline the patient was fairly quiet and had to be prompted to answer questions in any detail. He reported that his mood was fine and that recently he had been motivated to make some positive changes in his life including getting fitter. His Baseline mood scores were 4 for the HAM-D, 2 for the HAM-A, 6 for the DEX and 7 for the HADS-A and 5 for the HADS-D.

Week 8 Assessment: At Week 8 the patient showed signs of blunted mood, this was communicated both verbally (blunted emotional affect) and non-verbally (facial expression). When administered the SCID he reported having depressed mood for most of the day every day, with the last 3 weeks being particularly bad. He also talked of being a lot more irritated and was getting more annoyed with his family, describing a general feeling of being “pissed off”. He also reported that the physical side effects of treatment were causing him psychological distress. When asked about his motivation he reported a feeling of not looking forward to most things and that when he was around people he felt “flat”, which he put down to the fact that his life was having to revolve around treatment. He reported no problems with weight or appetite, however, he did have a problem with insomnia, with his average night’s sleep reduced by 3 hours per night. When asked about fatigue he mentioned that this was severely affected, with a feeling of leaden paralysis affecting him. He admitted to feeling “down on himself”, but this did not reach a level of clinical significance. His cognition was also severely affected, with his concentration being particularly affected. However he spoke of no suicidal ideation. The lack of emotional reactivity led to a hypothesis that the melancholic depressive subtype could have been what the patient was displaying as he met criteria for the loss of pleasure in almost all activities and a lack of reactivity to usually pleasurable stimuli, he spoke of no longer enjoying being around his grandchildren which was something that always used to make him happy. When asked further questions he then admitted that the mood he was experiencing was distinct from
anything he had ever previously experienced, and that he suffered from early morning
awakenings and that his mood was regularly worse in the mornings. He also displayed
marked psychomotor retardation.

**Week 8 Summary:** The patient met criteria for a MDE with melancholic
features (Depressed mood; a distinctly different mood, loss of interest in usual
activities (with a loss of reactivity to normally pleasurable stimuli), insomnia (with
early morning awakenings), psychomotor retardation, fatigue and cognitive problems
specifically with concentration. His HAM-D score was 25, his HAM-A score was 21,
his DEX score was 15 and his HADS-A score was 14 and his HADS-D score was 16.

**Follow-up:** At the Week 20 assessment the patient revealed that 4 weeks ago he
had been administered Cipramil by his treatment nurse, and that in the last week he
noticed that his mood had lifted. However, when the SCID was administered he still
exhibited the same depressed and irritated mood and diminished interest in previously
pleasurable activities as before; however, the leaden paralysis previously exhibited was
gone. He still also experienced insomnia, fatigue and concentration problems and had
developed appetite problems. Despite the official diagnosis still being one of a major
depressive episode, he no longer displayed melancholic features and his HAM-D was
reduced to 17, his HAM-A to 4, his DEX remained fairly stable at 17 and his HADS-A
score was reduced to 3 and HADS-D to 12. Following this assessment his mood
improved further and the patient was able to successfully complete 48 weeks of
treatment.
Patient 422

Background: A 40 year old married male with a history of substance abuse, he presented with genotype 3 of Hepatitis C and was at level 4 of fibrosis. He was prescribed 180µg of PEG-IFN weekly with 1200mg/day of Ribavirin, and was also taking Methadone.

Baseline Assessment: At Baseline the patient reported that his mood was normally labile, and that he had lost interest in things that had interested him since an injury a few years previously. Despite this, he did not meet the criteria for any depressive episode. His mood scores were slightly elevated compared to most patients at baseline, his HAM-D score was 15, his HAM-A score was 13, his DEX was 32 and his HADS-A score was 6 and his HADS-D score 5.

Week 8 Assessment: When the patient was asked about his mood he reported being put on Cipramil 2 weeks previously as he had become very agitated and that this had helped him to calm down slightly, he went on to explain that his mood was mostly characterised by this agitated state, and that he was “more wound up and snappy”. He spoke of a severely diminished interest in things that had normally interested him, something that had also affected him at baseline, but had become more pronounced with treatment. He had also lost a significant amount of weight, and his appetite was reduced. When asked about insomnia he stated that the last 2 weeks had been particularly bad, with him waking during the night and displaying early morning awakenings at 3am. He also admitted to displaying a psychomotor agitation that other people had noticed, and that he was suffering from extreme fatigue. When asked how he felt about himself he admitted to feeling down on himself, and guilty when he got agitated with his family, but this was subthreshold in intensity. In terms of his ability to think, he reported severe memory problems. However, he reported having no problems with suicidal ideation. As the patient was displaying anhedonia, anorexia and early morning awakenings further questions were asked to see whether a melancholic subtype of depression was present. He noted that the depression was a distinct mood state, and that his mood was regularly worse in the mornings.

Week 8 Summary: The patient met criteria for a MDE with melancholic features (Depressed mood; a distinctly different mood, loss of interest in usual
activities, insomnia (with early morning awakenings), psychomotor agitation, fatigue and cognitive problems which were related to his memory, as well as worse mood in the mornings. His HAM-D score was 22, his HAM-A score was 23, his DEX score was 31 and his HADS-A score was 6 and his HADS-D was 12.

Follow-up: At the Week 20 assessment the patient stated that his mood had improved yet he still found that he was extremely irritated, and he still had little interest in activities that he had previously enjoyed. His appetite was still extremely low, and he was continuing to lose weight, and was still experiencing insomnia. He was also still highly agitated, and experiencing high levels of fatigue. He met criteria for MDE (anhedonia, weight loss, insomnia, agitation, fatigue). His HAM-D score remained fairly constant at 31, as did his HAM-A at 24. His DEX score was 28, his scores HADS-A increased slightly to 9, and HADS-D decreased slightly to 9.
Patient 426

**Background:** A 32 year old single male with a history of substance abuse. He presented with genotype 3 of Hepatitis C and was at stage 3 of fibrosis. He was prescribed 1.5mg/kg of PEG-IFN2b and 1200mg per day of Ribavirin. He was also co-prescribed Methadone.

**Baseline Assessment:** At Baseline the patient appeared relaxed and stated that he was happy to be starting treatment, and had no problems or issues, this was reflected in his HADS-D score of 0 and HADS-A score of 0. He also only scored 1 on the HAM-D, 0 on the HAM-A and 0 on the DEX

**Week 8 Assessment:** At Week 8 the patient presented with a subsyndromal depression, he appeared more flat in affect and more agitated than he had done at baseline. He mentioned that his mood had deteriorated and that he was finding that he was more aggressive and angry with people, something that he had noticed become an issue in the last 3 weeks, he believed that this was due to the fact that things stressed him out more easily. He also spoke of finding activities that he used to enjoy harder to do as he had lost his “jump and go”, and that it took a long time for him to get going in the morning. When asked about appetite he spoke of having lost a lot of weight which was due to his decreased appetite. He spoke of his sleep being slightly disturbed, as he was waking more frequently during the night, but that he was able to go back to sleep. His energy levels were “very low” and he also spoke of having lost some of his self-esteem, which coincided with having lost pride in his appearance. His concentration levels were reported to be fine, but he did admit to having issues with his memory and found that he was experiencing a diminished ability to think. He also reported having no problems with psychomotor retardation or agitation, or suicidal ideation.

**Week 8 Summary:** The patient did not meet the criteria for a MDE; however as he met threshold for 4 items of depression (depressed mood, weight loss, fatigue and a diminished ability to think), and was subthreshold for three items of depression (anhedonia, insomnia and worthlessness) he met criteria for subthreshold depression. His HAM-D score increased to 17, his HAM-A increased to 10, his DEX increased to 14, and his HADS-A increased to 6 and his HADS-D increased to 12.
**Week 20 Assessment:** At Week 20 the patient presented with a MDE, which he reported was due to starting the anti-depressant Cipramil 4 weeks earlier. He started the anti-depressant as his mood had deteriorated; however he believed that the drug had caused his mood to worsen. He spoke of having depressed mood for most of the day nearly every day while on Cipramil, but that since he had stopped taking the drug his mood had started to improve, however, he still experienced significant irritation. He also spoke of a significant anhedonia that involved him not wanting to socialise or take care of himself. He mentioned that his weight had started to normalise slightly, however, his appetite was still low. His sleep had also deteriorated significantly, with him waking frequently during the night and finding that it took him between half an hour to an hour to return to sleep. He also displayed psychomotor retardation, speaking and moving more slowly than would be normal, which co-occurred with significant fatigue. This low mood was accompanied by negative cognitions that were centred around him feeling bad about himself. He also spoke of excessive guilt that was due to his irritated mood and that fact that he was shouting a lot at his children. However, he mentioned that his cognition had actually improved slightly and that he was experiencing no suicidal ideation.

**Week 20 Summary:** The patient met criteria for MDE (depressed mood, anhedonia, insomnia, psychomotor retardation, fatigue and feelings of worthlessness). His HAM-D score increased slightly to 21, and the HAM-A increased slightly to 16. His DEX score more than tripled to 44, and while his HADS-D score remained constant at 12 and his HADS-A rose to 10.

**Follow-up:** A week after the session, the patient mentioned that his low mood had improved since discontinuing the Cipramil treatment, and he did not require any psychological interventions.
3.4 Discussion

3.4.1 General Discussion

Case studies of those patients who developed a severe PAE were included in order to give a better insight to how IFN-α induced PAEs impact on patients, and the treatment that is undertaken in order to ameliorate these side-effects. The more severe PAE's appeared to occur in those patients who developed a hypomanic episode rather than those patients who became depressed, as the potential for engaging in risky behaviours, along with suicidal ideation when in the midst of a hypomanic episode make this a dangerous and often underappreciated PAE.

One paper describes the mood changes that occur during IFN-α as being best thought of as an overlap between hypomanic symptoms and depressive symptoms, with inner tension and anxiety being more severe symptoms than the depressed mood that would accompany treatment (Constant et al, 2005). This is something the echoes the findings from the case-studies, as the tension and anxiety experienced by those patients in a hypomanic episode were more severe than the depression experienced by the patients who developed MDD. This theory is also supported by the finding that those patients with a hypomanic episode displayed depressive symptoms, and those patients with a depression displayed irritable symptoms.

One of the reasons hypomania may have presented as a more severe PAE in patients studied here is because depression is an easily treated side-effect of IFN-α, and will often be ameliorated by anti-depressant medication (Kraus et al, 2007) (however, as for patient 426, this is not always the case). Case-studies conducted previously also indicate that the most effective therapy for IFN-α induced side-effects is with pharmacological therapy (see Table 3.1). However, hypomania is a more difficult side-effect to treat, especially in ex-substance abusers. Part of the reason that Patient 402 experienced such severe side-effects could have been due to the medication he had been prescribed, with the pleasant effect he experienced when taking the Lithium potentially leading to his subsequent relapse.

All patients spoken to during this study were receiving regular counselling and medical check-ups from their treatment nurses. These check-ups enabled any potential problems to be identified quickly, and where appropriate consultation with a psychiatrist was undertaken. For most patients, however, psychiatric therapy was not necessary as anti-depressant treatment was sufficient to improve their mood.
In terms of the impairment induced by PAEs, almost all patients described a significant impairment in social functioning that was caused mainly by the irritation that they experienced on treatment. However, the depressed patients would also show social withdrawal, and anhedonia, which led to them isolating from people around them. These two features of depressed mood fit in with previous research which indicates that the depression seen in medically-ill patients is generally comprised mainly of anhedonia, negative affect and somatic symptoms (Clark et al, 1998). Depressed patients were more likely to display symptoms consistent with sickness behaviour as part of their diagnosis (see Table 1.8) than patients who were experiencing a hypomanic episode. This meant that patients who were diagnosed with MDE would often meet certain criteria possibly due to the general IFN-α induced side-effects of treatment, rather than the effects of a pure depression, examples of these behaviours include fatigue, concentration difficulties, insomnia, appetite problems and anhedonia. This observation is backed up by the fact that two of the three depressed patients met criteria for a melancholic depression, which is the more neurovegetative subtype of depression (see Table 1.7).

However, those patients who developed a hypomanic episode would exhibit sickness behaviours alongside their hypomanic symptoms, with their symptoms rarely being caused by the sickness behaviour itself. This means that depressed patients can develop a diagnosis of depression simply through being sick, whereas, hypomania is separate from sickness behaviour and so the more severe PAE.

### 3.4.2 Implications of findings

The five case-studies conducted as part of this Chapter indicate that IFN-α induced PAEs cause significant impairment in social functioning. However, with appropriate treatment for the more moderate PAEs discontinuation of IFN-α therapy can be avoided. This is not always the appropriate course of action for all patients and where the PAE is causing a severe impairment in social functioning, and involves potentially harmful outcomes for the patient themselves (as was the case for patient 402), treatment should be discontinued.

Results also indicate that hypomania is a severe and often underappreciated PAE, that can cause harmful consequences for the individual, and that particular attention should be paid to this side-effect as well as the other more rare side-effects of
treatment, as the focus of clinicians will often primarily be on depression. However results suggest that the depression that occurs during IFN-α treatment could be due to patients meeting the criteria for a severe sickness behaviour rather than a pure depression. In order to assess this observation in further detail further analysis was conducted into the side-effects induced by IFN-α; specifically depression. This was done by interviewing patients who were taking, or had taken IFN-α in order to assess how they found the experience (Chapter 5), and then using this data to create a focused neuropsychological test battery (Chapter 6). Mood was then compared between patients who did and did not develop a PAE, and those patients who developed an IFN-α-induced depression compared to those patients with a primary depression in order to gain a better appreciation of the nature of the IFN-α-induced depression (Chapter 7).
CHAPTER 4

Validation of Interview in Healthy Controls and HCV patients
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4.1 Introduction

4.1.1 Use of qualitative interviews in psychology

The qualitative research interview can broadly be placed into one of three different types: the unstructured interview (based primarily on observation), the semi-structured interview (organised around a pre-determined set of questions) and the structured interview (organised around pre-determined questions and answers), with the first two providing mainly quantitative data and the third providing qualitative data (DiCicco-Bloom and Crabtree, 2006). A semi-structured or structured interview provides experimenters with the opportunity to test a hypothesis surrounding given variables, by having participants speak about these experiences and then in the case of the semi-structured interview, coding the resulting transcript to examine emerging themes with participants, or, in the case of structured interviews extracting data for statistical analysis (DiCicco-Bloom and Crabtree, 2006). Both types of interview offer advantages and disadvantages, while the semi-structured interview offers participants the opportunity to speak about a given subject more freely, the interpretation of their transcript by the researcher is often biased by the investigator (Warren and Carner, 2005). However, while the structured interview avoids this bias, it also means that the participant is more constrained in what they can say (Maughan, 2004).

An interview which combines both the structured and semi-structured interview allowing for both quantitative and qualitative data to be gathered would be especially useful where a-priori hypotheses have been generated and the interview is being used as a exploratory measure to assess the extent to which the investigated domains affect participant functioning, while also giving the participants the flexibility to speak about these domains in their own words.

4.1.2 Qualitative research on HCV

There have been a variety of studies examining the perceived impact of HCV on the individual using interviews and thematic analysis. Many of the studies found over-riding themes of stigmatisation (Butt et al, 2008; Conrad et al, 2009; Janke et al, 2008; Lally et al, 2008; Zickmund et al, 2003), adverse effects on physical health (Conrad et al, 2009; Crockett and Gilford, 2004; Glacken et al, 2001; Sgorbini et al, 2009), psychological side-effects such as depression and cognitive difficulties (Conrad et al, 2009; Sgorbini et al, 2009), fears of disease transmission (Conrad et al, 2009; Copeland,
2004; Crockett and Gilford, 2004), anxiety concerning the uncertain course of disease progression (Copeland, 2004; Davis and Rhodes, 2004), attempting to promote personal well-being (Crockett and Gilford, 2004; Glacken et al, 2001), feelings of wanting to keep the disease to themselves (Sgorbini et al, 2009) and feelings of isolation and social withdrawal (Conrad et al, 2009; Janke et al, 2008; Sgorbini et al, 2009).

The most replicated theme was that of stigmatisation, with women being particularly vulnerable (Crockett and Gifford, 2004; Zickmund et al, 2003). When people spoke about their feelings of being infected with HCV, they would often use words like ‘contaminated’ and ‘dirty’ (Fraser and Treloar, 2006; Glacken et al, 2001), with some people reporting that HCV diagnosis had changed the way they regarded themselves (Glacken et al, 2001). Patients described feeling stigmatised by both their friends and family and also healthcare professionals, likening it to being treated as though they had leprosy (Crockett and Gifford, 2004; Zickmund et al, 2003). The stigma that arose was sometimes due to the misconception that HCV was like HIV (Crockett and Gifford, 2004; Munoz-Plaza et al, 2008; Zickmund et al, 2003), and also its association with illicit drug use (Zickmund et al, 2003).

It was also found that intra-venous drug users (IVDUs) were more likely to normalise their illness through the belief that everyone they knew had it, and that being infected with HIV would be worse (Copeland, 2004; Davis and Rhodes, 2004; Wozniak et al, 2007). This population was also more likely to have a poor education around HCV (Copeland, 2004; Lally et al, 2008), but this was not limited to this population, with other people likening HCV to a terminal disease (Fraser and Treloar, 2006; Glacken et al, 2001).

In order to gain a rich insight into the changes in health, behaviour and psychological functioning that can accompany treatment with IFN-α, without being limited to the structure of many official diagnostic clinical interviews it was decided to develop and validate an interview in healthy control participants and patients with HCV who were not due to start treatment in order to assess the impact of HCV on the domains investigated.
4.2 Methods and Materials

4.2.1 Interview

A semi-structured interview that explored the domains of health, sleep, mood and cognition was designed and validated in healthy Control participants and patients with HCV (see Appendix III for copy of interview). A description of this interview and procedure for administration and scoring can be found in Chapter 2 of this thesis (section 2.3).

4.2.2 Participants

20 control participants (see Table 4.1 for demographic information) and 10 HCV patients (see Table 4.2 for demographic information) were recruited via Trinity College Dublin and St. James’s Hospital Hepatology centre. More information on patient and Control recruitment and inclusion and exclusion criteria is contained in Chapter 2, section 2.4.

### Table 4.1: Demographic data for Control participants

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Mean age ± SEM</th>
<th>Sex</th>
<th>Nationality</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>9</td>
<td>29.3 ± 2.1</td>
<td>M: 4 (44%) F: 5 (56%)</td>
<td>Irish: 5 (55%) British: 1 (15%) German: 1 (15%) Greek: 1 (15%)</td>
</tr>
<tr>
<td>41-60</td>
<td>11</td>
<td>57.2 ± 0.8</td>
<td>M: 6 (55%) F: 5 (45%)</td>
<td>Irish: 11 (100%)</td>
</tr>
</tbody>
</table>

Table showing demographic information for control participants, participants were split into two age groups in order to account for the health problems that become more frequent with older age.

### Table 4.2: Demographic data for HCV patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Sex</th>
<th>Age ± SEM</th>
<th>Nationality</th>
<th>Genotype</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>10</td>
<td>M: 3 (30%) F: 7 (70%)</td>
<td>52.8 ± 4</td>
<td>Irish: 8 (80%) American: 1 (10%) Polish: 1 (10%)</td>
<td>1: 8 (80%) 3: 2 (20%)</td>
<td>Transfusion: 6 (60%) IVDU: 2 (20%)</td>
</tr>
</tbody>
</table>

Table showing demographic information for patients with Hepatitis C. Where infected via transfusion, patient’s received HCV through a contaminated transfusion, where infected due to intravenous drug use (IVDU), the most likely cause of infection was through sharing contaminated needles.
4.3 Data analysis

The Shapiro-Wilks test of normality was run on each data set, in order to determine what analysis to run on the qualitative data. Where normality was demonstrated throughout the data set, independent t-tests were used to compare between-groups, and paired t-tests to compare within-groups. Where normality was not demonstrated the one-sample Kolmogorov-Smirnov analysis was used to test variability within a single sample and the Mann-Whitney test was used to compare between-groups (see section 2.2.4 for more information on statistical tests). Thematic analysis was conducted for qualitative analysis (see section 2.3.4)
Chapter 4: Interview validation

4.4 Results

4.4.1 Validation of interview in healthy Controls

4.4.1.1 Quantitative statistics

4.4.1.1.1 Normality of dataset

The normality of the dataset was assessed using the Shapiro-Wilks test (see Appendix VII); as most of the data were not normally distributed it was decided to use non-parametric tests to assess the data.

4.4.1.1.2 Within-group analysis

In order to determine which questions yielded the most variability within the control group a one-sample Kolmogorov-Smirnov analysis was run. See Table 4.3 for all results (Figures 4.1 to 4.8 show some of the results from each domain);

Table 4.3: Within-group variation for healthy Controls

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean ± SD</th>
<th>Kolmogorov-Smirnov Z</th>
<th>2-tailed significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>0.85 ± 0.81</td>
<td>1.128</td>
<td>P=0.16</td>
</tr>
<tr>
<td>Health limit activities</td>
<td>0.3 ± 0.47</td>
<td>1.96</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Health limit activities (vigorous)</td>
<td>0.65 ± 1.04</td>
<td>1.494</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Health limit activities (moderate)</td>
<td>0.1 ± 0.31</td>
<td>2.358</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Hours physical activity per week</td>
<td>8.3 ± 1.15</td>
<td>1.087</td>
<td>P=0.19</td>
</tr>
<tr>
<td>Hours physical exercise per week</td>
<td>1.15 ± 1.35</td>
<td>1.092</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>1.05 ± 1.05</td>
<td>1.303</td>
<td>P=0.67</td>
</tr>
<tr>
<td>Expect health to get worse</td>
<td>0.85 ± 0.81</td>
<td>1.238</td>
<td>P=0.93</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.22 ± 0.67</td>
<td>1.558</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>0.65 ± 1.57</td>
<td>1.617</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>0.45 ± 0.76</td>
<td>1.670</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Hours slept</td>
<td>0.45 ± 0.759</td>
<td>1.670</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Time in bed asleep</td>
<td>0.3 ± 0.571</td>
<td>2.014</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>0.95 ± 1.28</td>
<td>1.272</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Happiness</td>
<td>1.15 ± 0.745</td>
<td>1.028</td>
<td>P=0.24</td>
</tr>
<tr>
<td>Worry</td>
<td>1.2 ± 0.696</td>
<td>1.624</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Irritation</td>
<td>0.8 ± 0.616</td>
<td>1.464</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Anger</td>
<td>0.45 ± 0.61</td>
<td>1.662</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Memory</td>
<td>1 ± 0.858</td>
<td>1.02</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.95 ± 0.51</td>
<td>1.74</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Concentrate book</td>
<td>0.7 ± 0.571</td>
<td>1.566</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Concentrate film</td>
<td>0.7 ± 0.733</td>
<td>1.302</td>
<td>P=0.07</td>
</tr>
<tr>
<td>Concentrate boring</td>
<td>2 ± 0.858</td>
<td>1.020</td>
<td>P=0.25</td>
</tr>
</tbody>
</table>

Table showing the variability within the group for each quantitative question asked, where there is a significant difference between responses made it is indicated in bold. Those responses not in bold indicate those variables where answers were spread more equally between a variety of responses, whereas those questions where significance is observed meant the majority of participants responded to the question in a more similar fashion.
Figure 4.1: Overall health rating for Controls

Graph showing the number of participants that made each response for health ratings, there was a non-significant difference within the group for this question (P=0.16 see Table 4.1), with most participants rating their health as good ($n=5 \pm 0.36$), very good ($n=7 \pm 0.3$) or excellent ($n=8 \pm 0.29$), no participant rated their health in negative terms.

Figure 4.2: Physical limitation ratings for Controls

Graph showing the number of participants that made each response for how health limited the physical activities they could do, there was a significant difference within this group for this question ($**p<0.01$ see Table 4.4). The majority of participants stated that their health had no limiting effects on the physical activities they could do ($n=14 \pm 0.1$) with the rest of the participants stating they were sometimes limited a little ($n=6 \pm 0.19$). No participant believed their health impacted hugely on their ability to do physical activities.
Graph showing the number of participants that made each response for how fatigued they were, there was a significant difference within this group for this question (**p < 0.01 see Table 4.4). With only 1 participant stating that they felt fatigued (n=1 ± 0.45), with all other participants reporting no problems with fatigue (n=19 ± 0.1).

**Figure 4.4: Overall sleep quality ratings**

Graph showing the overall sleep quality for control participants, with higher scores indicative of more sleep problems. There was no significant difference within the group for this particular domain (P=0.08 see Table 4.4). The chart was skewed towards the left (see Appendix V) indicating fewer sleep problems with most participants overall sleep quality being 0 (n=9 ± 0.42), 1 (n=7 ± 0.48), 2 (n=2 ± 0.9), 3, (n=1 ± 1.3) and 5 (n=1 ± 1.28).
Figure 4.5: Happiness rating for Controls

Graph showing the number of participants that made each response for how happy they had been for the last month there was no significant difference within this group with responses ranging from a fair amount ($n=7 \pm 0.26$) to quite a lot ($n=9 \pm 0.23$) to extremely ($n=4 \pm 0.35$) ($P=0.24$; see Table 4.4).

Figure 4.6: Anxiety rating for Controls

Graph showing the number of participants that made each response for worried they had been for the last month there was a significant difference within the group for this question ($**p<0.01$, see Table 4.4). While participants responses ranged from not at all ($n=2 \pm 0.49$), not that much ($n=13 \pm 0.19$), a fair amount ($n=4 \pm 0.35$) and quite a lot ($n=1 \pm 0.7$), a significant majority of participants stated that they had not been that worried within the last month.
Graph showing the number of participants that made each response for how their memory had been for the last month, there was no significant difference within this group for this question ($P=0.25$; see Table 4.4). Variation in participant responding was split fairly equally between memory being excellent ($n=7 \pm 0.29$), good ($n=6 \pm 0.35$) or neither good nor bad ($n=7 \pm 0.36$).

Graph showing the number of participants that made each response for how their concentration had been for the last month, there was a significant difference within this group, with most participants ($15 \pm 0.13$) reporting that they had good concentration, with fewer participants rating their concentration as either excellent ($3 \pm 0.29$) or good ($2 \pm 0.26$) for this question ($**p<0.01$; see Table 4.4)
4.4.1.1.3 Comparison between age groups

The Mann-Whitney test was then run in order to see if there was a significant difference between age groups, with no significant differences being found due to age (see Table 4.4).

Table 4.4: Between-groups comparison: Young and Old

<table>
<thead>
<tr>
<th>Question</th>
<th>Mann-Whitney U</th>
<th>Z score</th>
<th>2-tailed significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>33</td>
<td>-1.337</td>
<td>P=2.3</td>
</tr>
<tr>
<td>Health limit activities</td>
<td>42.5</td>
<td>-0.669</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Health limit activities (vigorous)</td>
<td>43</td>
<td>-0.563</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Health limit activities (moderate)</td>
<td>40.5</td>
<td>-1.314</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Hours physical activity per week</td>
<td>38.5</td>
<td>-0.846</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Hours physical exercise per week</td>
<td>46.5</td>
<td>-0.239</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>26</td>
<td>-0.905</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Expect health to get worse</td>
<td>45</td>
<td>-0.375</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>No variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>49</td>
<td>-0.045</td>
<td>P=1</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>49</td>
<td>-0.045</td>
<td>P=1</td>
</tr>
<tr>
<td>Hours slept</td>
<td>48.5</td>
<td>-0.101</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Time in bed asleep</td>
<td>47.5</td>
<td>-0.219</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>48</td>
<td>-0.122</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Happiness</td>
<td>37.5</td>
<td>-0.983</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Worry</td>
<td>26.5</td>
<td>-2.062</td>
<td>P=0.08</td>
</tr>
<tr>
<td>Irritation</td>
<td>42.5</td>
<td>-0.611</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Anger</td>
<td>38</td>
<td>-1.014</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Memory</td>
<td>30</td>
<td>-1.571</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Concentration</td>
<td>45.5</td>
<td>-0.401</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Concentrate book</td>
<td>35</td>
<td>-1.278</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Concentrate film</td>
<td>43</td>
<td>-0.562</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Concentrate boring</td>
<td>30</td>
<td>-1.571</td>
<td>P=0.2</td>
</tr>
</tbody>
</table>

Table showing the difference between the younger and older age groups, the Mann-Whitney test was used and no significant difference was seen between the two groups. Fatigue could not be analysed as there was too little variability for that question.

A Chi-squared analysis was used to assess if there was an effect of age on categorical data collected during the interview. There was found to be no significant difference between the older and younger age group in relation to words used to describe health ($x^2(2, N=40)=0.808$, P=0.67), statements regarding sleep quality ($x^2(2, N=40)=6.95$, P=0.07), psychiatric history ($x^2(2, N=40)=2.22$, P=0.53), previous anxiety ($x^2(2, N=40)=2.78$, P=0.1), previous depression ($x^2(2, N=40)=0.194$, P=0.66), whether current mood state was different from normal for anxiety ($x^2(2, N=40)=0.737$, P=0.39), and happiness ($x^2(2, N=40)=2.17$, P=0.34), how irritated people were ($x^2(2, N=40)=0.02$, P=0.88), how angry they were ($x^2(2, N=40)=0.861$, P=0.35), whether
memory was different from usual ($x^2(2, N=40)=2.89, P=0.24$), and whether concentration was different than usual ($x^2(2, N=40)=0.9, P=0.34$).

### 4.4.1.2 Qualitative data

Using thematic analysis for each of the five domains investigated in the interview the themes listed in Table 4.5 emerged, in the health and mood domains. In the sleep, fatigue, and cognition domains not enough qualitative data were gathered to analyse as these domains were measured primarily with quantitative data.

**Table 4.5: Themes for healthy Controls**

<table>
<thead>
<tr>
<th>Category</th>
<th>Major theme</th>
<th>Minor theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>Health is viewed in terms of ailments</td>
<td>Where people have ailments the manageability of the ailment determines how they view their health.</td>
</tr>
<tr>
<td></td>
<td>Health is viewed in terms of taking care of oneself</td>
<td>People in the older age group have a more complex view of health.</td>
</tr>
<tr>
<td></td>
<td>Healthy people don’t think about their health</td>
<td>It is only when health is compromised that people think about it.</td>
</tr>
<tr>
<td></td>
<td>Health is a stable construct</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>Mood is externally driven.</td>
<td>Older people rate their younger selves as being more stressed, with career being the most common reason for previous anxiety.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The most common reasons for experiencing anxiety are money worries and career worries.</td>
</tr>
</tbody>
</table>

Table showing the major and minor themes that were extrapolated from the qualitative data gathered in the interview for the categories health, mood and personality. Data were not analysed for sleep, fatigue or cognition as there was insufficient qualitative data to analyse.
4.4.1.2.1 Themes in health

Theme 1: Health is viewed in terms of ailments (Minor theme: Where people have ailments the manageability of the ailment determines how they view their health)

When asked to describe the reasons that healthy people rated their health in the way they did, the most common reason cited was the fact that they did not have any ailments, 55% \( n=11 \) of the participants who rated their health from good to excellent did so because they did not have any ailments. With reasons such as: "I don’t know my Doctor" (Participant 62, F, age 57), “there is nothing wrong with me” (Participant 57, M, age 55) and: "I am not sufficiently unhealthy for it to be a cause for concern” (Participant 60, M, age 40) being given. Where participants did have an underlying medical condition it was the manageability of the condition that determined how they viewed their health, one participant had asthma, but described their health as very good as they had it: “under control” and they were mostly: “unaware” of the condition (Participant 61, F, age 36). Another participant with high blood pressure rated their health as excellent: “I can feel my blood pressure tablets are working” (Participant 67, M, age 60) and a patient who had arthritis rated their health as good stating that they were: “aware and dealing with it....because it can be dealt with” (Participant 70, M, age 54).

Theme 2: Health is viewed in terms of taking care of oneself (Minor theme: People in the older age group have a more complex view of health)

Another theme that emerged as important when people rated their health was how much care they took over themselves, both in terms of fitness levels and eating healthily, with 45% \( n=9 \) talking about these things when discussing their rating of their health. One participant who rated their health as good described their reasons thus: “I always see my health is relation to my fitness levels, and I am not fit at the moment, so I am not happy with that” (Participant 52, M, age 27: rated health as good). With other participants who rated their health slightly lower than they may have done otherwise also stating that: “I would like to play a bit more sport, but it’s not a serious problem” (Participant 56, M, age 23), and: “I find I could do that very easily up to the age of 50, and I can’t do it as easily anymore” (Participant 70, M, age 54). Where people rated their health more highly due to these factors they would talk about things such as: “I exercise almost every day. I try and eat healthily, using the triangle” (Participant 71, F, age 54: rated
health as very good); "I can get up and carry on and I think I am healthy for my age, I can carry on and do my exercises" (Participant 66, F, age 60: rated health as very good); "I take plenty of exercise and I usually eat healthy." (Participant 64, F, age 53: rated health as very good).

A minor theme that also emerged was that those people in the older age category were more likely to have a complex view of their health, talking about ailments, fitness and eating well: "I have a good quality of life, feel good, and can do most things" (Participant 65, F, age 60: rated health as excellent), whereas younger people tended to have a more simplistic view of their health: "there's nothing wrong with me" (Participant 51, F, age 25: rated health as very good).

**Theme 3: Healthy people don't think about their health (Minor theme: It is only when health is compromised that people think about it)**

When rating how their health affected their daily lives and being asked to pick which statement summed up their attitude towards their health most people chose the statement "My health does not bother me" (see Figure 4.9).

**Figure 4.9: Statements that describe how controls feel about health**

![Bar chart showing feelings towards health](chart.png)

When healthy people were asked to pick a statement to sum up how they best felt about their health and then describe the reason for their choice, the majority of participants chose the statement "my health does not bother me" ($n=13$), some chose the word "happy" ($n=4$), 1 patients chose the two statements "not bothered" and "happy", and 2 participants stated that none of the words summed up their feelings toward their health.
When asked to explain this decision in more detail two participants summed up the reasons: “If there was something wrong with me I would be, but there’s not so I don’t have to be” (Participant 51, F, age 25); “If I put my mind into it I would be like, ‘yeah it’s great’, but I don’t wake up in the morning like, ‘oh how healthy I am’, you know? So it doesn’t bother me. It’s grand” (Participant 54, M, age 35).

Where people did think about their health, it was in relation to their fitness levels rather than the lack of ailments that they presented with one participant saying they were: “happy with my health, I could exercise more” (Participant 59, F, age 30). Another minor theme that emerged within this major theme was that it was only when good health was compromised that people thought about their health, one participant recently experienced a fall and stated: “it doesn’t stop me from doing anything...it bothered me when I fell, that was the first time in my life that I have felt geriatric” (Participant 64, F, age 53) with another participant recovering from the flu saying: “When I am not sick and everything is fine and I feel better I am more happy, sure” (Participant 55, F, age 25). This minor theme was summed up by a participant talking about why their health did not bother them: “When it’s not right it’s not a good place to be....if you had something wrong with your health you wouldn’t be a happy camper” (Participant 57, M, age 55).

Theme 4: Health is a stable construct

When asked whether they thought their health would get worse over the next year 85% (n=17) of participants choosing the answer “possibly not” or “definitely not”. When asked why they had chosen that answer some people spoke about it in a vague manner: “I don’t forsee any reason it should get worse” (Participant 56, M, age 23: definitely not get worse); “I have no reason to think there will be a problem” (Participant 60, M, age 40; possibly not get worse).

Many people who gave the answer ‘possibly not’, spoke about the uncertainty of what may happen in the future, but not in terms of any illness that may arise from within themselves, but instead taking about external factors that would influence their health such as: “I am feeling fine at the moment, unless I get knocked down” (Participant 67, M, age 60). Only three participants spoke about the specifics of why their health may get worse because of intrinsic factors with two participants specifying their age (Participant 68, M, age 60: possibly get worse; Participant 57, M, age 53:
possibly not get worse), and the other speaking about their arthritis (Participant 70, M: possibly not get worse). For the most part however, people regarded their health as something that was going to remain stable: "allowing for the unexpected stuff" (Participant 71, F, age 54: possibly not get worse), with 25% of participants acknowledging that they took care of their good health: "I take relatively good care of myself" (Participant 65, F, age 60: possibly not get worse).

4.4.1.2.2 Themes in mood

Theme 1: Mood is externally driven.

When speaking about both current and past mood, it was dependent on events that were or had occurred in their life, with lower than normal mood being described as a: "present set back" (Participant 52, M, age 27), and people who maintain their mood talking about: "a realistic approach on things" (Participant 54, M, age 35). The most common reasons for changes in mood were career, money worries and family problems (see Figure 4.10 for a graph showing whether participants mood was different to usual). With 20% (n=4) of all participants reporting a significant episodes of anxiety being due to career related issues and 25% (n=5) reporting they had experienced a significant change in mood due to relationship or family issues. 44.4% (n=4) of the younger participants were worried about their career: "what am I going to do with my life?" (Participant 56, M, age 23), with those people who were retired stating that this was the reason for them being less worried than would be usual: "I'm retired now, so I have less pressure" (Participant 67, M, age 60); "I retired and lost a lot of the stress of life" (Participant 68, M, age 60).

Those people who were in the older age group, stated that they were now less worried than they would have been when they were younger: "As a youngster I would have been anxious a lot of the time, I wasn’t aware of it mind you, hindsight is wonderful" (Participant 66, F, age 60); "Possibly in my youth I got a bit more stressed, but then as age has set in you realise they aren’t as important as they may seem to be" (Participant 57, M, age 53).

Other reasons for current changes in mood were due to family and relationships with 20% of participants stating that this was the reason that their mood was lower and anxiety slightly higher than may be normal, and also financial worries which were
currently affecting 10% of participants (see Figure 4.10 to see how current mood in all participants differs to normal mood).

Where participants had experienced previous episodes of depression this was due to family (Participant 66, F, age 60), career problems (Participant 70, M, age 54) and a relationship break-down (Participant 52, M, 27), all of which resulted from a reaction to an external stressor rather than occurring endogenously.

In some cases mood was higher than would be normal with people getting engaged (Participant 59, F, age 30), family members getting engaged (Participant 67, M, age 60) and having being on holiday (Participant 68).

**Figure 4.10: Whether current mood different for Controls**

![Graphical representation of mood comparison](image)

Graphical representation of how participants rated their mood compared to normal. Most participants rated their happiness \(n=14\) and worry \(n=11\) as being the same as usual. However 9 participants rated their worry higher than normal, and 5 stated they were less happy than usual. 1 participant rated themselves as being happier than they would be normally.
4.4.2 Hepatitis C

4.4.2.1 Quantitative statistics

4.4.2.1.1 Normality of dataset

The dataset was run in order to check normality for each question, as results were mixed with half the data being distributed normally and half not. It was decided to run non-parametric sets for all analysis in this section (see Appendix V).

4.4.2.1.2 Within-groups comparison

A one-sample Kolmogorov-Smirnov analysis was run in order to assess the variability within the HCV group for each question, with no question yielding a significant result (see Table 4.6 for all results).

Table 4.6: Within-group variation for HCV patients

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean ± SD</th>
<th>Kolmogorov-Smirnov Z</th>
<th>2-tailed significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>2.33 ± 1</td>
<td>0.576</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Health limit activities</td>
<td>1.78 ± 1.09</td>
<td>0.618</td>
<td>P=0.84</td>
</tr>
<tr>
<td>Health limit activities (vigorous)</td>
<td>2.33 ± 1.5</td>
<td>0.6</td>
<td>P=0.87</td>
</tr>
<tr>
<td>Health limit activities (moderate)</td>
<td>0.78 ± 0.83</td>
<td>0.807</td>
<td>P=0.53</td>
</tr>
<tr>
<td>Physical health interfered social</td>
<td>1.56 ± 1.33</td>
<td>0.635</td>
<td>P=0.82</td>
</tr>
<tr>
<td>Social support</td>
<td>1.67 ± 1.5</td>
<td>0.6</td>
<td>P=0.86</td>
</tr>
<tr>
<td>Hours physical activity per week</td>
<td>7.89 ± 11.07</td>
<td>1.037</td>
<td>P=0.23</td>
</tr>
<tr>
<td>Hours physical exercise per week</td>
<td>0.44 ± 0.726</td>
<td>1.189</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>2.44 ± 1.24</td>
<td>1.02</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Expect health to get worse</td>
<td>1.44 ± 1.24</td>
<td>0.687</td>
<td>P=0.73</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.67 ± 2</td>
<td>1.243</td>
<td>P=0.09</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>1.22 ± 1.22</td>
<td>0.72</td>
<td>P=0.68</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>0.78 ± 0.83</td>
<td>0.807</td>
<td>P=0.53</td>
</tr>
<tr>
<td>Hours slept</td>
<td>Not computed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in bed asleep</td>
<td>Not computed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep quality</td>
<td>0.78 ± 0.833</td>
<td>0.807</td>
<td>P=0.53</td>
</tr>
<tr>
<td>Happiness</td>
<td>1.44 ± 0.882</td>
<td>0.745</td>
<td>P=0.64</td>
</tr>
<tr>
<td>Worry</td>
<td>1.78 ± 1.3</td>
<td>0.841</td>
<td>P=0.45</td>
</tr>
<tr>
<td>Irritation</td>
<td>1.11 ± 0.33</td>
<td>1.558</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Anger</td>
<td>0.78 ± 0.78</td>
<td>0.807</td>
<td>P=0.53</td>
</tr>
<tr>
<td>Memory</td>
<td>2 ± 0.866</td>
<td>0.628</td>
<td>P=0.83</td>
</tr>
<tr>
<td>Concentration</td>
<td>1.78 ± 1.3</td>
<td>0.841</td>
<td>P=0.48</td>
</tr>
<tr>
<td>Concentrate book</td>
<td>1 ± 0.866</td>
<td>1.167</td>
<td>P=0.13</td>
</tr>
<tr>
<td>Concentrate film</td>
<td>1.33 ± 0.866</td>
<td>0.950</td>
<td>P=0.33</td>
</tr>
<tr>
<td>Concentrate boring</td>
<td>2.44 ± 1.236</td>
<td>0.687</td>
<td>P=0.73</td>
</tr>
</tbody>
</table>

Table showing the variability within the group for each quantitative question asked, no question yielded a significant result, indicating results were spread between various responses for all questions.
4.4.2.1.3 Between-groups comparison (HCV and Controls)

The HCV group was compared to age-and-sex-matched healthy Control participants (HCV group 70% female, mean age 52.8 ± 4, n=10; Control group 70% female, mean age 47.1 ± 4.65, n=10) there was no significant difference between the ages of the two groups when assessed using an independent samples t-test (t(17)=1.45, P=0.16). Comparative data were assessed using the Mann-Whitney non-parametric test for independent samples for the scale data and the chi-square test for the categorical data. The only significant results were found in domains that explored perception of health (see Table 4.7 and Figures 4.11 to 4.15):

<table>
<thead>
<tr>
<th>Question</th>
<th>Mann-Whitney U</th>
<th>Z score</th>
<th>2-tailed significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>15.5</td>
<td>-2.714</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Health limit activities</td>
<td>20</td>
<td>-2.403</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Health limit activities (vigorous)</td>
<td>22</td>
<td>-2.192</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Health limit activities (moderate)</td>
<td>33</td>
<td>-1.525</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Hours physical activity per week</td>
<td>25</td>
<td>-1.897</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Hours physical exercise per week</td>
<td>32.5</td>
<td>-1.463</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Physical health interfered social</td>
<td>22.5</td>
<td>-2.447</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Social support</td>
<td>No comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>27</td>
<td>-1.826</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Expect health to get worse</td>
<td>36</td>
<td>-1.106</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16.5</td>
<td>-2.938</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>34</td>
<td>-1.299</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>36</td>
<td>-0.045</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Hours slept</td>
<td>40</td>
<td>-1.451</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Time in bed asleep</td>
<td>45</td>
<td>-0.61</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>49.5</td>
<td>-0.04</td>
<td>P=1</td>
</tr>
<tr>
<td>Happiness</td>
<td>47.5</td>
<td>-0.205</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Worry</td>
<td>45.5</td>
<td>-0.355</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Irritation</td>
<td>32.5</td>
<td>-1.511</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Anger</td>
<td>43</td>
<td>-1.576</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Memory</td>
<td>26.5</td>
<td>-1.881</td>
<td>P=0.07</td>
</tr>
<tr>
<td>Concentration</td>
<td>34.5</td>
<td>-0.957</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Concentrate book</td>
<td>36</td>
<td>-1.828</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Concentrate film</td>
<td>31</td>
<td>-1.279</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Concentrate boring</td>
<td>39.5</td>
<td>-1.474</td>
<td>P=0.7</td>
</tr>
</tbody>
</table>

Table showing the statistical comparison of qualitative interview results, with only those questions that explored perception of health yielding significant results (significance indicated in bold).
Figure 4.11: Overall health rating for Controls and HCV

Graph showing how patients with HCV and matched Control participants rate their health with higher scores being indicative of more impairment: 0 (excellent), 1 (Very good), 2 (Good), 3 (Fair), 4 (Poor). Results are presented as mean scores with the median response indicated by the purple line (HCV: mean=2.4 ± 0.3; median=2) (Control: mean=1.1 ± 0.2; median=1). There was a significant difference between the two groups U(19)=15.5, Z=-2.714, **p<0.01.

Figure 4.12: Physical limitation ratings for Controls and HCV

Graph showing how patients with HCV and matched Control participants rate impact of their health on their ability to do physical activities: 0 (Not at all), 1 (Sometimes, a little), 2 (Sometimes, a lot), 3 (Definitely, a little), 4 (Definitely, a lot). Results are presented as mean scores with the median response indicated by the purple line (HCV: mean=1.6 ± 0.4; median=1) (Control mean=0.4 ± 0.2; median=0). There was a significant difference between the two groups U(19)=20, Z=-2.403, *p<0.05.
**Figure 4.13: Vigorous physical limitation ratings for Controls and HCV**

Graph showing how patients with HCV and matched Control participants rate impact of their health on their ability to do vigorous physical activities: 0 (Not at all), 1 (Sometimes, a little), 2 (Sometimes, a lot), 3 (Definitely, a little), 4 (Definitely, a lot). Results are presented as mean scores with the median response indicated by the purple line (HCV: mean=2.1 ± 0.5; median=2) (Control mean=0.8 ± 0.3; median=1). There was a significant difference between the two groups U(19)=22, Z=-2.192, *p<0.05.

**Figure 4.14: Physical health interfere social for Controls and HCV**

Graph showing how patients with HCV and matched Control participants rate the impact of their health on their normal social activities with family and friends: 0 (No), 1 (A bit), 2 (Moderately), 3 (Quite a bit), 4 (Extremely). Results are presented as mean scores with the median response indicated by the purple line (HCV: mean=1.6 ± 0.4; median=2) (Control mean=0.1 ± 0.1; median=0). There was a significant difference between the two groups U(19)=22.5, Z=-2.447, *p<0.05.
Figure 4.15: Fatigue ratings for Controls and HCV

Graph showing how patients with HCV and matched Control participants rate severity of fatigue: 0 (Never), 1 (The last month), 2 (The last few months), 3 (The last year), 4 (The last few years). Results are presented as mean scores with the median response indicated by the purple line (HCV: mean=2.8 ± 0.6; median=4) (Control mean=0.2 ± 0.2; median=0). There was a significant difference between the two groups U(19)=16.5, Z=-2.938, **p<0.01.

Categorical data were analysed with a chi-squared analysis with only the question 'which of these words most closely describes how you feel about your health yielding a significant result ($\chi^2(4, N=20)=16.8$, p<0.01; see Figure 4.16). However for all other questions there were no significant differences: statements regarding sleep quality ($\chi^2(2, N=20)=5.11$, P=0.08), psychiatric history ($\chi^2(4, N=20)=2.29$, P=0.68), previous anxiety ($\chi^2(1, N=20)=3.33$, P=0.07), previous depression ($\chi^2(2, N=20)=4.267$, P=0.12), whether current mood state was different from normal for anxiety ($\chi^2(2, N=20)=0.228$, P=0.23), and happiness ($\chi^2(1, N=20)=2.4$, P=0.12), how irritated people were ($\chi^2(2, N=20)=1.059$, P=0.59), how angry they were ($\chi^2(2, N=20)=3.529$, P=0.17), whether memory was different from usual ($\chi^2(3, N=20)=2$, P=0.57), how forgetful people were ($\chi^2(2, N=20)=21.077$, P=0.58) and whether concentration was different than usual ($\chi^2(3, N=20)=2.961$, P=0.4).
Figure 4.16: Statements that describe how Controls and HCV patients feel about health

Graph showing the types of words that HCV patients and Control participants chose when considering how they felt about their health, with there being an overall significant effect of group on the types of words chosen ($\chi^2(4, N=20)=16.8$, $p<0.01$). The majority of HCV patients chose words that had a negative connotation ($n=9$, 90%), and the majority of control participants chose the statement ‘not bothered’ ($n=8$, 80%). Participants could choose the statement ‘my health does not bother me’, or words with negative connotations ‘my health makes me upset’, ‘my health makes me worried’, ‘my health makes me angry’, words with positive connotations ‘my health makes me happy’, or any other word that they felt summed up how they considered their health.
4.4.2.2. **Qualitative data**

After a thematic analysis on the interviews conducted the themes shown in Table 4.8 were found, no consistent themes emerged for sleep or cognition as there was very little qualitative data available to analyse.

<table>
<thead>
<tr>
<th>Category</th>
<th>Major theme</th>
<th>Minor theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>Fatigue is the main side-effect</td>
<td>HCV involves significant adjustment psychologically and physically</td>
</tr>
<tr>
<td></td>
<td>Interpretation of health is related to symptoms present</td>
<td>Acceptance of side-effects is important</td>
</tr>
<tr>
<td></td>
<td>Anger is commonly associated with thinking about HCV, with anger being directed differently (internally vs externally) depending on how infected</td>
<td>People often forget about HCV</td>
</tr>
<tr>
<td></td>
<td>Thinking about HCV is associated with complex emotions</td>
<td>There is a mental impact of the knowledge you have HCV</td>
</tr>
<tr>
<td></td>
<td>Other health issues are more important than HCV</td>
<td>State-infected women experienced traumatic diagnoses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Those people infected via transfusion or unknown means feel they did not deserve to get infected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>There is an element of denial associated with HCV</td>
</tr>
<tr>
<td>Social support</td>
<td>Level of social support received is linked to the understanding that other people have of HCV</td>
<td>Patients can experience mood swings</td>
</tr>
<tr>
<td>Mood</td>
<td>Mood changes rarely linked in directly with HCV</td>
<td>Spirituality is beneficial</td>
</tr>
</tbody>
</table>

Table showing the major and minor themes from the qualitative data gathered in the interview for the categories health, social support, mood and personality. Data were not analysed for sleep and cognition as there was not sufficient qualitative data to analyse.
Chapter 4: Interview validation

4.4.2.1 Themes in health

Theme 1: Fatigue is the main side-effect (minor theme: HCV involves adjustment physically and psychologically)

The most commonly reported side-effect of HCV (90%, 9 patients), and the one that most patients referred to as being the main, and often the only symptom they experienced was fatigue: "Because of the hepatitis I could be doing something normal and all of a sudden my energy is zapped from me and I have to go and lay down" (Participant 21, F age 65); "I don’t know I have it, except for I’m very tired" (Participant 27, F, age 63).

This fatigue is perceived to be very different from what other people of the same age may experience: "they don’t get tired, you know, erm, they don’t wake up with aches and pains, or just feeling like not getting out of bed" (Participant 23, F, age 60), and different to what they would have experienced prior to getting HCV: "I am tired, all the time tired and I was never like this before." (Participant 22, F, age 40). People describe this fatigue as impacting on their abilities to do activities as: "I have no stamina" (Participant 26, M, age 62), and it is something that occurs sporadically rather than being present constantly: "sometimes, some days I can get limited." (Participant 29, F, age 53).

Many people spoke about having to adjust to the illness: "when it does happen I’m well advised to just stop what I’m doing because that means the hepatitis is working its way into my system." (Participant 21, F, age 65), with participants speaking about having to accept the limitations that HCV induced fatigue can cause: "I have learnt to manage it, and not push the body so hard, and acceptance is really a very, very big part" (Participant 20, F, age 57), with this acceptance being a process that people go through: "in the early stages when I didn’t really have a handle on things, I did, you know, I was absolutely exhausted" (Participant 20, F, age 57).

Theme 2: Interpretation of health is related to symptoms present (minor theme: people often forget about HCV and there is a mental impact of the knowledge you have HCV)

Those patients who had fewer HCV induced side-effects tended to rate their health as better than those who perceived the HCV to be affecting their health: "I know I have the hepatitis, but yet it doesn’t, it’s not a major problem at this stage" (Participant 21, F,
age 65: health very good); “I have problems with my throat very often...I am weak and er, I have very big problems with my concentration....I am very tired” (Participant 22, F, age 40: health poor).

Many people seemed to almost forget that they had the HCV when rating their health: “cuz I don’t have any problems or anything like” (Participant 32, M, age 33: health fair), and would instead refer to other items such as fitness when rating their health. One patient who rated their health as good spoke about feeling that the HCV had no real impact on their health: “I don’t feel anything, like there’s any difference between this and if I was getting pains or anything so that doesn’t really bother me” (Participant 30, M, age 33) with other participants saying they would forget for the most part that they even had HCV: “It’s only when things start piping up you know, with aches and pains, like a few little stabs in the liver and things like that will you actually become very aware of it” (Participant 20, F, age 57: health good); “Cuz I don’t have any problems or anything like” (Participant 32, M, age 33: health fair).

It was also found that those patients who take care of their health also rate their health as better and seem to perceive their overall health as better: “I actually take great pride and care in my health” (Participant 20, F, age 57: health good). As some patients did not experience many HCV-related symptoms; they instead spoke of the knowledge of having a disease and this would in turn impact on how they rated their health: “The knowledge that I have the hepatitis c puts the mental factor on it” (Participant 30, M, age 33: health good).

Theme 3: Anger is commonly associated with thinking about HCV, with anger being directed differently (internally vs externally) depending on how infected (minor theme: state infected women experienced traumatic diagnoses and those people infected via transfusions or unknown means feel they did not deserve to get infected)

The most common statement that people with HCV agreed with when rating how they felt about their health was anger (see Figure 4.17), however, this anger was differentially directed depending on the mode of transmission, with those people who received infected blood products likely to direct their anger towards those people that had infected them. This was especially true of those women who were infected in the 1970’s via infected blood products: “yes it makes me angry at the bloody State”
(Participant 20, F, age 57); however some women had come to terms with that anger by thinking about in a more positive way: “If I hadn’t got that blood transfusion I would have died” (Participant 23, F, age 60).

A minor theme that emerged was that some patients got angry as they felt they did not deserve to get infected with HCV: “I never drunk in my life and I used to say, you know, ‘I will never have to worry about my liver’” (Participant 28, F, age 62). Another minor theme that emerged from this population was that they were still angry and upset about the way in which they found out they had HCV, with one particular patient recounting how her doctor had told her that her blood tests had come back clear but that: “the blood transfusion board sent me out all this literature on hepatitis c, and er, sure I didn’t realise why I was getting this in the post, because I was free, I was negative, and then my sister rang them and they said, no, that I was antibody positive and virus positive” (Participant 28, F, age 62). Other patients spoke about finding out while watching TV with their family: “horrific stuff. Absolutely horrific” (Participant 20, F, age 57), and when they went to give blood: “I gave blood and they found out that I had hepatitis and I hadn’t a clue. I wasn’t sick.” (Participant 21, F, age 65). There is also still anger about the way that they were treated by the healthcare professionals when they were first diagnosed: “I was told, ‘the best advice we can give you is to keep it to yourself and not tell anybody about it’” (Participant 28, F, age 62).

Those people who were infected via unknown means also experienced anger, which was also directed externally towards other people due to the uncertainty they felt over their infection: “Sometimes because of the hepatitis c, because they can’t tell me how I got it” (Participant 29, F, age 53), and also a nonspecific anger towards the illness itself: “angry because I can’t do like I did before” (Participant 22, F, age 40).

However, those people infected via sharing needles were the only group that directed their anger internally as they felt they were responsible for giving themselves the illness, feeling that they had a lack of personal strength which had put them into the position where they now had HCV: “Because I wish I was stronger, some people are stronger than me” (Participant 32, M, age 33); “Angry that I was stupid enough to use other people’s needles...angry that I put myself in a position to catch a disease like hepatitis c through my own stupidity” (Participant 30, M, age 33).
Theme 4: Thinking about HCV is associated with complex emotions

As well as anger there were a variety of other emotions also associated with the knowledge that patients had HCV, which for the most part were negative emotions (see Figure 4.17).

Many patients spoke about the variety of emotions they experienced when thinking about their diagnosis: “I am upset that I am ill...angry that I can’t do like I did before” (Participant 22, F, age 40); “When I talk about hep c, I seem to get this lump in my throat, you know, and I find it hard to swallow” (Participant 28, F, age 62).

Figure 4.17: How patients with HCV feel about health

When patients were asked to chose which of a variety of statements most closely represented how they felt about their health, most people chose more than one statement with the graph showing the total number of participants chose each response. Most participants chose statements with negative connotations with 8 people agreeing their health made them angry, 7 agreeing it made them worried and 6 agreeing it made them upset. However, 3 patients also said their health did not bother them, 2 saying it made them happy with 1 patient choosing none of the statements.

Some people spoke about worrying over their health, with the reasons for this ranging from the effects HCV has on their health and progression of the disease: “the liver. I don’t know what is going on...I can’t get rid of these thoughts in my brain about my illness” (Participant 22, F, age 40), to people finding out they have HCV: “the girl next to me is married to my first cousin and I am always afraid that if something comes in the post...it goes to her by mistake” (Participant 28, F, age 62). Some patients also agreed with the statement that their health made them upset, as they can feel like it is unfair that they have the illness: “I just wonder why I have all these things wrong with me” (Participant 27, F, age 63). However, some people actually spoke about their health
as not bothering them, and actually making them happy as it had relatively little impact on their lives: “I can do things, and I’m older now and I can still function” (Participant 21, F, age 65).

**Theme 5: Other health issues are more important than HCV (minor theme: there is an element of denial associated with HCV)**

As HCV was mostly asymptomatic in many patients, other than fatigue, it was found that some participants would rate their health in terms of other afflictions that they felt they had: “I smoke and I know I am very unfit” (Participant 30, M, age 33: health good), with many patients rating their health not purely in terms of HCV, but as: “an amalgamation of things” (Participant 26, M, age 62: health fair). One patient in particular spent time describing other health complaints she had and when asked where the HCV fitted into that she admitted: “I forgot about that” and went on to explain that: “I don’t even think I even think that much about my hepatitis c” (Participant 27, F, age 63: health fair). This patient went on to describe her belief that her age impacted on her health more than HCV: “I’m getting older, so sometimes I put it down, it’s because I’m getting older, and sometimes I look at people and say, ‘well I’m nearly better than her’” (Participant 27, F, age 63).

Some patients also justified their attitude towards their health by rating HCV on a continuum, and it coming out as being less of an issue than other health problems: “there’s worse out there with cancer, than we are, strokes....I know it’s life threatening but sure than is everything else, you could walk out in front of a bus and be killed or whatever” (Participant 23, F, age 60). Some patients even spoke about an element of denial which was associated with the way they viewed their HCV: “I suppose I just kind of forget about it you know” (Participant 28, F, age 62), with one patient actually stating that he did not have any health problems and instead rating his health based on his fitness levels: “cuz I don’t have any problems or anything like” (Participant 32, M, age 33: health fair). One participant spoke about the issue of denial directly in relation to adjusting to their diagnosis: “trying to deal with what I had was kind of like a denial because I didn’t know, understand what I had” (Participant 21, F, age 65), with other participants using a process of active denial, in order to forget about their illness: “you just push it further down.” (Participant 28, F, age 62).
4.4.2.2 Themes in social support

Theme 1: Level of social support received is linked to the understanding other people have of Hepatitis C

Most of the patients that were asked about how supportive their friends and family had been to them since finding out they had HCV, rated their support as very good or excellent: “they would listen” (Participant 20, F, age 57); “they would do anything for me, they would go out of their way” (Participant 26, M, age 62). This level of social support for the most part seemed to be related to the level of understanding that people around them had of HCV, with those people who had friends or family who understood HCV rating their social support as higher than those whose friends and family did not understand the illness: “They’re all there for me.... particularly the ones that know I have hepatitis c” (Participant 23, F, age 60: support excellent).

Those patients who spoke positively about their social support also mentioned the support that they had gotten from the hospital had helped them with their diagnosis a lot: “I would compliment James’s in relation to the care that they’re actually giving” (Participant 20, F, age 57: support excellent). However, where poor support had been received from a hospital, this impacted on patients’ overall perception of the support they had received; one patient referred to an incident where she visited the blood transfusion board to speak to a Doctor about her illness: “she was very nasty like, ‘if you cut yourself, you clean it up’” (Participant 21, F, age 65: support fair).

Some of the patients interviewed did not actively seek out social support, stating that the main reason was the lack of understanding of other people: “This hepatitis c belongs to me....I am too shy to talk about this illness because no-body understand” (Participant 22, F, age 40: support poor); “It ’s something I am trying to hide because I remember one of my friends saying ‘oh I wouldn’t drink out of cups or anything like that’” (Participant 28, F, age 62: support poor).

One patient spoke of the lack of understanding as being a result of poor education for other people regarding HCV, and the belief that HCV and HIV were similar illnesses: “I think they think it’s like....they’re going to get AIDS, and they’re a bit paranoid about that end of it because they’re ignorant about it” (Participant 29, F, age 53: support fair). This poor education and poor understanding was also reflected in the statement from another participant who told one family member about the illness:
"they don't know...I told me brother, but, like he doesn't seem very concerned"
(Participant 32, M, age 33: support poor).

4.4.2.2.3 Themes in mood

Theme 1: Mood changes rarely linked in directly with HCV (minor themes: patients can experience mood swings and spirituality is beneficial)

When talking about their mood most patients reported that their mood was good, however, 30% of patients \( (n=3) \) spoke about how HCV caused them to have mood swings: "I get these mood swings and I can be irritable." (Participant 28, F, age 62); “unless I'm in one of those mood swings where you can't think anything is good.” (Participant 23, F, age 60). One patient in particular believed that the illness impacted on her mood: “I think the problem is both the physical and psychological together...when I am in bad mood from this health” however, when spoken to more about this issue the low mood appeared to be related to her feelings about having HCV rather than the illness causing an endogenous depression: “the biggest difference is this bad mood...the self-esteem” (Participant 22, F, age 40). Despite this, the majority of patients \( (90\% \; n=9) \) reported that the illness had no current impact on their mood, but 50\% \( (n=5) \) of patients spoke of having a previous depression. However this depression appeared to occur endogenously for only one patient post HCV-infection: “I can't put my thumb on it....I just couldn't say, you know, what it was” (Participant 23, F, age 60), with one other patient specifying that the diagnosis and a marriage breakdown was the reason for her depression: “you're bloody well dealing with the state. You're dealing em, em, with a relationship, you know, as I've said you don't know which end of you is up” (Participant 20, F, age 57). For all the other patients, however, the depression was linked to life events. Where previous anxiety had occurred this was for the most part also linked in with life events other than HCV, however one patient in particular recalled experiencing a significant amount of anxiety when they were diagnosed as: “I thought I was going to die” (Participant 23, F, age 60).

A minor theme emerged whereby people turned to spirituality in order to help them with their mood and how they felt about their diagnosis, which they had felt to be very beneficial: “Years ago I asked Christ to come into my heart and be my saviour and I have confidence in him” (Participant 21, F, age 65). Another patient spoke about using spirituality in order to make herself more calm and through using techniques such as
yoga and Eastern medicine stating she had: "learned to breathe again" (Participant 20, F, age 20).
4.5 Discussion

4.5.1 Overview of interview results

The aim of this chapter was to assess and validate an interview in healthy Controls and patients with HCV in order to administer the interview to patients due to take IFN-α, and also use a variation of the interview with patients who have taken IFN-α to assess their experience retrospectively. The main issue that arose from the study with both the healthy Control participants and HCV patients was the amount of variability seen within the group as regards the Likert-style questions that examined the domains of health, fatigue and sleep, mood, personality and cognition (see Tables 4.3 and 4.6), especially for the HCV group, where there was no agreement between participants for any question asked, however, this variability within each group was explained through the thematic analysis conducted on the qualitative data that arose from the interview, thus demonstrating the importance of the thematic analysis for the IFN-α patients.

4.5.2 Healthy Control validation

Within the healthy control group, there seemed to be less variability than the HCV group, but there was still variability when asking participants about their overall health, how much activity they did per week, bodily pain, health expectations, sleep quality, happiness and memory (see Table 4.3). As there was no variation in responding between the two age groups studied (see Table 4.4), it was decided to analyse the group as a whole. The low number of participants tested would explain the variability for questions that looked at physical activity, as this is something that was not given a 'score', and instead was analysed purely on the number of hours people did per week, which means that a higher n would be needed to see significance for that particular domain. However, for all other questions, the results are explained through themes that emerged for the group. In the case of overall health, where responses differed between participants (see Figure 4.1), this could be explained by the themes that emerged for health perception, where it could be seen that some people view their health purely in terms of ailments they have and some view their health in terms of taking care of themselves; some participants that may have had no ailments rated their health lower because they felt that they did not take sufficient care of their health and others who did have ailments rated their health higher because they felt that they did take good care of themselves (see section 4.1.2.1). The concept of 'health' and what constitutes being
'healthy', was a very individual ideal, with each person having their own perception as to what made them healthy, and as such how they would rate their overall health. In the case of pain, there was again a variability as there was also a difference in perception as to what constituted 'mild' pain and 'moderate'. This idea of what constitutes health as being a very personal ideal, was further supported by the finding that questions that were more specific in their focus, and thus less open to individual interpretation, yielded significance, and so there was more consistency within the group’s responses. This could be seen for the health limiting activity questions (see Table 4.3 and Figure 4.2), where participants had to base their answer on personal experience rather than on their own interpretation of the question. The fatigue question also yielded a significant result with the majority of participants agreeing that they had no issues with tiredness, again, this could be due to the fact that this question was based less on interpretation as they were asked to compare themselves to someone else of their age and think whether they experienced more fatigue than them (see Figure 4.3). This issue of 'interpretation' could also explain why the cognition domain saw variability for the memory and some of the concentration questions, with overall concentration being significant (see Figures 4.6 and 4.7).

The sleep domain also yielded variable results with the individual components that constituted overall sleep quality yielding significance, but, the sleep quality question itself yielding non-significance (see Figure 4.4). There was not sufficient qualitative data to analyse this question in more depth, but, the reasoning that would explain this result is that for each of the individual component scores there could only be a score between 0 and 3 obtained, thus leading to fewer possible responses and thus less variability. However, for the overall sleep quality there was a possibility of 9 'scores', which automatically meant more possible variability, which would have been enhanced by the low number of people studied for this interview, there is a possibility that a higher n, would have led to decreased variability within this domain.

Mood also yielded different results with happiness being a highly variable construct, and anxiety a less variable one (see Figures 4.5 and 4.6), this is in part explained by the issue of 'interpretation', but is also explained through some of the thematic analysis, with mood shown to be a concept which is very much externally driven. Most people reported that the mood they were currently experiencing was as a direct result of things that were going on in their lives, with age also being partially
responsible for how much anxiety people were experiencing (see section 4.4.1.2.2). For the most part these mood issues could be explained by relationships with other people and finance, and as the climate that these interviews were conducted in was a financially tough one, this could have impacted on mood.

4.5.3 HCV patient validation

For the HCV group there was variability within all questions asked for quantitative analysis (see Table 4.6), this is partly explained by the low number of participants spoken to, however, the main thing that emerged from the thematic analysis was that the views that HCV patients held of their illness were complex and every individual interviewed had a different attitude towards their health, which had out-reaching implications for the other domains of sleep and fatigue, mood and cognition (see section 4.4.2.2.1).

When asked to rate their own health there was a large difference in perception of what their health constituted, and consistent with the Control group who spoke about health being viewed in terms of ‘ailments’, many of the HCV patients spoken to viewed their health in terms of the symptoms of HCV that they were currently experiencing, with those patients who were mostly asymptomatic rating their health as better than those who were currently experiencing side-effects due to their illness.

Another theme that emerged to explain inconsistency within the group as regards health, was that the only side-effect of HCV that many patients experienced was fatigue, and for many of those patients spoken to this was seen to be a manageable side-effect. This also fits in with a minor theme from the Control group where manageability of a condition determined the extent, to which it impacted on overall ratings of health. HCV was also rated by some participants as being less important than other health issues they had, and some patients would even forget that they had HCV until they experienced the fatigue or another side-effect. This also fits in with the theme from healthy Controls that only when health is compromised will people think about it, however, as people with HCV have the psychological knowledge that they have a serious underlying health condition this would impact on their ratings of health relative to healthy Controls, which is something that was observed when a comparison between the two groups was conducted. There was an overall effect of HCV on the health domain, with overall health, levels of impairment due to health, the impact of health on
social activities and fatigue all showing significance (see Figures 4.11 to 4.15 and Table 4.7).

When asked to speak about their health it also became clear that HCV patients had complex illness related cognitions (see Figure 4.17), which would impact on mood and health ratings, with anger, worry and being upset being the most common statements chosen by patients to describe how they felt about their health. As the majority of patients spoken to were either infected via transfusion or unknown means, these cognitions form an understandable part of patients view of their health, with anger being a particularly dominant emotion with many of the patients spoken to. The anger was directed towards the person, people, or organisation that was felt to be responsible for their infection. As such those people infected via intra-venous drug use felt they were responsible for giving themselves the illness and so directed their anger internally, those people who were infected via transfusions seemed be angry towards the people they felt had infected them, and finally those people infected via unknown means often did not know where to direct their anger, and so sometimes would direct it towards themselves, and sometimes towards the healthcare professionals dealing with their illness (see section 4.4.2.2.1). A comparison with healthy controls showed patients who had HCV were significantly more likely to choose words with a negative connotation to describe their health than healthy controls (see Figure 4.16). This lends support to the idea that it is health that is the central issue for HCV patients, and that they have a complex relationship with their illness.

Another domain where thematic analysis could partly explain variability in results is for mood. This is because some patients blamed HCV as having a direct effect on their mood, but for the most part, patients seemed to agree that it was external life events that were more important in determining their mood rather than some endogenous chemical effect of the HCV. At most, the only possible endogenous effect seemed to be through increasing mood lability rather than inducing a full depression. This is also partly supported by the fact that there was no significant difference between HCV patients and healthy Controls on any of the mood domains, despite evidence that HCV affects mood (Yovtcheva et al, 2001). This could in part be due to the low number of participants questioned, but the thematic results gathered seem to support the idea that mood is primarily driven externally for those patients with HCV, as was the case for control participants (see section 4.4.2.2.3).
The only theme that was specific to HCV and not comparable across groups was the social support question. When talking to patients it became clear that the social support received from other people was most beneficial when family and friends had an understanding of HCV, as where there was little or no understanding patients tended to feel very isolated, and tended to have more negative illness related cognitions (see section 4.4.2.2.2).

4.5.4 Limitations of interview results

For most of the domains, with both groups there is a huge amount of inter-group variability, which confounds any results that may be between different groups. This variability is mostly explained by the low number of participants tested and the variability in individual interpretation of questions.

The interview could also be perceived to be flawed by the highly standardised nature in which it was administered, with the fact that patients are required to answer certain Likert-style questions prior to describing any answer leading to a potential bias in results. However, it has been acknowledged by the researcher that the interview was designed to look at certain domains and questions, and rather than extrapolate novel themes from data we have attempted to focus our analysis in such a way that the emphasis is placed on the groups interpretation of the specified domains.

Another issue from using an interview with a mixed qualitative/quantitative design was that a good qualitative dataset is defined by the variability within a group, however a strong quantitative dataset is characterised by low within-group variability. The fact that the qualitative data within the interviews was so interesting and found a variety of themes impacted detrimentally on the quantitative data, which showed very little significance.

4.5.4 Implications for IFN-α interviews

One of the main problems that arose from the validation was the issues that arose from variability within each of the groups due to variability of how each participant interpreted each question. This issue will be remedied in the prospective IFN-α study as it shall be a within-groups design, however, in order to avoid this problem with the retrospective question it was decided to design a less structured interview, and only complete a thematic analysis with this group.
CHAPTER 5

Prospective and Retrospective IFN-α Interviews
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5.1 Introduction

There has been relatively little work done on investigating the effects of IFN-α on people using qualitative data. So far, studies have been conducted about the perception of treatment (Fraenkel et al., 2005; Treloar and Hopwood, 2008) and the reality of experiencing treatment (Janke et al., 2008; Treloar and Hopwood, 2008; Sgorbini et al., 2009). In terms of how people view treatment, it was sometimes believed that the experience of treatment would be worse than having HCV (Fraenkel et al., 2005); however, when at the start of treatment many people underestimate the side-effects that can occur and believe that adverse effects will not happen to them (Treloar and Hopwood, 2008).

People on treatment report feelings of depression (Janke et al., 2008; Sgorbini et al., 2009; Treloar and Hopwood, 2008), being more emotionally labile and irritable (Janke et al., 2008), with many people talking about withdrawing socially (Janke et al., 2008). Treatment also had a significant effect on people’s health, with fatigue being listed as a particularly difficult side-effect leading to individuals having to adapt to the new limitations they were experiencing (Sgorbini et al., 2009). In some cases being on treatment led people to question their own identity, as the person they were on treatment was not the person they had been before (Janke et al., 2008).

Rather than investigate the effects of treatment in a more informal way in order to assess how patients feel IFN-α impacted on them the majority of studies use structured clinical diagnostic interviews, that leave very little scope for exploring how patients perceive the treatment to have affected them. It was decided to use the interview validated in Chapter 3 of this thesis with patients before they start treatment and 8 weeks into treatment, as well as a less structured post-treatment interview to be conducted with patients who had been through treatment in order to gain a full appreciation of how patients felt IFN-α affected them, both prospectively and retrospectively.
5.2 Methods and Materials

5.2.1 Participants

Patients were recruited from St. James’s Hospital Hepatology Centre, via procedures laid out in Chapter 2 (section 2.4.3) (see Table 5.1 for demographic information). Inclusion criteria for the prospective study included being HCV positive and due to start treatment. For the post-treatment group inclusion criteria included having being on IFN-α previously.

### Table 5.1: Demographic data for IFN-α patients (prospective and retrospective groups)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Sex</th>
<th>Age ± SEM</th>
<th>Nationality</th>
<th>Genotype or Treatment response</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α</td>
<td>6</td>
<td>M: 3 (50%) F: 3 (50%)</td>
<td>41.7 ± 3.5</td>
<td>Irish: 4 (67%) British: 1 (11.5%) Polish: 1 (11.5%)</td>
<td>1: 3 (50%) 3: 3 (50%)</td>
<td>IVDU: 4 (67%) Unknown: 2 (33%)</td>
</tr>
<tr>
<td>Post IFN-α</td>
<td>15</td>
<td>M: 11 (73%) F: 4 (27%)</td>
<td>47.1 ± 2.3</td>
<td>Irish: 13 (86%) American: 1 (7%) Polish: 1 (7%)</td>
<td>SVR: 8 (53%) N/R: 4 (27%) Unknown: 3 (20%)</td>
<td>Transfusion: 5 (33%) IVDU: 9 (60%) Unknown: 1 (7%)</td>
</tr>
</tbody>
</table>

Table showing demographic information for the two groups studied for the effects of IFN-α, the post IFN-α group (retrospective group), and the IFN-α group (prospective group). For the post IFN-α group the response to treatment was either SVR (sustained viral response, HCV cleared); N/R (non-responder; HCV not cleared) and unknown (results for 6 month response not obtained).

5.2.2 IFN-α interviews

The interviews used for both the prospective and retrospective groups were based on the validation of interviews that took place in Chapter 4 of this thesis (see Appendix II for a copy of the interviews used). The main difference between the validation interviews and the prospective interview was that there was a section at the end of the interview that asked treatment-specific questions. Also at Week 8, patients were asked to rate whether their health, fatigue, mood and cognition had improved or disproved since commencing IFN-α.

The post-treatment interview was based on the domains investigated in all interviews, but took a less structured approach, and started with general questions regarding treatment before asking about the specific effects on the four main domains.
5.2.3 Administering the interview

All procedures for administering and scoring the interview were as completed for Chapter 4.
5.3 Data analysis

All analyses used were consistent with those that had previously been used in Chapter 4; with the prospective study being analysed using the Mann-Whitney test for between group comparisons and the Wilcoxon Signed-Rank test was used to compare within groups. The Chi-squared test was used for categorical comparisons. A thematic analysis was also conducted on this sample. For the retrospective study only a thematic analysis was conducted, as described in Section 2.3.4 of this thesis.
5.4 Results

5.4.1 Prospective IFN-α study

5.4.1.1 Qualitative data

5.4.1.1.1 Normality of data and analysis

Data were assessed using non-parametric tests due to the small number of participants studied; the non-normal distribution of data as assessed using the Shapiro-Wilks test also supported this decision (see Appendix V), with inconsistency emerging between items and often between sessions.

5.4.1.1.2 Comparison between IFN-α Baseline and HCV patients not due to commence treatment.

Participants due to take IFN-α were firstly compared to age-and-sex-matched HCV patients assessed in Section 4.4.2 who were not due to start treatment in order to see if the knowledge that treatment was due to start had any effect on any of the domains investigated in the interview (IFN-α group, 50% male mean age 41.7 ± 3.5, n=6; HCV group 50% male, mean age 46.3 ± 5.2, n=6). There was no significant difference between the ages of the two groups when assessed using an independent samples t-test (t(10)=-0.75, P=0.47). The two groups could not be matched fully for mode of infection however (IFN-α group; 67% (n=4) ex-IVDU, 33% (n=2) unknown infection: HCV group; 33% (n=2) ex-IVDU, 33% (n=2) transfusion infected, 33% (n=2) unknown infection. The two groups were firstly assessed using the Mann-Whitney test for independent samples (see Table 5.2) with there being no significant difference in any of the domains investigated.

When categorical data were then assessed using a Chi-square analysis, this also demonstrated that there was no significant difference between the groups in any of the following domains: words used to describe health ($\chi^2(2, N=12)=0$, P=1), sleep quality ($\chi^2(2, N=12)=1.143$, P=0.5), psychiatric history in family ($\chi^2(3, N=12)=4$, P=0.26), previous anxiety ($\chi^2(2, N=12)=2.5$, P=0.29), previous depression ($\chi^2(2, N=12)=1.2$, P=0.55), whether current mood state was different from normal for anxiety ($\chi^2(2, N=12)=0.667$, P=0.26), and happiness ($\chi^2(2, N=12)=1.867$, P=0.39), how angry they were ($\chi^2(1, N=12)=2.4$, P=0.12), whether memory was different from usual ($\chi^2(2, N=12)=1.2$, P=0.55), how forgetful people were ($\chi^2(1, N=12)=3.086$, P=0.08) and
whether concentration was different than usual ($\chi^2(2, N=12)=1.2$, P=0.55). Irritation could not be computed as it was a constant.

**Table 5.2: Statistical differences between patients due to start IFN-α and HCV patients not due to start treatment.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Mann-Whitney U</th>
<th>Z score</th>
<th>2-tailed significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>11</td>
<td>-1.187</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Health limit activities</td>
<td>14</td>
<td>-0.667</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Health limit activities (vigorous)</td>
<td>15</td>
<td>-0.5</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Health limit activities (moderate)</td>
<td>16.5</td>
<td>-0.267</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Hours physical activity per week</td>
<td>12</td>
<td>-0.969</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Hours physical exercise per week</td>
<td>14.5</td>
<td>-0.601</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Physical health interfered social</td>
<td>14.5</td>
<td>-0.626</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Social support</td>
<td>12</td>
<td>-1.076</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>11.5</td>
<td>-1.09</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Expect health to get worse</td>
<td>13</td>
<td>-0.819</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16.5</td>
<td>-0.268</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>16</td>
<td>-0.33</td>
<td>P=0.8</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>15.5</td>
<td>-0.433</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Hours slept</td>
<td>11.5</td>
<td>-1.251</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Time in bed asleep</td>
<td>9</td>
<td>-1.897</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>11</td>
<td>-1.154</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Happiness</td>
<td>13</td>
<td>-0.843</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Worry</td>
<td>11.5</td>
<td>-1.087</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Irritation</td>
<td>15</td>
<td>-1</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Anger</td>
<td>15.5</td>
<td>-0.433</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Memory</td>
<td>17.5</td>
<td>-0.087</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Concentration</td>
<td>14.5</td>
<td>-0.577</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Concentrate book</td>
<td>13.5</td>
<td>-0.802</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Concentrate film</td>
<td>14.5</td>
<td>-0.58</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Concentrate boring</td>
<td>16</td>
<td>-0.33</td>
<td>P=0.8</td>
</tr>
</tbody>
</table>

Table showing that there is no statistical difference caused by the knowledge a patient is due to start treatment with IFN-α in terms of health, fatigue, sleep, mood and cognition.

### 5.4.1.1.3 Comparison between Week 0 and Week 8 of treatment

Results from Week 0 and Week 8 of treatment were then compared using the Wilcoxon-Matched pairs test and the Chi-Square test for categorical data; there were significant increases in bodily pain ($Z(-1.414)$, $p<0.05$), levels of irritation experienced ($Z(-2.121)$, $p<0.05$) as well as a significant decrease in memory ($Z(2.06)$, $P<0.05$) and concentration ($Z(-2)$, $p<0.05$). These data are displayed in Table 5.3 and Figures 5.1 to 5.4.
Table 5.3: Statistical differences from Week 0 to Week 8 of IFN-α treatment

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean</th>
<th>Median</th>
<th>Z score</th>
<th>2-tailed significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health</td>
<td>1.83 ± 0.5</td>
<td>1.83</td>
<td>-1.58</td>
<td>P=0.06</td>
</tr>
<tr>
<td>Health limit activities</td>
<td>1.67 ± 0.4</td>
<td>2</td>
<td>-1.34</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Health limit activities (vigorous)</td>
<td>2 ± 0.6</td>
<td>2</td>
<td>-1.62</td>
<td>P=0.1</td>
</tr>
<tr>
<td>Health limit activities (moderate)</td>
<td>0.5 ± 0.2</td>
<td>0.5</td>
<td>-1.47</td>
<td>P=0.14</td>
</tr>
<tr>
<td>Hours physical activity per week</td>
<td>8.58 ± 4.4</td>
<td>5.75</td>
<td>-1.46</td>
<td>P=0.14</td>
</tr>
<tr>
<td>Hours physical exercise per week</td>
<td>1.17 ± 0.8</td>
<td>1</td>
<td>0</td>
<td>P=1</td>
</tr>
<tr>
<td>Physical health interfered social</td>
<td>1.17 ± 0.7</td>
<td>1</td>
<td>0</td>
<td>P=0.16</td>
</tr>
<tr>
<td>Social support</td>
<td>0.33 ± 0.2</td>
<td>0</td>
<td>-1.41</td>
<td>P=0.26</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>1.83 ± 0.5</td>
<td>2</td>
<td>-2.07</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 ± 0.5</td>
<td>3</td>
<td>-1.09</td>
<td>P=0.28</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>1.17 ± 0.3</td>
<td>1</td>
<td>-1.13</td>
<td>P=1</td>
</tr>
<tr>
<td>Hours sleep</td>
<td>0.83 ± 0.5</td>
<td>0.5</td>
<td>-0.27</td>
<td>P=0.41</td>
</tr>
<tr>
<td>Time in bed asleep</td>
<td>0.67 ± 0.3</td>
<td>0.5</td>
<td>-1.41</td>
<td>P=0.26</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>2.5 ± 0.9</td>
<td>2.5</td>
<td>-1.63</td>
<td>P=0.79</td>
</tr>
<tr>
<td>Happiness</td>
<td>1.33 ± 0.2</td>
<td>1.5</td>
<td>-1.41</td>
<td>P=0.16</td>
</tr>
<tr>
<td>Worry</td>
<td>2.17 ± 0.3</td>
<td>2</td>
<td>-1.63</td>
<td>P=0.1</td>
</tr>
<tr>
<td>Irritation</td>
<td>1 ± 0</td>
<td>1</td>
<td>-2.12</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Anger</td>
<td>0.83 ± 0.3</td>
<td>1</td>
<td>-0.18</td>
<td>P&lt;0.85</td>
</tr>
<tr>
<td>Memory</td>
<td>1.33 ± 0.3</td>
<td>1.5</td>
<td>-2.06</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Concentration</td>
<td>1.5 ± 0.4</td>
<td>1.5</td>
<td>-2</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Concentrate book</td>
<td>0.5 ± 0.2</td>
<td>0.5</td>
<td>-1.84</td>
<td>P=0.07</td>
</tr>
<tr>
<td>Concentrate film</td>
<td>1.17 ± 0.5</td>
<td>1</td>
<td>-1.34</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Concentrate boring</td>
<td>2.17 ± 0.5</td>
<td>2</td>
<td>-1.51</td>
<td>P=0.13</td>
</tr>
</tbody>
</table>

Table showing the results from the Wilcoxon-Matched pairs analysis ran on the results from Week 0 and Week 8 of the interview, with significant results being indicated by bold type. For both the mean and median, higher scores are indicative of more impairment for that particular question. Significant impairment was found for bodily pain, irritation, memory and concentration. Difficulty sleeping is not included as results were constant across weeks.
**Figure 5.1: Bodily pain experienced at Week 0 and Week 8 of IFN-α treatment**

Graph showing the difference between Week 0 and Week 8 in patients' perception of how much bodily pain they were experiencing: 0 (None), 1 (Very mild), 2 (Mild), 3 (Moderate), 4 (Severe), 5 (Very severe). Results are presented as mean scores with the median response indicated by the purple line (Week 0: mean=1.83 ± 0.5; median=2) (Week 8 mean=3 ± 0.6; median=3). There was a significant difference between the two groups (Z(-2.07), *p<0.05).

**Figure 5.2: Irritation experienced at Week 0 and Week 8 of IFN-α treatment**

Graph showing the difference between Week 0 and Week 8 in patients' perception of how easily irritated they had been for the last month: 0 (Not at all), 1 (Not that much), 2 (A fair amount), 3 (Quite a lot), 4 (Extremely). Results are presented as mean scores with the median response indicated by the purple line (Week 0: mean=1 ± 0; median=1) (Week 8: mean=2 ± 0.3; median=2). There was a significant difference between the two groups (Z(-2.121), *p<0.05).
Figure 5.3: Memory ratings at Week 0 and Week 8 of IFN-α treatment

Graph showing the difference between Week 0 and Week 8 in patients' perception in how their memory had been in the last month: 0 (Excellent), 1 (Good), 2 (Neither good nor bad), 3 (Not so good), 4 (Very bad). Results are presented as mean scores with the median response indicated by the purple line (Week 0: mean=1.33 ± 0.3; median=1.5) (Week 8: mean=2.67 ± 0.7; median=2.5). There was a significant difference between the two groups (Z=-2.06), *p<0.05.

Figure 5.4: Concentration ratings at Week 0 and Week 8 of IFN-α treatment

Graph showing the difference between Week 0 and Week 8 in patients' perception in how their concentration had been in the last month: 0 (Excellent), 1 (Good), 2 (Neither good nor bad), 3 (Not so good), 4 (Very bad). Results are presented as mean scores with the median response indicated by the purple line (Week 0: mean=1.5 ± 0.4; median=1.5) (Week 8: mean=2.17 ± 0.5; median=2.5). There was a significant difference between the two groups (Z=-2), *p<0.05.
Categorical data were then compared using a Chi-squared analysis; it was found that there was a significant difference in patients perception of how irritated ($\chi^2(1, N=12)=8.571, p<0.01$) they were (see Figure 5.5). However, for all the other domains there were no significant differences: words used to describe health ($\chi^2(4, N=12)=3.143, P=0.54$), sleep quality ($\chi^2(2, N=12)=3.111, P=0.21$), whether current mood state was different from normal for anxiety ($\chi^2(2, N=12)=0, P=1$), and happiness ($\chi^2(1, N=12)=0, P=1$), whether memory was different from usual ($\chi^2(1, N=12)=0.343, P=0.56$), how forgetful people were ($\chi^2(1, N=12)=1.5, P=0.22$) and whether concentration was different than usual ($\chi^2(2, N=12)=1.5, P=0.22$) and whether anger experienced was different ($\chi^2(2, N=12)=2.4, P=0.12$).

**Figure 5.5: Week 8 rating of irritation**

There is an overall effect of treatment on perception of how irritation levels compare to normal ($\chi^2(1, N=12)=8.571, p<0.01$). At Baseline, all patients rated their irritation levels as being the same as usual, however, at Week 8 5 patients rated their irritation levels as being higher than normal, with only one patient saying that their irritation levels had remained the same.
5.4.1.2 Qualitative data

For this thematic analysis it was decided to concentrate on all data related to IFN-α at week 0 as the effects of HCV have already been discussed in detail, as well as assessing the perceived effects of treatment at week 8. Emergent themes are presented in Table 5.4.

Table 5.4: Themes for IFN-α

<table>
<thead>
<tr>
<th>Category</th>
<th>Major theme</th>
<th>Minor theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>Starting treatment is associated with feelings of anxiety.</td>
<td>Anxiety is related to personal values and uncertainty of what will happen</td>
</tr>
<tr>
<td></td>
<td>Most people start IFN with a sense of optimism</td>
<td>The treatment is seen as a negative to get to a positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taking IFN will be life-changing</td>
</tr>
<tr>
<td>Health</td>
<td>IFN-α causes significant fatigue</td>
<td>Patients have to ‘ration’ their energy</td>
</tr>
<tr>
<td></td>
<td>IFN-α has an impact on perceived general health</td>
<td>Health is seen to go up and down and does not remain constant</td>
</tr>
<tr>
<td>Mood</td>
<td>IFN-α induces emotional lability; mood is not constant</td>
<td>Mood is different from depression</td>
</tr>
<tr>
<td></td>
<td>IFN-α causes irritability</td>
<td>IFN-α lowers tolerance threshold</td>
</tr>
<tr>
<td></td>
<td>Being on treatment is associated with IFN-α specific anxiety</td>
<td>IFN-α magnifies already existing problems in the mind</td>
</tr>
<tr>
<td>Social functioning</td>
<td>IFN-α causes social withdrawal</td>
<td>Other people don’t understand how IFN-α affects an individual</td>
</tr>
<tr>
<td>Cognition</td>
<td>IFN-α has effects on executive functioning and memory</td>
<td>Patients have to ‘ration’ their cognitive efforts</td>
</tr>
</tbody>
</table>

Table showing the themes that emerged from the pre treatment interview (pre-treatment), and the during treatment interview at week 8 of treatment in order to assess the perceived impact that starting the treatment had on the group as well as the effect of being on treatment. During treatment themes emerged for health, mood, social functioning and cognition. Sleep and personality were not analysed as not enough consistent data were gathered.
5.4.1.2.1 Pre-treatment themes

Theme 1: Starting treatment is associated with feelings of anxiety (Minor theme: anxiety related to personal values and uncertainty of what will happen)

Starting treatment is associated with unknown outcomes both in terms of what side-effects if any a patient will experience, and the uncertainty of whether they will achieve a SVR, this was summed up by one patient: "I know what can happen, and I also know what might not happen" (Participant 006, M, age 54). These concerns were also reflected in the anxiety that other patients were experiencing prior to treatment with one patient specifying she was: "worrying about the side-effects" (Participant 005, F, age 40), and another recognising that treatment would: "at times be very debilitating, like being chronically ill" (Participant 001, M, age 54). There was also the worry of treatment discontinuation due to side-effects: "will I be able to last?" (Participant 004, F, age 40). The anxiety was so severe in one patient that he had been experiencing panic attacks: "When I am thinking about my treatment and any side-effects I am a little scared because it will complicate my life" (Participant 002, M, age 33). When asked what they had heard about treatment most patients spoke about the negative connotations of treatment: "It's poison, erm, it can bloody near kill you things like that" (Participant 006, M, age 54), and that it was: "like being in your own private hell" (Participant 004, F, age 40). However, some patients recognised that this was a part of the treatment and that despite the uncertainty they believed thinking in terms of the worst possible scenario could be beneficial to them: "I faced the facts that I'm going to have these symptoms, so it's a bonus if I don't" (Participant 005, F, age 40).

For most patients their anxiety was specific to something that they valued in themselves; one patient who was due to start a course at college was worried about: "forgetting things, feeling slow all the time" (Participant 002, M, age 33), another patient who valued herself highly in terms of her ability to be a good mother to her children was upset: "knowing that you won't be able to play with your children and things like that" (Participant 003, F, age 33). For one patient the anxiety was specific to the fact that he valued the fact that he had given up substances a few years previously and had managed to turn his life around, but he was worried about being reliant on needles again: "I got home and opened the syringes and I thought, 'that's what it is', because when I was an intravenous drug user I always had syringes with me, you know, a big box full of em at one time, I was worried about getting back into that
mindset...it's all to do with the drugs, injecting, mind-altering substances, here we go again!" (Participant 006, M, age 54).

Theme 2: Most people start IFN-α with a sense of optimism (Minor theme: The treatment is seen as a negative to get to a positive and taking IFN-α will be life changing)

All of the patients interviewed spoke with a sense of optimism that the treatment would work for them regardless of genotype and likelihood of viral clearance: “It’s going to cure me” (Participant 002, M, age 33: Genotype 1, 50% chance of clearance); “I think I’ve got a very good chance of getting over it” (Participant 001, M, age 54: Genotype 1, 50% chance of clearance). However, in some patients there was an acknowledgement that their genotype would play a role in how likely they would be to clear the virus: “I am looking that in 6 months time the hepatitis could be out of me system...there’s a 90% chance” (Participant 005, F, age 40: Genotype 3, 85% chance of clearance); “I happen to have the worst type and, er, it’s harder to fight” (Participant 003, F, age 33: Genotype 1, 50% chance of clearance).

This optimism was not unrealistic, as many patients acknowledged that there was a chance it may not work: “now I feel optimistic, whatever happens, win, lose, or whatever” (Participant 006, M, age 54: Genotype 1, 50% chance of clearance). When speaking about the sense of optimism they felt regarding treatment, there was a minor theme that emerged where people spoke about the treatment as a negative (side-effects) to get to a positive (viral clearance): “it’s going to make it bad to make it good” (Participant 003, F, age 33); “It can bring you right down, but that’s the point of the stuff to bring you right down so that the other stuff can work on it and get rid of it” (Participant 006, M, age 54); “Just that little bit of bad, and then my life would improve” (Participant 002, M, age 33).

During the course of the interview it also became apparent that people viewed the start of treatment as a major event in their life: “I’m just dying to get it over and done with now, you know. I’m on the countdown now” (Participant 004, F, age 40) and that their life would not be the same for the time they take the treatment: “it’s kind of like I am going away for a while is the way that I feel” (Participant 003, F, age 33). However, some people view the anticipated change induced by treatment in a more philosophical way, and see it as an opportunity to test themselves: “coping with the
side-effects is a major part” (Participant 001, M, age 54), and also as an opportunity to learn more about themselves and grow: “I am going to feel that I am doing something in that I am growing” (Participant 002, M, age 33); “It’s going to be a journey....it’s a learning experience” (Participant 006, M, age 54).

5.4.1.2.2 Themes in Health

Theme 1: IFN-α cause’s significant fatigue (Minor theme: Patients have to ‘ration’ their energy)

When asked about the effect IFN-α had on their health, all patients spoke about a significant amount of fatigue that they had been experiencing and the impact that was having on their daily lives: “It’s been good enough, but I haven’t as much energy as I normally would...I find that if I run up the stairs like I’m out of breath.” (Participant 004, F, age 40); “I don’t feel like going for walks anymore...it’s like the mind is willing but the body is weak” (Participant 006, M, age 54).

This fatigue was often the main side-effect of treatment that patients spoke about: “I’m so tired, and mostly I’m tired, um, not much else really” (Participant 006, M, age 54); “Once I sit on me couch at home I won’t get off it, sure I won’t” (Participant 005, F, age 40). With one patient the fatigue was so bad that she had not left her bed for the previous two weeks and when asked to describe it she said: “there’s no word for the tiredness, it’s not tired, there’s no word in the vocabulary for it” and that her energy was so low that: “I can’t even put an earring in” (Participant 003, F, age 33).

The fatigue experienced was described as fluctuating, but it was also acknowledged that IFN-α caused their Baseline level of energy to be lower than would otherwise be normal: “My base-level has dropped you know, really significantly, and within that base-level I have gone up and down, but at the top of it, it is still way more tired than I ever was before” (Participant 001, M, age 54). This idea of Baseline energy being lower was echoed by another patient: “it’s like...you’re after doing the marathon already, but you’ve to do the marathon with everybody else.” (Participant 003, F, age 33). A minor theme that emerged within the fatigue theme was that some patients spoke as if they had a limited energy resource and that meant having to consciously decide what to ‘spend’ their energy resource on for that particular day: “I am redressing you know, an awful lot of my activities, er, and husbanding my energy quite consciously....I
have had to put quite a lot of work in, in the acceptance of the inescapable fact that I am not going to get everything done that I want to get done and I have to prioritise.” (Participant 001, M, age 54); “I can’t exert myself, like if I have something to do it takes over my whole day” (Participant 004, F, age 40).

**Theme 2: IFN-α has an impact on perceived general health (Minor theme: Health is seen to go up and down and does not remain constant)**

Many of the patients interviewed acknowledged that IFN-α had an impact on their general health: “it’s a bit like having the flu, flu-like symptoms, fuzzy headed...um, a few other aches and pains but not too bad, other than the itching skin” (Patient 006, M, age 54). For most patients there was an increase in the amount of bodily pain that they were experiencing: “I have joint pain, muscle pain, er, sores at the roof of my mouth, um, I have some kind of thing on the right side of my jaw at the moment, and occasional shooting pains” (Participant 001, M, age 54; moderate bodily pain). Five of the six patients interviewed also spoke of experiencing general aches and pains, consistent with those that would be experienced during the flu: “it’s strange because my muscles is like hurting me” (Participant 002, M, age 33; moderate bodily pain); “I had to put a pillow underneath me leg in bed because I couldn’t sleep, it’s like it’s me hip, me, all me joints on this leg, you know me knees, me thing and it’s just an ache or restless feeling” (Participant 004, F, age 40; moderate bodily pain); “the pain is indescribable, it is nothing I have ever felt before (Participant 003, F, age 33; severe bodily pain). However, health tended to fluctuate: “Some weeks, I am perfectly normal, like everything is fine, and sometimes, yeah it’s like different.” (Participant 002, M, age 33); “I am not as tired as I was, actually I feel that I am coming back to myself”(Participant 005, F, age 40).

**5.4.1.2.3 Themes in mood**

**Theme 1: IFN-α induces emotional lability; mood is not constant (Minor theme: Mood is different from depression and IFN-α magnifies already existing problems in the mind)**

When speaking to patients about how they felt IFN-α affected their mood, many spoke about experiencing a labile mood, as they were getting: “mood swings” (Participant 006, M, age 54). Patients spoke about getting more upset than they would do normally
with things that normally: “I’d get more upset, I can feel it in meself...irrational kind of upset like” (Participant 004, F, age 40). This enhanced emotional reaction was also spoken of by all the men interviewed in terms of being more easily moved to tears: “The kind of things that normally make me feel a little bit moved bring me to the point, you know, where I actually need the physical release of tears” (Participant 001, M, age 54); “When I am watching a movie and I see something sad I almost cry, you know, it’s like strange” (Participant 002, M, age 33); “I keep seeing things on the telly and sort of start crying, I don’t think it’s as bad as depression, it’s like, ‘oh God no, look what’s going on in the world’, because I feel a bit low in meself, I think it’s bothering me more.” (Participant 006, M, age 54).

When asked about this enhanced emotionality, one patient spoke of: “the borders have been expanded without a doubt” and that to experience being on IFN-α was: “to experience a lot of emotions to a greater degree than I normally would” (Participant 001, M, age 54). This emotional lability was seen to be mostly manageable by patients and distinct from depression: “I was thinking I was going to be...depressed you know, and everything is going to be awful, but actually I can still be normal, I can still work, and I can still like everything” (Participant 002, M, age 33). Mood was also viewed in relation to the physical effects of the treatment, rather than the treatment causing a pure depression: “it’s not like I’m all sad and all the treatment and all like that, but I am sad because of the effects, who likes to be in pain, I mean come on” (Participant 003, F, age 33). There was a general consensus that IFN-α affects mood and that Baseline psychological functioning would have an impact on this mood as treatment was described as magnifying already existing issues in people’s minds: “It’s like everything is magnified or something in your brain...a lot of thoughts go through your brain but you learn to deal with them...it’s kind of more of a struggle to be happier” (Participant 004, F, age 40).

Another patient also spoke of having to deal with these magnified negative emotions: “I have had invitations from my psyche to become depressed. I have had little tendrils of thoughts to obsess about and to spiral downwards with, you know, and so far I have been lucky enough to recognise them for what they are” (Participant 001, M, age 54).
Theme 2: IFN-α causes irritability (Minor theme: IFN-α lowers tolerance threshold)

The most consistent psychological effect of treatment on mood was on irritability, with all patients speaking about this specific side-effect: “I’m a lot snappier” (Participant 005, F, age 40), and how it was affecting them, with one patient rating this side-effect as the worst effect they were experiencing: “like going really angry really easily sometimes....I try to control but it is hard, that is the worst thing.” (Participant 002, M, age 33). This irritability was caused by innocuous activities that normally would not bother people: “things that used to, the children’s programmes I used to dance around to, now the squeaky bastards, oh I can’t even listen to it” (Participant 003, F, age 33); “it’s like I’m more impatient when I’m shopping, more touchy you know” (Participant 006, M, age 54). With one patient describing their tendency to get irritated as being due to a: “lower kind of tolerance threshold than usual” (Participant 001, M, age 54). One patient stated they were actively avoiding people because of this side-effect: “I could feel myself getting confrontational...I had to keep away from people because I knew I’d end up in an argument with me family over something ridiculous and stupid...I had to walk out of a room because I thought I was going to explode” (Participant 004, F, age 40). When speaking about irritability it was perceived not as being something where patients were constantly in a state of irritation, but instead something where they reacted more quickly to things, in line with the previous theme of emotional lability: “I am not irritable all the time like, when I get irritated, you know things set me off more....becoming irritated by something that wouldn’t normally irritate me that much” (Participant 001, M, age 54); “Sometimes I get aggravated...and the next day you could be grand” (Participant 003, F, age 33).

Theme 3: Being on treatment is associated with IFN-α specific anxiety

Most patients reported feeling some treatment specific anxiety related to cognitions associated with treatment, rather than being a direct effect of treatment itself. For some patients the anxiety was related to people finding out they were on treatment: “I am worried a bit if people see there is something wrong with me” (Participant 002, M, age 33), for others it was the uncertainty of side-effects and treatment outcome: “I’m still anxious because I don’t know what’s to come...you’re anxious to know like, you’re trying to do what you can, put all this work into it and then you get this kick in the
teeth” (Participant 003, F, age 33); “I kind of have this funny feeling of the next few weeks that it’ll be kind of, obviously you can only be strong so much, if something is overtaking you, it’s overtaking you” (Participant 004, F, age 40).

This uncertainty was summed up by one patient as: “nobody can say for certain you know, what side-effects you’re going to have, but, nobody can say for certain what’s going to happen anyway” (Participant 006, M, age 54).

Being on treatment did not result in a decrease in anxiety experienced relative to Baseline for the majority of patients with only one patient experiencing such a reduction: “I think I’m getting better, rather than before the treatment when you were thinking, ‘oh this is going to happen’, or, ‘you’re going to die’...they’re all positive thoughts now rather than negative, so.” (Participant 005, F, age 40).

5.4.1.2.4 Themes in social functioning
Theme 1: IFN-α causes social withdrawal (Minor theme: Other people don’t understand how IFN-α affects an individual)
Five of the six patients interviewed spoke of withdrawing socially from people around them: “I am more remote in some senses, I am more distant” (Participant 001, M, age 54). When speaking about this social withdrawal, some patients spoke about it as something that they were not motivated to engage in: “I don’t want to answer the phone, if someone’s ringing I don’t want to talk to them...I just don’t want to do anything.” (Participant 003, F, age 33); “I can’t be bothered to speak to some people, you know my sponsor phoned me up a couple of times to talk last week, and I just really could not be bothered to talk to anybody. So there’s a bit of isolation going on there, just a little bit” (Participant 006, M, age 54).

Another patient reported withdrawing specifically from his partner, which was due to spending all day at work having to interact with people, and needing to be alone when he got home: “I have to act in work to be healthy and normal to work with other people the same yeah, and I think that’s what I need yeah, just a break” (Participant 002, M, age 33). This sense that interactions with people drained energy was echoed by another patient: “I would stay in as much as I can so I don’t have to talk, or go out, or personality or anything, too much work to talk to people like” (Participant 003, F, age 33).
This feeling of isolation in part arose from a sense of: “feeling different to everybody” (Participant 004, F, age 40). With some people stating that people around them did not understand what treatment was like for them: “me son doesn’t believe in anything like that” (Participant 005, F, age 40). With the participant who felt the social isolation the most acutely going on to explain: “people just think that, ‘oh, she’s just losing the plot’, they don’t put it down to your medicine, because you look ok, they don’t realise it’s affecting your mental state too” (Participant 004, F, age 40).

5.4.1.2.5 Themes in cognition

Theme 1: IFN-α has effects on executive functioning and memory (Minor theme: Patients have to ‘ration’ their cognitive effort)

When talking about the side-effects of treatment four patients reported that the treatment had an effect on concentration and memory: “It’s like my brain is black with smoke...you cannot finish your sentence because you cannot concentrate on what you say” (Participant 002, M, age 33); “I am scattered, I have poor short-term and long-term memory” (Participant 001, M, age 54).

This concentration is something patients feel they have to ration as they find they can only maintain for a limited amount of time: “it’s only a couple of minutes really before I start feeling some strain” (Participant 001, M, age 54); “study and everything is good, but, personal life and things you know, and not work at home, and forgetting things that I should do” (Participant 002, M, age 33), with patients finding that it takes more effort to do things than it might do normally: “I haven’t got the concentration” (Patient 006, M, age 54). Another patient who had previously said her cognition was good admitting that: “I think I am starting to wane again” (Participant 004, F, age 40). As well as concentration another patient stated that they had lost some of their: “higher intellectual function” such as “wit and communicating on that level is not really available to me as it normally would be” (Participant 001, M, age 54).
5.4.2 Retrospective IFN-α study

5.4.2.1 Qualitative data

A semi-structured post-treatment interview was conducted with 15 patients. Only qualitative data were analysed from this interview, with major themes emerging within overall effects of treatment, health, sleep, mood, social functioning and cognition (see Table 5.5).

Table 5.5: Themes for post-treatment interview: effects of IFN-α

<table>
<thead>
<tr>
<th>Category</th>
<th>Major theme</th>
<th>Minor theme</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall perception</strong></td>
<td>Finishing treatment does not mean the end of side-effects</td>
<td>Severe adverse treatment-related health effects can impact on health long-term</td>
</tr>
<tr>
<td>of treatment</td>
<td>Treatment is a positive and negative experience with ratings based on treatment outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment can change people’s outlook on life</td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>Most commonly reported adverse health effect is fatigue</td>
<td>Fatigue shows a diurnal variation</td>
</tr>
<tr>
<td></td>
<td>Patients description of health effects of IFN-α comprise mainly of flu-related symptoms</td>
<td>Fatigue can lead to significant social impairment</td>
</tr>
<tr>
<td></td>
<td>Health is not explicitly improved by treatment</td>
<td>Severe adverse physical effects can occur during treatment</td>
</tr>
<tr>
<td>Sleep</td>
<td>IFN-α causes sleep disturbance</td>
<td>Sleep disturbance can continue past cessation of treatment</td>
</tr>
<tr>
<td>Mood</td>
<td>Most commonly reported mood effect is irritability</td>
<td>IFN-α causes a lowering of the threshold for coping with stressors</td>
</tr>
<tr>
<td></td>
<td>IFN-α causes mood to lower and can cause depression</td>
<td>Irritability and depression linked in to a labile mood</td>
</tr>
<tr>
<td></td>
<td>Anxiety is caused mainly by treatment related cognitions</td>
<td>The time between finishing treatment and finding out whether it worked is an anxiety provoking time</td>
</tr>
<tr>
<td>Social functioning</td>
<td>IFN-α causes social withdrawal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support of people who understand the side-effects of treatment is helpful</td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>IFN-α primarily affects concentration</td>
<td>Other executive functions can be impaired</td>
</tr>
</tbody>
</table>

Table showing the themes that emerged from the post-treatment interview that looked at the domains of overall perception of treatment, health, sleep, mood, social functioning and cognition.
Theme 1: Finishing treatment does not mean the end of side-effects (Minor theme: severe adverse treatment-related health effects can impact on health long-term)

One theme that emerged from half (n=8) of the participants was that finishing the treatment did not automatically mean a return to a pre-treatment level of functioning, with some participants reporting that it took them up to 18 months: “It would, it improved from a poor condition, not due to the hepatitis, but due to the effect of the treatment, to excellent, within a year and a half maybe, so it was a year and a half from the completion of treatment to what I would call optimal health” (Participant 107, M, age 48: 4 years post treatment).

Some participants did not seem to be prepared for the fact that recovery from treatment would be such a long process, and would feel the: “disappointment of not feeling much better much sooner” (Participant 001, M, age 54: 6 weeks post treatment). This was echoed by another patient who was only 3 months post-treatment: “I was, um, disappointed when I stopped taking the pills that I didn’t recover straightaway, do you know what I mean? It was a bit of a letdown... I’m still not sleeping, I’m not as happy as I was before” (Participant 103, M, age 36: 3 months post-treatment).

One patient in particular who had quit his job due to fatigue-related treatment complications was upset that he could still not return to his job 1 year post-treatment: “I didn’t expect myself to be off work this long” (Participant 110, M, age 48: 1 year post-treatment). In the case of two patients the lasting effects of treatment were psychological effects, with one patient specifying that it took him: “a couple of months” (Participant 101, M, age 34: 1 year post-treatment), and another stating: “I’m feeling a whole lot better, you know, but, erm, still very moody, very aggressive, er, you know?” (Participant 112, M, age 34: 6 months post-treatment). Those patients who had more recently finished a course of IFN-α could still be feeling the effects quite acutely: “I feel like there is a part of me that is still reassembling, you know? Physically, emotionally and psychologically” (Participant 001, M, age 54: 6 weeks post-treatment).

Those people who experienced severe side-effects during the treatment seemed to take a longer time to return to optimal health, with some reporting that treatment had left a lasting impact on their health: “Your body does come back a good lot, you know, your whole system kind of repairs if you like a good deal, you wouldn’t be back to normal totally” (Participant 105, F, age 54: cellulitus at week 18); “The thyroid damage, which
is probably permanent now, that’s what the endocrinologist thinks" (Participant 107, M, age 48: hypothyroidism at week 8)

**Theme 2: Treatment is both a positive and negative experience with ratings based on treatment outcome**

When asked whether treatment had been a positive or negative experience for them, most patients stated that it had been both a positive and negative experience with the overall perception related to treatment outcome (see Figure 5.6). For those patients who had achieved SVR, the experience was rated as both positive and negative, with the general consensus within the group being that the experience of the treatment itself was negative, but the outcome of the treatment (i.e., being clear of HCV) was positive: “It was positive in the end because it worked, but on it I felt it was very negative and nearly frightening” (Participant 104, F, age 55); “Being on the treatment, the end result to me was worth anything I went through, to be cleared, but being on it was awful, the end result was brilliant” (Participant 105, F, age 54).

This feeling that the treatment itself was negative but the outcome positive for patients who achieved SVR was echoed by one patient who recognised that treatment was a process, where the end result would define the interpretation of the process: “it was negative, I dunno, well it wasn’t as plain as negative because I knew it was part of a process, it was a treatment...but I knew from coming here and getting my updates it was working.” (Participant 101, M, age 34). As such, it would be expected that where SVR had not been achieved that the positive outcome would not accompany the negative process of treatment, and so treatment should be considered a mostly negative process, which is what was found (see Figure 5.6).

When asked why they had rated the experience as negative, the explanations seemed to revolve around a feeling that they had been punished in some way, with one patient spelling out the word: “A W F U L” (Participant 106, F, age 56) to describe her overall experience of treatment, and another explicitly stating: “The whole thing was like a punishment” (Participant 108, M, age 54). Patients also seemed to feel some resentment towards the interferon when it did not work for them: “I really got nothing out of it, and I couldn’t wait to get off it.” (Participant 113, F, age 57). However, one patient who rated the experience as both positive and negative acknowledged that the main thing was having tried: “I mean if it works it’s fucking great, but if it doesn’t at least you
tried.” (Participant 111, M, age 41). In line with the fact treatment perception is related to treatment outcome, where there is an unknown outcome, there is a less consistent interpretation of how treatment affected them. With one patient stating that the experience was positive: “I knew that's what made me tired, and sometimes depressed, but I knew that it is helping me, so always that is keeping me like you know, going” (Participant 002, M, age 33). Another patient stated that the experience was both positive and negative: “I am currently hep c negative so that's a positive...I feel like it's aged me” (Participant 001, M, age 54). The final patient rated the experience as being negative: “a very unpleasant experience....how can you poison someone and ask them if it's positive?” (Participant 103, M, age 36).

Figure 5.6: Ratings of treatment relative to treatment outcomes

Graph showing patients overall perception of how treatment affected them with treatment outcome investigated as a factor influencing perception of treatment. Of those 8 patients who achieved SVR (sustained viral response: HCV cleared), the majority (n=6) reported that it had been a positive and negative experience, with 2 patients reporting it had been a positive experience. For those patients where treatment did now work, it was mostly classified as a negative experience (n=3), with only 1 patient stating that it had been both positive and negative. For those patients who did not yet know whether treatment had been successful or not there was no consistency, with 1 patient agreeing with each of the three statements.

Theme 3: Treatment can change people's outlook on life

A smaller theme that emerged from treatment was that it seemed to be a pivotal moment in 40% (n=6) of the patients' lives, and something that actually led them to change their outlook on life itself. Some people stated that it had been an opportunity for them to grow psychologically and learn more about who they were: "I can know myself better,
and I can know my erm, other sides, so, that is fantastic like” (Participant 002, M, age 33: unknown treatment response); “It was a journey, yeah?....It probably wasn’t the best time in my life, but I think I have learnt a lot from it” (Participant 109, M, age 48: SVR). Two patients in particular who cleared the virus felt like they had a responsibility to live their lives to the fullest, one who contracted the virus through intravenous drug-use felt that he had been given a second opportunity, and the second who was infected through a blood transfusion, felt that the experience had made her stronger and that she shouldn’t waste it: “You know, you’ve been given this opportunity and you’ve got this responsibility to take advantage of it, and live your life the way it should be, you know, not fuck it up like, or waste it.” (Participant 101, M, age 34: SVR); “I think I’ve changed since. I’ve had a different outlook on life, and I put myself more, I think of myself more...you sort of realise life is for living and you’re only getting one go at this and you don’t know how long you’re going to have left” (Participant 104, F, age 55: SVR).

Some patients seemed to develop an awareness of social issues through treatment, with one patient stating that the anger he felt on treatment was because of a new awareness of social issues: “the way the whole of society is based on greed, innit? The whole thing is based on profit” (Participant 103, M, age 36: unknown treatment response). Another patient who developed an awareness of social issues did so due to the fact that he was given an opportunity to take a treatment that many people in the world would not be able to access: “you’re angry that the whole world can’t have this” (Participant 101, M, age 34: SVR). A final patient who developed such an awareness did so through becoming homeless while on the treatment, something which he explicitly blamed on IFN-α: “it changed everything, it changed the way I think, it raced me brain, er, it made me very, erm, aware of other people, it made me very aware of injustice” (Participant 108, M, age 54: treatment did not work).

5.4.2.1.2 Themes in health

Theme 1: Most commonly reported adverse health effect is fatigue (Minor themes: fatigue shows a diurnal variation and fatigue can lead to significant social impairment)

93% (n=14) of patients interviewed for this study reported that at some time during treatment they experienced significant fatigue. Often this symptom was reported to be
the most treatment-limiting side-effect experienced: “You can’t do nothing, you’re knackered, do you know what I mean? I’m a really physical person, and it just took me” (Participant 103, M, age 36); “I couldn’t do anything, I did absolutely nothing. I didn’t cook, I didn’t clean, I did nothing.” (Participant 104, F, age 55).

The fatigue was so bad that one patient likened it as having to fight your own body in order to be able to achieve anything: “you are more tired, and you have to fight with yourself actually” (Participant 002, M, age 33), with some patients stating that they were unable to even force themselves to do things they might normally: “I hadn’t got the energy even to force myself to do it.” (Participant 105, F, age 54). For a few patients the fatigue was both a physical and psychological phenomena: “you’re more tired then, and not just tired but less motivated you know?” (Participant 101, M, age 34); “I had no motivation, and I was fucking tired” (Participant 111, M, age 41). However, others felt the effect was purely physical: “mentally I wanted to do things, but physically I couldn’t” (Participant 102, F, age 54); “When I was on Interferon I couldn’t do anything like, I just couldn’t” (Participant 112, M, age 34). This fatigue seemed to have some diurnal variation as some participants mentioned that their levels of fatigue would be worse in the morning: “it was hard to wake up” (Participant 002, M, age 33); “in the morning, it takes ages to get going” (Participant 103, M, age 36), however, other participants found levels worse: “especially in the evenings” (Participant 105, F, age 54). For some participants the fatigue was so bad that it caused social and occupational impairment with three patients stating that the fatigue they experienced was the main reason that they had to give up their jobs, two of whom were builders: “Everything’s just walking, it’s rough terrain, climbing up ladders, scaffolds. You just can’t do it, you get exhausted” (Participant 103, M, age 36); “I didn’t have the oxygen levels to work in construction...I didn’t have the energy levels to do what I normally do, it was like hitting a brick wall” (Participant 110, M, age 48).

The fatigue also impacted on people’s ability to socialise: “I was a grumpy old fucker, yeah, I didn’t have time for people, I just didn’t want to be around people, I just wanted to sleep” (Participant 111, M, age 41), with one patient noting that this fatigue was also potentially responsible for the mood change he had experienced during treatment: “I think it’s all connected, you know, so if you’re tired, which you obviously are, not happy. I mean the happiest people aren’t often the tiredest people” (Participant 101, M, age 34).
Theme 2: Patients description of health effects of IFN-α comprise mainly of flu-related symptoms (Minor theme: Severe adverse physical effects can occur during treatment)

When asked to describe how their health was on treatment, most patients would talk about it being: “like the bad flu” (Participant 108, M, age 54). Flu-like symptoms were talked about by many patients: “I remember being tired, and the nausea...and headaches” (Participant 111, M, age 41); “I was so tired, the joint pains, and just nausea, was so sick I couldn’t eat anything. I went very thin” (Participant 104, F, age 55). However for the most part these flu-like symptoms were perceived to be a totally normal part of treatment: “I had the nausea, the normal symptoms that people get, the headaches” (Participant 113, F, age 57) and were often perceived to be: “at worst tolerable” (Participant 107, M, age 48). One patient described in detail the flu-like symptoms that accompanied the first few injections: “The first dose 8 hours later...it was flu-like symptoms, what, it was fever and hallucinating in bed at night and all kinds of stuff, and you knew, you were told to expect it, and it was alright, the second dose was way milder, the third dose was virtually undetectable...but again for those 3 weeks, maybe 4 weeks, I was definitely weak and lacking in energy” (Participant 107, M, age 48).

These flu-like symptoms often included an amalgamation of various symptoms, such as problems with the skin (see Figure 5.7 for the health issues talked about by patients): “I was feeling sick, and I had different problems. I had irritated skin for a few weeks, my gums were sore...I had sinus headaches a few times....my hair came out quite a bit, my skin was bad, and my face was dreadful I lost so much weight” (Participant 102, F, age 54). One patient felt like the dermatological effects of treatment were particularly hard to deal with “I’d say almost immediately your skin is affected, thrush I mean, stuff you’ve never had before, and rashes and itches.” (Participant 103, M, age 36).

As well as these flu-like symptoms there were also cases where patients spoke about severe adverse effects they had on treatment. One of these was a possible by-product of treatment, when a patient developed fluid in the legs after a long haul-flight: “when I got back I was stuck on the couch for probably about 5 weeks before the swelling came down” (Participant 110, M, age 48). The other two side-effects were acknowledged by doctors to be due to treatment with one patient developing
hypothyroidism: "my thyroid-stimulating hormone had gone down, so they put me on tablets for it...I felt otherworldly it was a bit weird, my sense of reality was a bit funny, and I was nervous about everything, and I was for the first time in my life afraid of the cold." (Participant 107, M, age 48). The other patient experienced cellulitis, and was the only patient for whom the side-effect was severe enough to warrant discontinuation of treatment: "I wasn't well at all on treatment, erm, I got cellulitis, and erm, it went actually from my toes to under my chin, yeah, I was very, very ill." (Participant 105, F, age 54).

**Figure 5.7: Reported physical symptoms of IFN-α**

The above graph shows those side-effects that patients interviewed post-treatment described when talking about how their health was on treatment. The most common side-effects of treatment recalled were fatigue (14/15 patients), flu-like symptoms (10/15 patients), weight loss (5/15 patients) and dermatological symptoms (5/15 patients). Other side-effects included ocular symptoms (2/15 patients) and hair loss (2/15 patients). The more severe physical effects of treatment are in purple with 1 patients each experiencing thyroid symptoms, cellulitis and fluid retention.

**Theme 3: Health is not explicitly improved by treatment**

When asked whether they felt their health had improved through treatment the majority of patients answered that they did not feel any different at the time of interview to how they did prior to treatment. One patient spoke in detail about this feeling: "Physically you don’t feel any better, ok, because you weren’t in bed lying there, you know like after a car crash, you weren’t lying in bed and now you’re grand again, you know what I mean? You didn’t notice it, like in your life, like you don’t go, ‘oh me liver’s killing me’ or anything like that. There’s no physical symptom of it, well not for me...people are
saying it worked so, you know you’re happy, but everything you feel is because you are told that by the doctor’s...it’s the information they’re giving you that makes you happy, it’s not what your body is telling you, it’s not how you feel.” (Participant 101, M, age 34).

The perception of health being better because of information provided by clinicians was something echoed across a number of participants: “I’d say it’s more or less the same, there wouldn’t be a huge, like really the only difference is that the nurses tell me that I have cleared the virus” (Participant 104, F, age 55). The feelings regarding perception of health were best summed up by a patient who did not yet know their results: “I didn’t even know I had hepatitis, so you know, what I mean, so all I’ve done, the only illness I know is taking interferon” (Participant 103, M, age 36).

As patients did not feel themselves that their health had improved, this could be reflected as a feeling of anxiety that their HCV-negative status was somehow wrong: “a little bit nervous, it was all a little too neat, that maybe it was going to come back...anxious, that is, that we could maintain the good result, not entirely believing that it would stay” (Participant 107, M, age 48), for this particular patient it took them three years post-SVR to accept that the HCV had gone.

5.4.2.1.3 Themes in sleep

Theme 1: IFN-α causes sleep disturbance (Minor theme: Sleep disturbance can continue past cessation of treatment)

73% (n=11) of patients interviewed reported that IFN-α caused sleep disturbance for them: “I just watched television, just couldn’t sleep” (Participant 113, F, age 57). However, the nature of this disturbance varied between patients; some patients reported a straightforward insomnia that they attributed directly to the effects of the drug: “I’d be there, and I’d be out of bed onto the computer, read a bit, just be like going around, and I used to be lying down during the day, but I wasn’t sleeping, I would just sort of rest because I couldn’t do anything” (Participant 104, F, age 55); “I wasn’t sleeping an awful lot, you know? Sometimes I would be driving, and I would be falling asleep just from tiredness, sheer tiredness...But em, I would be in bed then, and I just couldn’t sleep then, you know?” (Participant 112, M, age 34). Other patients, however, reported that the insomnia they experienced was an indirect consequence of the treatment; specifying that it was the result of anxiety due to illness related rather than a straightforward effect
of treatment: “It’s all the time worried, so that, it’s just because of that that you’re, you don’t sleep I think” (Participant 105, F, age 54). Another participant reported that he believed the insomnia that he experienced was an indirect effect of the drug in that he was having to get up more during the night due to the amount of water he was drinking on treatment: “It would probably be about 5 or 6 hours sleep, and I would have to get up a lot during the night because I was drinking so much” (Participant 110, M, age 48).

A final group that experienced sleep disturbance, believed they did so because their circadian rhythm was essentially no longer in the pattern it used to be: “You went to sleep for an hour, and it was more broken sort of pattern, there was no pattern, you know, the pattern was all sort of broken...different days, different times.” (Participant 101, M, age 34); “You’d be asleep at the wrong time, you know, in the morning, and then you couldn’t get out of bed. It was like your day had been turned upside-down.” (Participant 103, M, age 36).

One participant interviewed attributed his poor sleep to a combination of all the issues that were spoken about by other participants, believing that it was both a direct and indirect effect of treatment: “I was getting my rest during the day, and night-time I was just twisting and turning, maybe I was doing a lot of thinking, I was just thinking negative and in bed lying there, and I was kind of feeling nauseous and that keeps you awake.” (Participant 111, M, age 41). This belief was backed up by a patient who said he experienced no sleep problems during treatment, but only because he forced himself to stick to a routine: “I was sleeping better on the interferon...I tried to do for my body a routine, so always same time, and waking up at same time.” (Participant 002, M, age 33). Sleep disturbance impacted on the patients self-reported quality of life: “one of the things that takes you down, it’s like this, and not sleeping, I probably slept, I don’t know, I didn’t sleep a lot” (Participant 103, M, age 36).

Other patients (n=2), however, reported that they experienced hypersomnia rather than insomnia: “I did sleep because I often slept through the day, which wasn’t something that I would often do” (Participant 102, F, age 54); “23 fucking hours, honest to God, you would fall asleep, and er, that was it, there was no reason to get out of bed unless I had to go to the toilet” (Participant 108, M, age 54).

A minor theme that emerged was that even after a significant period of time had passed post-treatment, sleep could still be affected, “I find you wake up more easily” (Participant 101, M, age 34: 12 months post-treatment); “the sleeping still, it’s not as
bad as it was but I’m hoping that eventually it will get better.” (Participant 104, F, age 55: 18 months post-treatment); this disturbance was something that patients attributed directly to the effect of IFN-α: “I can’t fucking sleep anymore, I am extremely tired, er, before the interferon I wouldn’t know what you’d be talking about if you said you couldn’t sleep, and that’s fact, I do now.” (Participant 108, M, age 54).

5.4.2.1.4 Themes in mood

Theme 1: Most commonly reported mood effect is irritability (Minor themes: IFN-α causes a lowering of the threshold for coping with stressors and irritability linked in to a labile mood)

87% of patients interviewed reported that they experienced the side-effect of irritability during treatment: “I just became an angry, irritated person” (Participant 103, M, age 36); “I was like a ball of anger, I was just angry and pissed off” (Participant 111, M, age 41). This side-effect was the most commonly reported mood effect due to treatment (see Figure 5.8). When talking about this irritability, and the reasons why they felt they got so angry, there were two interrelated themes that emerged; the first revolved around the idea that the IFN-α caused a lowering of the threshold for coping with stressors: “Being sharp-tempered, much more so again....I ended up having roaring arguments....the barriers to express my anger were either flimsy or non-existent” (Participant 001, M, age 54).

The idea of a lowered threshold to deal with stressors was supported by patients who reported that they started seeing different traits in people that started to irritate them, as though their threshold for dealing with people was reduced: “my husband was annoying me and he was trying to do the best that he could, but erm, I could see all the bad things in him, things that I never saw before, and it was like I was awakened to different things and different people” (Participant 104, F, age 55).

The second reason this irritability seemed to occur was due to a labile mood, where participants described themselves as being more moody and more likely to overreact in situations where normally they could maintain their mood: “My mood was flashing, I can like go angry really easily, I can go annoyed really easily, so I was like more sensitive about feelings too sensitive I think.” (Participant 002, M, age 33).
Figure 5.8: Reported mood effects due to IFN-α

Graph showing the number of participants who reported that they experienced each of the mood effects listed above, and these were attributed directly to the effects of IFN-α. The most commonly experienced mood effect of treatment was irritability (13/15) followed by depressive symptoms (9/15), with the depression experienced severe enough to warrant suicidal thoughts in 2 patients. Other adverse mood effects experienced were anxiety (6/15), depersonalisation (2/15), disinhibition (2/15) and hypomanic symptoms (1/15).

One participant described the irritability experienced as being; "more intense" and also spoke of there being: "no consistency to what you would get angry about" (Participant 101, M, age 34); this, and the observation that mood goes to: "an extreme on treatment" (Patient 108, M, age 54) supported the idea of mood lability. The intensity of the irritability was described two patients as being so extreme that they described thoughts of killing other people: "Just bad mood all the time, very impatient, very aggressive, just wanted to kill people and stuff, you know?" (Participant 112, M, age 34); "I'd a very bad spin at one stage, I was so angry, and I mean I could understand people killing other people, a real anger with everybody, you know?" (Participant 106, F, age 56). These two themes of lowering of coping threshold and labile mood were bought together by the general consensus between participants that the things they would get irritated about: "stupid things" (Participant 002, M, age 33), that normally would not bother them: "At the time definitely, you're shorter temper, you lose, you sort of blow up over stupid things, things that, you know, in hindsight you would be embarrassed about, you know?" (Participant 101, M, age 34); "I was probably snapping, you know like, for little or nothing" (Participant 105, F, age 54); "Like I suppose the kids shouting and normal things like that, the noise, loud music, just stupid things really seemed to irritate me" (Participant 113, F, age 57).
Theme 2: IFN-α causes mood to lower and can cause depression (Minor themes: IFN-α causes a lowering of the threshold for coping with stressors and depression linked in to labile mood)

For 60% (n=9) of the sample spoken to for this interview, being on IFN-α caused them depressive symptoms, with the depression being so bad that in 13% (n=2), they spoke of having suicidal ideation. For the most part, however, the depressive symptoms experienced by patients were reported to be manageable, and not what they would consider to be a true depression: “I was depressed I would say, not total, you know, black depression you know, but something like grey” (Participant 101, M, age 34); “I couldn’t honestly say that I was in the depths” (Participant 102, F, age 54).

Some patients described their depression in terms of anhedonia: “I lost motivation, I’m, I’ve always got summot to do, it don’t matter where I am, I will be doing it. I just lost the will to do it like” (Participant 101, M, age 34); “I never felt content and happy on it, it was all I was kind of, struggled to do things, and struggling to get around and stuff like that” (Participant 112, M, age 34).

For some patients the depressive symptoms were linked in to a feeling of depersonalisation while on treatment: “The most profound effect was, you know, a loss of a realistic sense of self and the world” (Participant 001, M, age 54); “It’s not like unhappy, but a little bit, like squashed….sometimes I felt like I was behind the glass and everything was happening around me” (Participant 002, M, age 33). For two patients, the depression experienced was an indirect effect of treatment. One patient believed her mood stemmed from a lack of support and understanding from people around her: “I remember you know, feeling, ‘no-body gives a damn, no-body understands’” (Participant 106, F, age 56). The second patient spoke about his depressed mood being due to an inability to cope with the side-effects of treatment, which he believed caused him to re-enter substance-abuse in order to cope with the problems he was facing, which started a downwards spiral into a severe depression: “I was feeling tired, and then I was mad depressed, and um, I think at the end of it I was taking tablets and taking coke, and drinking heavily, by that time I just couldn’t sleep and everything was irritating, just didn’t see any fucking light ahead of me, just really down and had no interest in stuff” (Participant 111, M, age 41).
The reasons for the depressed mood seemed to be caused by similar processes to the irritability with a general lowering of the threshold to perceived stressors and labile mood both seeming to play a role in the mood experienced. In terms of the lowering of threshold, participants spoke of treatment magnifying their thoughts: “I feel like it opened up things, places that you didn’t want to go, it’s very hard” (Participant 104, F, age 55), and a lowering of the threshold to deal with things that normally did not bother them: “you were more sensitive...the least thing that normally you would push to one side with an answer or something, erm, it wasn’t the case, you would take it to heart so that you were very sensitive to things you know, and it would make you very sad and annoyed about something that was very small really” (Participant 105, F, age 54).

The idea of the depression being caused by a labile mood is supported by the fact that mood experienced was also not always consistent with mood swinging from low to high, with treatment making people: “extremely moody, swinging from hot to cold” (Participant 108, M, age 54): “I experienced moments of depression, not extended periods, but I was plunged very quickly, and then came out relatively quickly” (Participant 001, M, age 54). This is supported by the fact that one particular patient interviewed who had been on treatment four times experienced two severe psychiatric adverse events due to treatment, the first event was depression, and the second was hypomania: “I have been depressed on it they said...and another course of interferon made me elated. I mean it was the same interferon! The only sense I can make of that is that it is the person, it depends on how you are” (Participant 109, M, age 48). One patient also described having racing thoughts, consistent with a manic mood rather than a depressed mood: “it changed everything, it changed the way I think, it raced me brain”, however, when this participant was asked how the IFN-a had affected his mood he reported: “I went into a complete depression on Interferon” (Participant 108, M, age 54).

For two patients, the depression experienced was so severe that they described suicidal ideation; in the case of one patient they experienced thoughts of dying, but did not act on these thoughts: “it just takes away your reason for living...it makes you think, what’s the point?” (Participant 103, M, age 36). However, in the case of the second patient, the suicidal ideation was so bad that she had a plan for killing herself: “I did contemplate it yeah, I did, I thought of taking an overdose, and luckily I was attending a psychologist...and she just said, ‘C’ I can’t let you leave here’” (Participant 112, F, age
57). This particular patient had an underlying psychological problem, for which she had been attending a psychologist, but being on IFN-α seemed to make her problems more acute, lending additional support for the idea of a reduced threshold to stressors, with her developing an obsession with her own death: "I would wake up in the morning and I would get this smell, and I would say, 'that is the smell of death', and I really believed at that time that was me, and they were saying, 'why do you think you are going to die, there is no reason for it', and I would say, 'no, no, I know I am, I just know I am'" (Participant 112, F, age 57).

Theme 3: Anxiety is caused mainly by treatment related cognitions (Minor theme: The time between finishing treatment and finding out whether it worked is an anxiety provoking time)

The other main psychological effect that arose as a result of treatment with IFN-α was anxiety, with 40% (n=6) of patients reporting that they had experienced this side-effect on treatment. However, in the case of all patients interviewed anxiety was a result of treatment related cognitions, rather than a pure causal effect of the IFN-α itself: "You're always thinking, 'what if it doesn't work', and then you're thinking, 'well I'm not going to be any worse off" (Participant 101, M, age 34); "I suppose it's the worry of it, that you don't really know, are you going to clear it, is it going to get worse, and I suppose it's just that, the worry of it" (Participant 105, F, age 54).

One patient in particular attributed the anxiety he experienced on treatment to a hyper-vigilance of side-effects he was experiencing, which he put down to the emphasis on the negative effects of treatment when educated about treatment by healthcare professionals at Baseline: "they were up there....when you're on treatment you believe everything, because you've been told everything, but then your anxiety levels are up there because they've been brought there." (Participant 109, M, age 48). However, another patient attributed his increased anxiety levels to not expecting the negative side-effects that he ended up experiencing: "my body had gone through a change that I didn't really expect, I knew something was going to happen, but I didn't really know what it was going to be, and so my anxiety levels got high there" (Participant 110, M, age 48). Other reasons for increased anxiety on treatment were inability to cope with the side-effects of treatment: "general anxiety certainly went up...my normal coping skills were not quite as automatic or I had forgot them or they weren't working as well"
(Participant 001, M, age 54), and having more time to ruminate over things seemed to impact on anxiety levels for one patient: "I think it was because I had more time to think" (Participant 001, M, age 54). As well as treatment itself invoking anxiety, the period of time between finishing treatment to the six month follow-up, when patients discovered whether or not they had achieved SVR was a particularly anxious time: “Before I got my results, you know, I had to wait six months when it’s over for you to get your final results. So I only got that, erm, last month, you know, so for the couple of weeks coming up to it I was just anxious to know the results” (Participant 102, F, age 54). One patient who was currently awaiting his results reiterated this belief: “I am still worried that it is going to be alright, the results” (Participant 002, M, age 33).

5.4.2.1.5 Themes in social functioning

Theme 1: IFN-α causes social withdrawal

60% (n=9) of the patients interviewed stated that during treatment they withdrew from people around them: “You don’t wanna see people, if you don’t, there’s times like if someone comes to visit you, you’d be like, ‘oh no, don’t want to see them’, you know, so you get a lot of that while you’re on it...people noticed and I noticed” (Participant 101, M, age 34); “I was the one to he always upfront and there first, but no, it was the thing, I didn’t want to go out, and you lose friends, yeah, because you’re all the time saying and making excuses...they just don’t bother asking you” (Participant 105, F, age 54). In some cases, the patients noted that they had actively withdrawn from people around them: “I found meself isolating an awful lot on the, the old treatment” (Participant 111, M, age 41). Other patients put the social withdrawal they experienced down to a lackadaisical attitude that they developed directly as a result of treatment: “I was disengaged, socially disengaged, normally I would be perceived by people to be, you know, sort of talkative, engaging person in any company...but I wouldn’t be bothered when I was on the treatment” (Participant 107, M, age 48); “I just didn’t want to meet people” (Participant 113, F, age 57). This idea that Interferon changed their personality thus affecting their willingness to socialise was echoed by another patient: “I became withdrawn you know, I have a very outgoing personality” (Participant 108, M, age 54). However, others believed it to be an indirect effect, with two patients stating they withdrew due to their physical health: “If I wasn’t feeling very good I prefer to hide” (Participant 002, M, age 33); “It was a shock to me, and that’s when I started..."
getting a bit more seclusive” (Participant 110, M, age 48). Finally, one participant reported that he actively withdrew from people around him, as he did not want to be perceived to be a burden: “I really didn’t want to do nothing, didn’t want to be around anybody, you know real, I just wanted to be left alone, you know, like I didn’t really want to be a burden” (Participant 112, M, age 34).

Theme 2: Support of people who understand the side-effects of treatment is helpful

Another theme that emerged when talking about how IFN-α affected people socially was that the support of people who understood what they were going through was especially beneficial, such as the support received from the hospital: “They’re brilliant, there’s no word could describe how good they were” (Participant 102, F, age 54); “I am more grateful for getting the treatment, very grateful, and the nurses helped me through it so well, that it made the difference” (Participant 110, M, age 48).

It was also acknowledged that additional support at home was also important: “the support of their family is extremely important, and where you don’t have the patience they can have it for you....it is absolutely important because you have the back-up, and not only the support and care in the clinic, but you need it when you go home as well” (Participant 105, F, age 54). This support and understanding from family members, notably partners was seen to be important: “Me partner really knew what I was going through so she kind of helped me” (Participant 112, M, age 34); “It’s only now that I’m off it that I can see what it did affect, as I say, my children definitely, my husband was very good” (Participant 113, F, age 57).

Support also came from other sources such as support groups: “I had the girls at positive action, and they understood, and that makes, even someone not on treatment but with hepatitis c, it did make a difference, and you felt you could relate better to them than anyone in your family” (Participant 104, F, age 55). This type of support was something that some patients who did not have access to such a group felt was lacking from their treatment: “I would have liked to talk to somebody that was on the treatment, had gone through the treatment” (Participant 110, M, age 48); “Maybe if there was a support group run by facilitators for people in the hospital who want to sit around and talk about how their week is....they should have the option of coming in here” (Participant 111, M, age 41).
This meant that those people who had less understanding from their family had poorer social support and so felt the effects of the treatment more acutely, one patient whose Mother did not support him through his HCV diagnosis reported having poor social support: “she thinks I’ve got hepatitis, it’s self-inflicted, she’s one of them funny people” and he spoke of having a difficult time on treatment, to the point of suicidal thoughts: “it just takes your reason for living away...it makes you think what’s the point?” (Participant 103, M, age 36). Another participant whose family did not understand the effects of treatment was upset that the treatment-induced fatigue he was experiencing did not mean allowances were made for him: “I was still going out doing all the grocery shopping even though I didn’t have the energy, and that was just wearing me down more and more” (Participant 110, M, age 48).

5.4.4.2.1 Themes in cognition

Theme 1: IFN-α primarily affects concentration (Minor theme: Other executive functions may be impaired)

When asked how memory and concentration were affected on treatment 47% (n=7) of patients reported that their concentration would have been worse on treatment than it would be normally, and 27% (n=4) reported that IFN-α had an effect on their memory, with two participants reporting that memory impairment may have been caused by poor concentration: “You’ve got a bad memory because you haven’t got an attention, you haven’t got an ability to concentrate on anything” (Participant 103, M, age 36); “I was scatterbrained altogether...it was just that I couldn’t concentrate” (Participant 105, F, age 54).

Some patients spoke of an increased effort to concentrate when they were taking IFN-α: “it’s like you have to concentrate double times than normal” (Participant 002, M, age 33). This increased effort needed was seen to co-occur with an increased distractibility: “it was less focussed; it was more difficult, distraction, easily distracted” (Participant 101, M, age 34). This increased distractibility and effort was summed up by one patient as becoming like a goldfish: “You’re distracted. It’s hard to concentrate, do you know what I mean? It’s like being a goldfish, you can’t concentrate for long”(Participant 103, M, age 36).

Other patients spoke specifically about being unable to focus on things: “your mind, you know, it’s not focussing rightly” (Participant 105, F, age 54); with this
concentration impacting on two patients ability to do their job to the level they would normally: "While I was on treatment I wasn’t concentrating on anything, um, work, reading, keeping notes, following up on clients" (Participant 111, M, age 41); "I found it hard to read long passages or texts, you know, or to follow a line of argument or something when you’re reading, to stick to an arithmetic problem. I would give it a relatively cursory attention" (Participant 107, M, age 48).

Where memory impairment was spoken of, it was mostly for everyday things such as being: "More likely to forget peoples names" (Participant 001, M, age 54), with the majority of patients reporting that: "I didn’t notice anything untoward or strange that I couldn’t explain" (Participant 107, M, age 48).

Other executive problems were also described by some patients, with one patient who prided himself on being highly intellectual saying: "a couple of my abilities left me in a fashion….I had no sense of humour…my wit did not come to me. My ability to write deserted me" (Participant 001, M, age 54). Another participant spoke about losing the ability to do mental calculations: "you lose how quick you are, like doing a calculation in your head" (Participant 103, M, age 36).
5.5 Discussion

5.5.1 Overview of findings

Findings from this portion of the thesis are consistent with previous findings from studies that use more structured clinical interviews, with depression, irritability, and anxiety (see Table 1.4: Chapter 1) emerging as the main psychological domains that are affected by treatment with IFN-α. However, while the majority of research into IFN-α-induced side-effects concentrate primarily on depression (see Table 1.4), it is irritability that emerged from both groups as being the most common psychological side-effect. Despite irritability being more frequently observed it was the depression that was the more distressing side-effect of the two, with the retrospective interview demonstrating how severe this side-effect could become leading to suicidal ideation in two patients. The anxiety observed in both groups, was primarily due to treatment-related cognitions rather than being an endogenous phenomena, possibly explaining the lower rates of anxiety seen in patients relative to both depressive symptoms and irritability.

In line with previous studies, the most commonly reported health-induced side-effects from treatment were fatigue (Cotler et al., 2000; Khalili et al., 2000) and flu-like symptoms (Lindsay et al., 1998; McHutchinson et al., 1998), the former of which in particular seemed to be the most distressing of all the health-effects experienced in the absence of a severe physical adverse event. Sleep was something that yielded changeable results from the prospective to the retrospective groups, with the post-treatment group more likely to speak about disturbed sleep patterns as being a distressing side-effect of treatment. However, this observation could in part be explained by the issue of low numbers for the prospective group, and the lack of qualitative data for analysis. The final domain of cognition showed that it is executive functions, such as concentration, affected by treatment with IFN-α, with memory impairment being reported as being a result of poor concentration rather than a separate phenomena.

When speaking about the overall experience of treatment, both groups spoke of the importance of having social support from people who understood the experience that they were going through, in particular people who understood the psychological impact that IFN-α had on individuals. The support of the hospital emerged as being hugely important to participants, as education of side-effects and understanding treatment results were two things that seemed to help many of the patients through the
treatment. Another important social issue that arose was regarding social withdrawal with many patients in both groups speaking about withdrawing from people around them due to a lack of motivations as regards social interactions.

Many of these side-effects are an acknowledged part of the sickness behaviour syndrome (see Table 1.8), which is a collection of behaviour designed to decrease an organism's mood and activity, so that energy is specifically focused on fighting illness (Dantzer et al, 2008; Konsman et al, 2002).

5.5.2 Prospective IFN-α interview

For this group, there was a significant difference between Baseline and Week 8 in the amount of bodily pain experienced, irritation, memory and concentration. These differences were explained by results from the qualitative portion of the experiment as well as past research. In terms of bodily pain (see Figure 5.1), this was mostly due to the flu-like symptoms that often accompany treatment, which are primarily seen in the first few weeks of taking IFN-α (Lindsay et al, 1998; McHutchinson et al, 1998), this was reflected by the fact that when participants spoke about bodily pain it was more in terms of flu-like aches (see section 5.4.1.2.2). However, none of the other health domains yielded significance, even though participants spoke of increased fatigue and decreased ability to do normal activities; neither fatigue, nor any of the 'health impacted on physical activity' questions yielded significance (see Table 5.3). This could partly be explained by the minor theme that emerged, whereby, most participants said that their state of health was not a constant and varied from week to week. However, it is also explained by the low number of participants interviewed, with only 6 participants questioned. The previous chapter demonstrated the extent to which individual interpretation influenced within-group variability; with only six participants interviewed this was an insufficient number to overcome that particular limitation of the interview.

The only question that yielded significance in the psychological domain was the irritation question (see Figure 5.2), something that is gaining more interest from researchers as an important side-effect of treatment (see Table 1.4). Irritation was something that all participants spoke of when referring to how the treatment had affected them (see section 5.4.1.2.3). Patients described of the reason for this irritation in two similar ways; some patients spoke of their normal tolerance being lowered and others blamed the IFN-α as having a direct effect of their mood (see section 5.4.1.2.3).
As all participants experienced this side-effect, it would be expected that the result would yield significance despite the low number, however, for the other psychological questions where results were more variable this was not the case.

The reason that the depression question may not have yielded significant differences was that participants reported IFN-α as inducing a mood lability, whereby their mood was swinging instead of being constantly down. This lability meant that participants did not rate their mood as being significantly worse than it may be normally, as it was both worse and normal. The anxiety question may not have yielded significance as the worry that patients were experiencing was due primarily to worries concerning their treatment, rather than being a direct effect of the treatment. A larger number of participants may have also revealed a different result with quantitative data, as the IFN-α was reported as having an effect on mood, despite it being a non-significant one.

For the cognition domain, participants rated themselves to have a significant increase in memory impairment (see Figure 5.3) and concentration impairment (see Figure 5.4); however, when spoken to, it was concentration and executive functioning that they tended to speak of, instead of a pure mnemonic impairment. The fact that not all participants spoke of this impairment is in line with neuropsychological studies which find that there are variable results when examining memory and executive functioning (see Table 1.4), as well as large-scale studies reporting this as a side-effect that occurs for a minority of patients (Lindsay et al, 1998; McHutchinson et al, 1998).

For many of the domains, participants spoke of an adjustment that they went through in order to cope with these new side-effects especially for fatigue and cognition, by almost ‘rationing’ their energy and cognitive effort (see section 5.4.1.2.5). This idea of having to ‘ration’, also emerged when speaking about social functioning, as most participants felt themselves actively withdrawing from people around them, with some people specifying that their ‘effort’ would be spent while they were at work for example, meaning that the majority of withdrawal took place when the person was at home with friends or family (see section 5.4.1.2.4).

When speaking about their cognitions surrounding commencement of treatment, there was a general feeling of anxiety due to the uncertainty of what side-effects they may encounter and also whether the treatment would work, which was paired with a sense of optimism that the treatment would work for them. For the most part, patients
felt that the experience they were going through was tough, but it was ultimately going to be a worthwhile one (see section 5.4.1.2.1).

**5.5.3 Retrospective IFN-α interview**

Post-treatment, the overall experience of being on IFN-α was one that was viewed primarily in terms of treatment outcome (see Figure 5.6), with those people for whom treatment was successful being more likely to rate the experience as positive than those who either did not work, and the outcome was unknown. However, despite the positive outcome it was still acknowledged that the process of being on IFN-α was unpleasant and mostly negative with the main reasons for treatment being negative were the health effects and physical effects that people experienced, which at times were severe enough to warrant treatment discontinuation (Participant 105, cellulitis and Participant 113, depression).

The most common physical side-effect, and the one that caused the most significant social and occupational impairment was fatigue, with two patients having to give up their job due to this side-effect (Participants 103; 108; 110). This side-effect was considered by some people to be the central effect of treatment with many of the other side-effects such as decreased mood and social withdrawal being a direct result of this. This fatigue tended to have a diurnal variation, being worse in either the mornings or the evenings. The other main health effect, in line with what was found in the prospective interview, was that flu-like symptoms tended to predominate, however, these were felt to be a totally normal part of treatment (see section 5.4.2.1.5). Treatment was also acknowledged to cause sleep disturbance with many patients reporting that their circadian rhythm seemed to have been disturbed somehow (see section 5.4.2.1.3). This idea of circadian rhythm disturbance fits in with the diurnal variation in fatigue that many people experienced, suggesting that IFN-α had some effect on hypothalamic regions of the brain, which is supported by evidence that Interferons can lead to disruption of the HPA axis (Dafny and Yang, 2005; Turnbull and Rivier, 1999).

In terms of mood, there was also a general consensus with this population that the main psychological side-effect experienced was irritation (see Figure 5.8), with the main reasons for this irritation occurring being a decreased threshold to respond to stressors and increased emotional lability. This emotional lability and decreased threshold to deal with stressors also seemed to contribute to an increase in depressive symptoms.
consistent with what has been found in most of the literature (see Table 1.4), however, the depression experienced was not interpreted to be a major depression, but instead a general lowering of mood (see section 5.4.2.1.4). This lowering of mood was partly due to people feeling as though issues were magnified in their brain with their threshold for dealing with stressors significantly reduced and their mood more labile this often resulted in a general feeling of reduced mood, which when combined with the anhedonia that is a common part of sickness behaviour (Charlton, 2000), led patients to report that they experienced a depression. However, only two participants reported suicidal ideation due to treatment, with only one of these participants having a suicidal plan (Participant 113). As depression is very much a subjective experience, with the word 'depressed' actually being a common term used in the vernacular to describe a general feeling of low mood, results from this part of the interview should be interpreted with caution. In terms of anxiety, findings were very much consistent with the prospective interview, with anxiety being a result of negative cognitions and depressive symptoms seeming to arise more endogenously as a direct result of IFN-α. The feeling of anhedonia that accompanied treatment went hand in hand with the social withdrawal that many participants reported feeling while they were on the treatment. While this withdrawal is a completely natural part of sickness behaviour (see Table 1.8), it could have been seen by participants to be part of the ‘depression’ that they were experiencing.

Cognition was also reported to be affected by treatment and in line with the prospective interview it was mainly concentration and other executive functions that were affected over memory (see section 5.4.4.1.6). However, this did not affect everyone, with only half of patients reporting they suffered from this side-effect, in line with previous research which finds variable results with regards to cognition (see Table 1.4).

The other significant social theme that arose, was that of social support being especially useful where there was an understanding of side-effects from people around the patient, with family, especially partners being especially important in the supportive role.

After treatment, patients were often surprised and disappointed at the length of time that it took them to recover from treatment, with full recovery taking up to 18 months in some people. While this recovery was primarily for physical health, with sleep also being particularly affected, some participants would report still experiencing
psychological effects even six months post-treatment (see section 5.4.2.1.1). The time between finishing treatment and finding out final results is a particularly stressful time as the focus is no longer on getting through treatment, but instead on wondering whether the treatment itself was successful or not.

Patients reported that finishing treatment did not automatically lead to an explicit improvement in health. As HCV is mostly asymptomatic, prior to starting treatment many people did not feel ill, with the treatment itself often being more physically demanding than having HCV. This meant that the main way that people knew they had cleared the virus was by being told; for some patients this led to a sense of disbelief about results (see section 5.4.2.1.2).

For many people that went through treatment, it was seen as an opportunity for them to change their lives, and they used the overall experience however negative it may have been, to make some positive changes (see section 5.4.2.1.1).

5.5.4 Implications of findings

When speaking about their overall experience of treatment, a major theme that emerged was the importance of support from family, friends, and healthcare professionals who understood the realities of dealing with treatment. While most people interviewed were happy with the support they had received there were a number that felt that they needed more support, in terms of a support group, especially when they received little understanding from home. This support should also be received from employer as some of the side-effects especially fatigue and disturbed sleep can in extreme cases lead to people having the leave their jobs, especially where combined with cognitive and mood problems. There is little, or no, education currently provided for employers regarding the potential impact of this treatment on the productivity of their employees, and should this be made available, more allowances could be made.

Social support was especially important in the context of the psychological and physical adjustment that patients had to go through when they were on treatment, with the irony being that they were mostly asymptomatic when ill with HCV, but when taking IFN-α which reduced their viral load thus making them better, they actually felt significantly worse. This was something that most patients spoke of as being a hard concept to come to terms with, and as most side-effects came into play from very early on in treatment, it was a rapid adjustment they were required to undertake. This finding
is especially important in making healthcare professionals aware of the importance of adjustment disorders, and the importance of ensuring patients having sufficient coping skills to deal with this adjustment.

The mood lability observed in both groups, together with a reduced threshold for dealing with external stressors seemed to be the driving force behind the irritability and depression. This observation would in part explain the observation from other studies that an increased depression score at Baseline leads people to become more susceptible to develop depression (see Table 1.5), with the rationale being that where there are more depressive symptoms present at Baseline that a lowering of threshold plus increased lability would lead these vulnerable individuals to be more at-risk with regards to developing a depression. This was seen with one patient in the post-treatment group who had been attending a psychologist at Baseline for low mood, and who went on to develop severe suicidal ideation on treatment.

Where anxiety occurred in both groups, it was related primarily to treatment-specific cognitions, rather than a cytokine-induced anxiolytic state being induced. This observation could in part explain the variation in results from previous studies that have looked at anxiety (see Table 1.4), as patients experience a high level of treatment-related anxious cognitions at Baseline which either are enhanced when on treatment, or can be decreased. This variability between patients would explain variability within studies. There is anxiety experienced from the time that patients find out they are due to start treatment, to finding out their results 6 months post-treatment. The importance of understanding the nature of this treatment related anxiety is also of key importance for healthcare workers, who should be aware of the impact that starting a treatment with a plethora of potentially serious side-effects and uncertainty of treatment outcome leads to an enormous amount of strain on the individual.

There is also little research conducted on the long-term implications of IFN-α treatment, which as seen from this chapter can last for as long as 18 months. The support that patients receive post-treatment will often be less than when on treatment, as they are no longer seen to be the full-time responsibility of the healthcare workers, nor would other people be as willing to make allowances. It should be recognised by all people involved in the support of someone taking IFN-α that often the side-effects, and long-term psychological impact will last past the final injection.
5.5.5 Limitations of findings
These studies are again limited by the low number of participants interviewed, as well as individual interpretation of how to best answer a question, or what they believed was 'normal' for each domain spoken about. This was in part remedied by the within-groups design of the prospective interview and the non-quantitative design of the retrospective interview, however, the issue of low numbers for the prospective group in particular would mean that any quantitative results from that section should be interpreted with caution, as there would be too much within-group variability to show a completely accurate picture of the domains investigated.

The studies are also limited by the type of person that would take part in a project such as this. Many of the people who took part were motivated to take part in the study, and were not necessarily representative of the population of patients from the Hepatology Unit at St. James’s Hospital. This was a problem in particular for the post-treatment study, where many people who came forward to take part did so because they had experienced an issue on IFN-α that they wished to speak about. Thus emphasis should be placed on individuals interpretation rather than the quantitative data.

5.5.6 Conclusions
The main symptoms from treatment with IFN-α that are difficult to deal with are those that affect people physically and psychologically, with fatigue, irritability, depressive symptoms, social withdrawal and cognitive difficulties emerging as the domains with the most distress attached. Physically there is a general deterioration of health, which can affect people in a number of ways, but with flu-like symptoms and fatigue predominating. Psychologically, however, there is a lability of mood and lowering of threshold to deal with perceived stressors that can lead to an increased susceptibility to feeling depressed and irritable, with a feeling as though everything is magnified, and every emotion experienced is felt more intensely. Cognitively, there is a loss of mental flexibility with executive functioning becoming more strained. At its most severe these side-effects can lead to a significant social and occupational impairment that can be observed with many serious physical and psychological disorders, as such, the patient experience of taking IFN-α should not be underestimated and care taken to ensure that each patient has sufficient social support and education regarding the treatment-induced side-effect profile.
CHAPTER 6

Assessment of neuropsychological functioning in HCV, Depression and IFN-α: A short exploratory test-battery
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6.1 Introduction

Previous research using neuropsychological tests in patients taking IFN-α have yielded mixed results (see Table 1.4: Chapter 1). Significant findings include a decrease in performance for tests that involve the hippocampus such as the AVLT (Juengling et al, 2000; Lieb et al, 2006; Tanaka et al, 2006); and in tests that involve the PFC such as part B of the Trail-Making Test (TMT) (Hilsabeck et al, 2005). However, other PFC-focused neuropsychological batteries such as the CANTAB have yielded no significant results (Majer et al, 2008), with other researchers also finding no significant difference in the domains that they chose to test (Amodio et al, 2005). Often the only significant difference found in these test batteries is an increased reaction time (Kraus et al, 2005a; Majer et al, 2008).

These differential results are partially explained by the fact that cognitive difficulties are reported to happen in only 5-21% of patients (Fontana et al, 2007; Manns et al, 2001; McHutchison et al, 1998), thus leading to a large variability within each group equalling little, or no, significance.

The most commonly reported cognitive difficulty involves a decrease in concentration (Manns et al, 2001; McHutchison et al, 1998; interview results Chapter 4), implicating the PFC as being the area primarily affected by IFN-α (see Figure 4.1). This is backed up by data from fMRI imaging pinpointing this as the area of the brain where significant changes in blood flow can be observed during treatment relative to baseline (Capuron et al, 2005; Juengling et al, 2000).

Major depression has also been shown to have effects on tasks that examine functioning of the PFC, with domains such as executive functioning, attention and memory all showing significant impairment (Hammar and Ardal, 2009; Rogers et al, 2004). Also one of the main HRQOL issues that impacts on HCV patients is so-called ‘brain-fog’, where patients experience difficulties in executive functioning (Perry et al, 2008; Reimer et al, 2005).

The PFC is involved in diverse behaviours, many of which are affected by treatment with IFN-α including motivation, cognition and emotion (Faw, 2003) and also memory and attention (Kane and Engle, 2002) (see Figure 6.1).
As such tests that measure PFC functioning were chosen to assess what effects, if any, IFN-α has on neuropsychological functioning, a test of hippocampal functioning was also administered as the only test that has shown reproducible effects in this population is the AVLT. The PFC tests examine working memory (n-back), concentration (SART) and a general test of executive functioning (Stroop), elements of the Behavioural Assessment of Dysexecutive Syndrome (BADS) were also used. The hippocampal test is the Face-name pairs (FNP) task, which measures immediate and delayed recall for the associative learning of face-name pairs. The short test-battery incorporates self-rating measures with formal neuropsychological measures.
6.2 Materials and Methods

6.2.1 Participants

9 patients were recruited from the Hepatology Centre at St. James’s Hospital, Dublin and prior to commencing treatment so they could be assessed at Baseline and Week 8 of treatment. 14 patients who were 8 weeks into therapy for IFN-α were also recruited to be tested once for the comparative study (see Table 6.1 for demographic information). All patients were taking 180μg PEG-IFN-2b subcutaneously once per week, with a weight-based dose of Ribavirin (800-1200mg) once per day.

Table 6.1: Demographic data for participants

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>Gender</th>
<th>Education</th>
<th>Genotype (HCV)</th>
<th>Infection (HCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>46.35 ± 3</td>
<td>Male: 10 (50%) Female: 10 (50%)</td>
<td>14.7 ± 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>15</td>
<td>49.27 ± 3.2</td>
<td>Male: 5 (33%) Female: 10 (67%)</td>
<td>13.84 ± 0.5</td>
<td>Genotype 1: 10 (67%) Genotype 3: 5 (33%)</td>
<td>IVDU: 5 (33%) Transfusion: 9 (60%) Unknown: 1 (7%)</td>
</tr>
<tr>
<td>IFN-α repeated</td>
<td>9</td>
<td>40.67 ± 2.7</td>
<td>Male: 6 (67%) Female: 3 (33%)</td>
<td>13.4 ± 0.6</td>
<td>Genotype 1: 4 (45%) Genotype 3: 5 (55%)</td>
<td>IVDU: (78%) Unknown: (22%)</td>
</tr>
<tr>
<td>IFN-α once</td>
<td>14</td>
<td>40.86 ± 2.6</td>
<td>Male: 9 (64%) Female: 5 (36%)</td>
<td>13.07 ± 0.5</td>
<td>Genotype 1: 8 (57%) Genotype 3: 6 (43%)</td>
<td>IVDU: 10 (64%) Transfusion: 1 (7%) Unknown: 3 (29%)</td>
</tr>
<tr>
<td>Depressed</td>
<td>19</td>
<td>39.32 ± 2.8</td>
<td>Male: 13 (68%) Female: 6 (32%)</td>
<td>13.3 ± 0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table showing demographic information for all participants that took part in the neuropsychological testing session. Where appropriate for controls, and depressed patients, a matched sample of this population was taken and this is talked about specifically at the start of that particular results section.

20 Control participants were recruited from recruitment posters in St. James’s Hospital, an advertisement in the Irish Times newspaper and the Trinity College electronic notice board. Patients were matched for age and sex to patients from the HCV, Depressed and IFN-α cohort as much as possible (data for matched participants used is given in results section, for overall demographic data from all control participants see Table 6.1).

19 Depressed patients were recruited from St. Patrick’s Hospital Dublin (see Table 6.1 for demographic information). Patients were matched for age and sex to
patients from the IFN-α and Control cohort as much as possible (see each appropriate section for matching data).

All information regarding inclusion and exclusion criteria plus all recruitment procedures followed can be found in Chapter 2, section 2.4.

The IFN-α repeated measures experiment was terminated early at only 9 participants as there were problems with recruitment, follow-ups and the data was yielding very little significance in the expected direction (see section 6.4.3 and discussion).

6.2.2 Materials for test-battery

All participants took part in tests the measured memory and attention and were designed to focus attention on the PFC and hippocampus. The tests run included self-rating measures (EMQ and DEX questionnaire), pen and paper tasks (Key Search and Zoo Map tests) as well as the following computerised tests; Face-Name Pairs task, Stroop test, SART and N-back. For more details on all the tests run and the required materials see Chapter 2 section 2.2.3.
6.3 Data analysis

All data was first assessed for normality using the Shapiro-Wilks test, as most data showed normal variation it was decided to use parametric tests, and correct for any violations with modified degrees of freedom and p-values where appropriate. Results for the face-name pairs test were analysed using one-way ANOVA, where independent groups were compared and repeated-measures ANOVA when the same group was assessed. Independent groups were also assessed using an independent t-test, and the same groups using paired t-tests (see Chapter 2, section 2.2.4 for more information on statistical tests).
6.4 Results

6.4.1 HCV and age-matched Controls

15 HCV patients were compared to 15 age-education-and-sex-matched healthy Control participants (HCV: Mean age 49.2 ± 3.1, 33% male, mean years in education 13.3 ± 0.4; Control: Mean age 49.27 ± 3.2, 33% male, mean years in education 14.27 ± 0.5). There was no significant difference in the age of the HCV and Control groups when compared using an independent-samples t-test (t(28)=-0.02, P=0.9), or the years in education (t(26.03)=1.62, P=0.1).

6.4.1.1 Comparison of self-ratings: HCV and Control groups

The groups were firstly compared on self-ratings of memory using the EMQ (see Figure 6.2), and PFC problems using the DEX (see Figure 6.3). When assessed for perceived memory problems the HCV group rated themselves as having significantly more memory problems than the Control group (t(20.45)=2.92, p<0.01), (Figure 6.2), and also as having more dysexecutive problems than the Control group (t(28)=2.44, p<0.05), (see Figure 6.3).

Figure 6.2: Perceived memory problems with EMQ

Figure showing the average rating for the HCV group and Control group in the everyday memory questionnaire (EMQ). The patients in the HCV group rated their memory as being significantly more impaired, (6.54 ± 0.6), than the control group, (4.5 ± 0.31), **p<0.01.
In order to assess formally these perceived differences in PFC and memory function patients were assessed using various tests of PFC and hippocampal functioning.

6.4.1.2 Comparison of FNP between HCV and Control groups

Memory was assessed using the face-name task (see Figure 6.4). When the two groups were compared using one-way ANOVA there was no significant effect of group on block 1 ($F(1, 29)=1$, $P=0.3$), block 2 ($F(1, 29)=0.67$, $P=0.4$), block 3 ($F(1, 29)=0.01$, $P=0.9$), block 4 ($F(1, 29)=3.01$, $P=0.09$) and the delayed block ($F(1, 29)=3.7$, $P=0.06$).

When each group was assessed for learning using repeated-measures ANOVA, there was a significant effect of block on recall for the Control group ($F(4, 56)=5.68$, $p<0.01$). Bonferroni comparisons revealed that this was significant between block 1 ($M=1.47$, $SD=0.4$) and block 4 ($M=3.2$, $SD=0.5$).

When performance for the HCV group was assessed there was also a significant effect of block on recall ($F(4, 56)=4.97$, $p<0.01$) which post-hoc comparisons showed to be significant between block 1 ($M=1$, $SD=0.3$) and block 3 ($M=2.13$, $SD=0.4$) and also between block 1 and block 4 ($M=2.07$, $SD=0.4$) (see Figure 6.4) indicating that the HCV group showed improved recall over the final two learning blocks.
Figure 6.4: Effects of HCV on FNP

<table>
<thead>
<tr>
<th></th>
<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
<th>Block 4</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>1.47</td>
<td>1.6</td>
<td>2.13</td>
<td>2.07</td>
<td>1.47</td>
</tr>
<tr>
<td>CONTROL</td>
<td>1.47</td>
<td>2.07</td>
<td>2.2</td>
<td>3.2</td>
<td>1.67</td>
</tr>
</tbody>
</table>

Figure showing the mean recall of face-name pairs for the HCV and Control groups. Both groups showed improved learning from blocks 1 to 4. For the control group, recall increased from block 1, ($M=1.47$, $SD=0.3$), to blocks 2, ($M=2.07$, $SD=0.5$), and 3, ($M=2.2$, $SD=0.5$), and was significant at block 4, ($M=3.2$, $SD=0.5$). For the HCV group, recall also increased from block 1, ($M=1$, $SD=0.2$), to 2, ($M=1.6$, $SD=0.3$), and was significantly improved relative to block 1 at block 3, ($M=2.3$, $SD=0.4$), and block 4, ($M=2.07$, $SD=0.4$). When the two groups were compared there was no significant difference on performance for any of the blocks. However, the HCV group was significantly impaired in free recall of names ($p<0.05$).

When overall learning over the 4 blocks between the two groups was compared with an independent-samples t-test there was no significant difference ($t(28)=0.25$, $P=0.3$), with both groups showing similar learning (Control: $8.93 \pm 1.5$; HCV: $6.8 \pm 1.2$).

When delayed-free recall of names was assessed using an independent-samples t-test there a significant effect of group with free-recall being significantly impaired in the HCV group when compared to the Control group ($t(28)=2.57$, $p<0.05$; Control: $5.07 \pm 0.2$; HCV: $5.07 \pm 0.3$), (see Figure 6.5).

When face-recognition and name-recognition scores were assessed using an independent-samples t-test there was no effect of group on recognition scores. For face-recognition, there was no effect on correct number of faces identified ($t(28)=0.89$, $P=0.4$; Control: $5.73 \pm 0.1$; HCV: $5.87 \pm 0.09$) or correct foils identified ($t(28)=0$, $P=1$; Control: $7.33 \pm 0.3$; HCV: $7.33 \pm 0.3$). For name recognition, there was also no effect on the number of names correctly identified ($t(18.9)=0.63$, $P=0.1$; Control: $5.8 \pm 0.1$; HCV: $5.67 \pm 0.3$) or correct foils identified ($t(18.8)=1.21$, $P=0.2$; Control: $7.87 \pm 0.09$; HCV: $7.533 \pm 0.2$).
6.4.1.3 Comparison of PFC tests between HCV and Control groups

When the SART was assessed using an independent-samples t-test, there was an overall effect of group on accuracy ($t(14.87) = 2.32$, $p<0.05$), with the HCV group being significantly impaired on this task (see Figure 6.6).

Figure 6.6: Effect of HCV on SART test

Figure showing the mean accuracy for the SART, for the HCV group (89.04 ± 3.7), and the Control group (97.87 ± 0.7). The HCV group were significantly impaired at the task, when compared to controls (* $p<0.05$). This impairment was despite a notable difference in the mean for errors of omission for the two groups, (HCV: 33.4 ± 7.6; Control: 14.63 ± 5.4), $t(25.1)=2$, $P=0.06$. 

---

**Figure 6.5: Effects of HCV on delayed free-recall of names**

Figure showing the significant difference between delayed free-recall for the names participants saw in the FNP (maximum score: 6). The HCV group (4.07 ± 0.3) performed significantly worse at this task than the Control group (5.07 ± 0.2) (*$p<0.05$)
However, there was no effect of group on mean reaction time ($t(28)=1.86$, $P=0.07$; Control: $178.37 \pm 11.8$; HCV: $222.35 \pm 20.5$) or errors of omission ($t(25.1)=2$, $P=0.06$; Control: $14.63 \pm 5.5$; HCV: $33.4 \pm 7.6$) for the SART.

The groups were then compared on the Stroop test for relative performance on the congruent (i.e., word and colour matched), and incongruent, (i.e., word and colour mismatched) trials. When compared using an independent-samples t-test there was no significant difference in accuracy between-groups for congruent ($t(15.8)=1.29$, $P=0.2$; Control: $97.47 \pm 0.6$; HCV: $94.7 \pm 2.3$) and incongruent trials ($t(28)=0.5$, $P=0.6$; (Control: $68.53 \pm 7.7$; HCV: $63.8 \pm 8.2$), (see Figure 6.7).

When groups were assessed individually for respective differences between congruent and incongruent trials using paired-samples t-tests, there was a significant difference for the Control group ($t(14)=3.84$, $p<0.01$) and the HCV group ($t(14)=3.84$, $p<0.01$), (see Figure 6.7).

**Figure 6.7: Effect of HCV on the Stroop test**

![Figure showing the mean percentage correct for the HCV group and Control group for the Stroop task. There was no difference between-groups in performance, however, both groups were significantly worse at the incongruent trial when compared to the congruent trial (**p<0.01); HCV; Congruent 94.47 ± 2.3; Incongruent 63.8 ± 8.2. Control; Congruent 97.48 ± 0.6; Incongruent 68.53 ± 7.7.](image-url)

There was also no between-group difference for reaction time for congruent ($t(28)=0.42$, $P=0.7$; Control: $791.16 \pm 18.8$; HCV: $777.81 \pm 19.4$) and incongruent trials ($t(28)=0.5$, $P=0.06$; Control: $821.08 \pm 55.2$; HCV: $666.71 \pm 54.5$). When the assessed for within-group differences using a paired-samples t-test it was found that there was no effect of trial type on reaction time for the HCV group ($t(14)=0.5$, $P=0.6$). The HCV
group took longer to react in the congruent trials than the incongruent trials, however, this was not significant ($t(14)=2.04$, $P=0.06$).

When the N-back test was assessed using a one-way ANOVA, there was a significant difference between groups for the 0-back ($F(1, 29)=4.47$, $P<0.05$), and the 1-back ($F(1, 29)=6.03$, $P<0.05$), but not the 2-back ($F(1, 29)=1.5$, $P=0.2$), (see Figure 6.8).

When assessed for within-group differences using a repeated-measures ANOVA the Control group showed a significant effect of block on performance ($F(1.19, 16.6)=22.03$, $P<0.01$), with performance being significantly better in the 0-back ($M=99.87$, $SD=0.1$), when compared to the 1-back ($M=90.53$, $SD=2.6$), and the 2-back ($M=62.6$, $SD=7.4$), as well as performance being significantly better for the 1-back when compared to the 2-back.

For the HCV group there was also a significant effect of block on performance ($F(2, 28)=34.77$, $P<0.01$), with performance also being significantly better for the 0-back ($M=98.6$, $SD=0.6$) when compared to the 1-back ($M=73.07$, $SD=6.6$) and the 2-back ($M=51.07$, $SD=5.9$) as well as there being a significant difference between the 1-back and the 2-back.

**Figure 6.8: Effect of HCV on the N-back**

<table>
<thead>
<tr>
<th></th>
<th>0-back</th>
<th>1-back</th>
<th>2-back</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td>99.9**</td>
<td>90.5**</td>
<td>62.6**</td>
</tr>
<tr>
<td>HCV</td>
<td>98.6**</td>
<td>73.1**</td>
<td>51.1**</td>
</tr>
</tbody>
</table>

Figure showing performance for the N-back across the 0-back, 1-back and 2-back conditions. Both groups performed significantly worse as the task got more demanding (**$P<0.01$ see box at bottom of figure) (HCV: 0-back: 98.6 ± 0.6; 1-back: 73.07 ± 6.6; 2-back: 51.07 ± 5.9. Control: 0-back: 99.87 ± 0.1; 1-back: 90.53 ± 2.6; 2-back: 62.6 ± 7.4). There was a significant difference (*$P<0.05$) for the 0-back and 1-back between the groups, with the HCV group performing significantly worse for both conditions.
When compared for reaction times on the task, there was no significant difference between groups for the 0-back ($t(28)=1.03$, $P=0.3$; Control: 654.37 ± 27.6; HCV 701.19 ± 35.9), 1-back ($t(28)=1.16$, $P=0.3$; Control: 551.75 ± 51.1; HCV 623.7 ± 35.5) or the 2-back ($t(26.3)=0.99$, $P=0.3$; Control: 405.43 ± 53.3; HCV 347.35 ± 23.8).

Groups were finally compared for performance on the Key-search test and the Zoo-map test from the BADS. There was no significant difference in the Key-search test ($t(22.76)=1.65$, $P=0.1$; HCV: 10.53 ± 1.1; Control: 12.67 ± 0.7; Maximum score 16).

There was also no difference for version 1 of the Zoo-map test ($t(28)=0.49$, $P=0.5$; HCV: 2.27 ± 1.1; Control: 3.2 ± 0.8; Maximum score 8) or version 2 of the Zoo-map test ($t(28)=1.05$, $P=0.3$; HCV: 6.87 ± 0.7; Control: 7.67 ± 0.2; Maximum score 8), as well as the overall score ($t(28)=0.93$, $P=0.4$; HCV: 9.2 ± 6.2; Control: 10.87 ± 0.8; Maximum score 16).
6.4.2 Primary Depression and age-matched Controls

19 patients with a diagnosis of MDD were compared to 17 age-education-and-sex-matched Control participants (Depressed: Mean age 39.32 ± 2.8, 68% male, mean years in education 13.84 ± 0.5; Control Mean age 46.24 ± 3.2, 65% male, mean years in education 14.47 ± 0.5). There was no significant difference between the groups when assessed using an independent-samples t-test for age (t(34)=0.52, P=0.1), or education (t(34)=0.93, P=0.4). When gender was assessed using a chi-squared analysis, there was no significant difference between groups for the percentages of males and females, (χ²(1, N=35)=0.23, P=0.6).

6.4.2.1 Comparison of self-ratings: Depressed and Control groups

Participants were first compared for perceived memory and PFC dysfunction with independent-samples t-tests; Depressed patients rated themselves as having significantly more everyday memory problems (t(34)=3.71, p<0.01; Control 5.47 ± 0.5; Depressed 8.08 ± 0.5), (see Figure 6.9).

Figure 6.9: Perceived memory problems with EMQ

![Figure showing the mean rating that participants gave their everyday memory impairments. Depressed patients rated themselves as having significantly more memory problems than age-and-sex-matched controls, **p<0.01. (Depressed 31.68 ± 2.8; Control 18.9 ± 2.6)](image-url)
When the DEX test was assessed it was found that Depressed patients rated their dysexecutive problems as significantly higher than Control participants ($t(34)=3.37$, $p<0.01$; Control $18.9 \pm 2.6$; Depressed $31.68 \pm 2.8$) (see Figure 6.10).

**Figure 6.10: Perceived PFC problems with DEX**

![Figure showing the mean rating for the DEX questionnaire that each group gave for their perceived problems with domains that affect the PFC. The Depressed group rated their dysexecutive issues as significantly higher (**$p<0.01$**)) than the Control group (Depressed $31.68 \pm 2.8$; Control $18.9 \pm 2.6$).]

6.4.2.2 **Comparison of FNP between Depressed and Control groups**

When performance on the FNP test was measured between-groups using a one-way ANOVA, there was a significant effect of group at learning block 1 ($F(1, 35)=5.03$, $p<0.05$), block 4 ($F(1, 35)=7.19$, $p<0.05$) and the delayed recall block ($F(1, 35)=6.66$, $p<0.05$), (see Figure 6.11).

When groups were assessed individually using a repeated-measures ANOVA, there was an overall effect of block on learning for the Control group ($F(4, 64)=9.12$, $p<0.01$). Post-hoc tests showed a significant improvement in performance from block 1 ($M=1.77$, $SD=0.4$) to block 4 and also from block 1 to the delayed block ($M=3.24$, $SD=0.4$), (see Figure 6.11).

When the Depressed group was assessed there was also a significant effect of block on performance ($F(4, 72)=5.67$, $p<0.01$). Post-hoc tests showed that all significance was relative to performance in block 1 ($M=0.84$, $SD=0.2$) with improvements from this block been seen at block 2 ($M=1.58$, $SD=0.3$) block 3 ($M=1.9$, $SD=0.3$), block 4 ($M=3.24$, $SD=0.4$) and the delayed recall block ($M=3.24$, $SD=0.4$), (see Figure 6.11).
When assessed for total learning over the first four blocks using an independent-samples t-test, there was a significant difference between the two groups ($t(25.6)=2.35$, $p<0.05$), with the Depressed group recalling fewer faces than the Control group (Control: $10.71 \pm 1.61$; Depressed: $6.47 \pm 0.8$), (see Figure 6.12).

When the two groups were compared for delayed free recall of names for the task, there was a significant effect of group ($t(34)=2.43$, $p<0.05$), with the Depressed group recalling significantly fewer names (Control: $5.06 \pm 0.2$; Depressed: $4.26 \pm 0.2$), (see Figure 6.13).

Figure 6.11: Effect of Depression on FNP

Figure showing performance for the FNP task for the control and depressed groups, there were six faces to be recalled for each block. The depressed group were significantly worse at the task at blocks 1 (Depressed: $0.84 \pm 0.2$; Control: $1.76 \pm 0.4$), 4, (Depressed: $2.16 \pm 0.3$; Control: $3.76 \pm 0.5$) and the delayed recall block (Depressed: $1.95 \pm 0.3$; Control: $3.23 \pm 0.4$) $^*p<0.05$. There was no significant difference at blocks 2 (Depressed: $1.58 \pm 0.3$; Control: $2.35 \pm 0.5$) or 3 (Depressed: $1.89 \pm 0.3$; Control: $2.82 \pm 0.5$). When assessed for learning over the first four blocks, the control group performed significantly better in the last two blocks, when compared to the first two blocks. However, the depressed group only achieved significance in the last 3 blocks relative to the first block only ($^{**}p<0.01$, $^*p<0.05$).
Figure 6.12: Effect of Depression on overall learning

Figure showing that Depressed patients show significantly less total learning over the first four blocks (10.71 ± 1.61), when compared to matched Control participants (6.47 ± 0.8), *p<0.05. There was a maximum of 24 names to be recalled.

Figure 6.13: Effect of Depression on delayed free name-recall

Figure showing that Depressed patients recall significantly fewer faces after a half-hour delay (4.26 ± 0.2), than matched Control participants (5.06 ± 0.2), *p<0.05. There was 6 names to be recalled.
Despite there being a significant impact of Depression on the recall portion of the FNP task, there was no significant impact of Depression on any of the measures of recognition (see Figure 6.14), including the correct number of faces identified ($t(34)=0.85$, $P=0.4$; Control: 5.76 ± 0.1; Depressed: 5.63 ± 0.1) or correct face foils identified ($t(34)=0.008$, $P=1$; Control: 7.53 ± 0.3; Depressed: 7.53 ± 0.2). There was also no effect on the number of names correctly recognised ($t(26.1)=1.38$, $P=0.2$; Control: 5.82 ± 0.1; Depressed: 5.53 ± 0.2), or correct foils identified ($t(26.9)=1.14$, $P=0.3$; Control: 7.88 ± 0.08; Depressed: 7.68 ± 0.2).

**Figure 6.14: Impact of Depression on recognition component of FNP task**

![Figure showing average responses for the recognition portion of the FNP task. Despite there being a significant difference between the groups in learning and delayed recall (see Figure 6.10), there was no significant difference between the groups on any of the measures of face and name recognition, indicating that the depressed patients impairment in this task is specific to recall rather than recognition. For the correct names and faces participants could score a maximum of 6, and for the correct name and face foils participants could score a maximum of 8.]

**6.4.2.3 Comparison of PFC tests between Depressed and Control groups**

Groups were then compared on the SART task using an independent-samples t-test which showed there was a significant difference in overall accuracy ($t(34)=2.34$, $p<0.05$; Control: 98.35 ± 0.6; Depressed: 95.7 ± 0.9), (see Figure 6.15). However, there was no difference in reaction times ($t(34)=0.49$, $P=0.6$; Control: 168.49 ± 11.1; Depressed: 179.32 ± 18.5) or errors of omission ($t(34)=1.41$, $P=0.2$; Control: 13.91 ± 5.6; Depressed: 26.79 ± 7.1).
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Figure 6.15: Effect of Depression on SART

Figure showing the mean accuracy for the Depressed and Control groups for the SART. Depressed patients performed significantly worse at the task (*p<0.05), however, they did also have more errors of omission than the control group (Depressed: 26.79 ± 7.1; Control: 13.91 ± 5.6), and while this difference was not significant (P=0.2), it suggests that depressed patients were impaired on the task.

Groups were then compared for performance on the Stroop task using an independent-samples t-test. There was no significant difference between groups for congruent (t(21.1)=1.6, P=0.1; Control: 97.35 ± 0.6; Depressed: 94.2 ± 1.9) or incongruent trials (t(34)=0.91, P=0.4; Control: 68.88 ± 6.6; Depressed: 59.42 ± 7.9) (see Figure 6.16).

There was also no significant effect of group on average reaction times for both the congruent (t(34)=0.11, P=0.9; Control: 768.45 ± 21.3; Depressed: 765.65 ± 14.8) and incongruent conditions (t(34)=1.48, P=0.2; Control: 804.75 ± 46.8; Depressed: 713.31 ± 41.1).

When assessed individually to determine within-group differences in the task using a paired-samples t-test, there was a significant difference for both the Control group (t(16)=4.34, p=0.01) and the Depressed group (t(18)=5.14, p<0.01), for performance between congruent and incongruent trials (see Figure 6.16), however, there was no effect of condition on reaction times for the Control (t(16)=0.68, P=0.5), or Depressed group (t(18)=1.08, P=0.3).
Figure 6.16: Effect of Depression on the Stroop task

Figure showing mean accuracy for the congruent (word and colour matched) and incongruent (word and colour mismatched) trials for the Stroop task. There were no significant differences between the groups for performance on the task, however, for both groups there was a significant difference (**p<0.01) within-groups for accuracy on the congruent and incongruent trials (Depressed: Congruent: 94.21 ± 1.9; Incongruent: 59.42 ± 7.9; Control: Congruent: 97.35 ± 0.6; Incongruent: 68.88 ± 6.6).

When the N-back was assessed using a one-way ANOVA Depressed patients were significantly worse at the 0-back (F(1, 35)=5.71, p<0.05), but there was no significant difference for the 1-back (F(1, 35)=2.76, P=0.1) or the 2-back (F(1, 35)=0.04, P=0.8), (see Figure 6.17).

When compared for reaction times on the task, there was no significant difference between groups for the 0-back (t(34)=0.66, P=0.5; Control 616.19 ± 27; Depressed: 642.28 ± 28.6), or the 2-back (t(34)=1.44, P=0.2; Control 359.12 ± 54.1; Depressed: 456.16 ± 41.7). However, there was a significant difference in the 1-back, with the Depressed group being significantly slower than Controls (t(34)=2.04, p<0.05; Control 486.76 ± 54.5; Depressed: 620.27 ± 38.1).

When the within-groups difference in performance using a repeated-measures ANOVA, there was an overall effect of block on performance for the Control group (F(1.2, 19.2)=20.3, p<0.01). Post-hoc comparisons showed this was due to a decrease in accuracy from the 0-back (M=99.82, SD=0.1), to the 1-back (M=92.59, SD=2.4), and a further significant decrease relative to both the 0-back and 1-back for the 2-back (M=69, SD=6.4) (see Figure 6.17). When the Depressed group was assessed, there was again an overall effect of condition on performance (F(2, 36)=19.19, p<0.01), which again was due to a decrease in performance from the 0-back (M=98.94, SD=0.4), to both the 1-
back \((M=81.58, SD=5.9)\), and 2-back \((M=67.26, SD=5.5)\), with there also being a significant deterioration from the 1-back to the 2-back.

**Figure 6.17: Effect of Depression on the N-back**

Figure showing the differences between and within-groups for the N-back task. Depressed patients performed significantly worse at the 0-back \((^p<0.05)\) (Depressed: \(98.95 \pm 0.4\); Control \(99.88 \pm 0.1\)), however, there was no significant difference between the groups for either the 1-back, (Depressed: \(81.58 \pm 5.6\); Control \(92.59 \pm 2.4\)), or the 2-back, (Depressed: \(67.26 \pm 5.5\); Control \(69 \pm 6.4\)). When the groups were assessed for within-group differences in performance, the increasing difficulty in the task was reflected by a significant decrease in performance for both groups with performance in the 0-back being significantly better than both the 1-back and 2-back, but also, performance in the 1-back being significantly better than the 2-back \((^p<0.05 \ ^{**}p<0.01)\).

Finally, the two groups were compared for performance on the Key-search test and the Zoo-map test for the BADS, with control participants being significantly worse at the Key-search test \((t(26.5)=3, \ p<0.01)\; \text{Depressed:}\ 13.47 \pm 0.6; \text{Control:}\ 10.06 \pm 1; \text{Maximum score 16})\), version 1 of the Zoo-map test \((t(34)=2.07, \ p<0.05)\; \text{Depressed:}\ 4.63 \pm 0.7; \text{Control:}\ 2.12 \pm 1; \text{Maximum score 8})\), and the overall score for the Zoo-map test \((t(34)=2.09, \ p<0.05)\; \text{Depressed:}\ 12.42 \pm 0.8; \text{Control:}\ 9.06 \pm 1.4; \text{Maximum score 16})\). There was no significant difference between groups for performance on version 2 of the Zoo-map test \((t(17.13)=1.45, \ P=0.2)\; \text{Depressed:}\ 7.79 \pm 0.1; \text{Control:}\ 6.82 \pm 0.7; \text{Maximum score 8})\).
6.4.3 Comparison IFN-α patients Week 0 and Week 8

The IFN-α treatment groups (9 patients) were compared firstly using a repeated-measures design, and following this would then be compared to an age-sex-and-education-matched Control group (IFN-α: Mean age 40.67 ± 2.7, 78% male, mean years in education 13.44 ± 0.6, n=9; Control: Mean age 47.11 ± 4.1, 78% male, mean years in education 13.33 ± 0.7, n=9). There was no significant differences between groups when assessed using an independent t-test for age (t(16)=1.32, P=0.2), or years in education, (t(16)=0.12, P=0.9).

6.4.3.1 Comparison of self-ratings: IFN-α and Control groups

The IFN-α group was firstly compared for perceived memory and PFC functioning for Week 8 relative to Baseline using a repeated-measures t-test (see Figures 6.18 and 6.19), with there being no significant difference between perceived memory functioning from Week 0 to Week 8 (t(8)=2.01, P=0.08; Week 0: 5.67 ± 1; Week 8: 7.02 ± 0.6), (see Figure 6.18), or perceived PFC dysfunction (t(8)=2.09, P=0.07; Week 0: 15.67 ± 2.9; Week 8: 19.33 ± 3.6), (see Figure 6.19).

Figure 6.18: Perceived memory problems with EMQ from Week 0 to 8 of IFN-α treatment

![Figure showing the difference in ratings for memory problems, with higher scores being indicative of a greater perceived impairment. From Week 0 (5.67 ± 1) to Week 8 (7.02 ± 0.6) there was a slight increase in perceived impairment, however, this was not significant (P=0.08). There was also no difference between either Week 0 or Week 8 of treatment with the control group (5.87 ± 0.5).]
Each week was then individually compared to the Control group using an independent samples t-test, and it was found that there was no significant difference between the two groups for EMQ at Week 0 ($t(16)=0.17, P=0.9$), or Week 8 ($t(16)=1.45, P=0.2$), (see Figure 6.18), nor was there any significant difference for the DEX at either Weeks 0 ($t(16)=0.8, P=0.4$), or 8 ($t(16)=0.02, P=1$), (see Figure 6.19).

**Figure 6.19: Perceived PFC problems with DEX from Week 0 to 8 of IFN-α treatment**

![Mean DEX rating chart](image)

Figure showing the difference in ratings for dysexecutive symptoms, with higher scores being indicative of a greater perceived impairment. From Week 0 ($15.67 \pm 2.9$) to Week 8 ($19.33 \pm 3.6$) there was a slight increase in perceived impairment, however, this was not significant ($P=0.07$). There was also no significant difference at either week with the Control group ($19.44 \pm 3.7$).

### 6.4.3.2 Comparison of FNP between IFN-α and Control groups

Patients were then assessed for performance in the FNP task from Week 0 to Week 8, using repeated-measures ANOVA. There was no significant effect of week on performance ($F(1,8)=0.78, P=0.4$), however, there was a significant impact of block on performance ($F(4,32)=11.47, p<0.05$), with the block * week interaction having a significant effect ($F(4,32)=3.29, p<0.05$) (see Figure 6.20), however, there was no significant difference between any of the blocks between-weeks.

When then compared to the Control group individually using a one-way ANOVA it was found that at Week 0 there was no significant difference between any of the blocks; block 1 ($F(1, 17)=0.65, P=0.4$), block 2 ($F(1, 17)=0.11, P=0.7$), block 3 ($F(1, 17)=0.07, P=0.8$), block 4 ($F(1, 17)=0.98, P=0.3$), or the delayed block ($F(1, 17)=0.56, P=0.5$). Then when compared to Week 8, there was also no significant
difference between any of the blocks; block 1 ($F(1, 17)=1.69, P=0.2$), block 2 ($F(1, 17)=0.08, P=0.8$), block 3 ($F(1, 17)=0.02, P=0.9$), block 4 ($F(1, 17)=0.06, P=0.9$) or the delayed block ($F(1, 17)=0.14, P=0.7$), (see Figure 6.20).

When each week was examined individually using repeated-measures ANOVA over the five blocks, it was found that at Week 0 there was an overall effect of block on recall ($F(4, 32)=3.61, p<0.05$), which post-hoc tests showed to be significant between blocks 1 ($M=1, SD=0.4$) and 3 only ($M=2.22, SD=0.5$). When the group was assessed for overall learning at Week 8 there was again an overall effect of block on recall ($F(4,32)=10, p<0.01$), which Bonferroni comparisons revealed was significant between blocks 1 ($M=0.78, SD=0.2$) and 3 ($M=2.11, SD=0.4$), and 1 and 4 ($M=3.22, SD=0.5$) (see Figure 6.20). When the Control group was assessed there was no overall effect of block on performance ($F(4, 32)=2.42, P=0.07$).

**Figure 6.20: Effect of IFN-a treatment on FNP**

![Figure showing performance for the FNP task for Week 0 and 8 of IFN-a treatment, there were six faces to be recalled for each block. There was no significant difference between the weeks at blocks 1 (Week 0: 1 ± 0.4; Week 8: 0.78 ± 0.3), 2, (Week 0: 2 ± 0.3; Week 8: 1.56 ± 0.5) 3 (Week 0: 2.22 ± 0.5; Week 8: 2.11 ± 0.4) 4 (Week 0: 2.11 ± 0.5; Week 8: 3.22 ± 0.5) or for delayed recall (Week 0: 1.89 ± 0.6; Week 8: 2.89 ± 0.7). There was also no significant difference at either week with the control group, block 1 (1.57 ± 0.6), to 2, (1.78 ± 0.5), 3 (2 ± 0.7), 4 (3.11 ± 0.9), and the delayed block (2.56 ± 0.6). When assessed for learning over the blocks, at Week 0 participants performed significantly better in the third block, when compared to the first block. However, when on treatment the groups performed slightly better, showing significantly better recall at both blocks 3 and 4 relative to the first block (**p<0.01). However, the control group did not show an effect of block on performance (P=0.07).

When assessed for total learning over the first four blocks using a paired t-test, there was no significant difference between the two time-points ($t(8)=0.46, P=0.7$; Week 0: 7.33 ± 1.6; Week 8: 7.78 ± 1.3). There was again no significant difference with
the Control group (Control: 8.44 ± 2.3) at Week 0 (t(16)=0.4, P=0.7), or Week 8 (t(12.78)=0.26, P=0.8).

The two groups were then compared for free recall of names after a delay, and again there was no significant effect of IFN-α treatment (t(8)=0.69, P=0.5; Week 0: 4.22 ± 0.4; Week 8: 4.44 ± 0.3).

When then compared to the Control group (Control: 4.56 ± 0.3) there was no significant difference for Week 0 (t(16)=0.61, P=0.6), or week 8 (t(16)=0.25, P=0.8).

As recall did not yield any significance, recognition scores were then assessed using paired-samples t-tests, and it was found that there was a significant difference in face recognition from week 0 to week 8 (t(8)=2.8, p<0.05; Week 0: 5.89 ± 0.1; Week 8: 5.11 ± 0.3) There was, however, no significant difference in correct identification of face foils (t(8)=2.12, P=0.06; Week 0: 7.89 ± 0.1; Week 8: 6.78 ± 0.5), name recognition (t(8)=0.76, P=0.5; Week 0: 5.56 ± 0.3; Week 8: 5.22 ± 0.4), or correct identification of name foils (t(8)=1.32, P=0.2; Week 0: 7.89 ± 0.1; Week 8: 7.44 ± 0.3).

When compared to the Control group, the only significant difference was with the Week 8 group for face recognition (t(10.82)=2.75, p<0.05; Control: 5.89 ± 0.1; Week 8: 5.11 ± 0.3), (see Figure 6.21).

**Figure 6.21: Impact of IFN-α treatment on recognition component of FNP task**

Figure showing average responses for the recognition portion of the FNP task. Despite IFN-α patients performing slightly better in the recall condition, with increased learning (see Figure 56.20), they were significantly worse at identifying correct faces (Week 0: 5.89 ± 0.1; Week 8: 5.11 ± 0.3). They were also slightly worse at identifying correct face foils, however, this difference was not significant (P=0.06). For the correct names and faces participants could score a maximum of 6, and for the correct name and face foils participants could score a maximum of 8.
6.4.2.3 Comparison of PFC tests between IFN-α and Control groups

The patients were then assessed for performance on the SART task from Week 0 to 8. Accuracy remained fairly stable from Week 0 to 8 ($t(8)= 0.22, P=0.8$; Week 0: 93.78 ± 2.2; Week 8: 94.19 ± 2.2), with no difference been seen when the Control group (Control: 97.78 ± 1) was compared to Week 0 ($t(10.93)= 1.65, P=0.2$), and Week 8 ($t(16)=1.48, P=0.2$), (see Figure 6.22).

There was no significant difference in reaction time, despite Week 0 times being slower ($t(8)=1.5, P=0.2$; Week 0: 224.52 ± 33.1; Week 8: 156.72 ± 17.5); with there also being no difference in errors of omission ($t(8)= 0.71, P=0.5$; Week 0: 29.32 ± 10.4; Week 8: 21.37 ± 8.3).

There was no difference with the Control group, (Control: 172.93 ± 12.7), at Week 0 ($t(10.31)= 1.46, P=0.2$), or Week 8 ($t(16)= 0.75, P=0.5$). For errors of omission there was no significant difference with the Control group (Control: 9.39 ± 5), at Week 0 ($t(11.52)= 1.73, P=0.1$), or week 8 ($t(16)=1.23, P=0.2$).

Figure 6.22: Effect of IFN-α treatment on SART

Figure showing performance on the SART from Week 0 (93.78 ± 2.2) to Week 8 (94.19 ± 2.2), there was no significant difference in any of the comparisons performed for this test, including mean accuracy, which remained fairly constant. There was also no difference in performance at either week when compared to matched controls (97.78 ± 1).

The Stroop task was then analysed, and it was found that between-weeks there was no significant difference in accuracy for either congruent ($t(8)=0.58, P=0.6$; Week 0: 92.89 ± 3.8; Week 8: 95 ± 1.3), or incongruent trials ($t(8)=0, P=1$; Week 0: 65.11 ± 10; Week 8: 65.11 ± 12.6), (see Figure 6.23).
There was also no significant difference in reaction times for the congruent trials ($t(8)=1.14$, $P=0.3$; Week 0: $782.08 \pm 28.9$; Week 8: $817.12 \pm 19.1$), or incongruent trials ($t(8)=1.01$, $P=0.3$; Week 0: $752.83 \pm 72.3$; Week 8: $674.7 \pm 96.6$).

When compared to the Control group, there was no significant difference at Week 0 for congruent trials (Control: $96.78 \pm 0.9$), ($t(8.91)=1$, $P=0.3$), or incongruent trials, (Control: $68.22 \pm 10.7$), ($t(16)=0.21$, $P=0.8$). At Week 8 there was also no significant difference for both the congruent ($t(16)=1.1$, $P=0.3$), and incongruent trials ($t(16)=0.19$, $P=0.9$).

There was also no difference in reaction times between the Control group and treatment group for the congruent trials (Control: $802.07 \pm 24.5$), at either Week 0 ($t(16)=0.53$, $P=0.6$), or Week 8 ($t(16)=0.48$, $P=0.6$), or for incongruent reaction times, (Control: $777.03 \pm 56.5$), at week 0 ($t(16)=0.26$, $P=0.8$), or week 8 ($t(16)=0.91$, $P=0$).

**Figure 6.23: Effect of IFN-α treatment on the Stroop task**

Figure showing mean accuracy for the congruent (word and colour matched) and incongruent (word and colour mismatched) trials for the stroop task. There were no significant differences between any of the groups for performance on the task, however, for all groups there was a significant difference (*$p<0.05$, ***$p<0.01$) within-groups for accuracy on the congruent and incongruent trials (Week 0: Congruent: $92.89 \pm 3.8$; Incongruent: $65.11 \pm 9.9$) (Week 8: Congruent: $95 \pm 1.3$; Incongruent: $65.11 \pm 12.6$) (CON: Congruent: $96.78 \pm 0.9$; Incongruent: $68.22 \pm 10.7$).

When the difference between-trials for Week 0 and Week 8 were assessed there was an effect on accuracy between the congruent and incongruent trials both at week 0 ($t(8)=3.96$, $p<0.01$), and week 8 ($t(8)=2.61$, $p<0.05$), (see Figure 6.23). There was not a significant difference in reaction time at Week 0 ($t(8)=0.4$, $P=0.7$), or at Week 8...
For the Control group, there was a significant difference for accuracy ($t(8)=2.68$, $p<0.05$), (see Figure 6.23), but not for reaction time ($t(8)=0.38$, $P=0.7$).

The N-back task was then assessed using a repeated-measures ANOVA (see Figure 6.24), and there was an overall effect of block ($F(2, 7)=7.42$, $p<0.05$), but there was no effect of week ($F(1, 8)=0.39$, $P=0.5$), or block * week ($F(2, 7)=1.64$, $P=0.3$). When each week was then compared to the Control group using a one-way ANOVA there was no significant difference for the 0-back at Week 0 ($F(1, 17)=1$, $P=0.3$), or Week 8 ($F(1, 17)=2$, $P=0.2$); nor was there any difference for the 1-back at Week 0 ($F(1, 17)=0.008$, $P=0.9$), or 8 ($F(1, 17)=0.52$, $P=0.5$). Finally there was no difference for the 2-back at week 0 ($F(1, 17)=0.001$, $P=1$) or 8 ($F(1, 17)=0.001$, $P=1$) (see Figure 6.24).

Figure 6.24: Effect of IFN-α treatment on the N-back

![Graph showing the differences between and within-weeks for the N-back task. There was no significant difference between weeks for any of the blocks. However, at Week 0, performance was significantly better for the 0-back (99.56 ± 0.4), than the 1-back, (90.44 ± 2.8), or 2-back, (72.11 ± 7.1) (*p<0.05). While there was an overall significant effect of block for Week 8 (p<0.05), there was no significant difference between the 0-back (99.33 ± 0.5), 1-back (94.4 ± 2.5) or 2-back (73 ± 9.3), meaning overall performance was more similar between blocks than at week 0. There was a similar effect for the control group as there was again an overall significant effect of block on performance (p<0.05), but there was no significance between the 0-back (100 ± 0), 1-back (90.89 ± 4.3) or 2-back (72.44 ± 11).

When reaction time was compared between-weeks it was found that there was no significant difference for the 0-back ($t(8)=0.05$, $P=1$; Week 0: 654.74 ± 48.1; Week 8: 656.35 ± 33.4), 1-back ($t(8)=1.43$, $P=0.2$; Week 0: 546.14 ± 75.4; Week 8: 486.16 ± 54.3), or the 2-back ($t(8)=0.21$, $P=0.8$; Week 0: 358.26 ± 33.5; Week 8: 350.51 ± 43.6).
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There was also no significant difference with the Control group for the 0-back (Control: 628.47 ± 38.2) for week 0 (t(16)=0.43, P=0.7) or week 8 (t(16)=0.55, P=0.6), the 1-back (Control: 335.64 ± 76.8) at Week 0 (t(16)=0, P=1) or week 8 (t(16)=0.67, P=0.5), and finally for the 2-back (Control: 546.09 ± 71.5) at Week 0 (t(16)=0.27, P=0.8), or Week 8 (t(16)=0.17, P=0.9).

Repeated-measures ANOVAs were then performed individually at Week 0 and Week 8 to assess the effect of block on performance. At Week 0, there was an overall effect of block on performance (F(1.2, 9.8)=12.16, p<0.01), with performance for the 0-back (M=99.56, SD=0.4), being significantly better than both the 1-back (M=90.44, SD=2.8), and 2-back (M=72.11, SD=7.1). At Week 8 there was also an overall effect of block on performance (F(1.2, 9.8)=12.16, p<0.05); however, post-hoc comparisons showed only near significance (P=0.06) between block 1 (M=99.56, SD=0.4) and block 3 (M=72.11, SD=7.1). For the Control group, there was an overall effect of block on performance (F(1.2, 9.5)=5.55, p<0.05), however, post-hoc comparisons showed there to be no effect between individual blocks.

Finally, performance on the Key-search test and the Zoo-map test were compared between the weeks using paired t-tests. For the Key-search there was no significant difference between weeks (t(8)=0.16, P=0.9; Week 0: 12.33 ± 1.1; Week 8: 12.22 ± 0.9; Maximum score 16). However, the Control group were significantly worse at this task at both weeks 0 (t(16)=2.36, p<0.05), and 8 (t(16)=2.55, p<0.05) (Control: 8.67 ± 1.1).

There was also no difference within the IFN-α group for version 1 (t(8)=0.16, P=0.9; Week 0: 3.22 ± 1; Week 8: 3.33 ± 0.8; Maximum score 8), or version 2 of the Zoo-map test (t(8)=1.51, P=0.2; Week 0: 7.89 ± 0.3; Week 8: 7.67 ± 0.5; Maximum score 8), or the overall score for the Zoo-map test (t(8)=0.16, P=0.9; Week 0: 11.11 ± 1; Week 8: 11 ± 0.8; Maximum score 16).

When compared to the Control group there was no significant difference for any of the comparisons, for version 1 (Control: 1.89 ± 1); (Week 0: t(16)=0.96, P=0.4; Week 8, t(16)=1.14, P=0.3), version 2, (Control: 7.11 ± 0.4), (Week 0: t(9.3)=1.92, P=0.09; Week 8, t(10.84)=1.31, P=0.2), or the overall score, (Control: 9.22 ± 1.1; Week 0: t(16)=1.21, P=0.3; Week 8, t(16)=1.24, P=0.2).
6.4.4 Comparison between IFN-a patients, Depressed patients and controls.

In order to see how patients on IFN-α performed relative to patients with a primary depression, and matched control participants a comparative analysis was compared between these 3 groups, with 14 participants in each group. Groups were matched for age, sex and education, (Control: Mean age 46.36 ± 3.2, 64% male, mean years in education 14.21 ± 0.5; IFN-α: Mean age 40.85 ± 2.6, 64% male, mean years in education 13.07 ± 0.5; Depressed: Mean age 40.29 ± 2.6, 64% male, mean years in education 13.79 ± 0.5). When compared using a one-way ANOVA there was no significant difference between groups for age ($F(2,41)=1.39$, $P=0.3$), or education ($F(2,41)=1.25$, $P=0.3$). Further analysis was then conducted to compare HAM-D scores for the three groups and it was found that there was an overall significant difference between-groups ($F(2,41)=50.9$, $p<0.01$), with the Depressed group having a significantly higher score ($M=24.57$, $SD=2.2$) than the IFN-α ($M=12.5$, $SD=1.4$) or Control group ($M=2.36$, $SD=0.5$), and the IFN-α group having a higher score than the Control group (all comparisons significant at the $p<0.01$ level).

6.4.4.1 Comparison of self-ratings: IFN-α, Depressed and Control groups

The first comparison undertaken was to compare perceived memory and PFC problems between patients using one-way ANOVAs (see Figures 6.24 and 6.25). There was an overall significant impact of group on perceived memory impairment ($F(2,41)=5.87$, $p<0.01$), with the Depressed group rating their memory as significantly worse ($M=8.58$, $SD=0.6$) than the IFN-α ($M=6.3$, $SD=0.6$) or Control group, ($M=6.03$, $SD=0.5$). (see Figure 6.24).

There was also a significant effect of group on the DEX questionnaire ($F(2,41)=6.27$, $p<0.01$), with the Depressed group rating their PFC dysfunction as significantly greater ($M=33.07$, $SD=3.3$) than the IFN-α group ($M=20.07$, $SD=2.6$), or Control group ($M=20.64$, $SD=2.8$) (see Figure 6.25).
Figure 6.24: Perceived memory problems with EMQ between Control, IFN-α and Depressed participants

Figure showing that Depressed patients perceived their memory as significantly more impaired (8.58 ± 0.6) than patients taking IFN-α (6.3 ± 0.6: *p<0.05) or Control participants (6.03 ± 0.5: **p<0.01).

Figure 6.25: Perceived PFC problems with DEX between Control, IFN-α and Depressed participants

Figure showing that Depressed patients perceived themselves as having significantly more PFC dysfunction (33.07 ± 3.3) than patients taking IFN-α (20.07 ± 2.6: *p<0.05) or Control participants (20.64 ± 0.8: **p<0.01).

6.4.4.2 Comparison of FNP between IFN-α, Depressed and Control groups

When assessed for performance on the FNP task using a one-way ANOVA there was an overall significant effect at block 4 only ($F(2, 41)=3.32$, $p<0.05$), which post-hoc
comparisons showed to be due to a significant difference between the Control ($M=6.03$, $SD=0.5$) and Depressed groups ($M=6.03$, $SD=0.5$), (see Figure 6.26).

Each group was then assessed individually for overall learning using repeated-measures ANOVA. For the Control group there was an overall effect of block on performance ($F(4, 52)=5.74, p<0.01$), which was significant between block 1 ($M=1.71$, $SD=0.5$) and block 4 ($M=3.57$, $SD=0.5$). For the Depressed group there was also an overall effect of block on performance ($F(4, 52)=3.17, p<0.05$), which was significant between block 1 ($M=0.79$, $SD=0.2$) and block 3 ($M=1.93$, $SD=0.3$). For the IFN-α group there was also a significant effect of block on performance ($F(2.4, 31.2)=13.09, p<0.01$), which was significant when block 1 ($M=0.79$, $SD=0.2$) was compared to block 3 ($M=2.29$, $SD=0.3$) block 4 ($M=3$, $SD=0.4$) and the delayed block ($M=3$, $SD=0.6$).

**Figure 6.26: Effect of group on FNP**

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<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
<th>Block 4</th>
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Figure showing performance for the FNP task for the Control, IFN-α and Depressed groups. There were six faces to be recalled for each block. There was no significant difference between groups for blocks 1 (Control: $1.71±0.5$; IFN-α: $0.79±0.3$; Depressed: $0.79±0.2$), 2, (Control: $2.36±0.6$; IFN-α: $1.5±0.3$; Depressed: $1.5±0.3$) 3 (Control: $2.64±0.5$; IFN-α: $2.29±0.3$; Depressed: $1.93±0.3$) or for delayed recall (Control: $3.14±0.5$; IFN-α: $3±0.4$; Depressed: $1.86±0.3$). However, there was a significant difference for block 4 (Control: $3.57±0.6$; IFN-α: $3±0.6$; Depressed: $1.86±0.4$), which was significant between the Control and Depressed groups (*$p<0.05$). When assessed for learning over the blocks, at Controls performed significantly better in the fourth block, when compared to the first block (**$p<0.01$). The IFN-α group showed significantly better recall at blocks 3, 4 and the delayed block relative to the first block (**$p<0.01$). The depressed group showed significantly better performance for the third block relative to the first (*$p<0.05$).
When then compared for overall learning over the first four blocks, there was no significant difference between groups \(F(2, 41)=2.56, P=0.09; \) Control: \(10.29 \pm 1.9;\) IFN-\(\alpha\): \(7.57 \pm 1.1;\) Depressed: \(6.07 \pm 0.8\). When groups were compared for delayed free-recall of names there was an overall difference between-groups \(F(2, 41)=2.6, p<0.05\), which was due to the Depressed group \(M=4.21, SD=0.2\) recalling significantly fewer names than the Control group \(M=5.07, SD=0.2\), (see Figure 6.27).

**Figure 6.27: Effect of group on free-recall of names**

![Figure showing the effect of group on delayed free-recall of names for the FNP (maximum score 6). The Control group (5.07 ± 0.2) scored significantly higher than the Depressed group (4.21 ± 0.2) with the IFN-\(\alpha\) group (4.57 ± 0.3) showing no significant difference from either group.]

Groups were then compared for recognition performance. There was no significant difference between-groups for face recognition \(F(2, 41)=2.91, P=0.07\), name recognition \(F(2, 41)=0.64, P=0.5\), correct face foils identified \(F(2, 41)=2.17, P=0.2\), or correct name foils identified \(F(2, 41)=0.97, P=0.4\), (see Figure 6.28)
Figure 6.28: Impact of group on recognition component of FNP task

Figure showing the difference between groups for the recognition portion of the experiment. Despite showing a significant difference in recall performance in the FNP, Depressed and Control groups showed no significant difference for the recognition components of the FNP task. There was no significant difference for face recognition (Control: 5.79 ± 0.1; IFN-α: 5.29 ± 0.2; Depressed: 5.64 ± 0.1: maximum score 6) name recognition (Control: 5.79 ± 0.4; IFN-α: 5.5 ± 0.3; Depressed: 5.5 ± 0.2: maximum score 6) correct face foils identified (Control: 7.43 ± 0.4; IFN-α: 7 ± 0.3; Depressed: 7.79 ± 0.2: maximum score 8) or correct name foils identified (Control: 7.93 ± 0.2; IFN-α: 7.64 ± 0.2: Depressed: 7.64 ± 0.2: maximum score 8).

6.4.4.3 Comparison of PFC tests between IFN-α, Depressed and Control groups

When compared for overall performance on the SART with one-way ANOVA, there was a significant difference in overall accuracy ($F(2, 41)=4$, $p<0.05$), which post-hoc tests revealed was due to the IFN-α group ($M=92.55$, $SD=2.6$) performing significantly worse than the Control group ($M=98.29$, $SD=0.7$) (see Figure 6.29).

There was no significant difference between groups for reaction times ($F(2, 41)=0.85$, $P=0.4$; Control: 180.23 ± 10.5; IFN-α: 208.98 ± 20.5; Depressed: 175.23 ± 25), or errors of omission ($F(2, 41)=2.75$, $p=0.08$; Control: 8.25 ± 3.4; IFN-α: 26.23 ± 7; Depressed: 25.86 ± 7.6).
**Figure 6.29: Effect of group on the SART**

![Graph showing SART performance by group](image)

Figure showing the effect of group on SART performance. There was a significant difference (*p<0.05*) between the Control group (98.29 ± 0.7) and the IFN-α group (92.55 ± 2.6), however, there was no significant difference between either of these groups with the Depressed group (96.84 ± 0.7).

When then assessed for effect of group on performance in the Stroop test using one-way ANOVA, there was no significant effect of group for either the congruent ($F(2, 41)=1.75$, $P=0.2$), or incongruent trials ($F(2, 41)=0.48$, $P=0.6$), (see Figure 6.30). There was also no effect between-groups for reaction time in either congruent ($F(2, 41)=1.8$, $P=0.2$), or incongruent trials ($F(2, 41)=1.73$, $P=0.2$), (see Figure 6.30).

When groups were assessed individually using a paired-samples t-test in order to see what effect congruence had on performance the Control group performed significantly better in the congruent than incongruent condition ($t(13)=3.59$, $p<0.01$; Congruent: 97.21 ± 0.6; Incongruent: 68.43 ± 8.1), with there being no significant difference between-conditions for reaction time ($t(13)=0.43$, $P=0.7$; Congruent: 764.98 ± 22.1; Incongruent: 792.05 ± 57.1). When the IFN-α group was assessed, they also performed significantly better for congruent trials ($t(13)=4.42$, $p<0.01$; Congruent: 93.29 ± 1.6; Incongruent: 58.21 ± 9.1), with there also being a significant difference between-conditions for reaction time ($t(13)=2.23$, $p<0.05$; Congruent: 812.67 ± 16.4; Incongruent: 634.31 ± 73.9) (see Figure 6.31). Finally, when the Depressed group was assessed they also performed significantly better in congruent trials ($t(13)=4.92$, $p<0.01$; Congruent: 93.79 ± 2.2; Incongruent: 58.14 ± 8.4), with there being no significant difference between-conditions for reaction time ($t(13)=1.54$, $P=0.1$; Congruent: 770.29 ± 19.5; Incongruent: 685.32 ± 46).
Figure 6.30: Effect of group on the Stroop task

Figure showing effect of group on the Stroop task. There was no significant difference between groups for either congruent (Control: 97.21 ± 0.6; IFN-α: 93.29 ± 5.9; Depressed: 93.79 ± 2.2) or incongruent trials (Control: 68.43 ± 8.1; IFN-α: 58.21 ± 9.1; Depressed: 58.14 ± 8.4). All groups performed significantly better for congruent trials compared to incongruent trials (**p<0.01)

Figure 6.31: Effect of group on reaction times for Stroop task

Figure showing effect of group on reaction times for the Stroop task. There was no significant difference between groups for either congruent (Control: 764.98 ± 22.1; IFN-α: 812.67 ± 16.4; Depressed: 770.29 ± 19.5) or incongruent trials (Control: 792.05 ± 57.1; IFN-α: 634.31 ± 73.9; Depressed: 685.32 ± 46.1). When each group was assessed individually there was no effect between-conditions for the Control group or Depressed group, however, there was a significant difference for the IFN-α group, who responded significantly faster on the incongruent trials (*p<0.05). Unlike the control group, both the Depressed and IFN-α groups showed faster responding on the incongruent trials.

When the N-back was assessed there was no difference between groups for the 0-back (F(2, 41)=1.76, P=0.2), 1-back (F(2, 41)=1.52, P=0.2) or 2-back (F(2, 41)=0.58,
P=0.6), (see Figure 6.32). There was also no significant difference in reaction times between groups for the 0-back ($F(2, 41)=0.56$, $P=0.6$), 1-back ($F(2, 41)=1.38$, $P=0.3$), or 2-back ($F(2, 41)=2.33$, $P=0.1$).

Groups were then assessed individually to see what impact block had on performance using repeated-measures ANOVA. The Control group showed an overall significant effect of block on performance ($F(1.2, 15.3)=13.16$, $p<0.01$), where performance for the 0-back ($M=99.86$, $SD=0.1$) was significantly better than the 1-back ($M=91.43$, $SD=2.8$) and 2-back ($M=71.14$, $SD=7.5$), with performance in the 1-back also significantly better than the 2-back. For the IFN-α group there was an overall effect of block on performance ($F(1.2, 15.4)=35.5$, $p<0.01$), with performance for the 0-back ($M=99.57$, $SD=0.3$) being significantly better than the 1-back ($M=92.43$, $SD=2.6$) and 2-back ($M=60.57$, $SD=7.4$). For the Depressed group, there was also an overall effect of block on performance ($F(2, 26)=17.6$, $p<0.01$), which was significant between the 0-back ($M=99$, $SD=0.5$) and 2-back ($M=82.71$, $SD=6.5$), as well as the 1-back ($M=65.57$, $SD=5.8$) and 2-back (see Figure 6.32).

Figure 6.32: Effect of group on N-back

<table>
<thead>
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<tr>
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<td>99.6</td>
</tr>
<tr>
<td>Depressed</td>
<td>99</td>
</tr>
</tbody>
</table>

Figure showing performance in the N-back task for the Control (0-back: 99.86 ± 0.1; 1-back: 91.43 ± 2.8; 2-back: 71.14 ± 7.5), IFN-α (0-back: 99.57 ± 0.3; 1-back: 92.43 ± 2.6; 2-back: 60.57 ± 7.4), and Depressed groups (0-back: 99 ± 0.5; 1-back: 82.71 ± 6.5; 2-back: 65.57 ± 5.8). There was no overall difference between groups at each block. However, within groups there was a significant effect of block on performance. The Control group performed better in the 0-back than 1-back (**p<0.01) and 2-back (**p<0.01), and also significantly better in the 1-back than the 2-back (*p<0.05). The IFN-α group performed significantly better in the 0-back than the 1-back (*p<0.05) and the 2-back (**p<0.01). The Depressed group performed significantly better in the 0-back than the 2-back (**p<0.01).
Finally, all groups were compared for performance on the Key-search test and Zoo-map test using one-way ANOVA. When the Key-search test was assessed it was found that there was an overall effect of group on the score \( F(2, 41)=6.83, p<0.01 \), with the Control group being significantly worse at this task \( M=9.23, SD=1.1 \) than the Depressed group \( M=13.43, SD=2.1 \) and the IFN-\( \alpha \) group showing no significance compared to either group \( M=12, SD=2.5 \).

There was also a significant effect for scores for the Zoo-map version 1 \( F(2, 41)=3.25, p<0.05 \), which was again due to the Control group \( M=1.43, SD=4.2 \) scoring significantly lower than Depressed group \( M=4.79, SD=0.8 \) with IFN-\( \alpha \) showing no significance \( M=2.93, SD=0.8 \). When groups were compared on scores for Zoo-map version 2 there was no significant difference \( F(2, 41)=2.47, P=0.1 \); Control: 6.57 ± 0.8; IFN-\( \alpha \): 7.79 ± 0.1; Depressed: 7.86 ± 0.4).

There was also a significant difference in overall scores for the Zoo-map test \( F(2, 41)=3.61, p<0.05 \), which was due to the significantly lower score of the Control group \( M=8.14, SD=1.7 \) when compared to the Depressed group \( M=12.64, SD=0.9 \), with IFN-\( \alpha \) showing no significance when compared to both groups \( M=10.71, SD=3.1 \).
6.5 Discussion

6.5.1 Overview of results

- Patients with HCV perceive themselves to have significantly more memory problems than controls, but the only part of the FNP to be affected is delayed free-recall.
- Patients with HCV perceive themselves to have significantly more PFC problems, something backed up by them having significantly lower scores on the SART and 0-back and 1-back conditions for the N-back.
- Depression causes the most impairment in the FNP task, but this is limited to recall, with recognition remaining unaffected.
- Depression also causes significant impairment in the SART and 0-back condition for the N-back
- Relative to Baseline patients taking IFN-α only show a significant impairment in face recognition, despite improving in overall FNP performance at Week 8 relative to Week 0.
- All patient groups (HCV, IFN-α and Depressed) had longer reaction times for congruent than incongruent trials on the Stroop, unlike the Control group who took longer on congruent trials, although this difference rarely reached significance.
- Depressed patients perceived their memory and PFC dysfunction to be significantly worse than IFN-α patients, however, there was no significant difference between these two groups on any of the measures of PFC function.
- The Control group tended to be worse at the Key-search test, scoring significantly lower marks than the HCV group, Depressed group and IFN-α group. They also tended to be significantly impaired at version 1 of the Zoo-map test.
6.5.2 Effect of HCV on tests

In line with previous studies which indicate that HCV can cause an impairment in executive functioning (Perry et al., 2008; Reimer et al., 2005), findings from this chapter indicate that HCV patients perceive themselves as having significantly more dysexecutive problems than Controls (see Figure 6.3), something which is backed up by findings that they show an impairment relative to the Control group for the SART and N-back.

HCV patients show a slight but significant impairment in attention, as seen in the SART (see Figure 6.6). There are two parts to the test that require concentration from participants. The first one being to remember to press the spacebar on the cross after every number, rather than on the number itself, with failure to do so resulting in errors of omission; the second was to remember to withhold responding for the 'target' number. HCV patients had significantly more errors of omission than the Control group, and as there was no significant difference in reaction times between the groups, it could be ascertained that patients forgot to make the response at the correct time, rather than being significantly slower at the task and not responding in time. Despite showing significantly more errors of omission, the HCV group also demonstrated increased levels of commission (i.e., pressing the spacebar for the target number when they were required to omit their response). This could not be due to patients being too slow to press for the previous number as should this have been the case there would have been significantly fewer levels of omission. It can therefore be assumed that in this small sample of HCV patients that there was a small, but significant impairment in attention.

The other PFC test to yield significance for this group was the N-back test (see Figure 6.8), where patients with HCV showed an impairment at the 0-back and 1-back. With this test, in order to conclude that working memory is affected it would be expected that performance in the 1-back and 2-back be significantly worse, with the 0-back not showing any difference, as this is a Baseline condition relative to which subsequent performance is determined. There are two reasons why this may have occurred. The first is that HCV patients demonstrate slower processing speed (which would explain the significant difference seen for the 0-back), and so are slower to respond leading to incorrect responses, should this be the case however, significantly slower reaction times would be expected, and this was not the case, although they were slightly slower for both the 0-back and 1-back, but faster for the 2-back. This theory
could also be backed up by the observation that HCV patients show a similar decrease in performance to the Control group, but that their performance is always below the Control group. Meaning that as the task gets harder the HCV group gets worse, but they could potentially always be processing the information just below the Control group. The second is that patients do show impairment in working memory, and that significance for the 2-back was not seen due to the increased variability in responses for this block seen for both groups. The HCV group were also worse at the 2-back, but due to the standard error of the means for both groups being larger, this could not reach significance. The only way to ascertain which of these two the correct assumption is would be to run the test again in a much larger sample, so that variability could be decreased.

There was no impairment for the Stroop task relative to the Control group for the HCV group. However, the HCV group were faster to respond to incongruent than congruent trials, unlike the Control group who responded to congruent trials slightly faster (none of these effects were significant). The observation that the high-conflict situation of incongruence had little effect on response times could mean that HCV patients do not display a dissociation that would be observed with Control participants, parts of the brain which could be responsible for this include the parietal cortex (Larson et al., 2009) and frontal and parietal regions (West, 2003). In order to assess this potential dissociation, and the part of the brain responsible a potential experiment where the two groups are assessed in an fMRI machine while performing the Stroop task could be undertaken. It would also be necessary to test more participants in order to see whether this dissociation could reach a level of significance.

For the Zoo-map and Key-search tests the HCV group actually showed superior performance to the Control group; indicating that HCV may not have a severe impact on frontal functioning. This hypothesis could only be confirmed, however, by testing a large group of participants on the full BADS battery, as there is not sufficient evidence to draw a conclusion from here.

When rating memory, the HCV group rated themselves as having significantly more memory problems than the Control group (see Figure 6.2). However, when compared for performance on the FNP task there was no significant difference between groups (see Figure 6.4), with the only domain of this task to yield significance being delayed free-recall of names (see Figure 6.5). This could mean that the HCV memory
impairment could be specific to verbal memory, rather than associative memory, something which would have to be assessed in greater detail using a larger cohort with more specific tests.

However, results from this section do support existing literature which confirms that the two main neuropsychological impairments seen in HCV are impaired attention and impaired verbal memory (Weissenborn et al, 2009).

6.5.3 Effect of Depression on tests
Depressed patients rated their memory as being significantly more impaired than the Control group (see Figure 6.9) and also the IFN-α group (see Figure 6.24). Of all the groups tested, Depressed patients showed the most impairment in the FNP task when compared to Control participants (see Figures 6.11 to 6.13; 6.26 and 6.27). This impairment was seen for both the associative aspects of face-name recall, and also the verbal memory aspect of delayed free-recall of names. When assessed individually, it could be seen that the Depressed group were learning over the course of the task (as indicated by a significant increase in recall relative to block 1), however, their responses were always at a significantly lower level than the Control group, even for the first block (see Figure 6.11). This impairment was specific to the recall and learning portions of the experiment, not to the recognition portion of the experiment (see Figures 6.14 and 6.28). This suggests that Depressed patients are impaired in verbal-recall and associative-recall, but that the impairment does not affect recognition. This dissociation could be investigated in more detail using the remember/know paradigm, as previous studies have shown that Depressed patients do also show an impairment in recognition, but not familiarity (Drakeford et al, 2009). This distinction could not be made using this data gathered, however, should this be remedied in the future a more accurate idea of neural substrates potentially involved in the observed dissociation could be ascertained.

Depressed patients also showed impairment in the SART task relative to Control participants where despite increased errors of omission, they also displayed significantly more errors of commission (as indicated by a significantly reduced accuracy for the task). As reaction-times between-groups were non-significant it could be assumed that the difference is due to an attentional impairment rather than a processing impairment. This observation fits in nicely with other research indicating that executive functioning
is impaired in major depression (Porter et al, 2007), indeed, one of the criteria in the DSM-IV for depression is a significant impairment in concentration.

Performance on the N-back was only significantly affected for the 0-back, indicating that rather than displaying an impairment in working memory, that patients were impaired in psychomotor processing (see Figure 6.17). However, as patients did show a relative decrease in performance for the 1-back especially, repeat-testing for this group could yield a more accurate result.

As seen in the HCV group the Depressed group were also faster in responding for incongruent than congruent trials. Previous research has shown that MDD has an effect on Stroop performance, and that reaction times are slower for incongruent than congruent trials (Kertzman et al, 2009). This observation is said to be due to the fact that severity of depression does not affect responding in incongruent trials, that instead specific MDD subgroups will show impairment in this condition (Kertzman et al, 2009; Stordal et al, 2005), something we could not assess due to the low n. However, there was no overall difference between-groups for performance in congruent or incongruent trials (see Figures 6.16 and 6.30).

The final comparison undertaken was for the Key-search and Zoo-map tests, and again the Control group performed significantly worse. This could mean that either the impairment in executive functioning for depression does not generalise to the BADS battery, or that these two tests alone are insensitive measures of PFC function.

**6.5.4 Effect of IFN-α on tests**

When assessed from Week 0 to Week 8 there was no significant difference seen in any of the neuropsychological tests conducted, other than the face recognition component of the FNP task, suggesting that a more extensive test-battery should be conducted with neuropsychological tests that assess areas of the brain involved in face recognition such as prefrontal, lateral temporal and medial temporal regions (Leveroni et al, 2000). However, in line with many other studies conducted where investigation of neuropsychological functioning was undertaken prior to and during IFN-α treatment, there was no significant difference between time-points (see Table 1.4). In fact for many of the tests investigated in this short test battery, performance actually improved slightly (but non-significantly) from Baseline to treatment (see Figures 6.20; 6.22; 6.23 and 6.24), possibly due to a practice-effect. In order to assess whether a practice-effect takes
place, a repeated-measures design should have been conducted for Control participants. Another possibility is that IFN-α has little, or no effect on the tests investigated here, and that the variation seen from week-to-week, was simply a natural variation in performance that occurs in all participants (again a repeated-measures Control design would be needed to confirm this).

A potential reason that no significant effects were observed from Baseline to treatment is because cognitive difficulties only occur in 5-21% of patients (Fontana et al, 2007; Manns et al, 2001; McHutchison et al, 1998). This would mean that in order to fully assess the impact of cognitive impairment that it would be necessary to study a large number of patients and compare those patients who do and do not develop self-reported cognitive difficulties on treatment in order to assess the exact nature of this impairment. However, a large part of being able to conduct this type of experiment would be identifying firstly those tests that would be yield significance and target the correct areas of the brain.

In order to assess the similarities, or difference between the neuropsychological impairments (or lack thereof) seen in IFN-α-induced sickness-behaviour and MDD, the Depressed and IFN-α groups were compared with one another and also a matched Control group. The only significant difference between the IFN-α and Depressed group was for self-ratings of memory and PFC dysfunction (see Figures 6.24 and 6.25), for all other tests there was a non-significant difference. However, for many tests both these groups would show significance with the Control group instead. The Depressed group were worse at the recall components of the FNP task compared to Controls (see Figures 6.26 and 6.27). The IFN-α group was, however, significantly worse at the SART task than Controls (see Figure 6.29). However, this difference was probably due to HCV rather than a direct effect of IFN-α as there was no significant difference in performance on the SART from week 0 to week 8 of treatment (see Figure 6.22), however, the HCV group was significantly impaired on this task relative to Controls (see Figure 6.6). In order to say that an observed effect was due to IFN-α rather than HCV, it would be necessary to see an effect that was significant for the IFN-α group, significant for the repeated-measures IFN-α group at Week 8 relative to Baseline, but was not significant for the HCV group. This was not the case for any test, although the observed dissociation in reaction times for congruent and incongruent trials for HCV, Depressed and IFN-α patients at Weeks 0 and 8, reached a level of significance in those patients.
taking IFN-α only (see Figure 6.31). This implicates frontal and parietal regions as being areas that future neuropsychological test batteries could concentrate on.

6.5.5 Limitations of results

Results are limited by the low number of patients in each group, especially for the repeated IFN-α study. However, due to problems for recruitment for this study, and the lack of significance observed the decision was taken to terminate this study early in order to concentrate on other studies. As so few participants were studied for the repeated-measures IFN-α study any significant results should be interpreted with caution.

As the tests chosen also targeted impairment for HCV (especially the PFC tests), it would have been difficult to see any changes from Baseline to treatment, unless the impairment was severe. This was not the case in the participants that took part in the repeat neuropsychological study for IFN-α (with the only significant impairment being for face recognition). This could, in part, explain why no significance was seen, as the tests chosen targeted HCV in general, rather than being specific to potential IFN-α-induced impairment.

The comparison conducted between the Depressed and IFN-α treatment group was a spurious one, and could be criticised as being inappropriate as Depressed patients had a significantly higher HAM-D score than IFN-α participants. However, it was felt that in order to gain an appreciation of general IFN-α-induced neuropsychological side-effects and compare them against the neuropsychological impairments induced by Depression, that this was a necessary comparison to undertake. Future research could potentially use a more appropriate comparison by comparing those patients who become Depressed on IFN-α to patients with a primary Depression in order to see how similar or different the two disorders may be in terms of neuropsychological impairments. The group that become Depressed on IFN-α could then be compared to those patients who do not become Depressed on IFN-α, in order to see if this distinction has an impact on cognitive performance. As both Depressed and IFN-α patients complain of concentration difficulties and other executive impairments, a large test-battery which focuses more specifically on various areas on the PFC could be conducted.
6.5.6 Implications of results

Results from this Chapter indicate that HCV and Depression are two disorders that impact on executive functioning and aspects of recall. However, IFN-α does not cause a significant impairment in any of the tests investigated here, other than face-recognition (although due to the small number of participants this result should be interpreted with caution).

Results from this Chapter have provided a useful insight into potential test-batteries that could be conducted in the future with a larger battery that investigates a variety of PFC areas potentially yielding some interesting results. When the appropriate tests have been selected, a comparison between IFN-α patients (Depressed and non-depressed), with patients with a primary MDD, could potentially yield interesting results and tell us more about the differences or similarities between a primary Depression and IFN-α-induced Depression.
CHAPTER 7

Assessment of the IFN-α induced mood change: Comparison of a primary and secondary IFN-α-induced Depression
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Chapter 7: Mood effects of IFN-α

7.1 Introduction

Literature identifies a number of neuropsychiatric side-effects that can be attributed to therapy with IFN-α (see Figure 7.1); these have been discussed extensively in the introduction to this thesis.

*Figure 7.1: Psychiatric side-effects associated with IFN-α*

When attempting to classify the depression that occurs in patients taking IFN-α, there are varying schools of thought. Some researchers believe the IFN-α-induced mood disorder is best thought of as a combination of depressive and Hypomanic symptoms (Constant *et al.*, 2002); others that the mood consists of depressive-specific and neurovegetative features (Raison *et al.*, 2005b), and some believe it may be better classified as an atypical form of depression that has yet to be defined (Pasquini *et al.*, 2008). The best way to classify the mood change and assess its relationship with depression would be to directly compare the IFN-α-induced depression with a primary depression. Thus far there have been two such studies conducted in patients taking IFN-α for malignant melanoma.

Capuron *et al.*, (2009) used a factor analysis on the 17-item HAM-D, and found that both sets of patients loaded on similar items, with the only difference being that those patients with a primary depression were significantly more likely to feel guilty...
than those patients who became depressed on IFN-α. However, the study conducted by Pasquini et al. (2008), instead broke the HAM-D down into subscales, and then compared the types of symptoms across the two groups. They found that there were significant differences between the two groups, with those patients taking IFN-α being significantly less likely to experience negative cognitions than patients with a primary depression.

In order to better understand the neurobehavioural syndrome induced by IFN-α, the aim of this chapter is to administer depression and anxiety scales to patients taking IFN-α at Weeks 0, 8 and 20, and break-down the types of symptoms that patients experience at each time-point. These measures will then be compared to a primary depression cohort to see how similar or different it may be. We will also focus on those patients that become depressed on treatment and compare them to age-sex-and-HAM-D-matched participants in order to see how these two types of depression compare.
7.2 Methods and Materials

7.2.1 Participants

39 patients due to start treatment with IFN-α were recruited from the Hepatology Unit at St. James's Hospital Dublin; however, only 35 participants were followed up to Week 8, and 20 participants followed up to Week 20 (see Figure 7.2 for drop-out rates). All patients were taking 180μg PEG-IFN-2b subcutaneously once per week, with a weight-based dose of Ribavirin (800-1200mg) once per day. Participants were recruited as set out in Chapter 2 (section 2.4), using the same criteria (see Table 7.1 for demographic information).

23 matched depressed patients were recruited from St. Patricks Hospital and 29 control participants were also recruited (see Chapter 5 for information on recruitment and Table 7.2 for demographic information). Data for matched participants is given at the start of each results section where appropriate.

*Figure 7.2: Drop-out rates for IFN-α mood study*

Figure showing the dropout rates for the IFN-α study. 39 patients were recruited at baseline, however, 4 patients were removed from the week 8 analysis (one patient presented with MDD at baseline, one discontinued treatment at week 4 due to intolerance of side-effects of treatment, one did not return for their week 8 visit, and one patient had their start date pushed back for medical reasons. 35 patients were therefore assessed at week 8, however, 15 patients dropped out of the study before the week 20 visit. 5 patients dropped out due to treatment side-effects leading them to discontinue treatment. For 3 patients the side-effects were psychological (drug relapse, depression and hypomania), and for 2 patients the reasons were physical (both severe haematological effects). 8 patients were noncompliant to the study and did not return for their follow-up visits. A final 3 patients were discontinued from treatment by their nurse as they were not responding to the IFN-α.
Table 7.1: Demographic data for IFN-α patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>Gender</th>
<th>Genotype</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 8 week follow-up</td>
<td>35</td>
<td>37.8 ± 1.4</td>
<td>M: 22 (63%)</td>
<td>1: 16 (46%)</td>
<td>IVDU: 30 (86%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 13 (37%)</td>
<td>3: 19 (54%)</td>
<td>Unknown: (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1: 16 (46%)</td>
<td>3: 19 (54%)</td>
<td></td>
</tr>
<tr>
<td>0 to 20 week follow-up</td>
<td>20</td>
<td>40.8 ± 1.9</td>
<td>M: 15 (75%)</td>
<td>1: 9 (45%)</td>
<td>IVDU: 17 (85%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 5 (25%)</td>
<td>3: 11 (55%)</td>
<td>Unknown: (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1: 9 (45%)</td>
<td>3: 11 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Table showing demographic data for patients who took part in the mood study for IFN-α. All patients who took part in the 20 week study were also part of the 8 week study, however, due to large drop-out rates the data was analysed separately.

Table 7.2: Demographic data for all groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean age</th>
<th>Gender</th>
<th>Mean HAM-D score</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α (week 8)</td>
<td>35</td>
<td>37.8 ± 1.4</td>
<td>M: 22 (63%)</td>
<td>15 ± 1.25</td>
</tr>
<tr>
<td>IFN-α (week 20)</td>
<td>20</td>
<td>40.8 ± 1.9</td>
<td>M: 15 (75%)</td>
<td>14.55 ± 1.36</td>
</tr>
<tr>
<td>Control</td>
<td>29</td>
<td>40.83 ± 2.4</td>
<td>M: 16 (55%)</td>
<td>2.83 ± 2.25</td>
</tr>
<tr>
<td>Depressed</td>
<td>23</td>
<td>42.35 ± 2.4</td>
<td>M: 17 (74%)</td>
<td>23.74 ± 1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F: 6 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

Table showing the demographic information for all participants recruited for this portion of the thesis. Groups were matched for age, when assessed using a one-way ANOVA, $F(3, 106)=0.9, P=0.4$. They were also matched for gender when using a chi-squared analysis, $\chi^2(6, N=109)=6.74, P=0.3$. However, HAM-D scores were significantly different ($F(3, 106)=45.1, p<0.01$). The differences in the HAM-D scores lay between all groups except the two IFN-α groups when post-hoc comparisons were used.

All procedures for this experiment had full ethical approval from the St. James’s Hospital Research Ethics Committee, the St. Patrick’s Hospital Ethics Committee, and the School of Psychology, Trinity College Dublin, Ethics Committee (see Appendix IV).

7.2.2 Mood scales

The scales used for mood assessment in this chapter were the SCID, HAM-D, HAM-A, HADS and DEX (see Appendix I). These are described in Chapter 2 (Sections 2.2.1 and 2.2.2).
7.3 Data analysis
Data was first assessed for normality using the Shapiro-Wilks test, and as normality was established for most data it was decided to use parametric tests to assess data, with adjusted degrees of freedom being used where appropriate. Between-groups data were assessed using independent sample t-tests and one-way ANOVAs. To assess the data within a group, repeated-measures ANOVAs or paired t-tests were used. All data were checked for homogeneity of variance and where appropriate, if this assumption was violated, modified degrees of freedom were used (all analysis is described in Chapter 2, section 2.2.4).

7.3.1 Breakdown of HAM-A
The HAM-A was broken down into items that measured anxious cognitions (anxious, tension, fears, concentration), somatic symptoms (insomnia, muscular symptoms, sensory symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms), and behaviour (anxious behaviour, depressed behaviour). These domains were then assessed at each time-point using a one-way ANOVA, and then each domain compared across each week using a repeated-measures ANOVA.

7.3.2 Breakdown of HAM-D
The HAM-D was broken down into those items that measured mood (mood, motivation, anxiety psychic), behaviour (psychomotor agitation, psychomotor retardation), somatic items (appetite, fatigue, appetite, libido, early insomnia, middle insomnia, late insomnia, anxiety somatic, hypochondriasis, diurnal variation) and negative cognitions (guilt, suicide, insight, depersonalisation, paranoia, compulsiveness, helplessness, hopelessness, worthlessness). These four domains were then compared from week-to-week using repeated-measures ANOVA to see if there was an overall effect of week on each domain, and then a one-way ANOVA was used to assess whether there was a significant difference in the proportion of symptoms explained by a particular domain.
Chapter 7: Mood effects of IFN-α

7.4 Results

7.4.1 Mood change from Weeks 0 to 8

7.4.1.1 Effect of treatment on mood scores

Prior to assessing the individual mood scores it was decided to see if treatment had any effect on psychiatric adverse events (PAEs), and a chi-squared analysis showed a significant increase in the number of psychological disorders from Week 0 to Week 8 ($\chi^2(1, N=70)=11.67, p<0.01$), (see Figure 7.3).

A comparison was made between age-and-sex-matched Control participants where appropriate (IFN-α group: 63% male, mean age 37.8 ± 1.4, $n=35$; Control group (n=29): 53% male, mean age 40.8 ± 2.4, $n=29$). There was no significant difference between groups for gender when measured using a Chi-squared analysis ($\chi^2(1, N=64)=0.39, P=0.53$), or age when using a independent pairs t-test ($t(45.9)=-1.1, P=0.3$).

**Figure 7.3: SCID assessment at Weeks 0 and 8 of IFN-α treatment**

![Bar chart showing mood disorders](chart.png)

Figure showing the number of participants who met criteria for diagnosis of a mood disorder assessed using SCID. At Week 0, no patient met criteria for a psychological disorder, however, by Week 8 two (6%) met criteria for Major Depression, and six (17%) were experiencing a subsyndromal depression, with two (6%) meeting criteria for a Hypomanic episode. However, the majority of patients ($n=25, 71\%$) remained free of any official psychiatric or subsyndromal psychiatric disorder.

Initial analysis was conducted to ascertain whether there was a significant effect of treatment on mood scores by using a paired t-test. There was an overall significant effect of week of treatment on HAM-D scores ($t(47)=-5, p<0.01$), HAM-A scores
Chapter 7: Mood effects of IFN-α

(\(t(47)=-2.7, \ p<0.01\)), the HADS-D (\(t(47)=-4.4, \ p<0.01\)), and the DEX (\(t(47)=-2.1, \ p<0.05\)). However, there was no significant effect of week on the HADS-A (\(t(47)=-0.8, \ P=0.4\)). Patients were also compared to Control participants using independent-samples t-tests for each separate comparison, with all comparisons yielding significance (see Figures 7.4 to 7.7 for results).

**Figure 7.4: Effect of IFN-α on HAM-D scores over 8 weeks**

There is an overall effect of week on HAM-D scores, \(t(47)=-5, \ p<0.01\), with a significant increase from Week 0 (8.2 ± 1.33) to Week 8 (15 ± 1.25). There is a significant difference between healthy control participants (2.83 ± 2.25) and Week 0 of IFN treatment \(t(40.4)=3.81, \ p<0.01\), and Week 8 \(t(41.2)=9.13, \ p<0.01\), (**\(p<0.01\)).

**Figure 7.5: Effect of IFN-α on HAM-A scores over 8 weeks**

There is an overall effect of treatment on HAM-A scores from Week 0 (8.9 ± 1) to Week 8 (12.2 ± 1.3), \(t(47)=-2.7, \ p<0.01\). There is also a significant difference between control participants (3.6 ± 0.6) with IFN-α at Week 0 \(t(53.48)=-4.2, \ p<0.01\), and Week 8 \(t(48.67)=5.93, \ p<0.01\), (**\(p<0.01\)).
There is an overall effect of week on treatment on HADS-D scores from Week 0 (3.8 ± 0.5) to Week 8 (7.14 ± 0.7), $t(47) = -4.4$, $p < 0.01$. However, there is not a significant effect on HADS-A scores, $r(47) = -0.8$, $P = 0.4$, from Week 0 (7.2 ± 0.7) to Week 8 (7.74 ± 0.7). However, there was a significant difference for HADS-D scores between the control group (2.1 ± 0.3) and IFN-α scores at Week 0 $t(58.47) = 2.87$, $p < 0.01$ and Week 8 $t(47.78) = 6.33$, $p < 0.01$. There was also a significant difference when the control (5.2 ± 0.6) and IFN-α groups were compared for anxiety at Week 0 $t(62) = 2.2$, $p < 0.05$ and 8 $t(62) = 2.65$, $p < 0.01$, (**$p < 0.01$).

There is significant increase in DEX scores from Week 0 (18.6 ± 2) to Week 8 (21.1 ± 1.9), $t(47) = -2.1$, $p < 0.05$. There was also a significant difference between the control group (15.97 ± 1.5) and the IFN-α group at Week 0, $t(59.39) = 1.1$, $p < 0.05$, and Week 8, $t(60.72) = 2.1$, $p < 0.05$, (*$p < 0.05$).
7.4.1.2 Effect of treatment breakdown of mood scores

Firstly, it was decided to measure each individual question asked as part of this experiment in order to see which questions yielded significance from Week 0 to 8 using a paired t-test, all those questions that showed a significant increase or decrease are shown in Table 7.3.

Results from this table indicate that many of the items where a significant effect is seen from Week 0 to Week 8 are somatic items, or items that measure depressed mood (see Table 7.3). It was therefore decided to break down the HAM-A into three domains that measured anxious cognitions, somatic symptoms and behaviour, with the HAM-D being broken down into four domains that looked at depressed mood, behaviour, somatic symptoms and negative cognitions. By breaking both of these scales down it was hoped that it would be possible to ascertain what proportion of the HAM-A and HAM-D scores comprised each of these domains.
## Table 7.3: Table showing items yielding significance from Week 0 to 8.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Question</th>
<th>Mean (± SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-A</td>
<td>Insomnia</td>
<td>Week 0: 0.63 ± 0.8</td>
<td>2.253</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.37 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concentration/memory</td>
<td>Week 0: 0.74 ± 0.9</td>
<td>-3.833</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.51 ± 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic (sensory)</td>
<td>Week 0: 0.43 ± 0.7</td>
<td>-4.845</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.89 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic (cardiovascular)</td>
<td>Week 0: 0.29 ± 0.6</td>
<td>-3.311</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.51 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic (respiratory)</td>
<td>Week 0: 0.26 ± 0.5</td>
<td>-2.095</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.57 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic (gastrointestinal)</td>
<td>Week 0: 0.54 ± 0.8</td>
<td>-2.452</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.77 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic (genitourinary)</td>
<td>Week 0: 0.34 ± 0.6</td>
<td>-2.678</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.8 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic (other)</td>
<td>Week 0: 0.34 ± 0.7</td>
<td>-3.648</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.8 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depressed mood</td>
<td>Week 0: 0.4 ± 0.7</td>
<td>-3.567</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.9 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>Depressed mood</td>
<td>Week 0: 0.31 ± 0.7</td>
<td>-2.074</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.69 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Work and activities</td>
<td>Week 0: 0.4 ± 0.8</td>
<td>-6.458</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.46 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic GI (Appetite loss)</td>
<td>Week 0: 0.17 ± 0.5</td>
<td>-3.51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.49 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic general (Fatigue)</td>
<td>Week 0: 0.49 ± 0.6</td>
<td>-5.202</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.26 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>Week 0: 0 ± 0</td>
<td>-4.115</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.46 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Libido</td>
<td>Week 0: 0.31 ± 0.6</td>
<td>-3.347</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.97 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia early</td>
<td>Week 0: 0.37 ± 0.6</td>
<td>-2.59</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.8 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety somatic</td>
<td>Week 0: 0.63 ± 0.6</td>
<td>-4.825</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.23 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypochondrisis</td>
<td>Week 0: 1.09 ± 0.9</td>
<td>-3.309</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.6 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychomotor retardation</td>
<td>Week 0: 0.26 ± 0.5</td>
<td>-2.052</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.51 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td>Week 0: 0.31 ± 0.53</td>
<td>-4.098</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.83 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Helplessness</td>
<td>Week 0: 0.2 ± 0.5</td>
<td>-2.797</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.54 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>I still enjoy the things I used to enjoy</td>
<td>Week 0: 0.6 ± 0.8</td>
<td>-2.953</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.17 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I can laugh and see the funny side of</td>
<td>Week 0: 0.29 ± 0.6</td>
<td>-2.915</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>things</td>
<td>Week 8: 0.69 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I feel cheerful</td>
<td>Week 0: 0.46 ± 0.6</td>
<td>-3.311</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.9 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I feel as if I am slowed down</td>
<td>Week 0: 1 ± 0.8</td>
<td>-5.587</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.97 ± 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I look forward with enjoyment to things</td>
<td>Week 0: 0.51 ± 0.7</td>
<td>-2.121</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.94 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEX</td>
<td>Apathy and a lack of drive</td>
<td>Week 0: 0.89 ± 0.9</td>
<td>-2.927</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.54 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disturbed impulse control</td>
<td>Week 0: 0.77 ± 0.9</td>
<td>-2.927</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.29 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shallowing of affective responses</td>
<td>Week 0: 1.49 ± 1</td>
<td>2.541</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 0.97 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aggression</td>
<td>Week 0: 1.11 ± 1</td>
<td>-2.321</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 1.54 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distractibility</td>
<td>Week 0: 1.54 ± 1</td>
<td>-2.625</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8: 2.03 ± 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table shows significant questions for each questionnaire. The higher the mark the more impairment that has been experienced in that particular domain; HAM-A, HAM-D, and DEX maximum score of 4 per question (libido for HAM-D, maximum 2). The HADS has a maximum score of 3 per question. Items specific to 'sickness behaviour' are indicated in bold, depression in italics. Most of the items scored highly on overlap between sickness behaviour and depression (somatic and mood effects).
There was an overall effect of domain on proportion of symptoms for Week 0 $F(1.33, 45.3)=21.52, p<0.01$, which post-hoc comparisons revealed to be significant between all domains (*p<0.05, **p<0.01); anxious cognitions, ($M=51.54, SD=4.7$), somatic symptoms, ($M=29.97, SD=3.8$), and behaviour ($M=12.77, SD=1.9$) (see Figure 7.8). There was also an effect of domain at Week 8 $F(1.55, 52.52)=43.35, p<0.01$, which again was due the significant difference between the three domains of cognition, ($M=33.82, SD=1.3$), somatic symptoms, ($M=52.34, SD=2.3$), and mood, ($M=10.99, SD=1.6$), (see Figure 7.8).

*Figure 7.8: Breakdown of HAM-A symptoms, within-week comparisons (8 week)*

Figure showing the proportions at Week 0 and Week 8 explained by a particular domain for the HAM-A. At week 0 the majority of symptoms were anxious cognitions; however at Week 8 the significant majority of symptoms were somatic symptoms.
When a repeated-measures ANOVA was used to assess the effect of domain between week there was an overall effect of treatment on domains, which was explained mainly by the significant increase in somatic symptoms and significant decrease in anxious cognitions ($F(1.28, 43.45)=17.66, p<0.01$), (see Figures 7.8 and 7.9).

**Figure 7.9: Comparison of HAM-A symptoms, between-week comparisons (8 Week)**

From Week 0 to Week 8 there was a significant difference in the proportion of symptoms explained by the somatic and anxious cognition domains, $F(1,34)=54.22, p<0.01$ (**). Both these domains also showed a significant difference when compared with the proportions explained by behaviour symptoms, $F(1,34)=37.12, p<0.01$ (somatic); $F(1,34)=4.38, p<0.05$ (anxious cognitions). This means that the main difference in proportion of symptoms is explained by the decrease in anxious cognitions and increase in somatic symptoms.

There was an overall effect of domain on proportion of symptoms for Week 0 ($F(1.87, 63.56)=41.67, p<0.01$), which Bonferroni comparisons revealed to be mainly due to somatic symptoms ($M=52.55, SD=4.6$), when compared to mood ($M=14.82, SD=2.1$), behaviour ($M=5.55, SD=1.7$), and negative cognitions ($M=15.94, SD=2.9$), with there also being a significant difference between mood and behaviour (see Figure 7.10). There was also an effect of domain at week 8 ($F(1.9, 64.68)=131.12, p<0.01$), which again was due to the majority of symptoms being explained by somatic symptoms ($M=59.29, SD=2.5$), when compared to mood ($M=19.18, SD=1.5$), behaviour ($M=8.75, SD=1$), and negative cognitions ($M=12.78, SD=1.9$). There was also a significant difference between mood and behaviour.
There was significance in the proportion of symptoms explained by a particular domain (*p<0.05, **p<0.01), for both Week 0 and Week 8 the significant majority of symptoms were in the 'somatic symptoms' category, with there also being significantly more mood symptoms when compared to behaviour. For Week 0, the proportions in the pie chart are different to the mean scores as many patients scored 0 across many of the domains, thus the mean score of each domain is different to the percentage proportion of each domain.
When domains were compared between weeks, there was no overall significant effect of treatment \( F(1.78, 60.28)=1.51, P=0.2 \), (see Figure 7.11)

**Figure 7.11: Comparison of HAM-D symptoms, between-week comparisons (8 week)**

Graph showing the difference in proportions of symptoms domains from Week 0 to 8. There was no overall effect of treatment on the domains investigated \( F(1.78, 60.28)=1.51, P=0.2 \), meaning although there was a significant increase in the HAM-D score from Week 0 to Week 8 (see Figure 7.4), this was not reflected in any significant increase in any of the domains.
7.4.2 Mood change between Weeks 0, 8 and 20

7.4.2.1 Effect of treatment on mood scores

The effect of treatment on psychiatric diagnoses can be seen in Figure 7.12: at Week 0 no patient met criteria for any DSM-IV diagnosis, however, by Week 8, two patients met the criteria for major depression and by Week 20, three patients met the criteria. When assessed using a Chi-squared analysis there was a significant difference in the number of PAE’s from Week 0 to Week 8 ($\chi^2(1,N=40)=10, p<0.01$), however, there was no significant difference from Week 8 to Week 20 ($\chi^2(1,N=40)=0.11, P=0.7$).

**Figure 7.12: SCID assessment Weeks 0, 8 and 20 of IFN-α treatment**

![Graph showing mood change between Weeks 0, 8, and 20](image)

Figure showing the number of participants who met criteria for diagnosis of a mood disorder assessed using SCID. At Week 0, no patient met criteria for a psychological disorder, however, by Week 8 two (10%) met criteria for Major Depression, and five (25%) were experiencing a subsyndromal depression, with one (5%) meeting criteria for a Hypomanic episode. By Week 20, the patient experiencing a Hypomanic episode, had recovered from this and was now experiencing subsyndromal depression, and one patient who had been experiencing subsyndromal depression had developed a major depression. However, the majority of patients ($n=12; 60\%$ experienced no significant psychiatric difficulty during treatment).

Results for each individual week were compared to scores from age-and-sex-matched healthy control participants (IFN-α group: 75% male, mean age 38.9 ± 2; Control group 75% male, mean age 39.7 ± 3). There was no significant difference between the ages of the two groups ($t(31.55)=-0.25, P=0.8$). Results were compared using independent samples t-tests.
Repeated-measures ANOVA were used to assess the effect of week of treatment on mood scores with Bonferroni post-hoc comparisons. There was an overall effect of treatment on HAM-D scores ($F(2,38)=15.29$, $p<0.01$), and also HAM-A scores ($F(2,38)=3.86$, $p<0.05$). For the HADS there was a significant effect of week on depression ($F(2,38)=9.15$, $p<0.01$), but not for anxiety ($F(2,38)=1.25$, $P=0.3$). There was no significant effect of week on the DEX questionnaire ($F(1.42,26.94)=3.49$, $P=0.06$), (see Figures 7.13 to 7.16)

**Figure 7.13: Effect of IFN-α on HAM-A scores over 20 weeks**

![Figure 7.13: Effect of IFN-α on HAM-A scores over 20 weeks](image)

There was an overall effect of week of treatment on HAM-A scores post hoc testing revealed the only significant difference to be between baseline ($M=7.4$, $SD=0.96$) and Week 8 ($M=11.4$, $SD=1.42$), but not Week 20 ($M=10.35$, $SD=1.59$). There was a significant difference between the control group ($M=3.03$, $SD=0.63$) and the IFN-α group for Week 0 ($t(38)=3.78$, $p<0.01$, Week 8 $t(26.47)=5.36$, $p<0.01$ and Week 20 $t(24.75)=4.16$, $p<0.01$, (*$p<0.05$, **$p<0.01$)
Chapter 7: Mood effects of IFN-α

Figure 7.14: Effect of IFN-α on HAM-D scores over 20 weeks

There was an overall effect of week of treatment on HAM-D scores $F(2,38)=15.29$, $p<0.01$, with a significant increase in scores from baseline ($M=7.7$, $SD=1.3$) to Week 8 ($M=14.65$, $SD=1.37$) and Week 20 ($M=14.55$, $SD=1.36$). Comparison with control participants ($M=2.55$, $SD=0.45$) also yielded significant results for each week, Week 0 $t(31.54)=-0.25$, $p<0.01$, Week 8 $t(22.71)=3.79$, $p<0.01$, and Week 20 $t(22.36)=8.43$, $p<0.01$, (**$p<0.01$)

Figure 7.15: Effect of IFN-α on HADS scores over 20 weeks

There was an overall effect of week of treatment on scores for the HADS-D, $F(2,38)=9.15$, $p<0.01$, from Week 0, ($M=3.8$, $SD=0.55$), to Week 8, ($M=7.2$, $SD=1$), and Week 20, ($M=7.15$, $SD=0.94$). However there was no overall effect of week on the HADS-A, $F(2,38)=1.25$, $P=0.3$, from Week 0, ($M=6.4$, $SD=0.7$), to Week 8, ($M=7.45$, $SD=0.9$), and Week 20, ($M=7.8$, $SD=0.9$). When compared to control participants ($M=4.9$, $SD=0.7$) the HADS-A was not significant at week 0, $t(38)=1.5$, $P=0.1$, but was at Weeks 8, $t(38)=2.24$, $p<0.05$, and 20, $t(38)=2.47$, $p<0.05$. When compared to control participants ($M=2.1$, $SD=0.3$) depression scores were significant at Weeks 0 $t(30.42)=2.7$, $p<0.05$, 8 $t(22.77)=4.88$, $p<0.01$ and 20 $t(23.19)=5.07$, $p<0.01$, (**$p<0.01$)
There was not an overall effect of week of treatment on DEX scores \( F(1.42,26.94)=3.49, P=0.06 \). The mean score at Week 0 \( (M=19.2, SD=2.93) \), did not differ significantly from Week 8 \( (M=21.15, SD=2.79) \) or Week 20 \( (M=24.7, SD=3) \). When compared to control participants \( (M=17.15, SD=1.74) \) the only significant difference was at Week 20 \( t(30.46)=2.17, p<0.05 \), (*p<0.05)

7.4.2.2 Effect of treatment on breakdown of mood scores

As there was no significant difference between any of the domains from Weeks 8 to 20 on treatment, it was decided to break down individual mood scores for the HAM-A and HAM-D only to see whether the domains remained constant through treatment. Results were analysed using repeated-measures ANOVAs.

For the HAM-A at Week 0 there was an overall significant difference between all domains \( F(2,38)=16.4, p<0.01 \), which was significant for all comparisons between anxious cognitions \( (M=53.52, SD=5.6) \), somatic symptoms \( (M=27.51, SD=4.36) \) and behaviour \( (M=13.96, SD=2.7) \). At Week 8, there was also an overall effect of domain \( F(2,38)=22.49, p<0.01 \), with significance between all domains, anxious cognitions \( (M=31.99, SD=3.9) \), somatic symptoms \( (M=51.43, SD=4.45) \) and behaviour \( (M=11.59, SD=2.11) \). At Week 20, there was a significant difference between all domains \( F(2,38)=25.5, p<0.01 \), but this was only significant between behaviour \( (M=13.44, SD=3.13) \) and the two other domains of somatic symptoms \( (M=48.29, SD=5.85) \), and anxious cognitions \( (M=38.27, SD=7.11) \), (see Figure 7.17).
When HAM-D for the 20 week study were broken down into proportions it was found that the results across each week were fairly similar, with around 50% of symptoms being somatic, 35% due to anxious cognitions and 15% due to behaviour, at Week 20 the majority were somatic and negative cognitions (*p<0.05, **p<0.01)

There was an overall effect of week on each of the domains (F(2.68, 50.9)=5.16, p<0.01), which showed significance from Week 0 to 8, and 0 to 20, however, there was no difference in domains from Weeks 8 to 20 (see Figure 7.18).
The main contrast that yielded significance was when Somatic symptoms were compared to the other domains over each week. When somatic symptoms were compared to behaviour at Week 8 ($F(1,19)=20.81, p<0.01$) and Week 20 ($F(1,19)=5.43, p<0.05$) and anxious cognitions also at Week 8 ($F(1,19)=12.68, p<0.01$) and 20 ($F(1,19)=12.68, p<0.01$). However between Week 8 to 20, there is no significant difference between the somatic and behaviour ($F(1,19)=0.37, p=0.55$) or somatic and anxious cognition ($F(1,19)=0.44, P=0.52$) domains. Overall, differences in domain were explained mainly by a decrease in anxious cognitions and an increase in somatic symptoms, (**p<0.01).

When the HAM-D was investigated, at Week 0 there was an overall significant difference between all domains ($F(3,79)=45.54, p<0.01$), which was significant for all comparisons with somatic symptoms, ($M=62.01, SD=5.37$), for behaviour, ($M=5.87, SD=2.64$), negative cognitions, ($M=15.9, SD=3.49$) and mood, ($M=14.55, SD=2.92$) (see Figure 7.19).
Figure 7.19: Comparison of HAM-D symptoms, within-week comparisons (20 week)

Three pie charts showing the proportion of patients HAM-D scores that are explained by the domains of mood, behaviour, somatic symptoms and negative cognitions at Weeks 0, 8 and 20. There is an overall difference in domains week 0, 8 and 20, which is significant mainly at the somatic domain, which explains over 60% of HAM-D symptoms over each week (*p<0.05, **p<0.01).

At Week 8, there was also an overall effect of domain (F(3,79)=90.15, p<0.01), which again showed significance between somatic symptoms and all other items (M=60.53, SD=3.47), mood (M=18.67, SD=2.2), behaviour (M=8.02, SD=1.57) and...
negative cognitions ($M=12.78$, $SD=2.54$), as well as between mood and behaviour. At Week 20, there was a significant difference between all domains ($F(3,79)=56.33$, $p<0.01$), again between somatic symptoms, ($M=60.14$, $SD=5.05$) and the two other domains of mood ($M=18.83$, $SD=2.26$) behaviour, ($M=7.21$, $SD=1.9$) and negative cognitions ($M=13.83$, $SD=2.52$) (see Figure 7.19). When results were compared between-weeks using a repeated-measures ANOVA, there was no effect of week on any measure of domain ($F(2.77, 52.57)=0.257$, $p=0.84$), (see Figure 7.20), despite an overall increase in the HAM-D score from Weeks 0 to 8, and 0 to 20 (see Figure 7.13).

**Figure 7.20: Comparison of HAM-D symptoms, between week comparisons (20 week)**

Figure showing the overall effect of week on each of the domains, there is no significant effect of treatment on the proportion of symptoms explained by mood, behaviour, somatic symptoms and cognition. With the proportion of symptoms explained by each domain remaining constant.
7.4.3 Comparison of patients who did and did not experience psychiatric adverse events on treatment

Patients who did and did not develop PAEs on treatment were compared for demographics using a Chi-squared analysis. Of those people experiencing PAEs at Week 8, 30% (n=9) of patients infected via needles, and 20% (n=1) infected via unknown sources developed an adverse event ($\chi^2(2, N=35)=0.41, P=0.8$). 25% (n=4) of patients with genotype 1, and 31.6% (n=6) of patients with genotype 3 developed psychiatric disorders ($\chi^2(2, N=35)=1.8, P=0.4$), as did 36% (n=8) of men and 15% (n=2) of women ($\chi^2(4, N=35)=5.42, P=0.2$). When split into age ranges, 17% (n=1) of 20-30 year olds, 27% (n=4) of 31-40 year olds and 42% (n=5) of 41-50 year olds developed APEs ($\chi^2(6, N=35)=2.46, P=0.9$). Finally, when assessed for history of self-reported mood disorders, 44% (n=4) of patients who had a previous mood disorder experienced a PAE on treatment, whereas 56% of patients who also had a psychiatric history did not develop a PAE, ($\chi^2(2, N=20)=1.63, P=0.4$).

At Week 20, 41.2% (n=7) of patients infected through needles developed a PAE, compared to 33% (n=1) of patients infected via unknown means, ($\chi^2(2, N=20)=0.85, P=0.7$). Genotype had an equal effect on development of depression with 4 patients (40%) from genotype 1 and genotype 3 developing a PAE, ($\chi^2(2, N=20)=1.14, P=0.5$). Gender also had no effect on developing depression with 40% of men (n=4) and 40% of women (n=2) developing a PAE, ($\chi^2(2, N=20)=1.23, P=0.5$). Age also had a negligible effect with 33% (n=1) of 20-30 year olds, 44% (n=4) of 31-40 year olds and 50% (n=3) of 41-50 year olds developing a PAE, ($\chi^2(6, N=20)=4.46, P=0.6$). In terms of psychiatric history, those patients who had a history of mood disorders were non more likely to develop depression than those who did, with 43% (n=3) of patients who developed a PAE having a psychiatric history, and 57% (n=4) of patients who did not develop a PAE also having a psychiatric history ($\chi^2(2, N=20)=4.53, P=0.1$).

Patients were then compared to those patients who did not develop PAEs at baseline using an independent-samples t-test, at Week 8 (see Table 7.4) and Week 20 (see Table 7.5). There was a significant difference between the group that did not become depressed and the subsyndromally depressed group at Week 8 only for the HAM-D ($t(29)=-2.1, p<0.05$), and the depression portion of the HADS ($t(29)=-4.2, p<0.01$). There was a difference between the group who developed no PAEs and the
major depressed group at Week 8 for the HAM-D ($t(25)=-2.3$, $p<0.05$), HAM-A ($t(25)=-2.6$, $p<0.05$), and HADS-D ($t(25)=-3.6$, $p<0.05$). When compared to hypomanic patients, there was again only a significant difference at Week 8 in the HAM-D ($t(25)=-2.2$, $p<0.05$), HAM-A ($t(25)=-2.4$, $p<0.05$), and for the HADS-A ($t(25)=-3.3$, $p<0.01$), and depression ($t(24)=2.9$, $p<0.01$) categories.

**Table 7.4: Comparison of average scores for patients who developed PAEs at week 8 with those who did not.**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>No PAE (mean ± SEM) n=25</th>
<th>Subsyndromal depression (mean ± SEM) n=6</th>
<th>Major depression (mean ± SEM) n=2</th>
<th>Hypomanic episode (mean ± SEM) n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>8.28 ± 1.7</td>
<td>7 ± 3.1</td>
<td>9.5 ± 5.5</td>
<td>9.5 ± 3.5</td>
</tr>
<tr>
<td>Week 8</td>
<td>12.6 ± 1.4</td>
<td>19 ± 1.6 *</td>
<td>24.5 ± 0.5 *</td>
<td>24 ± 4 *</td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>9.12 ± 1.4</td>
<td>7 ± 2.5</td>
<td>11 ± 3</td>
<td>9.5 ± 3.5</td>
</tr>
<tr>
<td>Week 8</td>
<td>10.24 ± 1.4</td>
<td>13.17 ± 1.7</td>
<td>22 ± 1 *</td>
<td>23.5 ± 7.5 *</td>
</tr>
<tr>
<td>HADS-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>7.4 ± 0.8</td>
<td>6.5 ± 2</td>
<td>6.5 ± 0.8</td>
<td>7.5 ± 1.5</td>
</tr>
<tr>
<td>Week 8</td>
<td>6.8 ± 0.8</td>
<td>8.17 ± 1.5</td>
<td>10 ± 4</td>
<td>16 ± 1 *</td>
</tr>
<tr>
<td>HADS-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>3.8 ± 0.6</td>
<td>3.83 ± 1.1</td>
<td>5 ± 0</td>
<td>2 ± 0</td>
</tr>
<tr>
<td>Week 8</td>
<td>5.32 ± 0.7</td>
<td>11.5 ± 1.1 **</td>
<td>14 ± 2 **</td>
<td>10 ± 2 **</td>
</tr>
<tr>
<td>DEX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>18.36 ± 2.4</td>
<td>20 ± 5.9</td>
<td>19 ± 13</td>
<td>17.5 ± 6.5</td>
</tr>
<tr>
<td>Week 8</td>
<td>19.04 ± 2.3</td>
<td>26 ± 4.2</td>
<td>23 ± 8</td>
<td>30 ± 1</td>
</tr>
</tbody>
</table>

Table showing the differences in mean results for those patients who did, and did not, develop PAEs 8 weeks into treatment. Significant differences are indicated in bold (* $p<0.05$, ** $p<0.01$). There was no difference with the no PAE group at baseline for any of the groups, despite the MDE and Hypomanic groups both having slightly raised HAM-D and HAM-A scores, and the MDE group also having slightly raised HADS-D scores. The main differences occurred at Week 8, with all groups showing a significant difference on the HAM-D and HADS-D scores. The MDE group showed additional differences on the HAM-A scores, with the Hypomanic group showing the most difference with all scores showing significance except for the DEX.

When the results were computed for the 20 Week follow-up, there was a significant difference between the non-PAE group and the subsyndromally-depressed group at Week 8 for the HAM-D ($t(15)=-2.9$, $p<0.05$), HAM-A ($t(15)=-2.2$, $p<0.05$) and HADS-D ($t(15)=-3.1$, $p<0.01$). There was also a difference with the group that developed MDE, as there was a significant difference at Week 8 for the HAM-D score ($t(14)=-2.79$, $p<0.05$), and the HADS-D ($t(6.44)=-4.28$, $p<0.01$).
Table 7.5: Comparison of average scores for patients who developed PAEs at week 20 with those who did not.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>No PAE (mean ± SEM) n= 13</th>
<th>Subsyndromal depression (mean ± SEM) n= 4</th>
<th>Major depression (mean ± SEM) n= 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>7.23 ± 1.5</td>
<td>10 ± 3.8</td>
<td>6.67 ± 4.3</td>
</tr>
<tr>
<td>Week 20</td>
<td>11.62 ± 1.4</td>
<td>19.75 ± 2.1 *</td>
<td>20.33 ± 1.8 *</td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>7.54 ± 1</td>
<td>7 ± 2.7</td>
<td>7.33 ± 4.1</td>
</tr>
<tr>
<td>Week 20</td>
<td>7.77 ± 1.8</td>
<td>15.5 ± 2.6 *</td>
<td>14.67 ± 5.8</td>
</tr>
<tr>
<td>HADS-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>6.38 ± 0.7</td>
<td>7.75 ± 2.5</td>
<td>4.67 ± 1.9</td>
</tr>
<tr>
<td>Week 20</td>
<td>6.92 ± 1.1</td>
<td>11 ± 2.2</td>
<td>7.33 ± 2.2</td>
</tr>
<tr>
<td>HADS-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>3.69 ± 0.7</td>
<td>4.5 ± 1.5</td>
<td>3.33 ± 1.7</td>
</tr>
<tr>
<td>Week 20</td>
<td>5.08 ± 1</td>
<td>11 ± 1.6 **</td>
<td>11 ± 1 **</td>
</tr>
<tr>
<td>DEX</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>20.15 ± 3.9</td>
<td>20.15 ± 3.9</td>
<td>12.67 ± 9.8</td>
</tr>
<tr>
<td>Week 20</td>
<td>21.62 ± 3.7</td>
<td>31 ± 6.5</td>
<td>29.67 ± 7.8</td>
</tr>
</tbody>
</table>

Table showing the differences in mean results for those patients who did, and did not, develop psychiatric adverse events 20 weeks into treatment. There was no a significant difference in patients who did, and did not, develop a PAE, with a diagnosis of depression leading to significantly higher scores on the HAM-D and HADS-D. However, only those patients who had a subsyndromal depression had a significantly higher HAM-A score than the Non-PAE group.

7.4.4.1 Breakdown of mood scores for patients who did and did not develop psychiatric adverse events

Those questionnaires that consistently yielded significance were compared between those who did and did not develop a PAE. There was a non-significant difference between those patients who developed a MDE and subsyndromal depression on treatment for the HAM-D at Week 8 (*t*(5)=-1.85, *P*=0.1), and 20 (*t*(5)=-0.2, *P*=0.8), as well as the HADS-D; Week 8 (*t*(5)=-2.34, *P*=0.06); Week 20 (*t*(5)=0, *P*=1). It was therefore decided to combine these two groups in all further analysis in order to increase the normality of the data through an increased *n*. It was also decided to analyse data from Week 8 only as there were no significant difference in the depressed group from Week 8 to Week 20 for the HAM-D (*t*(13)=0.12, *P*=0.9; Week 8: 20.38 ± 1.5; Week 20: 20 ± 1.3) or HADS-D (*t*(13)=0.83, *P*=0.4; Week 8 12.12 ± 1; Week 20: 11 ± 0.9). The individual questions that yielded significance for all questionnaires are shown for comparisons with patients who developed depression and hypomania (see Table 7.6).
Table 7.6: Table showing items yielding significance from Week 0 to 8, comparison between patients who did, and did not develop PAEs

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>No PAE (n=25)</th>
<th>Depression (n=8)</th>
<th>Hypomania (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td></td>
<td>t-value</td>
<td>t-value</td>
<td>t-value</td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious mood</td>
<td>0.92 ± 0.2</td>
<td>1.88 ± 0.4 **</td>
<td>-2.7</td>
</tr>
<tr>
<td>Tension</td>
<td>0.68 ± 0.1</td>
<td>1.88 ± 0.4 **</td>
<td>-4.1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.2 ± 0.2</td>
<td>2.5 ± 0.5 **</td>
<td>-9.9</td>
</tr>
<tr>
<td>Genitourinary symptoms</td>
<td>0.56 ± 0.1</td>
<td>1.37 ± 0.2 **</td>
<td>-3.2</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0.56 ± 0.2</td>
<td>1.63 ± 0.3 **</td>
<td>-3.3</td>
</tr>
<tr>
<td>Anxious behaviour</td>
<td>0.64 ± 0.2</td>
<td>2 ± 0 **</td>
<td>-3.2</td>
</tr>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0.44 ± 0.2</td>
<td>1.38 ± 0.4 *</td>
<td>-2.6</td>
</tr>
<tr>
<td>Work and activities</td>
<td>1.24 ± 0.1</td>
<td>2.13 ± 0.1 **</td>
<td>-4.6</td>
</tr>
<tr>
<td>Somatic (GI)</td>
<td>0.4 ± 0.1</td>
<td>0.88 ± 0.1 **</td>
<td>-2.8</td>
</tr>
<tr>
<td>Insomnia (late)</td>
<td>0.2 ± 0.08</td>
<td>0.5 ± 0.5 **</td>
<td>-4.2</td>
</tr>
<tr>
<td>Libido</td>
<td>0.8 ± 0.2</td>
<td>1.63 ± 0.3 *</td>
<td>-2.7</td>
</tr>
<tr>
<td>Guilt</td>
<td>0.24 ± 0.08</td>
<td>0.5 ± 0.5 **</td>
<td>-2.8</td>
</tr>
<tr>
<td>Anxiety psychic</td>
<td>0.64 ± 0.1</td>
<td>1.63 ± 0.3 **</td>
<td>-3.4</td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel tense or wound up</td>
<td>1.08 ± 0.2</td>
<td>2.5 ± 0.5 *</td>
<td>-2.4</td>
</tr>
<tr>
<td>I get a sort of frightened feeling like something awful is about to happen</td>
<td>1 ± 0.2</td>
<td>2.5 ± 0.5 *</td>
<td>-2.2</td>
</tr>
<tr>
<td>Worrying thoughts go through my mind</td>
<td>0.84 ± 0.1</td>
<td>3 ± 0 **</td>
<td>-4</td>
</tr>
<tr>
<td>I get a sort of frightened feeling like butterflies in the stomach</td>
<td>0.76 ± 0.2</td>
<td>2.5 ± 0.5 **</td>
<td>-3.1</td>
</tr>
<tr>
<td>I get sudden feelings of panic</td>
<td>0.76 ± 1.4</td>
<td>2 ± 0 *</td>
<td>-2.4</td>
</tr>
<tr>
<td>I still enjoy the things I used to enjoy</td>
<td>0.8 ± 0.2</td>
<td>2.25 ± 0.3 **</td>
<td>-3.9</td>
</tr>
<tr>
<td>I can still laugh and see the funny side of things</td>
<td>0.44 ± 0.1</td>
<td>1.38 ± 0.3 **</td>
<td>-3.7</td>
</tr>
<tr>
<td>I feel cheerful</td>
<td>0.68 ± 0.1</td>
<td>1.5 ± 0.3 **</td>
<td>-2.9</td>
</tr>
<tr>
<td>I have lost interest in my appearance</td>
<td>0.36 ± 0.1</td>
<td>1.5 ± 0.5 **</td>
<td>-0.7</td>
</tr>
<tr>
<td>I look forward with enjoyment to things</td>
<td>0.56 ± 0.1</td>
<td>2 ± 0.3 **</td>
<td>-4.6</td>
</tr>
<tr>
<td>I can enjoy a good book, or radio, or TV show</td>
<td>0.52 ± 0.2</td>
<td>1.63 ± 0.4 **</td>
<td>-2.6</td>
</tr>
<tr>
<td>DEX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confabulation</td>
<td>1.2 ± 0.7</td>
<td>1.5 ± 0.5 **</td>
<td>-2</td>
</tr>
<tr>
<td>Disturbed impulse control</td>
<td>1.04 ± 0.2</td>
<td>2 ± 0.3 *</td>
<td>-2.2</td>
</tr>
<tr>
<td>Shallowing of affective responses</td>
<td>0.76 ± 0.2</td>
<td>1.87 ± 0.3 **</td>
<td>-2.7</td>
</tr>
<tr>
<td>Lack of concern</td>
<td>0.64 ± 0.1</td>
<td>2 ± 0 **</td>
<td>-10.7</td>
</tr>
<tr>
<td>Inability to inhibit responses</td>
<td>0.56 ± 0.1</td>
<td>2 ± 0 **</td>
<td>-10.1</td>
</tr>
<tr>
<td>Unconcern for social rules</td>
<td>0.76 ± 0.2</td>
<td>2 ± 0 **</td>
<td>-2.1</td>
</tr>
</tbody>
</table>

Table showing those items that depressed patients and patients with hypomania scored significantly more highly on than those participants who did not develop a PAE. Higher scores for each question indicate more dysfunction for that particular domain. The HAM-A, HAM-D, and DEX maximum score of 4 per question (libido for HAM-D, maximum 2). The HADS has a maximum score of 3 per question. Depressed patients tended to score more highly on items related to mood, however, hypomanic patients tended to score more highly on items related to anxiety.
Chapter 7: Mood effects of IFN-α

It was then decided to analyse what individual questions showed a significant increase from Week 0 to Week 8, and occurred in all patients equally regardless of whether a PAE occurred. It was hoped that this analysis would yield a collection of side-effects that can be attributed to the general IFN-α syndrome. This was achieved by determining which items showed significance in Table 6.3 (general mood changes) but not in Table 6.6 (patients who developed a PAE).

Table 7.7: Items specific to the general IFN-α induced syndrome

<table>
<thead>
<tr>
<th>HAM-A</th>
<th>HAM-D</th>
<th>HADS</th>
<th>DEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration/ memory impairment</td>
<td>Somatic (general)</td>
<td>I feel as if I am slowed down</td>
<td>Apathy</td>
</tr>
<tr>
<td>Somatic (sensory)</td>
<td>Somatic weight loss</td>
<td></td>
<td>Aggression</td>
</tr>
<tr>
<td>Somatic (cardiovascular)</td>
<td>Somatic insomnia (early)</td>
<td></td>
<td>Distractibility</td>
</tr>
<tr>
<td>Somatic (respiratory)</td>
<td>Somatic anxiety (somatic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic (GI)</td>
<td>Hypochondriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic (Other)</td>
<td>Psychomotor retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic (general)</td>
<td>Agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Helplessness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel as if I am slowed down</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table showing those side-effects that occurred equally among all patients, as they showed significance for the overall mood breakdown, but not between those patients who did and did not develop a PAE. Those side-effects which can be said to be specific to the general syndrome induced by IFN-α comprise mainly somatic, mood and cognitive effects. These effects are all associated with 'sickness behaviour' but not necessarily depression (see table 1.7; Chapter 1).

Patients who did and did not develop PAEs were then compared in terms of symptom breakdown for the HAM-D and HAM-A at Baseline and Week 8. Symptom domains were compared between groups using a one-way ANOVA, and within-groups using repeated-measures ANOVA.

Groups were initially assessed at Week 0 in order to see if there was any difference between groups for any of the domains, however, for the HAM-A there was no significant difference between any of the groups for anxious cognitions \((F(2,34)=0.05, P=1);\) No PAE: 50.77 ± 5.3; Hypomanic: 56.41 ± 10.3; Depressed: 52.74 ± 12.8), somatic symptoms \((F(2,34)=0.65, P=0.5);\) No PAE: 32.67 ± 4.6; Hypomanic: 27.56 ± 15.4; Depressed: 22.13 ± 7.4) or mood \((F(2,34)=0.09, P=0.9);\) No PAE: 12.55 ± 2.3; Hypomanic: 16.03 ± 0.9; Depressed: 12.63 ± 11.7. There was also no difference in the HAM-D for mood \((F(2,34)=0.07, P=0.9);\) No PAE: 14.29 ± 2.6; Hypomanic: 16.03 ± 0.6; Depressed: 16.14 ± 4.9), behaviour \((F(2,34)=0.48, P=0.6);\) No PAE: 6.48 ± 2.3; Hypomanic: 0 ± 0; Depressed: 4.05 ± 2.2), somatic symptoms \((F(2,34)=0.05, P=1);\) No PAE: 52.14 ± 5.3; Hypomanic: 48.72 ± 17.9; Depressed: 54.78 ± 11.7) or negative
cognitions ($F(2,34)=1.41, P=0.3$; No PAE: $17.44 \pm 3.6$; Hypomanic: $27.56 \pm 10.9$; Depressed: $8.36 \pm 4.3$).

At Week 8 there was an overall effect of group on the HAM-A in the behaviour domain between the non-PAE and Depressed groups ($F(1,32)=4.2, p<0.05$). There was no significant difference between the non-PAE and Hypomanic group at Week 8 (see Figure 7.21).

Figure 7.21: Symptom breakdown for the HAM-A, comparison between the non-PAE group, Depressed group and Hypomanic group (Week 8)

For the non-PAE group there was an overall effect of domain ($F(1.48, 36.87)=30.97, p<0.01$), which was significant for all comparisons between somatic symptoms ($M=53.65, SD=4.2$), behaviour ($M=9.12, SD=1.9$) and anxious cognitions, ($M=33.39, SD=4$) (see Figure 7.22). There was also a significant effect of domain on the depressed group ($F(2,12)=27.9, p<0.01$), which Bonferroni comparisons showed to be significant between behaviour ($M=15.18, SD=2.7$) and both anxious cognitions, ($M=35.12, SD=2.1$) and somatic symptoms, ($M=49.71, SD=3.2$) (see Figure 7.22). Due to the low $n$ in the Hypomanic group, reliable results could not be computed, although mean results are shown in Figure 7.22.
Figure 7.22: Symptom breakdown for the HAM-A, comparison within the non-PAE group, Depressed group and Hypomanic group (Week 8)

Figure showing the proportion of symptoms at Week 8 that are made up by a particular domain for each group. For the PAE group the majority the symptoms are split equally between each domain. For the depressed group, the significant majority of symptoms are somatic and negative cognitions. The results for the hypomanic group could not be computed due to a low n, and insufficient degrees of freedom for the repeated ANOVA analysis required, (*p<0.05).
The HAM-D showed an overall effect of group between the non-PAE and Depressed group for the mood domain \( (F(1, 32)=5.4, p<0.05) \), and the non-PAE and Hypomanic group for the negative cognition domain \( (F(1, 32)=5.13, p<0.05) \), (see Figure 7.23).

**Figure 7.23: Symptom breakdown for the HAM-D, comparison between the non-PAE group, Depressed group and Hypomanic group (Week 8)**

Figure showing the symptom breakdown for the HAM-D at Week 8 for the non-PAE group; mood \((17.4 \pm 1.8)\); behaviour \((8.99 \pm 1.3)\); somatic symptoms \((61.7 \pm 3.2)\); negative cognitions \((11.87 \pm 2.1)\). The Depressed group: mood \((25.07 \pm 1.5)\); behaviour \((8.85 \pm 1.1)\); somatic symptoms \((54.59 \pm 3.1)\); negative cognitions \((11.48 \pm 3.2)\), and the Hypomanic group: mood \((17.86 \pm 7.1)\); behaviour \((5.35 \pm 5.4)\); somatic symptoms \((47.5 \pm 2.5)\); negative cognitions \((29.29 \pm 0.7)\). Depressed patients showed a significantly higher depressed mood than the non-PAE group, \( *p<0.05 \). Hypomanic patients also experienced significantly more negative cognitions than the non-PAE group, \( *p<0.05 \).

When a within-groups ANOVA was carried out for the non-PAE group there was an overall effect of domain on the symptom breakdown \( (F(1.84, 44.22)=94.3 p<0.01) \), which post-hoc comparisons showed to be significant between the somatic domain \((M=61.74, SD=3.2)\), with the domains of mood \((M=17.4, SD=1.8)\), behaviour \((M=8.99, SD=1.3)\) and negative cognitions \((M=11.87, SD=2.1)\), with there also being a difference between depressed mood and behaviour (see Figure 7.24).

For the Depressed group there was also an overall effect of domain on the symptom breakdown \( (F(3, 21)=56.4, p<0.01) \), which was significant when the somatic \((M=54.6, SD=3.1)\) and mood domains \((M=25.1, SD=1.5)\) were compared to one another and also the behaviour \((M=8.85, SD=1.1)\) and negative cognition domains, \((M=11.49, SD=3.2)\) (see Figure 7.24).
Figure 7.24: Symptom breakdown for the HAM-D, comparison within the non-PAE group, Depressed group and Hypomaniac group (Week 8)

Figure showing the proportion of symptoms for the HAM-D at Week 8 that are made up by a particular domain for each group. For the PAE group the majority the symptoms are somatic, with mood only being significant when compared to behaviour. For the Depressed group, the significant majority of symptoms are somatic and mood based, explaining 80% of the symptoms of the depressed patients HAM-D when added together. The results for the Hypomaniac group could not be computed due to a low n, and insufficient degrees of freedom for the repeated ANOVA analysis required.
7.4.4 Further analysis with IFN-α Depressed group

As the focus of this thesis is on depression, it was decided to do further analysis on the Depressed group only, concentrating on results from the HAM-D. This was done for both the 8 Week and 20 Week study in order to see if there was any effect of week on depression ratings. The HAM-D scores were assessed from Week 0 to 8 using repeated-measures ANOVA for the non-PAE group, and then the Depressed group. For the non-PAE group there was not an overall effect of week on mean proportions of domains \( F(3,72)=2.05, P=0.1 \), (see Figure 7.25).

Figure 7.25: Symptoms breakdown for the HAM-D, between-week comparison Weeks 0 to 8; non-PAE group.

Figure showing the relative proportion of symptoms explained by a particular domain from Week 0 to Week 8 for the non-PAE group. There was no significant difference between mood (week 0: 14.3 ± 2.6 ; week 8: 17.4 ± 1.8); behaviour (week 0: 6.5 ± 2.3 ; week 8: 8.9 ± 1.3); somatic symptoms (week 0: 52.1 ± 5.3 ; week 8: 61.7 ± 3.2); and negative cognitions (week 0: 17.4 ± 3.6 ; week 8: 11.9 ± 2.1).

When the effect of week on symptom breakdown was done for the Depressed group, there was also no effect of week on symptoms present \( F(3,21)=0.41, P=0.7 \), (see Figure 7.26), despite a significant raise in the overall HAM-D score \( t(7)=-4.2, p<0.01 \) from a mean score of 7.62 ± 2.5 at Week 0 to 20.38 ± 1.5 at Week 8.
Figure 7.26: Symptoms breakdown for the HAM-D, between-week comparison Weeks 0 to 8; Depressed group.

Figure showing the relative proportion of symptoms explained by a particular domain from Week 0 to Week 8 for patients taking IFN-α who developed depression. There was no significant difference between mood (Week 0: 25.8 ± 4.9; Week 8: 25.83 ± 1.5); behaviour (Week 0: 10.79 ± 2.2; Week 8: 8.85 ± 1.1); somatic symptoms (Week 0: 54.78 ± 11.7; Week 8: 54.59 ± 3.1); and negative cognitions (Week 0: 16.72 ± 4.3; Week 8: 11.49 ± 3.2).

As the breakdown of mood scores shows that the proportion of mood domains for the HAM-A and HAM-D remains stable, whereas significance levels for the total mood score increases significantly on treatment it was then decided to analyse HAM-D results from the 20 week study, however, when analysed with the repeated-measures ANOVA there was no effect ($F(1.6, 10)=1.402, P=0.2$), (see Figure 7.27). Despite this, the figure showed a relative change from Week 0 to 8, with no effect from 8 to 20, it was decided to analyse these patients from Week 0 to 8 only, with this repeated-measures comparison not yielding significance either ($F(1.4, 8.5)=3.68, P=0.08$), possibly due to the large amount of variation at baseline.
Figure 7.27: Symptoms breakdown for the HAM-D, between week comparison Weeks 0 to 20; Depressed group.

Figure showing the difference in the mean proportion of symptoms in the HAM-D explained by a particular domain for depressed patients. From Week 0 to Week 20, and also Week 0 to 8, there is no significant effect of week on overall proportions between mood (Week 0: 13.56 ± 4.8; Week 8: 22.81 ± 1.6; Week 20: 18.6 ± 3.3), behaviour (Week 0: 4.17 ± 2; Week 8: 9.5 ± 1.7; Week 20: 9.72 ± 2.3), somatic symptoms (Week 0: 68.73 ± 8.9; Week 8: 53.2 ± 2.7; Week 20: 55 ± 5.7) and negative cognitions (Week 0: 18.6 ± 3.9; Week 8: 14.4 ± 4; Week 20: 16.67 ± 4.4). The main reason for effects observed is the large variability at baseline, somatic symptoms explain 68.7 ± 8.9 of their symptoms, which decreases to 53.2 ± 2.7 at Week 8. The proportion of symptoms explained at Week 8 and Week 20 by somatic symptoms (and all other symptoms) is more consistent with that found in Figure 7.21, as are all the other domains of mood behaviour and negative cognitions.
7.4.5 Mood breakdown for primary Depressed group

The HAM-A and HAM-D were assessed in the Depressed patient group in order to determine what domains characterised the total score for each group. For the HAM-A, there was a significant effect of domain on the overall HAM-A score ($F(1, 21)=6.83$, $p<0.05$). This was due to the significantly more symptoms being explained by anxious cognitions ($M=42.94$, $SD=2.8$) than behaviour ($M=42.94$, $SD=2.8$); however, there was no significant difference between somatic symptoms ($M=42.94$, $SD=2.8$) and any other domain (see Figure 7.28).

**Figure 7.28: Symptom breakdown for the HAM-A, primary Depressed group**

![Pie chart showing symptom breakdown for the HAM-A in the primary depressed group](image)

Figure showing the proportions of the HAM-A that was explained by each domain in the primary depression group. The only significant difference was between anxious cognitions and behaviour, with the majority of symptoms being explained by anxious cognitions, and partly by somatic symptoms.
When the HAM-D was broken down, there was an overall effect of domain on mood score ($F(3, 21)=15.38, p<0.01$). This difference was explained by the significant majority of symptoms being somatic ($M=31.82, SD=2.5$) and negative cognition symptoms ($M=32.54, SD=3.2$) when compared to mood symptoms ($M=19.18, SD=1.6$) and behaviour symptoms ($M=10.63, SD=7.1$), (see Figure 7.29).

**Figure 7.29: Symptom breakdown for the HAM-D, primary depressed group**

Figure showing the proportion of symptoms explained by each symptom domain for the HAM-D. The significant majority of symptoms are explained by the somatic and negative cognition domains, which account for nearly 70% of the symptoms experienced.
7.4.6 Comparison of patients with a primary and secondary IFN-a-induced depression

It was decided to look at all patients who developed a depression on treatment, as there was no effect of treatment from Week 8 to 20 on the domains investigated (see Figure 7.27). Where patients were depressed at both time-points, the data where the HAM-D was higher was used. One patient who developed a depression (Patient 411) was excluded from the analysis as he had previously suffered from a hypomanic episode. Patients who developed a depression on treatment were compared to age-sex- and-HAM-D-matched depressed participants (IFN-a group: 78% male, mean age 40.89 ± 2.9, mean HAM-D 20.89 ± 1.3, n=9; Depressed group 78% male, mean age 37.78 ± 5.6, mean HAM-D 23.33 ± 2.8, n=9). When assessed using an independent samples t-test there was no significant effect between the ages (t(12.04)=0.5, P=0.6) or the HAM-D scores (t(11.1)=-0.79, P=0.4) of the two groups. The first comparison between the two groups was to assess whether there was any significant difference in any of the other tests used in the mood battery using an independent-samples t-test, even when HAM-D scores were matched (see Table 7.8), and there was no significant difference for any of the tests used.

### Table 7.8: Differences between questionnaires for the primary and secondary IFN-a-induced Depressed groups

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>IFN-a-induced depression</th>
<th>Primary depression</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td>20.89 ± 1.3</td>
<td>23.33 ± 2.8</td>
<td>-0.79</td>
<td>P=0.4</td>
</tr>
<tr>
<td>HAM-A</td>
<td>15.67 ± 2.2</td>
<td>13.11 ± 1.9</td>
<td>0.89</td>
<td>P=0.4</td>
</tr>
<tr>
<td>HADS-A</td>
<td>8.89 ± 1</td>
<td>11.56 ± 1.1</td>
<td>-1.79</td>
<td>P=0.09</td>
</tr>
<tr>
<td>HADS-D</td>
<td>10.33 ± 1.3</td>
<td>11.22 ± 1.3</td>
<td>-0.49</td>
<td>P=0.6</td>
</tr>
<tr>
<td>DEX</td>
<td>31.22 ± 3.1</td>
<td>27.33 ± 3.7</td>
<td>0.81</td>
<td>P=0.4</td>
</tr>
</tbody>
</table>

Table showing the difference between the mean scores for the group that became depressed on IFN-a and the matched depressed group. The groups were matched for scores across all questionnaires used in the data analysis, even though the depressed group tended to score slightly higher on all questionnaires except for the HAM-A.

Once established that the two groups were matched across all domains the first comparison undertaken was to compare the scores for each question asked as part of the mood battery, including scores for the SCID, using an independent-samples t-test. There was at least one significant question within each questionnaire (see Table 7.9).
### Table 7.9: Differences in individual questions between the primary and secondary IFN-α-induced Depressed groups

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>IFN-α induced depression (n=9)</th>
<th>Primary depression (n=9)</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get a sort of frightened feeling like something bad is about to happen</td>
<td>0.78 ± 0.2</td>
<td>2 ± 0.3 *</td>
<td>-2.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious mood</td>
<td>0.11 ± 0.1</td>
<td>1.67 ± 0.5 *</td>
<td>-3.21</td>
</tr>
<tr>
<td>Fears</td>
<td>2.11 ± 0.4 **</td>
<td>0.31 ± 0.2</td>
<td>4.24</td>
</tr>
<tr>
<td>Concentration/ memory</td>
<td>1.78 ± 0.2 *</td>
<td>1 ± 0.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>1.33 ± 0.3 *</td>
<td>0.56 ± 0.3</td>
<td>2.82</td>
</tr>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic (general)</td>
<td>1.3 ± 0.2 *</td>
<td>0.78 ± 0.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Anxiety (somatic)</td>
<td>1.78 ± 0.2 *</td>
<td>1 ± 0.4</td>
<td>2.14</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>0.44 ± 0.2</td>
<td>1.22 ± 0.3 *</td>
<td>-2.37</td>
</tr>
<tr>
<td>Worthlessness</td>
<td>0.22 ± 1.5</td>
<td>1.78 ± 0.6 *</td>
<td>-2.54</td>
</tr>
<tr>
<td>DEX</td>
<td>1.8 ± 0.4 *</td>
<td>0.11 ± 0.1</td>
<td>-2.39</td>
</tr>
<tr>
<td>SCID</td>
<td>1.13 ± 0.3</td>
<td>2.38 ± 0.3 **</td>
<td>-3.75</td>
</tr>
</tbody>
</table>

The above table shows where significant differences lie between the group that are depressed after taking IFN-α and the group that has a primary Depression. Despite the two groups been matched equally across all questionnaires there were some significant differences between individual questions asked. The stars indicate the level of significance, and also where the significant increase occurs (* p<0.05, ** p<0.01). The HAM-A, HAM-D, and DEX maximum score of 4 per question (libido for HAM-D, maximum 2). The SCID is marked according to the following criteria (1=absent, 2=subthreshold, 3=definite). The IFN-α group scored significantly more highly on measures related to the somatic side-effects of depression (sensory symptoms, somatic (general) and anxiety somatic), , having significantly more fears, perceived memory problems and being more prone to confabulation. The Depressed group tended to score significantly higher on measures of negative cognition (suicidal ideation and worthlessness), as well as measures of mood (anxious mood) and some neurovegetative symptoms (psychomotor retardation).

In order to assess the observation that IFN-α depressed patients may load more onto somatic items than depressed patients, and depressed patients may load more onto negative cognition items than IFN-α patients (see Table 7.8) a one-way ANOVA was undertaken in order to compare the symptom domains of anxious cognitions, somatic symptoms and behaviour for the HAM-A, and also the domains of mood, behaviour, somatic symptoms and negative cognitions for the HAM-D.
Groups were firstly compared using a one-way ANOVA in order to see if there was an overall effect of group, and then using repeated-measures ANOVA in order to assess the within-group breakdown of symptoms.

For the HAM-A there was no effect of group on anxious cognitions ($F(1,17)=1.13, P=0.3$), somatic symptoms ($F(1,17)=2.37, P=0.1$), or behaviour ($F(1,17)=1.04, P=0.3$), (see Figure 7.30).

**Figure 7.30: Symptom breakdown for the HAM-A, comparison between the primary and secondary IFN-α-induced Depressed groups**

Graph showing the difference in mood scores between the group that became depressed on IFN-α treatment and the group with a primary depression. There was no difference between either of the groups for anxious cognitions (IFN: $32.12 \pm 3.5$; Depressed: $42.03 \pm 5.1$), somatic symptoms, (IFN: $51.83 \pm 3.5$; Depressed: $37.96 \pm 6.7$), or behaviour, (IFN: $16.06 \pm 2.5$; Depressed: $32.12 \pm 3.5$).
When the two groups were then assessed for individual differences within their groups for each symptom domain, there was an overall significant difference for the group that became depressed on IFN-α ($F(2,16)=22.12$, $p<0.01$), but there was no overall effect for the primary depressed group ($F(2,16)=2.29$, $P=0.1$), (see Figure 7.31).

**Figure 7.31: Symptom breakdown for the HAM-A, comparison within the primary and secondary IFN-α-induced Depressed groups**

There was a significant effect of domain on the HAM-A for the group that became depressed on IFN-α which was explained mainly by the majority of symptoms being somatic or negative cognitions. Bonferroni comparisons showed there to be significance between behaviour ($M=17.25$, $SD=2.8$) and both anxious cognitions ($M=1.08$, $SD=3.4$) and somatic symptoms ($M=51.67$, $SD=3.4$). However for the primary Depressed group symptoms were spread equally among the domains of behaviour ($M=38.25$, $SD=5.8$), somatic symptoms ($M=40.68$, $SD=6.5$), and anxious cognitions ($M=21.96$, $SD=3.7$), *$p<0.05$, **$p<0.01$.

The HAM-D was then broken down in a similar way in order to see if any differences lay between the two groups. When the two groups were compared using a one-way ANOVA there was an overall significant effect between the two groups for
negative cognitions \( (F(1, 17)=18.41, p<0.01) \), somatic symptoms \( (F(1, 17)=29.35, p<0.01) \), and mood \( (F(1, 17)=12.96, p<0.01) \). Significantly more of the IFN-\( \alpha \) Depressed groups HAM-D scores were made up of somatic symptoms \( \text{IFN: } 54.25 \pm 2.8 \); \text{Depressed: } 29.86 \pm 3.2 \) and mood symptoms \( \text{IFN: } 24.87 \pm 1.23 \); \text{Depressed: } 15.45 \pm 2.14 \) when compared to the primary Depression group. However, significantly more of the primary Depressed groups score was made up of the negative cognition domain \( \text{Depressed: } 34.7 \pm 2.7 \); \text{IFN: } 13.25 \pm 3.8 \) (see Figure 7.32). There was no difference for the behaviour domain \( (F(1, 17)=01.96, P=0.2; \text{IFN: } 7.63 \pm 1.23 \); \text{Depressed: } 12.6 \pm 3.11 \). This is despite the two groups being matched for overall HAM-D scores, \((t(9.96)=-0.96, P=0.4)\).

**Figure 7.32: Symptom breakdown for the HAM-D, comparison between the primary and secondary IFN-\( \alpha \)-induced Depressed groups**

![Symptom breakdown for the HAM-D, comparison between the primary and secondary IFN-\( \alpha \)-induced Depressed groups](image)

Figure showing the difference in domains that explain total the HAM-D score for the group that became depressed on IFN-\( \alpha \), and those that had a primary depression. Significantly more of the depressed IFN-\( \alpha \) groups overall score comprised of somatic and mood symptoms than the primary depressed group, however, significantly more of the Depressed groups score is made up of negative cognitions when compared to the IFN-\( \alpha \) Depressed group. There was no difference between groups in the behaviour domain.

When the groups were investigated individually there was a significant effect of domain on the breakdown of mood scores for the HAM-D for the group that became depressed on IFN-\( \alpha \) \( (F(3, 24)=63.25, p<0.01) \); this was due to the significant majority of symptoms being explained by somatic symptoms, \( M=54.25, SD=3 \), and mood, \( M=24.87, SD=1.3 \), when compared to behaviour, \( M=7.64, SD=1.3 \) and negative cognitions, \( M=13.25, SD=2.9 \) (see Figure 7.33). There was also a significant overall
effect of domain for the Depressed group \(F(3, 24)=8.12, p<0.01\). This was explained by the majority of symptoms being made up of somatic symptoms \((M=29.86, SD=3.4)\), and negative cognition symptoms \((M=34.7, SD=4.1)\), when compared to mood \((M=15.46, SD=2.3)\) and behaviour \((M=12.86, SD=3.4)\) (see Figure 7.33).

**Figure 7.33**: Symptom breakdown for the HAM-D, comparison within-groups for the primary and secondary IFN-α-induced Depressed groups

Figure showing the proportion of the HAM-D explained by the domains of mood, behaviour, somatic symptoms and negative cognitions. For the IFN-α group, significantly more of their symptoms were explained by somatic and mood symptoms, however, for the primary depressed group significantly more of the symptoms were explained by the somatic and negative cognition domains.
7.5 Discussion

7.5.1 Overview of results

- IFN-α causes a significant increase in PAEs, notably Depression and Hypomania.
- Despite a significant increase in HAM-D scores from Weeks 0 to 8 for all patients, there is no significant difference in the proportion of these scores explained by mood, behaviour, somatic symptoms and negative cognitions.
- When the HAM-A score is broken down from Week 0 to Week, there is a significant increase in somatic symptoms at Week 8 and a significant decrease in anxious cognitions.
- At Week 8 the majority of both the HAM-A and HAM-D scores is explained by somatic symptoms.
- The general mood change in patients taking IFN-α comprises symptoms of sickness-behaviour (see Table 7.7).
- The general mood change induced in patients taking IFN-α is distinct between those patients who do and do not develop a PAE.
- There is no difference at baseline for those patients who do and do not develop PAEs.
- Those patients who develop a hypomanic mood show more negative cognitions than patients who do not develop a PAE.
- Those patients who develop a depression have significantly more of their total HAM-D score explained by depressed mood than those patients who do not develop a PAE.
- There is no significant difference for the IFN-α Depressed group or the non-PAE group for the proportion of HAM-D scores which comprise each domain from Week 0 to Week 8.
- For those patients with a primary depression the significant majority of the HAM-D score is explained by somatic symptoms and negative cognitions.
- Patients who developed an IFN-α-induced depression have significantly more of their HAM-D score made up of depressed mood and somatic symptoms than patients with a primary depression.
• Those patients who have a primary depression have significantly more of their HAM-D score made up of negative cognitions than those patients who developed a depression on IFN-α.

### 7.5.2 Support from previous studies


However, very little research has sought to elucidate the type of depression that occurs following administration of IFN-α, in terms of the types of symptoms that patients experience and how this relates back to a primary depression. Results from this chapter seem to support the idea that the depression induced by IFN-α is distinct from a primary depression, and also distinct from the general ‘sickness behaviour’ syndrome which IFN-α causes in the majority of patients regardless of PAE’s.

### 7.5.3 General mood change induced by IFN-α

IFN-α was found to cause a general increase in anxiety and depression scale scores for the HAM-A, HAM-D and HADS-D from Week 0 to 8 (see Figures 7.4 to 7.7), however, not for Weeks 8 to 20 (see Figures 7.13 to 7.16). There was no significant increase in the HADS-A for Week 0 to 8 (see Figure 7.6), or Weeks 0 to 20 (see Figure 7.15). The reason for the increase in the HAM-A, but not the HADS-A became apparent when the data for the breakdown of symptoms was analysed. It was shown that on treatment, the proportion of symptoms explained by the somatic domain increased to over 50% (see Figures 7.8; 7.9; 7.17; 7.18), with anxious cognitions
decreasing (see Figures 7.9 and 7.18). As the HAM-A is comprised mainly of somatic items (8 items, 57%) which any kind of illness would load highly onto, and the HADS-A is designed to avoid items which illness would load highly onto (Zigmond and Snaith, 1983), it can be assumed that the significant increase in the HAM-A score is due mainly to a significant increase in somatic symptoms, rather than anxious cognitions or anxious behaviour. When the HAM-D was then analysed in order to see where the significant differences lay, it was found that from Week 0 to 8 and Week 0 to 20 there was no difference in any of the domains investigated (see Figures 7.10; 7.11; 7.19; 7.20). The fact that there was a significant increase in symptoms that was not necessarily backed up by a significant increase in any domain, suggests that IFN-α causes a general increase in symptoms already present, that it enhances the state the patient presented with at Baseline.

When each individual question was assessed for significance from Week 0 to Week 8, it was found that those items that were significant tended to be primarily related to mood and somatic symptoms (see Table 7.3); which are those items that tend to occur in sickness behaviour (see Table 1.8). Thus the behaviour change seen in IFN-α is characterised primarily by a depressed mood, anhedonia and social withdrawal. There was also a significant increase in many somatic items, with many of these items also been linked in to sickness behaviour (fatigue, psychomotor slowing and insomnia). Results from this table show that IFN-α does induce a general ‘sickness behaviour’ syndrome, characterised by depressed mood and somatic symptoms, and that many of the items of sickness behaviour also overlap with the symptoms of depression. However, those items where significance is found in Table 7.3 (general mood changes) but not Table 7.6 (patients who developed PAE) are more specific to the ‘general sickness behaviour syndrome’ which accompanies IFN-α, as these side-effects occur in all patients equally (see Table 7.7 for these symptoms). These particular symptoms comprise mainly somatic effects, which supports the data found in this chapter which indicates that in patients administered the HAM-D and HAM-A, around 50% of their symptoms will be explained by somatic side-effects (see Figures 7.8 to 7.11 and 7.17 to 7.20).

In order to better understand what the main differences were in those patients who developed a PAE, versus those who did not, more analysis was done comparing these two groups.
7.5.4 Differences between general mood change and PAE's for patients taking IFN-α

Treatment with IFN-α caused a significant increase in PAE's that was not specific to the time-point, be it 8 or 20 weeks (see Figures 7.3 and 7.12). The most common PAE was subsyndromal depression, which did not significantly differ from MDE in terms of depression scores (see Tables 7.4 and 7.5). The second most common PAE was major depression, which occurred in a total of 3 patients, followed by hypomanic mood which occurred in 2. When those groups who did and did not develop a PAE were compared it was found that patients who developed a depression were more likely to score highly on mood items, whereas patients who were experiencing a hypomanic episode were more likely to score highly on items related to anxiety, which again fits with the observations of Constant et al., (2005) (see Table 7.6).

When overall demographic information was compared for those patients who did and did not develop a PAE, there were no significant differences found. There were also no significant differences at Baseline between any groups; however, those patients who went on to develop a depression did have slightly elevated HAM-D, HAM-A and HADS-D scores, which is something that has been observed in previous studies (see Table 1.5). Those patients who did develop a depression were no more likely than those patients who did not develop a depression to have a psychiatric history, suggesting that it is factors that are present at baseline that are important for the development of a depression rather than a general history of mood disorders.

The symptom breakdown for the HAM-A and HAM-D, showed that the only difference for the HAM-A was that depressed patients showed significantly more anxiety behaviour symptoms (see Figure 7.21), and that the Depressed groups HAM-A showed a similar number of somatic and anxious cognition items, whereas the non-PAE group showed significance between all items (see Figure 7.22). The HAM-D yielded more interesting results, showing that those patients who experienced a hypomanic episode showed increased negative cognitions relative to the non-PAE group, and that those patients who developed a depression showed a significantly increased depressed mood, (see Figure 7.23 and 7.24). For those patients who developed a hypomanic episode their within-groups scores could not be computed due to a low n, however, when the non-PAE and Depressed group were looked at, it was found that within-groups the significant majority of the non-PAE group was made up of somatic
symptoms, however, the majority of the Depressed groups symptoms were made up of somatic symptoms and depressed mood (see Figure 7.24).

The Depressed group were then investigated in more detail in order to see whether there was any increase in any of the domains from Baseline to Week 8 and 20 of treatment. Data from the 8 week study showed that there was no difference in any of the domains, consistent with what was found in the non-PAE group (see Figures 7.25 and 7.26). However, when the same data was analysed for the 20 week study it was found that there was a slight decrease in somatic symptoms and relative increase in mood symptoms (see Figure 7.27). This was explained mainly by the large amount of somatic symptoms at Baseline, which was not consistent with the 8 week study. When the results at Week 8 were compared within both groups, it was seen that the results were more similarly distributed (see Figures 7.25 and 7.27). This again suggests, in line with the previous findings, that IFN-α causes an increase in symptoms already present at baseline, rather than causing new symptoms to develop, this potentially explains findings from previous studies where psychiatric risk factors been implicated in the development of IFN-α induced depression (see Table 1.5). It is possible that many patients who become depressed on treatment, have the pre-disposition to become depressed at baseline, and that IFN-α somehow exploits this pre-disposition, possibly through some cytokine mediated pathway; this idea shall be explored in Chapter 7.

All data points to the possibility that IFN-α-induced depression is primarily a disorder of mood and somatic symptoms; however, in order to gain a finer appreciation of this depression it was decided to compare the IFN-α-induced depression with patients who were hospitalised with a primary depression.

7.5.5 Differences between IFN-α-induced Depression and a primary Depression

When the HAM-A and HAM-D scores were broken down for all depressed patients tested it was found that the HAM-A score was comprised mainly of anxious cognitions (see Figure 7.28), which was different to all IFN-α patients as their scores seemed mostly comprised of somatic symptoms (see Figures 7.8 and 7.17) and their HAM-D score comprised mostly of the depressed mood and negative cognition domains (see Figure 7.29), which again differed from the IFN-α group as their score tended to comprise mostly of mood and somatic symptoms (see Figure 7.24)
In order to better understand the difference between these groups the patients depressed on IFN-α were compared to age-sex-and HAM-D matched patients with a primary depression, who were also matched across all other domains. When individual questions were compared between the two groups, it was found that the patients depressed on IFN-α tended to score more highly on somatic items, as well as items linked to perceived memory problems and confabulation. However, the patients who had a primary depression, scored more highly on measures of negative cognitions (most notably depression and worthlessness), and also psychomotor retardation (see Table 7.9). However, for the most part, there seemed to be very little difference between the two groups. When the HAM-A was broken down into mood domains there was no overall difference between the two groups (see Figure 7.30), however, the patients taking IFN-α had significantly less of their symptoms explained by the behaviour domain when their own score was assessed, and the primary depression group had their proportion of HAM-A score split evenly between all domains (see Figure 7.31).

The most interesting results from this comparison came from the HAM-D breakdown, with patients taking IFN-α, with patients on IFN-α scoring significantly higher on the somatic symptoms and depressed mood domains, and the primary depression group scoring significantly higher on the negative cognition domain (see Figure 7.32). When the results for each group was broken down individually it was found that the IFN-α score comprised mostly of depressed mood and somatic symptoms, whereas the primary depression score comprised mostly of negative cognitions and somatic symptoms (see Figure 7.33). The finding that primary depression comprises of significantly more negative cognitions than IFN-α induced depression backs up findings from Pasquini et al, (2008) with additional support coming from the work of Clark et al, (1998) who found that medically-ill patients who presented with a co-morbid depression tended to show more anhedonia and negative affect. However, results from the Capuron et al, (2009) study found that the two types of depression were similar when using a factor analysis. The main issue with the Capuron study was that they used a 17-item HAM-D, which did not have the additional negative cognition items contained within the HAM-D used for this study. When conducting the analysis for this study, it became apparent that factor analysis was not the ideal way to analyse data for a questionnaire such as the HAM-D, as there are such a limited number of potential responses (0-4), and as such unless there was a large
difference between the two groups, which data from the comparison of individual questions showed there was not (see Table 7.9), that type of analysis would be very unlikely to pick up any differences, as such, the type of analysis conducted here, where overall proportions of symptoms were analysed would yield a more reliable result. The fact that the change in mood which occurred in patients taking IFN-α was primarily a consequence of the mood fits in with the theory of Charlton (2000), who believed that the change in mood seen in depression was the result of the underlying physical state of the individual, as prior to taking IFN-α the patients were relatively healthy and had no mood problems, however, when taking the treatment their underlying physical state changed, which in turn could have impacted on their mood.

This meant that the main difference in the depression exhibited by the two groups was in terms of depressed mood and negative cognitions, with the depression seen in IFN-α defined primarily in terms of an increase in depressed mood. However, this depressed mood does not seem to co-occur with an increase in negative cognitions meaning that it differs significantly from a primary depression, which would affect negative cognitions to a greater extent than depressed mood (see Figure 7.33). In order to better explain how the two groups compare see Figure 7.34.

Figure 7.34: Contribution of domains to primary and secondary IFN-α induced Depression

Figure showing the contribution of the three main domains that comprise the HAM-D score for both the primary Depression and IFN-α induced Depression. For both groups a significant proportion of symptoms (Dep: \( F(3, 24)=8.12, p<0.01 \); IFN: \( F(3, 24)=63.25, p<0.01 \)) are made up of Somatic symptoms (Dep: 29.86 ± 3.4; IFN: 54.25 ± 3), and the smallest amount of behaviour symptoms (so it is not included in the diagram). However, for the IFN-α Depressed group, a significant proportion of their score is made up of mood symptoms (24.87 ± 1.3), and for the primary Depressed group a significant proportion of their score is made up of negative cognitions (34.7 ± 4.1).
7.5.6 Limitations of results

The results are first and foremost limited by the low number of patients that took part in the study, as where PAE’s did occur there were very few patients to compare. In particular those results from patients with a Hypomanic episode should be interpreted with caution as there were only two patients that developed this side-effect. The study was also limited by the high number of drop-outs from Weeks 8 to 20, this was partly due to treatment side-effects, and partly due to the poor compliance rate of patients.

The study was also limited by the fact that only specified time-points were used to speak to patients, a more flexible approach where patients were spoken to on a weekly basis could have yielded more data, as some patients developed a depression between Weeks 8 to 20 that could not be investigated due to the limits enforced by study design.

Another issue is that results are constrained by the questionnaires used. Should a more extensive test-battery have been used, this could have picked up on additional items. In future a questionnaire for physical health such as the SF-36 should be used in conjunction with mood questionnaires, and this could yield more information about the somatic effects that seemed to comprise the majority of symptoms for the IFN-α group.

7.5.7 Implications of results

Results indicate that IFN-α causes a significant increase in PAE’s and a general behavioural syndrome which consists primarily of somatic items (fatigue, weight loss), cognitive items (concentration/memory impairment) and mood items (aggression and apathy). Where a hypomanic episode occurs this tends to load highly onto anxiety items, and is distinct from the depression that can occur on treatment. Results also show that subsyndromal depression is the main PAE induced by treatment, and that this is a disorder that should not be overlooked as it is largely similar to IFN-α induced MDD. Where the IFN-α induced depression occurs, this is mainly due to a general reduction in mood (depressed mood, anhedonia) that is distinct from a primary depression, with this type of depression loading more onto negative cognitions. Results also show that hypomania is a rare, but severe PAE that is less manageable and has consequences for morbidity that are just as high as for a MDD.

The fact that those patients who develop a PAE tend to develop a specific set of side-effects discernible from the general sickness-behaviour means that these items are
those that healthcare-professionals monitoring individuals taking IFN-α should be on the lookout for, as they indicate a greater mood dysfunction, and thus a greater likelihood of a PAE being diagnosed.
CHAPTER 8

Discussion
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8.1: Synopsis of results

The aim of this thesis was to characterise the neurobehavioural syndrome induced by IFN-α in patients with HCV using qualitative and quantitative methodology. The main findings are outlined below:

- IFN-α causes significant impairment in social, occupational, psychological and physical functioning.
- The main reported physical side-effect of HCV is fatigue, and the main psychological side-effect is labile mood.
- The main reported physical side-effect of IFN-α is fatigue, and the main psychological side-effect is irritability.
- IFN-α causes a general behavioural syndrome which is consistent with sickness behaviour in all patients.
- IFN-α causes an increase in symptoms present at Baseline, most notably mood and somatic symptoms.
- IFN-α can cause PAEs in some patients, with the most common being depression.
- The IFN-α-induced depression is primarily a disorder of mood and somatic symptoms.
- Primary depression is primarily a disorder of negative cognitions and somatic symptoms.
- Commencing and finishing IFN-α treatment are both stressful times for patients due to the uncertainty of side-effects and treatment outcome.
- Patients with HCV and depression show neuropsychological impairment when compared to age-and-sex matched controls.
- IFN-α patients report having more memory and executive problems when interviewed, however, when assessed with a short neuropsychological test-battery there is no observable difference from Baseline to Week 8 or with Controls.
8.2: General Discussion

8.2.1 Overview of results

Results from this thesis back-up previous findings which show that IFN-α is a drug which is a potent inducer of sickness-behaviour (Dantzer and Kelley, 2007; Myint et al, 2009; Patten, 2006), mood change (Capuron and Dantzer, 2004: see Table 1.4), fatigue (Cotler et al, 2000; Khalili et al, 2000) and in some cases severe PAE’s such as MDD (Constant et al, 2005; Loftis et al, 2004; McHutchinson et al, 1998; Schaefer et al, 2003; Manns et al, 2001: see Table 1.4 and Figure 6.1).

In severe cases, adverse events associated with IFN-α treatment led to treatment discontinuation, with 9% (n=3) of patients discontinuing treatment due to psychological adverse events after Week 8. Physical side-effects led to treatment discontinuation for 8% of patients (n=3), with one patient discontinuing at Week 4 and an additional two patients after Week 8 (n=2). The most severe treatment-induced side-effects that led to discontinuation were hypomania and severe haematological side-effects, with both patients requiring hospitalisation (see Figure 7.2).

This thesis also explored IFN-α-mediated psychological changes by interviewing patients about their personal experience of IFN-α, breaking down mood scores in order to ascertain which aspects of a depression and anxiety scale are increased or decreased and conducting neuropsychological tests which focus on the PFC, with the latter two dimensions also being conducted in patients with a primary depression. Results indicated that IFN-α causes a variety of occupational, social and emotional disturbances, as verbalised by patients themselves when interviewed prospectively and retrospectively in Chapter 5. There is also a change in mood which accompanies IFN-α treatment that can be seen clearly after only 8 weeks of treatment. In some cases the mood change is so severe that a psychiatric disorder can be diagnosed. The PAE of major depression occurred in 8% (n=3) of patients, with 17% (n=6) exhibiting a subsyndromal depression and 6% (n=2) developing hypomanic mood, the majority of these side-effects occurred at Week 8. At Week 20, three patients had been discontinued from treatment due to psychological side-effects (depression, drug relapse and hypomania), with 15% of the patients left in the study (n=3) being diagnosed with MDD, and 25% (n=5) exhibiting a subsyndromal depression.

The mood change accompanying a PAE is distinct from the mood change that occurs for those patients who do not develop PAEs. Patients who become depressed on
treatment showed a significantly lower mood, and those who were hypomanic showed more anxious and negative cognitions (see Figures 7.23 and 7.24 and Table 7.6). When all questionnaires were assessed, and those questions that occurred equally among all patients ascertained, there was a general behavioural syndrome seen in all patients taking IFN-α which comprised mainly of the symptoms of sickness-behaviour (Dantzer et al, 2008; Konsman et al, 2002). These symptoms comprised various somatic symptoms, concentration problems, memory impairments, fatigue, agitation, helplessness, apathy and aggression (see Table 7.7). Psychological items such as irritation and concentration and memory impairments were also spoken about by patients in the interview.

The most commonly reported psychological side-effect of treatment, as measured by self-report (Chapter 5) was irritation; this side-effect which has been gaining increasing attention from researchers (Constant et al, 2005; Khalili et al, 2000; Kraus et al, 2003, 2005a; Lotrich et al, 2007; Maddock et al, 2004; Manns et al, 2001; McHutchinson et al, 1998; Preau et al, 2008; Russo et al, 2005). Almost all patients interviewed reported that they experienced increased irritability at some point during treatment, and rather than being associated specifically with the IFN-α-induced depression, this was a side-effect that seemed to occur in all patients (see Chapter 5, sections 5.4.1.2.3 and 5.4.2.1.4); this observation could have interesting implications for classifying the IFN-α-induced mood change (see section 8.2.3)

The mood change that occurred for the majority of patients taking IFN-α, seemed to be an enhancement of Baseline functioning, as qualitative data from Chapter 7 shows that while there was a significant increase in HAM-D scores from Week 0 to Week 8, that there was no significant difference in the proportion of this score explained by mood, behaviour, somatic symptoms and negative cognitions. This finding was backed up by qualitative findings from Chapter 5 where patients indicated that the mood change that accompanied IFN-α was due to mood lability and an increased sensitivity to things. They described issues as being magnified in their brain: “It’s like everything is magnified or something in your brain...a lot of thoughts go through your brain but you learn to deal with them...it’s kind of more of a struggle to be happier” (Participant 004, F, age 40). This idea of IFN-α magnifying pre-existing problems is also backed up by the finding that the main reported physical side-effect of HCV in Chapter 4 of this thesis was fatigue and the main psychological side-effect was mood swings, both of which
were among the main reported physical and psychological side-effects of IFN-α in Chapter 5. These observations lead to a proposed mechanism whereby IFN-α is having an effect on some system, which in turn leads individuals to become more sensitive to stress-inducing stimuli (this shall be discussed in more detail during this discussion).

Despite the results from the quantitative and qualitative chapters fitting together for mood results, there was a different outcome when it came to cognition. Within Chapter 5 patients reported having problems with both memory and concentration due to treatment, however, when tested using a short neuropsychological battery in Chapter 6 that investigated these two domains, there was no significant effect of treatment, other than on face recognition (see section 6.4.3). This was potentially explained by patients during Chapter 5, when they spoke of having a 'cognitive reserve'; so while their memory and attention were reported to be worse than normal, they could maintain a normal level of functioning for a short time when suitably motivated to do so. Another possibility is that cognitive problems only occur in up to 20% of patients (Fontana et al, 2007; Manns et al, 2001; McHutchinson et al, 1998), meaning that 80% would maintain a normal level of functioning. Together these two theories could explain why despite self-report of dysfunction in this area, there was no actual dysfunction seen. However, it could also be the case that the tests chosen to investigate the PFC were not suitable, as there were variable effects of treatment on the DEX questionnaire. This could mean that the cognitive impairment in IFN-α patients is either very broad, and so would not be picked up by the few neuropsychological test used in Chapter 6, or, it could be very specific, meaning a highly focused neuropsychological test-battery could be needed. In either case, further investigation would be warranted.

The fact that significance was observed for face recognition was interpreted with caution due to the low n. Instead these results are proposed to be used as a basis for forming a more focused and extensive neuropsychological battery. When the Depressed and IFN-α groups were compared directly there was no significant difference between groups. However, when then compared to matched-Controls, there seemed to be a greater impact of depression than IFN-α on many of the tests (see section 6.4.4). Where differences occurred between the IFN-α and Control groups, this was mostly explained by the effects of HCV rather than the IFN-α.

One of the main aims of this thesis was to investigate the depression which can be induced by IFN-α, in order to see how similar or different it may be to a primary
depressive disorder, for which patients are hospitalised. The main chapter investigating this hypothesis was Chapter 7, with patients depressed on IFN-α being compared to age-sex-and-HAM-D matched Depressed patients. Despite having similar scores for all mood scales administered, when the HAM-D was broken down into the four domains, it was found that patients depressed on IFN-α had significantly more of their mood score made up of depressed mood, and the primary Depressed group had significantly more of their mood made up of negative cognitions, with both groups showing significant somatic symptoms (see Figures 7.32 and 7.33). This finding indicates that the underlying mood disorder caused by IFN-α, is a general lowering of mood, rather than the low mood and distortion in cognition that often accompanies a MDD (see Table 1.6).

8.2.2 Impact of HCV on individual
In order to ascertain which effects were specific to IFN-α, patients who also had HCV, but were not due to start treatment were assessed for the interview and neuropsychological functioning chapters.

When spoken to individually, it became obvious that there is a complex psychological relationship for patients who have HCV with knowledge of their illness. Previous research has indicated that HCV is associated with a reduced HRQOL (Carta et al, 2007; Hauser et al, 2004), and that HCV side-effects are not limited to the physical side-effects (Conrad et al, 2009; Crockett and Gilford, 2004; Glacken et al, 2001; Sgorbini et al, 2009), such as fatigue (Kallman et al, 2007), but that there may also be an impact on psychological issues such as depression (Yovtcheva et al, 2001), a feeling of being stigmatised (Butt et al, 2008; Conrad et al, 2009; Janke et al, 2008; Lally et al, 2008; Moore et al, 2009; Zickmund et al, 2003) and cognition (Perry et al, 2008; Reimer et al, 2005).

When interviewed in Chapter 4 the main issues that patients spoke of were issues associated with HCV, such as fatigue, cognitions associated with the knowledge of disease, method of transmission and social support. Patients reported that the main health-related side-effect was fatigue: “I don’t know I have it, except for I’m very tired” (Participant 27, F, age 63), something which they perceived to be significantly different from other people of their age. This backs up previous research showing that the main effect that HCV has on HRQOL is in terms of fatigue (Kallman et al, 2007). As this was
the main health effect, patients tended to rate other health issues as being more important than HCV: “there’s worse out there with cancer, than we are, strokes...I know it’s life threatening but sure than is everything else, you could walk out in front of a bus and be killed or whatever” (Participant 23, F, age 60), and they would often forget about the illness: “I don’t feel anything, like there’s any difference between this and if I was getting pains or anything so that doesn’t really bother me” (Participant 30, M, age 33).

The main impact of HCV seemed to be a psychological one, with cognitions around transmission leading to feelings of anger for almost all patients, with anger being directed towards that person or organisation people felt to be responsible for their disease: “yes it makes me angry at the bloody State” (Participant 20, F, age 57: infected via transfusion); “Angry that I was stupid enough to use other people’s needles...angry that I put myself in a position to catch a disease like Hepatitis C through my own stupidity” (Participant 30, M, age 33: infected via IVDU). Other cognitions associated with the knowledge of the illness were mostly negative, such as anxiety and feeling upset.

When asked about mood, very few patients believed that the HCV had a direct influence of their mood, with only one patient reporting that they had suffered from an endogenous depression post-infection that was not linked in to any stressful life events: “I can’t put my thumb on it...I just couldn’t say, you know, what it was” (Participant 23, F, age 60). For all other patients, the low mood could be attributed directly to some other stimulus. The main reported mood-effect was an emotional lability in 30% of patients: “I get these mood swings and I can be irritable.”(Participant 28, F, age 62); “unless I’m in one of those mood swings where you can’t think anything is good.” (Participant 23, F, age 60).

Instead of the direct stigmatisation reported in previous qualitative studies (Butt et al, 2008; Conrad et al, 2009; Janke et al, 2008; Lally et al, 2008; Zickmund et al, 2003), people reported that the social support they received was a direct result of the understanding of people around them. With those people who had support and understanding from people rating their social support as better: “They’re all there for me.... particularly the ones that know I have Hepatitis C” (Participant 23, F, age 60: support excellent), than those people whose friends and family did not seem to understand HCV: “This Hepatitis C belongs to me....I am too shy to talk about this
illness because no-body understand” (Participant 22, F, age 40: support poor). Rather than attributing the lack of understanding of other people to stigmatization, patients instead were more likely to talk about the poor education of other people as regards the illness: “I think they think it’s like....they’re going to get AIDS, and they’re a bit paranoid about that end of it because they’re ignorant about it” (Participant 29, F, age 53: support fair).

While cognition was something that patients with HCV did not explicitly believe to be worse than other people during the interview, when assessed using the EMQ, they reported a significantly greater memory impairment and PFC dysfunction than Control participants (see Figures 6.2 and 6.3). However, when tested using the FNP task the only significant difference between the two groups was for delayed free-recall, with all recognition and associative learning conditions intact. This suggested that there was an impairment in verbal recall, something which has been shown to be affected by HCV in other studies (Weissenbom et al, 2009).

The significant difference in the SART test (see Figure 6.6) was deemed attentional, as patients made significantly more errors of commission, despite a significantly higher rate of errors of omission. HCV patients were also significantly worse at the 0-back and 1-back tasks. This was suggested to be due to either processing speed as performance was always just below the Control group, or, it was a working memory impairment and significance was not seen in the 2-back due to increased variability in that task for the two groups. It is also possible that the issue could have been due to impaired attention with patients finding the easier n-back conditions hard to concentrate on. The findings of significance in these two tasks, agrees with research where patients with HCV describe having ‘brain fog’ (Perry et al, 2008; Reimer et al, 2005); this encompasses a series of impairments in executive functions such as attention, concentration working memory and mental flexibility (Forton et al, 2001; Kramer et al, 2002; Hilsabeck et al, 2002; Weissenborn et al, 2004), all of which are reliant on the PFC. Further work with HCV patients should be conducted in this area in order to validate these findings as there is such a low n.

In short, results from this thesis indicate that HCV has associated with it a number of important psychological issues, in terms of how patients perceive their illness, neurocognitive effects and occasional effects on mood. It also backs up previous
research where patients perceive the psychiatric and medical co-morbidities of their illness as having a greater effect than the illness itself (Hauser et al, 2004).

8.2.3: Impact of IFN-α on individual

Results from this thesis confirm that the process of taking IFN-α is challenging, both physically and psychologically. Evidence is provided that treatment-related side-effects are not exclusive to the 24-week or 48-week window where patients are taking the treatment. Prior to starting treatment there are treatment-related anxious cognitions, and post-treatment there is not the automatic return to Baseline functioning that many patients seemed to expect: "I was, um, disappointed when I stopped taking the pills that I didn't recover straightaway, do you know what I mean? It was a bit of a letdown...I'm still not sleeping, I'm not as happy as I was before" (Participant 103, M, age 36: 3 months post-treatment). Despite these observations, the most severe side-effects still occurred while the patient was on treatment.

When assessed for mood, it was revealed that almost all patients experienced a behavioural syndrome which comprised mainly of sickness behaviours (see Figure 8.1). These behaviours occurred in almost all patients, regardless or not of whether a PAE was experienced.

When the HAM-D was assessed in all patients, it became clear that the largest proportion of symptoms that comprised the total score were somatic symptoms, and this did not change from Baseline to Week 8 (see Figures 7.10 and 7.11), or indeed to Week 20 (see Figures 7.19 and 7.20). This indicated that there was an enhancement of symptoms present at Baseline occurring while on treatment. This is supported by evidence from Chapters 4 and 5 which indicated that the main physical side-effect of HCV is fatigue: "Because of the Hepatitis I could be doing something normal and all of a sudden my energy is zapped from me and I have to go and lay down" (Participant 21, F age 65), which is also the main physical side-effect of IFN-α: "I'm so tired, and mostly I'm tired, um, not much else really" (Participant 006, M, age 54). Likewise, the main psychological side-effect of HCV is a labile mood where patients describe getting easily irritated and depressed: "I get these mood swings and I can be irritable."(Participant 28, F, age 62). The main psychological side-effects of IFN-α are irritation: "I just became an angry, irritated person" (Participant 103, M, age 36), labile mood: "extremely moody, swinging from hot to cold" (Participant 108, M, age 54) and
depressive symptoms: "I lost motivation, I'm, I've always got summot to do, it don't matter where I am, I will be doing it. I just lost the will to do it like" (Participant 101, M, age 34). The main difference that is observed with these side-effects is that prior to treatment they occur sporadically, whereas on treatment they occur more often or are present most of the time. The symptoms that increase from Baseline to treatment were sickness behaviours, indicating that patients with HCV show mild symptoms of sickness behaviour, but that these are exacerbated by treatment.

Figure 8.1: General IFN-α-induced behavioural syndrome

This idea of IFN-α increasing symptoms present at Baseline was described in two ways by patients. Some patients spoke of issues that had always being present, but they had previously been able to ignore coming to the forefront of their mind: "I feel like it opened up things, places that you didn't want to go, it's very hard"
(Participant 104, F, age 55). Another way it was described was in terms of increased sensitivity, as though IFN-α was reducing the threshold to cope with stressors: "you were more sensitive...the least thing that normally you would push to one side with an answer or something, erm, it wasn’t the case, you would take it to heart so that you were very sensitive to things you know, and it would make you very sad and annoyed about something that was very small really" (Participant 105, F, age 54).

This is not to say that there are no new symptoms that occur when taking IFN-α, many of the patients when interviewed at Baseline reported no influenza-like symptoms or many of the other side-effects listed in Figure 8.1. The proposal we have is that IFN-α causes a general increase in those symptoms present as Baseline, along with additional sickness-related behaviours that are induced by the pro-inflammatory cytokines and chemokines that increase when patients take IFN-α (see Section 1.2.4).

We therefore speculate that pro-inflammatory cytokines such as IFN-α could induce a change in mood that increases patients sensitivity to stressful stimuli. Where at Baseline patients are capable of suppressing certain thoughts or ignoring certain stimuli, it seems that on IFN-α they become incapable of the same thing, exhibiting increased sensitivity and labile mood. This reduction in threshold to stressful stimuli could be likened to that which occurs prior to a primary depression (see Figure 8.2), with IFN-α somehow biologically inducing this reduced threshold through mediating effects on 5-HT, growth factors and the HPA axis (This idea is discussed in section 8.2.5). This could be investigated in future experiments with a full assessment of biological (cytokines, serotonin, growth factors, HPA axis etc) and cognitive risk-factors (coping styles, attributional styles etc) been undertaken at Baseline and then assessed for their relative impact on levels of depression.
Figure 8.2: Interaction between vulnerability, stress and factors that maintain depression

Figure showing the interplay between vulnerability to depression (defined here as a genetic/biological vulnerability and a cognitive vulnerability) and stress leading to a depressed mood. This mood is then maintained by the depressed somatic state, the relationships they have with other people, their action and the negative cognitions they display. Adapted from Carr and McNulty (2006), with cognitive vulnerability introduced as a vulnerability-factor (Abramson, 1989; Beck, 1967, 1987). We propose that IFN-α may somehow biologically reduce the vulnerability threshold while possibly interacting with pre-existing cognitive vulnerabilities.

While the HAM-D revealed that the IFN-α-induced mood change was an enhancement of Baseline functioning, the HAM-A yielded slightly different results. There was also a significant increase in HAM-A scores from Week 0 to 8, however, when mood scores were broken down it was revealed that at Baseline the majority of symptoms experienced were anxious cognitions, yet at Week 8, the majority of symptoms were somatic symptoms (see Figure 7.8). This suggests that at Baseline patients experienced a significant amount of anxious cognitions, however, at Week 8 these thoughts were decreased and that the somatic effects of treatment eclipse both anxious cognitions and anxious behaviours (see Figure 7.9). This is in part explained by the somatic focus of the HAM-A, where 57% of questions focus on somatic symptoms. It would thus be expected that once any patient was experiencing any kind of illness that the symptoms of sickness behaviours would load onto somatic items, which is what was seen at Week 8 of treatment. This observed effect on anxiety is probably due to somatic
symptoms eclipsing anxious cognitions as when interviewed patients revealed that the anxiety they experienced prior to, during and after treatment was due to treatment-related cognitions. Prior to starting treatment anxious cognitions were due to the uncertainty of what side-effects could occur, and also the uncertainty of whether the treatment would work: “*I know what can happen, and I also know what might not happen*” (Participant 006, M, age 54); patients also experienced anxious cognitions when on treatment due to the uncertainty of treatment outcome: “*I suppose it’s the worry of it, that you don’t really know, are you going to clear it, is it going to get worse, and I suppose it’s just that, the worry of it*” (Participant 105, F, age 54). This uncertainty prevailed in the six month period post-treatment, while patients waited to hear whether they had achieved SVR. These results suggest that the HAM-A is an insufficient tool for the IFN-α population as it is not sensitive enough to focus on the anxious cognitions that often accompany treatment; instead this test focuses on somatic items and the increase in score seen was probably due to the physical side-effects of treatment.

In terms of neuropsychological functioning while on treatment, many patients when interviewed reported that they experienced cognitive difficulties in executive functioning and memory: “*You’ve got a bad memory because you haven’t got an attention, you haven’t got an ability to concentrate on anything*” (Participant 103, M, age 36). However, when tests of attention, memory (long-term and working memory) and a general test of executive functioning were employed, there was no significant difference seen for any of the domains tested, other than for face recognition (see Figure 6.21). However, this effect was only seen for the repeat-testing session, and not when a separate group of participants were compared to Controls and Depressed patients (see Figure 6.28), meaning that this effect could have been a by-product of the low \( n \) tested rather than a true, reproducible effect. One potential reason that no effect could have been seen was explained in the interviews, with some patients stating that they could maintain normal cognitive functioning for a short period of time, however, it took a greater amount of effort than it would do normally: “*it’s like you have to concentrate double times than normal*” (Participant 002, M, age 33). This would mean that patients would be able to demonstrate a ‘normal’ level of performance, but that it would take them more effort to do so than it may do normally. As the test-battery employed was designed to reduce fatigue-effects by being shorter than a classical test-battery, this
could have enabled patients to maintain a normal level of functioning for the short test durations, even though they were experiencing some cognitive difficulties. The issues described by patients in the interview were mostly executive impairments: "you lose how quick you are, like doing a calculation in your head" (Participant 103, M, age 36); "While I was on treatment I wasn't concentrating on anything, um, work, reading, keeping notes, following up on clients" (Participant 111, M, age 41). This means that there is also the possibility that the test-battery employed was insufficient to pick up on cognitive difficulties, however, it could also possibly mean that the poor cognition is a by-product of fatigue rather than an organic memory impairment. In order to ascertain this, it would be necessary to test patients in longer and shorter versions of the same task, in order to see how important fatigue effects are.

One important finding from the interview as regards patient-care was the perceived importance of social support for those people taking IFN-α; however, this social support was most effective when received from people who understood the process of treatment. This is because almost all patients developed side-effect that close friends and family could find hard to deal with unless they understood why they may occur (see Figure 8.1) such as irritation and social withdrawal: "I was disengaged, socially disengaged, normally I would be perceived by people to be, you know, sort of talkative, engaging person in any company,...but I wouldn't be bothered when I was on the treatment" (Participant 107, M, age 48). When talking to patients, the most important support was received from the hospital and family: "the support of their family is extremely important, and where you don't have the patience they can have it for you....it is absolutely important because you have the back-up, and not only the support and care in the clinic, but you need it when you go home as well" (Participant 105, F, age 54). When patients felt that they were not receiving the support they should this impacted on their experience of treatment, with those patients for whom allowances were not made experiencing more problems on treatment: "I was still going out doing all the grocery shopping even though I didn't have the energy, and that was just wearing me down more and more" (Participant 110, M, age 48). When assessing the impact of IFN-α on the individual there is a tendency to forget the impact of the social environment on mood, as well as those changes occurring internally, yet the effects of social support on the individual should not be underestimated.
8.2.4 Examining IFN-α-induced PAEs

Results from this thesis indicate that IFN-α treatment is associated with the potential development of PAEs, with 6% ($n=2$) of patients developing MDD, 17% ($n=6$) exhibiting a subsyndromal depression and 6% ($n=2$) having developed a hypomanic episode by Week 8. At Week 20 of those 20 patients left in the study 15% ($n=3$) were diagnosed with MDE, and 25% ($n=5$) exhibited a subsyndromal depression.

These PAEs are associated with distinct behaviours, mood and cognitions from those patients who do not develop a PAE. Those patients who develop hypomanic mood showed significantly more negative cognitions when compared to the non-PAE group (see Figure 7.23). They also show a significant higher score for questions that relate to anxious cognitions and aspects of PFC dysfunction (see Table 7.6). The Depressed group, however, show significantly more anxious behaviours (HAM-A: see Figure 7.21) and depressed mood (HAM-D: see Figure 7.23), when compared to the PAE group; also showing significantly higher scores for questions that related to depressed mood, and some of the more depression specific somatic side-effects such as decreased libido and late insomnia (see Table 7.6).

As seen in the previous section there is a collection of behaviours that almost all patients develop when taking IFN-α (see Figure 8.1), these behaviours also occur in those patients who develop a PAE with additional psychological complications coming into play (see Figure 8.3). For IFN-α-induced depression the main symptom that differentiates this group from the non-PAE, and Hypomanic groups is increased severity of depressed mood. For IFN-α-induced hypomania the main symptoms that differentiated this group from the non-PAE and Depressed groups were anxious and negative cognitions.

The idea that there is a general IFN-α-induced syndrome which comprises of behavioural, mood, somatic and cognitive symptoms with PAEs involving additional mood or cognitive symptoms is an expansion of two theories. The first is of Raison et al, (2005b) who proposed that the mood change observed in IFN-α patients was the result of two overlapping syndromes (neuro-vegetative and depression-specific). The second is Constant et al, (2006), who propose that the mood change observed is best thought of as an overlap between hypomanic and depressive symptoms. We propose that the mood change observed in IFN-α patients is a syndrome which comprises primarily of somatic and mood symptoms but also involves some cognitive and
behaviour symptoms (see Figure 8.1). The general mood change which occurs involves both depression-specific and hypomaniac symptoms, however the IFN-α-induced depression we observed is an enhancement of the depression-specific and neurovegetative symptoms proposed by Raison et al. (2005b), and the hypomania an enhancement of the syndrome described by Constant et al. (2006) with additional cognitive distortions.

**Figure 8.3: Difference in IFN-α-induced Depression and Hypomania**

![Figure showing the difference between the two main PAEs observed in this thesis based on results from Chapter 6. The two PAEs are distinguishable, as IFN-α-induced Hypomania is primarily a disorder of cognition, and IFN-α-induced depression is primarily a disorder of mood. However, both groups will also experience the same general IFN-α-induced syndrome as the non-PAE group. The main mood symptom linking all three groups together was irritation.]

The idea that the Depressed and Hypomaniac groups exhibit symptoms differently is backed up from results from both the interview Chapter and the case-studies Chapter. When patients were diagnosed with a hypomaniac episode, they described having racing thoughts and engaging in risky behaviours, however, depressed patients would describe a lack of energy and general low mood (see Chapter 6). This low mood was characterised by patients in the interview primarily in terms of anhedonia: “I never felt content and happy on it, it was all I was kind of, struggled to do things, and struggling to get around and stuff like that” (Participant 112, M, age 34).

The mood symptom that linked all three groups together was irritation. Almost all patients interviewed in Chapter 4 and 5 spoke of an increase in irritation, meaning that rather than being considered a by-product of the IFN-α-induced depression, that
irritation should be considered part of the general IFN-α-induced behavioural syndrome. This idea again builds on the theory of Constant et al., (2005) who proposed that the mood change induced by IFN-α would best be thought of as a syndrome with overlapping hypomanic and depressive symptoms. Rather than these two syndromes, we propose that the general IFN-α-induced syndrome could be thought of as an overlapping sickness behaviour /irritable-labile/depressive mood syndrome; with additional cognitive items occurring for hypomanic patients and the depression seeming to be an enhancement of certain aspects of the general mood syndrome such as the depressed mood and somatic symptoms.

The fact that IFN-α-induced hypomania and depression exhibit in different ways could have important implications for diagnosis and treatment. IFN-α-induced hypomania is primarily a disorder of cognition and somatic symptoms which echo the findings from patients with a primary MDD (see Figures 7.28 and 7.29). This places IFN-α-induced hypomania in the same severity category as those patients who were hospitalised for MDD, leading to the proposition that hypomania is a serious and often underappreciated side-effect of treatment. This side-effect should be monitored in much the same way as many clinicians would monitor for depression, as while IFN-α-induced depression was the more common side-effect in this study, the hypomania was the more serious in terms of consequences for the patient (see Chapter 6). As hypomania is primarily a disorder of cognition, it could be the case that the best therapy for patients with this side-effect to undergo would be a more cognitive-based therapy rather than a pure pharmacological therapy. However, future study of this side-effect and the best course of treatment would be warranted before any real recommendations for therapy could be made.

IFN-α-induced depression exhibits primarily in terms of mood, with symptoms such ashedonia and more depression-specific somatic symptoms prevailing in these patients (this shall be discussed more in the next section). As this depression exhibits primarily in terms of mood, it is potentially a better idea to use pharmacological therapy in these patients as there is little effect of IFN-α on negative cognitions and so cognitive therapy may not have the same impact as it may in those people whose depression arises primarily with negative cognitions. This suggestion is backed up by data which reports that the most effective way to ameliorate IFN-α-induced depression is with the use of anti-depressants (Kraus et al., 2007). While none of the patients in the mood study
developed a severe MDD that is not to say that it does not occur in patients that take IFN-α. One patient interviewed in Chapter 5 developed a severe MDD while on treatment that caused her to experience strong suicidal ideation: "I did contemplate it yeah, I did, I thought of taking an overdose, and luckily I was attending a psychologist...and she just said, 'C I can't let you leave here'" (Participant 112, F, age 57).

There was no identifiable difference at Baseline between those patients who did and did not develop a PAE (see Table 7.4 and Table 7.5); although the PAE groups did show slightly raised scores. While no Baseline risk factors could be identified, one patient summed up a possible reason for occurrence of these PAEs when interviewed: "I have been depressed on it they said...and another course of interferon made me elated. I mean it was the same interferon! The only sense I can make of that is that it is the person, it depends on how you are" (Participant 109, M, age 48). This echoes back to the idea presented in section 8.2.3 that IFN-α increases symptoms present as Baseline, which was also seen in Primary Depressed group when the HAM-D was broken down (see Figure 7.26).

8.2.5 Classifying the IFN-α-induced depression

In order to fully appreciate the nature of the IFN-α-induced depression it was decided to conduct an analysis whereby this depression would be compared to patients who did not develop any psychological complications through IFN-α therapy in order to ascertain which side-effects of treatment could be considered normal, and which could be considered to be part of the IFN-α-induced depression. This depression would then be compared to a primary depression, in order to then ascertain how similar or different these two disorders were, with the hope being that once all these comparisons had been undertaken a better understanding of the nature of IFN-α-induced depression could be achieved.

When compared to those patients who did not develop a PAE, IFN-α-induced depression seemed to involve significantly more symptoms of depressed mood and somatic symptoms (see Table 7.6 and Figure 7.23). This depressed mood tended to comprise mainly of symptoms that could be related back to anhedonia as well as items related to mood being lower than normal.
When then compared to patients with a primary depression who were matched for age-sex-and-HAM-D scores, the main difference that occurred with this group was that patients with a primary depression exhibited significantly more negative cognitions, whereas those patients with an IFN-α-induced depression exhibited significantly more depressed mood items (see Figures 7.32 and 7.33). Despite both groups having a significant proportion of their total HAM-D score made up of somatic symptoms, the IFN-α group still had significantly more of their score made up of these symptoms when compared to patients with a primary depression (see Figure 7.33). The observation that IFN-α-induced depression is mainly a disorder of mood and somatic symptoms supports findings from Chapter 3, where two of the three patients who developed a MDD on treatment, actually developed a melancholic depression (neuro-vegetative depression), with this disorder exhibiting primarily in terms of mood and somatic symptoms over negative cognitions (see Table 1.7). There is also evidence from the case-studies that the diagnosis of depression could have resulted from patients meeting criteria that were also symptoms of sickness behaviour (see Table 1.8), with depressed mood being one of the main psychological symptoms of sickness behaviour.

These findings also fit with those of Pasquini (2008) and Clark (1998), who found that negative cognitions were the primary symptoms that comprised a primary depression, and that IFN-α patients were significantly less likely to experience these symptoms (Pasquini, 2008), with a co-morbid medical illness leading to a depression characterised by mood symptoms, specifically anhedonia and low positive affect (Clark et al., 1998).

This depressed mood, characterised by anhedonia can be likened to that seen in a more endogenous, melancholic depression (Abramson et al., 1989), which is also characterised by the neuro-vegetative symptoms that echo sickness-behaviours (see Table 1.8). There is further evidence that these two disorders may be similar as melancholic depression involves increased immune activation (Rothermundt et al., 2001). This evidence suggests that cytokines such as IFN-α have an effect on those depressive symptoms which result from sickness behaviour such as low mood and neuro-vegetative symptoms, and they have a negligible impact on negative cognitions.

This leads to a hypothesis whereby IFN-α-induced depression could be fundamentally different to a primary depression (see Figure 8.4), with the depression induced by IFN-α potentially being an extreme form of sickness behaviour comprised of
depressed mood and somatic symptoms; whereas a primary depression is the result of somatic symptoms and cognitive distortions. In order to gain a better appreciation of this hypothesis a more extensive study needs to be conducted where IFN-α-induced depression is compared to all the different subtypes of MDD, as it could be found that Melancholic depression and IFN-α-induced depression are similar entities.

However, results for the IFN-α patients are possibly confounded by the fact that only mild-to-moderate depression was observed in the patients, which could explain in part the lack of negative cognitions observed.

Figure 8.4: Contribution of domains to primary and secondary IFN-α-induced Depression

Figure showing the contribution of the three main domains that comprise the HAM-D score for both the primary Depression and IFN-α induced Depression. For both groups a significant proportion of symptoms (Dep: \( F(3, 24)=8.12, p<0.01 \); IFN: \( F(3, 24)=63.25, p<0.01 \)) are made up of Somatic symptoms (Dep: \( 29.86 \pm 3.4 \); IFN: \( 54.25 \pm 3 \)), and the smallest amount of behaviour symptoms (so it is not included in the diagram). However, for the IFN-α Depressed group, a significant proportion of their score is made up of mood symptoms (24.87 ± 1.3), and for the primary Depressed group a significant proportion of their score is made up of negative cognitions (34.7 ± 4.1).

In the previous section we discussed the possibility that rather than having a pure causal impact on mood, that cytokines could instead lower the threshold for dealing with stressful stimuli. This would mean that the underlying psychological and biological state that the individual presents with at Baseline could determine how they respond to treatment. There is a general acknowledgement that depression is linked in to a reduction in the ability to deal with stressful life-events; with serotonin, the HPA-axis and growth factors all being identified as possible biological factors (see section 1.3.3).
All these factors have been shown to be influenced by pro-inflammatory cytokines (see Figure 8.5), thus, when levels of pro-inflammatory cytokines are raised there is a decrease in those chemicals that help us to maintain Baseline functioning, leading to an increased sensitivity to psychological stressors. However, it must be pointed out that this theory is purely speculative and would need formal testing via a study that specifically investigates the biological and cognitive vulnerability factors that could impact on depression.

**Figure 8.5: Cytokine-mediated pathways that influence CNS**

Diagram showing how cytokines affects factors that the CNS through a complex relationship the relationship with monoamines, growth factors and stress based on Anisman (2009) and Hayley et al, (2005). Stressors and cytokines both increase the amount of CRH, both in the CNS and peripherally, which in turn activates ACTH and cortisol (CORT) levels. CRH also has a bi-directional relationship with serotonin (5-HT) levels, and Gamma aminobutyric acid (GABA) acts as a mediator for this process. 5-HT levels are also influenced by the production of IDO, which favours the production of the neurotoxin kynurenine (Kyn) over 5-HT. This stressor system (in red) and IDO-Kyn pathway (in green) both lead to a reduction in 5-HT. Cytokines also influence oxidative and apoptotic mechanisms, leading to a reduction in growth factors such as BDNF, which in turn leads to impaired neuroplastic processes and decreased neurogenesis (neuroplastic pathway in purple), as well as cytokines having an indirect effect on growth factor levels, stress has also been shown to have a direct effect. The culmination of these three pathways can lead to the development of major depression.

We also speculate that cognitive factors could also play a role in the development of the IFN-α-induced depression (see Figure 8.2). This could be because certain patients were more able to employ cognitive protective factors than others. These factors could be those described by Nolen-Hoeksema et al, (1991, 2004), who
states that those people more likely to develop and sustain a depression are those who rumin ate over their condition, whereas those people who can effectively use distractive coping where they concentrate on pleasant or neutral thoughts and actions are less likely to become depressed. For the patients taking IFN-α this could mean that instead of using distractive coping to deal with their side-effects, that they would instead ruminate on these side-effects, leading to a downward spiral where their mood would get lower and they would feel like their side-effects were getting worse. These poor internal coping factors along with a lack of social support could lead to a cognitive vulnerability that has yet to be assessed in literature. The importance of these factors, in conjunction with biological risk-factors could be ascertained in future studies.

When compared on the HAM-A there was no significant difference between-groups (see Figure 7.30), however, when the groups were examined individually, the proportions of domains were split more equally for the Primary Depression group. Yet the IFN-α-induced Depression group had the majority of their symptoms made up of somatic symptoms (see Figure 7.31). This is potentially due to the reason discussed earlier in this thesis that supposes that due to the emphasis of the HAM-A on somatic symptoms, that any patient displaying any illness will load preferentially onto these items.

In line with the findings from the general IFN-α-induced behavioural syndrome, it was found that the patients who became depressed on IFN-α did not show a relative increase in any of the individual symptom domains from Week 0 to Week 8, despite a significant increase in mood scores (see Figure 7.26 and 7.27). This lends further support to the idea that IFN-α magnifies symptoms present at Baseline with additional treatment-related factors coming into play.

Those patients who developed a primary and secondary IFN-α-induced depression could not be directly compared on tests of neuropsychological functioning as none of the patients that became depressed on IFN-α were willing to take part in the neuropsychological study. However, when those patients taking IFN-α were compared to depressed patients there was no significant difference between the two groups in any of the tests used, except those tests that were self-report measures. In general, however, when compared to Controls, Depressed patients tended to be significantly worse at many of the tests (see Chapter 6).
As suggested previously, there may have been little impairment in the neuropsychological tests due to increased cognitive effort being employed by IFN-α patients, it could be further suggested that due to the nature of depression that these patients are not capable of inducing the same cognitive effort, however, this is something that would need to be tested formally. When interviewed the main cognitive difficulties expressed by patients who were or had taken IFN-α were with concentration and memory: “You’ve got a bad memory because you haven’t got an attention, you haven’t got an ability to concentrate on anything” (Participant 103, M, age 36). Interestingly, a significant impairment in concentration and memory is one of the criteria for depression in the SCID (see Appendix I). This could mean that these two groups do have more in common than has been revealed in this thesis, and so further investigation could yield some potentially interesting results.
8.3 Methodological issues

The low number of patients recruited was in part due to the difficulty of working with this population of patients as even when recruited for a study the drop-out rates were high (see Figure 7.2). For the depressed patients it was often the case that they would not want to take part in this study because they wished to focus on their treatment, or did not feel like they had the energy to be able to take part in such a study. For the IFN-α and HCV patients, the fact that they were recruited from an out-patient clinic meant that patients rarely wanted to stay behind to do research as they had jobs to return to.

The main issue with all studies conducted as part of this thesis was the low number of patients investigated. As with any study that has results based on a low number from a target population, results should be interpreted with caution, and only when the results have been repeated in a larger sample population can the results said to be true. This is particularly true of the interview studies, where the results mostly comprised of new findings. However, the mood and neuropsychological chapters results fit well with existing literature suggesting that these results can be assessed with more confidence.

This issue was predominantly noticeable for the interview chapters, where the low numbers of participants mixed in with the high inter-group variability, meant that any quantitative results from these chapters were rarely significant, and didn’t tend to show any trends. Instead, the qualitative results for these chapters should be concentrated on, as these sections would explore the variability that existed between-participants by creating and expanding on themes.

Another potential problem with this thesis is that the interviews conducted with IFN-α patients were not conducted in patients with a primary depression. This is because it was felt by the investigator that it would not be ethical to interview depressed in-patients about their mood when they were in the hospital to receive therapy for their problems. The similarities between the cognitive therapy environment and research interview environment were felt to be too strong, with the potential for issues to arise that the experimenter would be ill-equipped to deal with.

Another issue was the broad range, but shallow assessment of a wide variety of topics, from a qualitative patient assessment to quantitative assessments of mood and neuropsychological functioning. In order to gain a more detailed appreciation of any
topic it is necessary to focus primarily on one area and examine that area in detail. The main focus of this thesis was to try and appreciate the nature of the mood change induced by IFN-α, and whether the labelling of this mood change as a depression was an appropriate label by comparing a wide range of issues between two groups of patients, one who had an IFN-α-induced depression, and the other who had a primary diagnosis of MDD. The main issue with this comparison was that it was only viable for the mood chapter of this thesis, and even then only three patients developed a MDD on IFN-α treatment so it was necessary to combine this group, with a group of patients who developed a subsyndromal depression where 3 of 4 of the criteria for a MDE were met, and a further 2 met at a subsyndromal level. It could thus be argued that this did not yield an appropriate comparison as the majority of patients who developed an IFN-α-induced depression, were not actually depressed according to SCID criteria. This merging of groups was justified by the similarities in depression scores between the two groups, which were significantly different to those patients who did not develop a PAE on treatment.

One of the major flaws with this thesis could be said to be the lack of cytokine assessment, as fundamentally the cytokine theory of depression has been assessed without investigating cytokines. There was a substantial amount of time spent during this PhD on collecting such data for both the primary-depressed and IFN-α-induced depressed patients, however, when analysed the data was confounded by a variety of factors and the methodology employed was unsuccessful and found little significance (see Appendix VIII). As such this data was omitted from the thesis, but in future, an experimental design could be undertaken where the respective contributions of both biological and cognitive vulnerability factors could be assessed.

The neuropsychological comparison that was undertaken could only be carried out between all patients on IFN-α and depressed patients, as no patient who took part in the neuropsychological study developed a significant PAE. This issue meant that the appropriate comparison (i.e., between patients depressed taking IFN-α and patients with a primary depression) could not be undertaken, meaning that there were no real implications of the similarities between those two groups for the neuropsychological study.
8.4 Future directions

There are a number of studies that could be undertaken based on the interesting results the comparison between primary depressed patients, and patients with a secondary IFN-α-induced depression have shown. A larger scale study with a greater number of patients depressed on IFN-α, and a much larger number of primary depressed patients could explore the difference in groups between different sub-types of depression, with classic MDD, melancholic, atypical, paranoid and even a depressed episode for bi-polar patients all being compared to the depression induced by IFN-α in order to gain a much richer insight into the type of mood disorder that those patients develop when they become ‘depressed’ taking IFN-α, and whether it could be likened more to a melancholic depressive episode than a classical MDD. This comparison could be further enhanced by examining cytokine levels in the depressed patients before they are medicated and examining which cytokines are enhanced in this population when in the depressive episode in comparison to when they are remitted, and then see whether these cytokines overlap with the cytokines that correlate with mood that are enhanced in those patients taking IFN-α.

There is also the possibility to conduct research into the influence of cytokines on mood by conducting an extensive biological analysis that would investigate the relative importance of cytokines identified in literature. An extensive study would include more participants, and analyse a variety of factors not just limited to cytokines, so that the idea of a pro-inflammatory reduced threshold could be investigated formally.

There would be the possibility when conducting a biological analysis to use the breakdown of mood symptoms methodology employed here to assess the relative contribution of each cytokine to the different mood domains. This could tell us more about whether the higher levels of cytokines generally seen in both IFN-α and a primary depression is due to the cytokine having an effect on a subset of symptoms such as the somatic or mood symptoms, or if they have a direct impact on cognitions or behaviour.

Another comparison to undertake could be to assess the relative importance of cognitive factors and biological factors in IFN-α-induced depression. It may not always be possible to observe differences in biological factors at Baseline for those patients who do and do not develop depression as this does not take cognitive factors into account. The relative importance of external support (e.g., support groups), and internal support (e.g., Cognitive therapy), could be assessed for their possible roles in protecting
against IFN-\(\alpha\)-induced depression. These could then be compared to the more biological anti-depressant type therapies that are traditionally employed.

As well as the comparison for mood and cytokines, the comparison in neuropsychological functioning could also potentially yield interesting results should a more appropriate comparison be used. This would mean that all patients complete a Baseline assessment (be that prior to treatment for IFN-\(\alpha\) patients, or, when remitted for depressed patients), then those patients who become depressed on IFN-\(\alpha\) would undertake the same test battery as depressed patients, and a comparison then undertaken. It would also then be possible to compare those patients who become depressed on IFN-\(\alpha\), to those who do not become depressed in order to ascertain whether the depression itself could lead to a greater cognitive impairment that could be likened more to the impairment seen by those patients with a primary depression (i.e., whether the depression removes the proposed 'motivation/cognitive reserve' factor that patients taking IFN-\(\alpha\) appear to have).

A better designed and more extensive neuropsychological test battery could also yield more significant results, as data from the interview does suggest that PFC dysfunction could occur during treatment with IFN-\(\alpha\). This test battery could be designed around the BADS, including the DEX questionnaire which is administered to partners, as they could potentially observe more PFC dysfunction than the participant would be willing to admit to. An additional way to assess whether the PFC is affected would be to do an fMRI study utilising a test known to affect this region of the brain. Results could be compared from Baseline to Treatment in order to see if blood flow changes in the PFC for that task.

We also proposed that IFN-\(\alpha\)-induced cognitive difficulties could be the result of fatigue rather than a pure organic impairment. A way that this could be assessed would be to administer the same tests in two groups, but administer short versions of the test in the first condition, and longer versions of the same tests in the second condition. Groups could then be compared for potential differences.

Another potentially interesting neuropsychological comparison would be to design a test battery which looks specifically at the emotional lability that patients taking IFN-\(\alpha\) appear to develop. This would mean designing a battery that included a variety of tests that looked at emotional reactivity in patients taking IFN-\(\alpha\), and following the Baseline assessment compare those patients taking IFN-\(\alpha\) who do and do
not become depressed to patients with a primary depression in order to see if there is a significant difference between the two groups in the way that they react to emotional stimuli.

The interview conducted with patients gave a more detailed and personal insight into the effect that being on a treatment such as IFN-α has on the individual, both prospectively and retrospectively. As the qualitative section of the interview yielded such variation, a more semi-structured design with more participants could tell us more about how these patients feel the treatment impacted on their lives, a combination of both the retrospective and prospective designs could provide a more rounded picture of the side-effects patients experience, and which they feel are the most limiting, be that physical or psychological.

Results from this thesis, and more contemporary research into IFN-α also suggests that it is the irritation experienced by people taking this drug which may be the more commonly experienced psychological effect of treatment. Further research could investigate this side-effect in more detail, and a comparison (in particular with those patients who have a more atypical depression), could provide useful insight into categorizing the mood disorder that those patients taking IFN-α develop.

There is evidence from this thesis that the depression induced by IFN-α is significantly different to a primary depression, and any future research in this area could potentially elucidate the mood disorder that occurs during IFN-α, and as such, a more appropriate diagnostic tool that clinicians could use, as well a list of side-effects to be given to patients regarding which psychological side-effects they should expect to experience, and which would need them to seek out further guidance from healthcare professionals.
8.5 Conclusions

IFN-α causes impairment in social and occupational functioning which can impact on people physically, psychologically, or both. The focus of this thesis was to assess the impact that being on IFN-α had on the individual qualitatively and quantitatively.

When interviewed both prospectively and retrospectively there was much evidence that IFN-α has a significant impact on patients, which lasts past the final injection. Patients described a mood change that involved a labile mood, irritability and depressive symptoms. There is also evidence that there are a number of anxious cognitions that patients experience prior to, during and following treatment that centre around the uncertainty of side-effects and treatment-outcome. There was also further evidence provided that HCV itself is associated with a variety of psychological, physical and cognitive difficulties that occur in isolation from the effects of IFN-α that have been investigated in this thesis. The most commonly reported side-effect of both IFN-α and HCV is fatigue, which causes a significant amount of impairment for all patients, especially those on treatment. The interview also showed the importance of social support for both patients on treatment, and HCV patients.

We have provided evidence for a theory which proposes that the IFN-α-induced mood change is the result of an increase of symptoms that are present at Baseline along with additional pro-inflammatory cytokine induced sickness behaviours which potentially lower the threshold to deal with stressful stimuli. This mood change is characterised by mood lability and irritation and is accompanied by additional behavioural, somatic and cognitive symptoms. This behavioural syndrome occurs in almost all patients that take IFN-α, with additional factors that come into play when patients develop a PAE. The most severe PAE seen in this study was hypomania, which induces negative and anxious cognitions, and can lead to serious outcomes for the patient. The most common PAE was depression, with the IFN-α-induced depression exhibiting as a disorder of depressed mood and somatic symptoms.

The depression that can occur in patients taking IFN-α is distinct from both the general IFN-α-induced behavioural syndrome and a primary depression. Those patients who present with a primary depression have a disorder which is primarily a disorder of negative cognitions whereas those patients with an IFN-α-induced depression present with significantly more depressed mood symptoms.
We also propose that the depression seen in patients taking IFN-α could be interpreted to be an extreme form of sickness behaviour that shares common core features (anhedonia and neurovegetative symptoms) with melancholic depression. However, further research between these two groups is warranted.

There was no significant difference in neuropsychological functioning for those patients taking IFN-α, however, there is an acknowledgement that the test battery used was insufficient to pick up on any difficulties that may have occurred. There is also evidence provided that HCV is associated with attention and verbal recall problems, and depression leads to impairment in attention and recall. While there is no difference observed in the neuropsychological tests, patients taking IFN-α describe having problems with executive functions and memory, meaning that a better designed and more extensive neuropsychological test battery has the potential to reveal more about the exact mechanisms which may underlie these impairments. The two main reasons given for the lack of significance for IFN-α patients are because memory impairments are reported to occur in only 20% of patients, and patients also described having to put more cognitive effort into maintaining normal function, potentially meaning that patients are able to maintain a level of normal functioning with increased effort.
References


• Gaudiano, B. A. (2006). Review: cognitive behavioural therapy is an effective treatment for depression, panic disorder, and generalised anxiety disorder, but may be less effective in severe cases. *Evid Based Ment Health, 9*(3), 80.


References

References


• Lindsay, K. L. (2002). Introduction to therapy of hepatitis C. *Hepatology, 36*(5 Suppl 1), S114-120.


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APPENDIX I

Copy of neuropsychological and psychiatric tests
HAD Scale

Answer/Record Sheet

Initials: ___________ Date: _______ Group: ________

Testing session: _______ Participant Number: _______

Read each item carefully and circle the reply which comes closest to how you have been feeling in the last week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up'
   a) Most of the time
   b) A lot of the time
   c) Time to time, occasionally
   d) Not at all

2. I still enjoy the things I used to enjoy
   a) Definitely as much
   b) Not quite as much
   c) Only a little
   d) Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen
   a) Very definitely and quite badly
   b) Yes, but not too badly
   c) A little, but it doesn't worry me
   d) Not at all

4. I can laugh and see the funny side of things
   a) As much as I always could
   b) Not quite so much now
   c) Definitely not so much now
   d) Not at all

5. Worrying thoughts go through my mind
   a) A great deal of the time
   b) A lot of the time
   c) From time to time but not often
   d) Occasionally

6. I feel cheerful
   a) Not at all
   b) Not often
   c) Sometimes
   d) Most of the time

7. I can sit at ease and feel relaxed
   a) Definitely
   b) Usually
   c) Not often
   d) Not at all

8. I feel as if I am slowed down
   a) Nearly all of the time
   b) Very often
   c) Sometimes
   d) Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach
   a) Not at all
   b) Occasionally
   c) Quite often
   d) Very often

10. I have lost interest in my appearance
    a) Definitely
    b) I don't take so much care as I should
    c) I may not take quite as much care
    d) I take just as much care as ever

11. I feel restless as if I have to be on the move
    a) Very much indeed
    b) Quite a lot
    c) Not very much
    d) Not at all

12. I look forward with enjoyment to things
    a) As much as I ever did
    b) Rather less than usual
    c) Definitely less than I used to
    d) Hardly at all

13. I get sudden feelings of panic
    a) Very often indeed
    b) Quite often
    c) Not very often at all
    d) Not at all

14. I can enjoy a good book or radio or TV programme
    a) Often
    b) Sometimes
    c) Not often
    d) Seldom
# Dex Questionnaire

Self-rating

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your own experience.

<table>
<thead>
<tr>
<th>Subject’s name</th>
<th>Date</th>
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<thead>
<tr>
<th>Statement</th>
<th>Rarely</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Fairly often</th>
<th>Very often</th>
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</thead>
<tbody>
<tr>
<td>I have problems understanding what other people mean unless they keep things simple and straightforward.</td>
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<td>Never</td>
<td>Occasionally</td>
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<td>I act on what I think, doing the first thing that comes to mind.</td>
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<td>I sometimes talk about events or tasks that never actually happened, but believe did happen.</td>
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<td>I have difficulty thinking ahead or planning for the future.</td>
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<td>I sometimes get overexcited about things, and can be a bit over the top of things.</td>
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<td>I get events mixed up with each other, and get confused about the correct order of events.</td>
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<td>I have difficulty realizing the extent of my problems and am unrealistic about the future.</td>
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<tr>
<td>I am lethargic, or unenthusiastic about things.</td>
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<td>Never</td>
<td>Occasionally</td>
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<td>I do or say embarrassing things when in the company of others.</td>
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<td>Never</td>
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<td>Fairly often</td>
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<td>I really want to do something one minute, but couldn’t care less about it the next.</td>
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<td>Never</td>
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<th>Occasionally</th>
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<tr>
<td>I have difficulty showing emotion.</td>
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<td>I lose my temper at the slightest thing.</td>
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<td>Never</td>
<td>Occasionally</td>
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<td>I am unconcerned about how I should behave in certain situations.</td>
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<td>I find it hard to stop repeating saying or doing things once I’ve started.</td>
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<td>I tend to be very restless, and can’t sit still for any length of time.</td>
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<td>I find it difficult to stop myself from doing something even if I know I shouldn’t.</td>
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<td>I will say one thing, but will do something different.</td>
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<td>I find it difficult to keep my mind on something, and am easily distracted.</td>
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<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Fairly often</td>
<td>Very often</td>
<td></td>
</tr>
<tr>
<td>I have trouble making decisions, or deciding what I want to do.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Fairly often</td>
<td>Very often</td>
<td></td>
</tr>
<tr>
<td>I am unaware of, or unconcerned about, how others feel about my behaviour.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Occasionally</td>
<td>Sometimes</td>
<td>Fairly often</td>
<td>Very often</td>
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</tbody>
</table>

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A. Mood Episodes

MAJOR DEPRESSIVE EPISODE

Now I am going to ask you some more questions about your mood.

A1

In the past month...

...has there been a period of time when you were feeling depressed or down most of the day, nearly every day? (What was that like?)

IF YES: How long did it last? (As long as 2 weeks?)

A2

...what about losing interest or pleasure in things you usually enjoyed?

IF YES: Was it nearly every day? How long did it last? (As long as 2 weeks?)

CRITERIA FOR MAJOR DEPRESSIVE EPISODE

NOTE: Criterion B (i.e., does not meet criteria for a Mixed Episode) has been omitted from the SCID.

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Notes: In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

If neither A1 nor A2 is "+" during the current month, check for past Major Depressive Episode by asking questions A1 and A2 again looking for lifetime episodes, beginning with "Has there EVER..."

IF AT LEAST ONE PAST DEPRESSED PERIOD: Have you had more than one time like that? Which one was the worst?

If neither A1 nor A2 has ever been "+," go to A16, page 8 (Manic Episode).
### A. Mood Episodes

FOR THE FOLLOWING QUESTIONS, FOCUS ON THE WORST 2-WEEK PERIOD:

During [2-WEEK PERIOD]...

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>... how was your appetite? (What about compared with your usual appetite? Did you have to force yourself to eat? Eat [less/more] than usual? Was that nearly every day? Did you lose or gain any weight? How much? Were you trying to lose weight?)</td>
<td>A3</td>
</tr>
<tr>
<td>... how were you sleeping? (Trouble falling asleep, waking frequently, trouble staying asleep, waking too early, OR sleeping too much? How many hours a night compared with usual? Was that nearly every night?)</td>
<td>A4</td>
</tr>
<tr>
<td>... were you so fidgety or restless that you were unable to sit still? (Was it so bad that other people noticed it? What did they notice? Was that nearly every day?)</td>
<td>A5</td>
</tr>
<tr>
<td>IF NO: What about the opposite—talking or moving more slowly than is normal for you? (Was it so bad that other people noticed it? What did they notice? Was that nearly every day?)</td>
<td></td>
</tr>
<tr>
<td>... what was your energy like? (Tired all the time? Nearly every day?)</td>
<td>A6</td>
</tr>
</tbody>
</table>

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) **NOTE:** ALSO CONSIDER BEHAVIOR DURING THE INTERVIEW

(6) fatigue or loss of energy nearly every day
A. Mood Episodes

**A7**  
... how did you feel about yourself?  
(Worthless? Nearly every day?)

... what about feeling guilty about things 
you had done or not done? (Nearly every 
day?)

**A8**  
... did you have trouble thinking or 
concentrating? (What kinds of things did it 
interfere with? Nearly every day?)

IF NO: Was it hard to make decisions 
about everyday things?

**A9**  
... were things so bad that you were thinking 
a lot about death or that you would be better 
off dead? What about thinking of hurting 
yourself?

IF YES: Did you do anything to hurt 
yourself?

**A10**

(7) feelings of worthlessness or excessive 
or inappropriate guilt (which may be 
delusional) nearly every day (not merely 
self-reproach or guilt about being sick)

NOTE: CODE "-" IF ONLY LOW 
SELF-ESTEEM

(8) diminished ability to think or 
concentrate, or indecisiveness, nearly 
every day (either by objective account or 
as observed by others)

(9) recurrent thoughts of death (not just 
fear of dying), recurrent suicidal ideation 
without a specific plan, or a suicide 
attempt or a specific plan for committing 
suicide

AT LEAST FIVE OF A(1)--A(9) ARE 
"+" AND AT LEAST ONE OF THESE 
IS ITEM A(1) OR A(2).

If A10 above is "-" (i.e., fewer than five are "+"), ask the following if unknown:

Have there been any other times when you've been depressed and had even more of the symptoms 
that we've just talked about?

If "yes," go back to A1, page 3, and ask about that episode.
If "no," go to A16, page 8 (Manic Episode).
Appendix

A. Mood Episodes

A11 IF UNCLEAR: Has [the depression/OWN WORDS] made it hard for you to do your work, take care of things at home, or get along with other people?

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

If A11 above is "-" (i.e., symptoms not clinically significant), ask the following if unknown:

Have there been any other times when you've been depressed and it had more of an effect on your life?

If "yes," go back to A1, page 3, and ask about that episode.

If "no," go to A16, page 8 (Manic Episode).

A12 Just before this began, were you physically ill?

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition.

Just before this began, were you taking any medications?

Etiological general medical conditions include degenerative neurological illnesses (e.g., Parkinson's disease), cerebrovascular disease (e.g., stroke), metabolic conditions (e.g., vitamin B12 deficiency), endocrine conditions (e.g., hyper- and hypothyroidism, hyper- and hypoadrenocorticism), viral or other infections (e.g., hepatitis, mononucleosis, HIV), and certain cancers (e.g., carcinoma of the pancreas).

IF YES: Any change in the amount you were taking?

Just before this began, were you drinking or using any street drugs?

Etiological substances include alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phenycyclidine, sedatives, hypnotics, anxiolytics. Medications include antihypertensives, oral contraceptives, corticosteroids, anabolic steroids, anticancer agents, analgesics, anticholinergics, cardiac medications.

If there is any indication that the depression may be secondary (i.e., a direct physiological consequence of a general medical condition or substance), go to page 20 and return here to make a rating of "-" or "+."

If A12 above is "-" (i.e., mood is due to substance or general medical condition), ask the following:

Have there been any other times when you've been depressed and it was not because of [GENERAL MEDICAL CONDITION/SUBSTANCE USE]?

If "yes," go back to A1, page 3, and ask about that episode.

If "no," go to A16, page 8 (Manic Episode).
A Mood Episodes

A13 IF UNKNOWN: Did this begin soon after someone close to you died?

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss [death] of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

If A13 above is "-" (i.e., the depressed mood is better accounted for by Bereavement), ask the following:

Have there been any other times when you’ve been depressed and it was not because of the loss of a loved one?

If "yes," go back to A1, page 3, and ask about that episode.
If "no," go to A16, page 8 (Manic Episode).

A14 IF UNKNOWN: Have you had (SYMPTOMS RATED "+" ABOVE) in the past month?

CRITERIA A, C, D, AND E ARE "+" (MAKE A DIAGNOSIS OF MAJOR DEPRESSIVE EPISODE)

A15 How many separate times have you been [depressed/OWN WORDS] nearly every day for at least 2 weeks and had several of the symptoms that you just described, such as [SYMPTOMS OF WORST EPISODE]?

Total number of Major Depressive Episodes, including current (CODE 99 if too numerous or indistinct to count)
Appendix I: Neuropsychological and mood tests

SCID-CV Administration Booklet

A. Mood Episodes

HYPOMANIC EPISODE

If UNKNOWN: When you were [high/irritable/OWN WORDS], did it last for at least 4 days?

Have you had more than one time like that? (Which time were you the most [high/irritable/OWN WORDS]?)

FOR ITEMS A31–A37 ON PAGES 13 AND 14, FOCUS ON THE MOST EXTREME EPISODE.

If A30 is "—" (i.e., never any periods of elevated or irritable mood lasting at least 4 days), go to A45, page 17 (Dysthymic Disorder).

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.

CRITERIA FOR HYPOMANIC EPISODE

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

- inflated self-esteem or grandiosity
- decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

During [PERIOD OF MOST EXTREME HYPOMANIC SYMPTOMS]...

- how did you feel about yourself? (More self-confident than usual? Any special powers or abilities?)
- did you need less sleep than usual? IF YES: Did you still feel rested?
- were you much more talkative than usual? (Did people have trouble stopping you or understanding you? Did people have trouble getting a word in edgewise?)
- were your thoughts racing through your head?
- were you so easily distracted by things around you that you had trouble concentrating or staying on one track?
A. Mood Episodes

A36 ...how did you spend your time? (Work, friends, hobbies? Were you so active that your friends or family were concerned about you?)

IF NO INCREASED ACTIVITY: Were you physically restless? (How bad was it?)

A37 ...did you do anything that could have caused trouble for you or your family? (Buying things you didn't need? Anything sexual that was unusual for you? Reckless driving?)

A38 (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

A36 (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

AT LEAST THREE OF B(1)-B(7) ARE "+" (OR FOUR IF MOOD IS IRRITABLE AND NOT ELEVATED) A38

If A38 is "-" (i.e., fewer than three are "+"), ask the following:

Have there been any other times when you were [high/irritable/OWN WORDS] and had even more of the symptoms that we've just talked about?

If "yes," go back to A30, page 13, and ask about that episode. If "no," go to A45, page 17 (Dysthymic Disorder).

A39 IF UNKNOWN: Is this very different from the way you usually are? (How were you different? At work? With friends?)

If A39 is "-" (i.e., characteristically "hypomanic"), ask the following:

Have there been any other times when you were [high/irritable/OWN WORDS] and you were really different from the way you usually are?

If "yes," go back to A30, page 13, and ask about that episode. If "no," go to A45, page 17 (Dysthymic Disorder).
Appendix I: Neuropsychological and mood tests

SCID-CV Administration Booklet

A. Mood Episodes

A40 If UNKNOWN: Did other people notice the change in you? (What did they say?)

D. The disturbance in mood and the change in functioning are observable by others.

If A40 is "-" (i.e., not observable by others), ask the following:

Have there been any other times when you were [high/irritable/OWN WORDS] and other people did notice the change in the way you were acting?

If "yes," go back to A30, page 13, and ask about that episode.

If "no," go to A45, page 17 (Dysthymic Disorder).

A41 If UNKNOWN: At that time, did you have serious problems at home or at work (school) because you were [SYMPTOMS] or did you have to go into a hospital?

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

If A41 is "-" (i.e., severe enough to cause marked impairment, etc.) AND either hospitalization was required or duration was 1 week or longer, go back to A17, page 8, and recode "+" for that item, then continue with the rest of the ratings for Manic Episode. Otherwise, if there was marked impairment in functioning but duration was less than 1 week, skip to A45, page 17, and eventually code "2" for item D12, page 49.

A42 Just before this began, were you physically ill?

Just before this began, were you taking any medications?

IF YES: Any change in the amount you were taking?

Just before this began, were you drinking or using any street drugs?

F. The symptoms are not due to the direct physiological effects of a substance (i.e., a drug of abuse, a medication) or a general medical condition.

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder but are considered Substance-Induced Mood Episodes.

Refer to list of possibly etiological general medical conditions and substances included with item A27 (page 11).
A. Mood Episodes

If A42 above is "-" (i.e., the hypomania is due to a substance or general medical condition), ask the following:

Have there been any other times when you were [high/irritable/OWN WORDS] and you were not [physically ill/taking medication/using SUBSTANCE]?

If "yes," go back to A30, page 13, and ask about that episode.
If "no," go to A45, page 17 (Dysthymic Disorder).

A43 IF UNKNOWN: Have you had [SYMPTOMS RATED "+" ABOVE] in the past month? CRITERIA A, B, C, D, E, AND F ARE "+"

MAKE A DIAGNOSIS OF HYPOMANIC EPISODE

A44 How many separate times were you [high/irritable/OWN WORDS] and had [ACKNOWLEDGED HYPOMANIC SYMPTOMS] for a period of time?

Total number of Hypomanic Episodes (CODE 99 if too indistinct or numerous to count)

YOU ARE FINISHED EVALUATING MOOD EPISODES. GO TO MODULE B (PSYCHOTIC AND ASSOCIATED SYMPTOMS), B1 (PAGE 25).
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
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<tbody>
<tr>
<td>&quot;Is there anything you look forward to?&quot;</td>
<td>1) Why?</td>
</tr>
<tr>
<td>&quot;Have you stopped doing anything you used to do?&quot;</td>
<td></td>
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<tr>
<td>&quot;You feel there has been a change in your ability to do things&quot;</td>
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<tr>
<td>&quot;How has your mood been during the past week?&quot;</td>
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<tr>
<td>&quot;1. Work &amp; Activities&quot;</td>
<td></td>
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<tr>
<td>&quot;How long have you been feeling this way?&quot;</td>
<td>1-4) How long have you been feeling this way?</td>
</tr>
<tr>
<td>&quot;Have you been crying at all?&quot;</td>
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<tr>
<td>&quot;COMMUNICATIVE? Every day? All day?&quot;</td>
<td></td>
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<tr>
<td>&quot;In the last week how often have you had a depressed mood?&quot;</td>
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<tr>
<td>&quot;When your mood been like this past week?&quot;</td>
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</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working, communication and work relationships</td>
<td>4</td>
</tr>
<tr>
<td>Visually bearable</td>
<td>3</td>
</tr>
<tr>
<td>Communicative           (social expression) Positive, score</td>
<td>2</td>
</tr>
<tr>
<td>Comprehensible           (social expression) Positive, score</td>
<td>1</td>
</tr>
<tr>
<td>Doctor's opinion on diagnosis</td>
<td>0</td>
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</tbody>
</table>

**Assessment no.**

**Date**

**Patient's number**

**Patient's name**
Appendix I: Neuropsychological and mood tests

- Has there been any change in your interest in sex this week?
- How has your interest been in sex this week?
- Are you not depressed?
- Is something you have thought about much?
- Is that unusual for you?

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- Have you gained any of the weight back?
- Do you think your clothes are any looser on you?
- How much?

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- Have you lost any weight since this last weight?

- Weight Loss

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- This week, have you felt any heaviness in your limbs, back or head?
- This week, have you had any dizziness, headaches, muscle aches?

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<td>2</td>
<td>1</td>
<td>0</td>
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- Have you been tired all the time?
- How has your energy been this past week?

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- What about compared to your usual appeal?

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- Somatic symptoms (g3)

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- Somatic symptoms (g4)

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</table>
**Appendix 1: Neuropsychological and mood tests**

If you feel really out of it, what time do you usually wake up?  

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What time do you usually wake up (before you get depressed)?

For the last time, this past week?

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<tr>
<td>2</td>
<td>3</td>
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</table>

What time have you been waking up in the morning?

**5. Insomnia diary (BEFORE 6TH NIGHT SUFFICIENT)**

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</table>

Have you felt your sleeping has been restless or disturbed some nights?

When you get back to bed, are you able to fall right back asleep?

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<tbody>
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<td>2</td>
<td>3</td>
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</table>

What do you do? (only go to the bathroom?)

In the middle of the night? (7) do you get out of bed?

During the last week, have you been waking up

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<tr>
<td>2</td>
<td>3</td>
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</table>

*Insomnia Middle (up to 4 AM)*

How many nights this week have you had trouble falling asleep?

(7) nights after you go to bed, how long have you lain in bed before you fall asleep?

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<tbody>
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<td>0</td>
<td>1</td>
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<tr>
<td>2</td>
<td>3</td>
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</table>

How have you been sleeping over the last week?

**7. Insomnia Early**

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<tbody>
<tr>
<td>0</td>
<td>1</td>
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<tr>
<td>2</td>
<td>3</td>
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</tbody>
</table>
## Appendix 1: Neuropsychological and mood tests

<table>
<thead>
<tr>
<th>Question</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. Anxiety Psychie</td>
<td>0, 1</td>
</tr>
<tr>
<td>Things you would mind someone worry about?</td>
<td></td>
</tr>
<tr>
<td>Have you been worrying about the little unimportant things?</td>
<td></td>
</tr>
<tr>
<td>Have you been feeling especially tense or irritable this past week?</td>
<td></td>
</tr>
<tr>
<td>11. Suicide</td>
<td>0, 1</td>
</tr>
<tr>
<td>Have you actually done anything to hurt yourself?</td>
<td></td>
</tr>
<tr>
<td>What about having thoughts of killing or even killing yourself?</td>
<td></td>
</tr>
<tr>
<td>This past week have you had thoughts that life is not worth living?</td>
<td></td>
</tr>
<tr>
<td>Do you feel you're being punished by being sick?</td>
<td></td>
</tr>
<tr>
<td>Have you thought that you've brought this illness on yourself in some way?</td>
<td></td>
</tr>
<tr>
<td>You've done or don't?</td>
<td></td>
</tr>
<tr>
<td>Have you been feeling guilty about anything that</td>
<td></td>
</tr>
<tr>
<td>Feeling you've done things wrong, let others down?</td>
<td></td>
</tr>
<tr>
<td>Have you been especially critical of yourself this past week?</td>
<td></td>
</tr>
<tr>
<td>10. Feelings of guilt</td>
<td>0, 1</td>
</tr>
</tbody>
</table>

**Example:**

12. Anxiety Psychie

- 0: No difficulty
- 1: Some difficulty
- 2: Significant difficulty
### Appendix I: Neuropsychological and mood tests

<table>
<thead>
<tr>
<th>Question</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on observation</td>
<td></td>
</tr>
<tr>
<td>15. Insight</td>
<td></td>
</tr>
<tr>
<td>(Y) Like what for example, how often has that happened?</td>
<td></td>
</tr>
<tr>
<td>Really do you feel?</td>
<td></td>
</tr>
<tr>
<td>Have you found yourself asking for help with things that you could</td>
<td></td>
</tr>
<tr>
<td>Do you complain about how you feel physically?</td>
<td></td>
</tr>
<tr>
<td>How have your physical health or how your body is working?</td>
<td></td>
</tr>
<tr>
<td>In the last week, how much have your thoughts been focused on</td>
<td></td>
</tr>
<tr>
<td>1. Hypochondrias</td>
<td></td>
</tr>
<tr>
<td>How bad have they gotten? How much of the time, how often have you got them?</td>
<td></td>
</tr>
<tr>
<td>How much have these things been bothering you this past week?</td>
<td></td>
</tr>
<tr>
<td>Having to urinate frequently    ﶚ ﹫ Sighing    ﹫ Sweating</td>
<td></td>
</tr>
<tr>
<td>Headaches    ﹫ Migraines   ﹫ Hypersomnolent    ﹫ Cramps</td>
<td></td>
</tr>
<tr>
<td>Dry mouth    ﹫ Clogger    ﹫ Diffusion    ﹫ Cramps</td>
<td></td>
</tr>
<tr>
<td>In this last week, have you had any of these physical symptoms?</td>
<td></td>
</tr>
<tr>
<td>1. Anxiety Some</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix I: Neuropsychological and Mood Tests

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much worse do you feel? A little bit or a lot worse?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. At any particular time of day - morning or evening?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. This past week, have you been feeling better or worse overall?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 18. Dual Variation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in doing xeroxing, writing, drawing, and mental arithmetic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in doing mental arithmetic, writing, and drawing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in doing mental arithmetic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal speed and thought</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 17. Agitation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete stop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incessant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 16. Psychomotor Retardation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired ability to concentrate, decreased motor activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor slowing manifested in difficulty speaking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal speed and thought</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Compulsive Symptoms

(7) Can you give me an example?

In the past week, have there been things you've had to do over and over again, like checking the locks on the doors several times?

(7) Tell me about it.

Was anything to give you a hard time or to hurt you?

This past week, have you felt that anyone...

2.0. Paranoid Symptoms

(7) How often this week has that happened?

(7) How bad has that been?

Of all of the things that other people in some strange way...

Everything is unreal -- or you're in a dream...

In the past week, have you ever suddenly had the feeling that...

15. Depersonalization or Dissociation
Appendix I: Neuropsychological and mood tests

<table>
<thead>
<tr>
<th>Total Score</th>
<th>(tA)</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression of Worthlessness</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Volume loss in no good of interest</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Depression only increases loss of self esteem</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Positive states of self esteem on questions</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Do you feel that you are worth nothing at all, either to yourself or others?**
- **(a) How often did you feel this way in the past week?**
- **(b) Did you feel that you are in no good of interest?**
- **(c) Did you feel that others are better than you?**
- **(d) Do other people whom you know and respect see you as good as other people whom you know and respect?**
- **(e) During the past week, have you felt that you are worth less?**

<table>
<thead>
<tr>
<th>2.4 Worthlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>(tA)</td>
</tr>
<tr>
<td>Volume loss in no good of interest</td>
</tr>
<tr>
<td>Depression only increases loss of self esteem</td>
</tr>
<tr>
<td>Positive states of self esteem on questions</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- **(a) When people tell you that you will be well (or stay well), do you feel reassured?**
- **(b) Do you have this doubt all the time?**
- **(c) Do you doubt that things will improve for you?**
- **(d) This past week, were you optimistic or pessimistic about your future?**

<table>
<thead>
<tr>
<th>2.3 Hopelessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>(tA)</td>
</tr>
<tr>
<td>Volume loss in no good of interest</td>
</tr>
<tr>
<td>Depression only increases loss of self esteem</td>
</tr>
<tr>
<td>Positive states of self esteem on questions</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- **(a) Simple activities like going outside or eating?**
- **(b) Did you need the physical help of others to complete?**

<table>
<thead>
<tr>
<th>2.2 Helplessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>(tA)</td>
</tr>
<tr>
<td>Volume loss in no good of interest</td>
</tr>
<tr>
<td>Depression only increases loss of self esteem</td>
</tr>
<tr>
<td>Positive states of self esteem on questions</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- **(a) Did other people have to urge you to lead to your responsibilities?**
- **(b) Were those feelings so bad that you would say you felt helpless?**
- **(c) Were routine activities thwarted when you felt overwhelmed?**
- **(d) In the past week, did you feel you had trouble coping?**
### Appendix I: Neuropsychological and mood tests

#### 1. Anxious mood

Have you been worrying about anything this past week?

(Y) What sorts of things have been worrying you?

(Y) Have these thoughts affected you in your day to day life?

(Y) How often?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Small worries and insecurities</td>
</tr>
<tr>
<td>2</td>
<td>In a state of anxiety, which may find hard to control, but worrying is still about minor matters doesn't affect daily life</td>
</tr>
<tr>
<td>3</td>
<td>Clear state of anxiety that occasionally affects daily life</td>
</tr>
<tr>
<td>4</td>
<td>Feeling of dread clearly interferes with daily life</td>
</tr>
</tbody>
</table>

#### 2. Tension

Have you felt tense this week?

(Y) Have you felt nervous?

(Y) Have you found it difficult to relax?

(Y) Have these feelings interfered with your daily life?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Reports being slightly more tense and nervous</td>
</tr>
<tr>
<td>2</td>
<td>Patient is clearly unable to relax and full of inner unrest, which finds difficult to control, but it does not affect daily life</td>
</tr>
<tr>
<td>3</td>
<td>The tension and unrest occasionally interfere with daily life</td>
</tr>
<tr>
<td>4</td>
<td>Tensions and unrest clearly interfere with daily life and work</td>
</tr>
</tbody>
</table>
3. Fears

Is there anything that you are scared of?

Note

(Y) How do you feel when you encounter ______
Do you think of ______ often when you are not exposed to it?

(Y) Does this fear interfere with your daily life and work?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Has fears but not of phobic intensity</td>
</tr>
<tr>
<td>2</td>
<td>Experiences phobic anxiety but is able to fight it</td>
</tr>
<tr>
<td>3</td>
<td>Finds it difficult to fight or overcome the phobic anxiety, occasionally affects daily life</td>
</tr>
<tr>
<td>4</td>
<td>Phobic anxiety clearly interferes with daily life</td>
</tr>
</tbody>
</table>

4. Insomnia

Have you been having trouble sleeping this week?

(Y) Can you describe a typical night’s sleep to me? How many hours per night have you slept?

Only ask these questions if previous response is not enough to get a score from

(Y) Have you had trouble falling asleep? Have you been waking during the night?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Sleep duration slightly reduced, no change in sleep depth</td>
</tr>
<tr>
<td>2</td>
<td>Sleep duration and depth reduced, sleep is more superficial and somewhat disturbed</td>
</tr>
<tr>
<td>3</td>
<td>Sleep duration and depth markedly changed, sleep only totals a few hours</td>
</tr>
<tr>
<td>4</td>
<td>Sleep is so shallow that patients only speak of dozing or short periods of slumber, no real sleeping</td>
</tr>
</tbody>
</table>
5. Difficulties in concentration and memory

How has your memory been this week?
How has your concentration been this week?
(Refer to interview answers)

<table>
<thead>
<tr>
<th>0</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slight/doubtful difficulties in memory and concentration</td>
</tr>
<tr>
<td>2</td>
<td>Even with a major effort it is difficult to concentrate on daily routine</td>
</tr>
<tr>
<td>3</td>
<td>Pronounced difficulties with concentration and memory (e.g., reading newspaper or tv programme)</td>
</tr>
<tr>
<td>4</td>
<td>During interview obvious concentration and memory impairment</td>
</tr>
</tbody>
</table>

6 General somatic symptoms: Muscular

Have you experienced any unusual pain, stiffness or soreness in your muscles this week?
(Y) Where have you been experiencing this pain?

Why are you experiencing this pain?
How much does this pain interfere with your daily life?

<table>
<thead>
<tr>
<th>0</th>
<th>Absent/ No more stiff or sore than usual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slightly more stiff/ sore than usual</td>
</tr>
<tr>
<td>2</td>
<td>The symptoms have the characteristic of pain</td>
</tr>
<tr>
<td>3</td>
<td>Muscle pain interferes to some extent with patient’s daily life and work</td>
</tr>
<tr>
<td>4</td>
<td>Muscle pain present most of the time and clearly interferes with daily life and work</td>
</tr>
</tbody>
</table>
7. General somatic symptoms: Sensory
Have you experienced any of these symptoms in the last week;
Getting tired easily____ Feeling weak____ Ringing in your ears____
Blurring of your vision____ Hot and cold flashes____ Prickling sensations____
(Y) Why did these things happen?
(Y) Is this different from usual for you?
(Y) How often have these symptoms occurred in the last week?
Do they interfere with your daily life and work?

<table>
<thead>
<tr>
<th></th>
<th>Absent</th>
<th>Doubtful whether more pronounced than usual</th>
<th>Sensations of pressure lead to ringing in ears, visual disturbance, prickling sensations</th>
<th>These symptoms interfere somewhat with daily life and work</th>
<th>Symptoms are present most of the time and clearly interfere with life and work</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. Cardiovascular symptoms
In the last week have you experienced of these symptoms;
Racing heartbeat____ Heart palpitations____ Chest pain____
Tightness in your chest____ Throbbing in your blood vessels____ Fainting____
(Y) Why did these things happen?
(Y) Is this different from usual for you?
(Y) How often have these symptoms occurred in the last week?
Do they interfere with your daily life and work?

<table>
<thead>
<tr>
<th></th>
<th>Absent</th>
<th>Doubtful whether more pronounced than usual</th>
<th>1 or more symptoms are present but they are controllable</th>
<th>Occasionally these symptoms are hard to control and interfere with life and work</th>
<th>Symptoms are present most of the time and clearly interfere with life and work</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9. Respiratory symptoms
In the last week have you experienced any of these symptoms;
Constriction/contraction in chest  Difficulty catching breath  Sighing
Choking sensations
(Y) Why did these things happen?
(Y) Is this different from usual for you?
(Y) How often have these symptoms occurred in the last week?
Do they interfere with your daily life and work?

<table>
<thead>
<tr>
<th></th>
<th>Absent</th>
<th>Doubtful whether more pronounced than usual</th>
<th>1 or more symptoms are present but they are controllable</th>
<th>Occasionally these symptoms are hard to control and interfere with life and work</th>
<th>Symptoms are present most of the time and clearly interfere with life and work</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
<td>Doubtful whether more pronounced than usual</td>
<td>1 or more symptoms are present but they are controllable</td>
<td>Occasionally these symptoms are hard to control and interfere with life and work</td>
<td>Symptoms are present most of the time and clearly interfere with life and work</td>
</tr>
</tbody>
</table>

10. Gastro-intestinal symptoms
In the last week have you experienced any of these symptoms;
Diarrhoea  Heartburn  Nausea
Abdominal rumbling  Throbbing in your blood vessels  Faintness
(Y) Why do you think these things happened?
(Y) Is this different from usual for you?
(Y) How often have these symptoms occurred in the last week?
Do they interfere with your daily life and work?

<table>
<thead>
<tr>
<th></th>
<th>Absent</th>
<th>Doubtful whether more pronounced than usual</th>
<th>1 or more symptoms are present but they are controllable</th>
<th>Occasionally these symptoms are hard to control and interfere with life and work</th>
<th>Symptoms are present most of the time and clearly interfere with life and work</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
<td>Doubtful whether more pronounced than usual</td>
<td>1 or more symptoms are present but they are controllable</td>
<td>Occasionally these symptoms are hard to control and interfere with life and work</td>
<td>Symptoms are present most of the time and clearly interfere with life and work</td>
</tr>
</tbody>
</table>
11. Genito-urinary symptoms

Women: In the last month have you noticed anything different about your periods?

Men: In the last week have you been experiencing any difficulties with sex?

(Y) Is this different from usual for you?

Can you describe these difficulties to me?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Doubtful whether present, or different</td>
</tr>
<tr>
<td>2</td>
<td>One or more symptoms present but do not affect daily life and work</td>
</tr>
<tr>
<td>3</td>
<td>Occasionally these difficulties affect daily life and work</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms are present most of the time and clearly affect daily life and work</td>
</tr>
</tbody>
</table>

12. Other autonomic symptoms

In the last week have you experienced any of these symptoms;

Dryness of your mouth______Blushing______Getting very pale______

Sweating______Dizziness______

(Y) Why do you think these things happened?

(Y) Is this different from usual for you?

(Y) How often have these symptoms occurred in the last week?

Do they interfere with your daily life and work?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Doubtful whether more pronounced than usual</td>
</tr>
<tr>
<td>2</td>
<td>1 or more symptoms are present but they are controllable</td>
</tr>
<tr>
<td>3</td>
<td>Occasionally these symptoms are hard to control and interfere with life and work</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms are present most of the time and clearly interfere with life and work</td>
</tr>
</tbody>
</table>
### 13. Depressed mood
*(Refer to HAM-D)*

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Doubtful whether more sad, or only vaguely more so</td>
</tr>
<tr>
<td>2</td>
<td>More sad than usual, but lacks helplessness and hopelessness</td>
</tr>
<tr>
<td>3</td>
<td>Clear non-verbal signs of depression and/or hopelessness</td>
</tr>
<tr>
<td>4</td>
<td>Severe depressed mood which dominates interview</td>
</tr>
</tbody>
</table>

*Based on observation*

### 14. Behaviour during interview

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Does not appear anxious</td>
</tr>
<tr>
<td>1</td>
<td>Doubtful whether patient is anxious</td>
</tr>
<tr>
<td>2</td>
<td>Moderately anxious</td>
</tr>
<tr>
<td>3</td>
<td>Markedly anxious</td>
</tr>
<tr>
<td>4</td>
<td>Overwhelmed by anxiety (e.g., shaking and trembling all over)</td>
</tr>
</tbody>
</table>

Total Score:
### Appendix I: Neuropsychological and mood tests

<table>
<thead>
<tr>
<th>Participant Number:</th>
<th>Session:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louise</td>
<td>Karen</td>
</tr>
<tr>
<td>Karen</td>
<td>Carol</td>
</tr>
<tr>
<td>Lucy</td>
<td>Amy</td>
</tr>
<tr>
<td>Elaine</td>
<td></td>
</tr>
</tbody>
</table>

#### BLOCK 1
- Amy
- Karen
- Louise
- Elaine

#### BLOCK 2
- Lucy
- Carol
- Louise
- Karen

#### BLOCK 3
- Amy
- Karen
- Carol
- Louise

#### BLOCK 4
- Elaine
- Lucy
- Karen
- Amy
### DELAYED FACE-NAME RECALL

<table>
<thead>
<tr>
<th>Date:</th>
<th>Subject Number:</th>
<th>Age:</th>
</tr>
</thead>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amy</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Karen</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Carol</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Louise</td>
<td></td>
</tr>
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NAME RECALL

Date: ___________  Subject Number: ___________  Age: ___________

1. ___________
2. ___________
3. ___________
4. ___________
5. ___________
6. ___________

Extras: ___________  ___________  ___________  ___________

Total Correct: ___________

Face-Name Recall Score: ___________  ___________
Face Recognition Score: ___________  ___________
Name Recall Score: ___________  ___________

FACE RECOGNITION
## FACE RECOGNITION

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<tr>
<td>Megan:</td>
<td>Yes / No</td>
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**Zoo Map Test** Version 1

**Rules**

Imagine that you are going to visit a zoo. Your task is to plan a route in order to visit the following (not necessarily in this order):

- Elephant house
- Lion's cage
- Llama enclosure
- the Café
- the Bears
- Bird sanctuary.

When planning your route the following rules must be obeyed:

- start at the entrance and finish with a picnic
- you may use the shaded paths as many times as you like but the unshaded ones only once
- you may take only one Camel ride.
**Zoo Map Test Version 1**

**Rules**

Imagine that you are going to visit a zoo.

Your task is to plan a route in order to visit the following (not necessarily in this order):

- Elephant house
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- Llama enclosure
- the Café
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When planning your route the following rules must be obeyed:

- start at the entrance and finish with a picnic
- you may use the shaded paths as many times as you like but the unshaded ones only once
- you may take only one Camel ride.
Appendix I: Neuropsychological and mood tests

BADS Scoring  
Zoo Map Test  
Answer/Record Sheet

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<td>Group:</td>
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Zoo Map Test Scoring:

**VERSION 1**

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</tr>
<tr>
<td>Llamas</td>
<td>Llamas / Café / Elephants</td>
<td>B -</td>
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<tr>
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<td>Elephants / Café</td>
<td>C -</td>
</tr>
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<td>Café / Elephants / Llamas</td>
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<tr>
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<td>E -</td>
</tr>
<tr>
<td>Lions</td>
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<tr>
<td>Birds</td>
<td>Bird Sanctuary</td>
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<tr>
<td>Number of deviations from the path (i.e. cutting across grass)</td>
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<tr>
<td>Number of failures to make a continuous line</td>
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<td>Number of inappropriate places visited</td>
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<tr>
<td>TOTAL</td>
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Planning time | 151 | Total time | 194 | Version 1 raw score = SEQUENCE SCORE - TOTAL ERRORS | 8 |
Appendix I: Neuropsychological and mood tests

BADS Scoring
Zoo Map Test
Answer/Record Sheet

Initials: K-M    Date: 21/08/09

Group: Testing session:  

Participant Number: 451    Score: 16

Zoo Map Test Scoring:

**VERSION 1**

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Errors | Score
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Total number of occasions path used more than once | 8
Number of deviations from the path (i.e. cutting across grass) | 8
Number of failures to make a continuous line | 8
Number of inappropriate places visited | 8

**TOTAL** | 8

Planning time 151 | Total time 194

Version 1 raw score = SEQUENCE SCORE - TOTAL ERRORS | 8
Key Search Test

Subject's name: RM (313)
**BADS Scoring**
**Key Search Test**
**Answer/Record Sheet**

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<tr>
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<td><strong>16</strong></td>
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</table>
APPENDIX II

Poster of FNP age effect
Lifespan changes in hippocampal- and frontally-driven memory: trajectories of decline and their relationship to cortisol levels

Joanne Feeney¹, S.M. O'Mara¹
¹Trinity College Institute of Neuroscience and School of Psychology

Introduction

There is now evidence that a gradual age-related decline in many facets of cognition begins as early as young adulthood (Park et al., 2002). The factors influencing the course of this decline are not yet clear. Biological changes, such as increased production of glucocorticoids with age, may play a role in susceptibility to cognitive impairment, as elevated cortisol levels have been shown to adversely affect memory performance (Lee et al., 2007).

Our primary aim was to examine changes in associative memory performance in a cohort of young and middle aged individuals, as evidence suggests that type of memory may be particularly vulnerable to the effects of aging (Naveh-Benjamin, 2000).

A second aim was to investigate task performance in relation to cortisol levels. We hypothesized that increased production of cortisol may adversely affect task performance in older individuals.

Methods & Materials

Healthy participants aged 20-64 (20-29 N=20; 30-39 N=18; 40-49 N=19; 50-64 N=22) performed a Face-Name pairs associative memory task (Zeineh et al., 2003), as part of a larger study.

Participants viewed 8 female faces consecutively, each paired with a name. They were given 4 blocks of repeated learning, with memory being tested after each block. Participants also performed a delayed recall task approximately 20 mins later.

Discussion

We observed age-related impairments in task performance in the 40s and 50-64 age groups compared to the 20s and 30s groups. Differences on name recall and face recognition individually were only evident between the 20s and 50-64 age groups. This suggests that a deficit in binding a particular face to a particular name develops earlier than other facets of long-term memory. Interestingly there were no significant differences between the 20s and 30s groups on any of the measures.

Pre-test levels of cortisol were found to be related to encoding success only in individuals aged 40-64, with higher levels of cortisol predicting poorer face-name encoding performance. There was no significant relationship between cortisol and any of the other measures, nor between cortisol and task performance in the 25-39 year olds. These results suggest that higher levels of cortisol are having a negative impact on associative memory ability in the over 40s, and are likely to be contributing to the task impairment in this group.

References

This research was funded by the Health Research Board.
Appendix III

Copy of interviews
HCV and Control interview

Participant number:

Group number:

This interview is designed so that I may try and understand how you feel about your health, your sleep, your mood, personality and memory. This is so I can see if your results are different to those people who have Hepatitis C and also to those people who have to use the treatment Interferon alpha.

In general anything you tell me will be in complete confidence, however if during the course of this interview something is said which may be a cause for concern and means that you own health and wellbeing or that of some-one else may be at risk I will advise you on how you can get help concerning this with the help of the counselling service at Trinity College Dublin. However the results from this interview shall be in an anonymous format and your name will never be used in relation to the data gathered from this interview.

I am going to record the interview so that it may be typed up. Once the interview has been typed up, a copy of it shall be stored on the computer, and it shall be deleted from the recorder.

Some questions may seem fairly personal and if you really don’t want to answer them then please just let me know.

I would appreciate it if you could answer all questions as truthfully as possible.

The first few questions I am going to ask you concern your health.

If you were to rate your own health would you rate it as;

1. Excellent □
2. Very good □
3. Good □
4. Fair □
5. Poor □

Can you explain your reasons for describing your health in this way?

Does your state of health limit the physical activities that you can do?

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Can you list some activities that are affected?
Vigorous activities (Running, lifting heavy objects, strenuous sports)

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Moderate activities (Moving table, pushing vacuum cleaner, playing golf)

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

How much physical activity do you get per week in hours? This includes things like walking, or if you have a job that is physically demanding.

What type of activities do you do?

How much exercise do you get per week in hours? This includes things such as running or going to the gym.

What type of exercise do you get?

Has your physical health interfered with your normal social activities with family, friends, neighbours, work colleagues etc?

1. No □
2. A bit □
3. Moderately □
4. Quite a bit □
5. Extremely □

THE FOLLOWING QUESTION SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes why do you think this is?

HCV ONLY

How supportive would you say your friends and family have been to you during your illness?

1. Excellent □
2. Good □
3. Fair □
4. Poor □
5. Have had no support □
Appendix III: Interviews

How much bodily pain have you had in the last month?

1. None □
2. Very mild □
3. Mild □
4. Moderate □
5. Severe □
6. Very severe □

Do you agree with any of these statements in relation to how you feel about your state of health? You can answer

1. My health makes me worried □
2. My health makes me upset □
3. My health makes me angry □
4. My health makes me happy □
5. My health doesn’t bother me □

What other words describe the way that you feel?

Why does that word/ those words remind you of your health?

How much do you agree with the following statement?

"I expect my health to get worse over the next year"

1. Definitely yes □
2. Possibly yes □
3. Unsure □
4. Possibly not □
5. Definitely not □

Why do you think that is?

Do you experience difficulties with tiredness above and beyond something that you would consider normal for someone of your age?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If you are having difficulties with tiredness (if you answered yes) how long have you been like this?

1. During the last week □
2. During the last month □
3. During the last few months □
4. During the last year □
5. During the last few years □
Appendix III: Interviews

How long exactly have you been feeling tired for?

Why do you think you have been experiencing problems with tiredness?

Have you been sleeping well over the last month?

1. Yes □
2. No □

How many nights per week on average do you have difficulty sleeping?

1. 7 nights a week □
2. 4-6 nights a week □
3. 1-3 nights a week □
4. 0 (no difficulty sleeping) □

Do you agree with any of these statements in relation to how you normally sleep?

1. I have difficulty falling asleep □
2. I wake up during the night □
3. I wake up early and I can’t go back to sleep □
4. I sleep fine and have no problems □

What time do you normally go to bed at?

How long after getting into bed does it take you to fall asleep?

What time do you normally wake up at?

How long after waking up does it take you to get out of bed?

The next portion of the experiment has questions in it which shall ask you about your mood and personality.

Did a member of your family ever get diagnosed as having a psychiatric disorder and have to go and see a psychiatrist or get put onto medication for their mood?

Would you describe yourself as more of an optimist (someone who always looks at the bright side of things) or pessimist (someone who always sees things negatively)?

1. Optimist □
2. Pessimist □

Why does that word describe you more?

How would you rate how happy you have been over the last month?
1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS SAD.

If it is different what has happened to make you feel this way?
OR
If you are sad and usually feel sad why do you think you normally feel this way?

How long have you felt this way?

What caused you to feel this way?

Have you previously experienced any episode of depression in your life that has lasted a week or more?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If you answered yes why did it happen?

How long were you depressed for?

Why did the depression last for so long?

Have you ever being diagnosed by a doctor as having depression?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

When was this?

Would you describe yourself as someone who is calm or easily stressed out?
1. Calm □
2. Easily stressed □

Why does that word describe you more?

How would you rate how worried you have been over the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS ANXIOUS.

If it is different what has happened to make you feel this way?
OR
If you normally feel anxious anyway why do you think this is?

How long have you felt this way?

What caused you to feel this way?

Have you previously experienced any episodes of anxiety in your life that have lasted a week or more?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If you answered yes why did it happen?

How long were you anxious for?

Why did the anxiety last for so long?

Have you ever being diagnosed by a doctor as having an anxiety disorder?

1. Yes □
2. No □
THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

When was this?

Have you ever been diagnosed by a medical doctor as having any other psychiatric disorder?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes which disorder was it?

When did it occur?

Would you rate yourself as someone who is easily irritated?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes what sort of things irritate you?

Would you say that this irritation is irrational?

1. Yes □
2. No □

How irritated would you say you have been for the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Do you get easily angry?

1. Yes □
2. No □
THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

Is this anger above and beyond what you would consider normal?

1. Yes □
2. No □

What sorts of things make you angry?

How angry would you say you have been for the last month?
1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

If you had to say that one of the following statements would sum up how you have been feeling over the last month, which one would most closely represent you?

1. I have felt happy □
2. I have felt quiet □
3. I have felt sad □
4. I have felt worried □
5. I have felt angry □
6. Other, please specify? □

Explain why you chose that word/ those words?

The next few questions are going to ask you about your memory and attention.

How would you rate how your memory has being over the last month?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □
THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If it is different what sorts of things have been happening recently that didn’t happen before?

OR

If it is normally bad anyway why would you say this is?

How long has your memory being this way?

What do you think caused your memory to get this way?

During the last month have you been at all forgetful, misplacing things and forgetting names?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes can you give me some specific examples?

How would you rate how your ability to concentrate has being over the last month?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If it is different what sorts of things have been happening recently that didn’t happen before?

How long has your concentration being this way?

What do you think caused your concentration to get this way?
Appendix III: Interviews

Now I am going to give you a few examples of activities that involve concentration, could you rate how easily you find it to concentrate when doing the following things?

a. Reading a book or magazine
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (Have to keep re-reading passages) □

b. Watching a film or TV show with a complicated plotline
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (get easily lost, cannot remember any of the character names) □

c. Doing something you consider boring
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (Just cannot concentrate at all) □

Thank you for taking the time to answer these questions for me
0 month interview IFN-α

Patient number:

Group number:

This interview is designed so that I may try and understand how your illness makes you feel and how you feel about the fact that you have to use the treatment Interferon alpha. In general anything you tell me will be in complete confidence, however if during the course of this interview something is said which may be a cause for concern and means that you own health and wellbeing or that of some-one else may be at risk I will advise you on how you can get help concerning this with the help of the consultant hepatologist (Dr. Norris). However the results from this interview shall be in an anonymous format and your name will never be used in relation to the data gathered from this interview. Some questions may seem fairly personal and if you really don’t want to answer them then please just let me know. I would appreciate it if you could answer all questions as truthfully as possible.

The first few questions I am going to ask you concern your health.

If you were to rate your own health would you rate it as;

1. Excellent □
2. Very good □
3. Good □
4. Fair □
5. Poor □

Can you explain your reasons for describing your health in this way?

Does your state of health limit the physical activities that you can do?

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Can you list some activities that are affected?

Vigorous activities (Running, lifting heavy objects, strenuous sports)

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Moderate activities (Moving table, pushing vacuum cleaner, playing golf)
Appendix III: Interviews

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

How much physical activity do you get per week in hours? This includes things like walking, or if you have a job that is physically demanding.

What type of activities do you do?

How much exercise do you get per week in hours? This includes things such as running or going to the gym.

What type of exercise do you get?

Has your physical health interfered with your normal social activities with family, friends, neighbours, work colleagues etc?

1. No □
2. A bit □
3. Moderately □
4. Quite a bit □
5. Extremely □

THE FOLLOWING QUESTION SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes why do you think this is?

How supportive would you say your friends and family have been to you during your illness?

1. Excellent □
2. Good □
3. Fair □
4. Poor □
5. Have had no support □

Why have you given that answer?

How much bodily pain have you had in the last month?
Do you agree with any of these statements in relation to how you feel about your state of health? You can answer

1. My health makes me worried □
2. My health makes me upset □
3. My health makes me angry □
4. My health makes me happy □
5. My health doesn’t bother me □

What other words describe the way that you feel?

Why does that word/those words remind you of your health?

How much do you agree with the following statement?

“I expect my health to get worse over the next year”

1. Definitely yes □
2. Possibly yes □
3. Unsure □
4. Possibly not □
5. Definitely not □

Why do you think that is?

Do you experience difficulties with tiredness above and beyond something that you would consider normal for someone of your age?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If you are having difficulties with tiredness (if you answered yes) how long have you been like this?

1. During the last week □
2. During the last month □
3. During the last few months □
4. During the last year □
5. During the last few years □

How long exactly have you been feeling tired for?
Appendix III: Interviews

Why do you think you have been experiencing problems with tiredness?

Have you been sleeping well over the last month?

1. Yes □
2. No □

How many nights per week on average do you have difficulty sleeping?

1. 7 nights a week □
2. 4-6 nights a week □
3. 1-3 nights a week □
4. 0 (no difficulty sleeping) □

Do you agree with any of these statements in relation to how you normally sleep?

1. I have difficulty falling asleep □
2. I wake up during the night □
3. I wake up early and I can’t go back to sleep □
4. I sleep fine and have no problems □

What time do you normally go to bed at?

How long after getting into bed does it take you to fall asleep?

What time do you normally wake up at?

How long after waking up does it take you to get out of bed?

The next portion of the experiment has questions in it which shall ask you about your mood and personality.

Did a member of your family ever get diagnosed as having a psychiatric disorder and have to go and see a psychiatrist or get put onto medication for their mood?

Would you describe yourself as more of an optimist (someone who always looks at the bright side of things) or pessimist (someone who always sees things negatively)?

1. Optimist □
2. Pessimist □

Why does that word describe you more?

How would you rate how happy you have been over the last month?
1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS SAD.

If it is different what has happened to make you feel this way? 
OR
If you are sad and usually feel sad why do you think you normally feel this way?

How long have you felt this way?

What caused you to feel this way?

Have you previously experienced any episode of depression in your life that has lasted a week or more?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If you answered yes why did it happen?

How long were you depressed for?

Why did the depression last for so long?

Have you ever being diagnosed by a doctor as having depression?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

When was this?

Would you describe yourself as someone who is calm or easily stressed out?
Appendix III: Interviews

1. Calm □
2. Easily stressed □

Why does that word describe you more?

How would you rate how worried you have been over the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS ANXIOUS.

If it is different what has happened to make you feel this way?

OR

If you normally feel anxious anyway why do you think this is?

How long have you felt this way?

What caused you to feel this way?

Have you previously experienced any episodes of anxiety in your life that have lasted a week or more?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If you answered yes why did it happen?

How long were you anxious for?

Why did the anxiety last for so long?

Have you ever being diagnosed by a doctor as having an anxiety disorder?

1. Yes □
2. No □
THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

When was this?

Have you ever been diagnosed by a medical doctor as having any other psychiatric disorder?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes which disorder was it?

When did it occur?

Would you rate yourself as someone who is easily irritated?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes what sort of things irritate you?

Would you say that this irritation is irrational?

1. Yes □
2. No □

How irritated would you say you have been for the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Do you get easily angry?

1. Yes □
2. No □
THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

Is this anger above and beyond what you would consider normal?

1. Yes □
2. No □

What sorts of things make you angry?

How angry would you say you have been for the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

If you had to say that one of the following statements would sum up how you have been feeling over the last month, which one would most closely represent you?

1. I have felt happy □
2. I have felt quiet □
3. I have felt sad □
4. I have felt worried □
5. I have felt angry □
6. Other, please specify? □

Explain why you chose that word/those words?

The next few questions are going to ask you about your memory and attention.

How would you rate how your memory has been over the last month?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □
THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If it is different what sorts of things have been happening recently that didn’t happen before?

OR

If it is normally bad anyway why would you say this is?

How long has your memory being this way?

What do you think caused your memory to get this way?

During the last month have you been at all forgetful, misplacing things and forgetting names?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes can you give me some specific examples?

How would you rate how your ability to concentrate has being over the last month?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If it is different what sorts of things have been happening recently that didn’t happen before?

How long has your concentration being this way?

What do you think caused your concentration to get this way?
Now I am going to give you a few examples of activities that involve concentration, could you rate how easily you find it to concentrate when doing the following things?

a. Reading a book or magazine
   1. Excellent □
   2. Good □
   3. Neither good nor bad □
   4. Not so good □
   5. Very bad (Have to keep re-reading passages) □

b. Watching a film or TV show with a complicated plotline
   1. Excellent □
   2. Good □
   3. Neither good nor bad □
   4. Not so good □
   5. Very bad (get easily lost, cannot remember any of the character names) □

c. Doing something you consider boring
   1. Excellent □
   2. Good □
   3. Neither good nor bad □
   4. Not so good □
   5. Very bad (Just cannot concentrate at all) □

Now I am going to ask you a few questions regarding your feelings about starting your treatment on Interferon alpha

Do you agree with any of these statements in relation to how you feel about taking the treatment Interferon alpha?

1. It makes me worried □
2. It makes me upset □
3. It makes me angry □
4. It makes me happy □
5. It makes me excited □
6. I feel optimistic □
7. I feel pessimistic □
8. It doesn’t bother me □

What other words describe the way that you feel?

Why do you feel that way about taking Interferon?

What have you heard about Interferon alpha?

Where did you hear that?

What is your overall impression of what you feel being on Interferon alpha will be like?
Do you feel that taking Interferon will impact on your life in a positive or negative way?

1. Positive □
2. Negative □

Why do you feel that way?

Are there any major concerns that you have about starting treatment with Interferon-alpha?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

What are your main concerns?

Thank you for taking the time to answer these questions for me.
8 week interview IFN-α

Patient number:

Group number:

This questionnaire is again designed so that I may better understand your illness and how it makes you feel. A lot of the questions will be ones that you heard when you came to visit me last time. I want you to try and answer all these questions thinking of how you have felt in the last month.

In general anything you tell me will be in complete confidence, however if during the course of this interview something is said which may be a cause for concern and means that you own health and wellbeing or that of some-one else’s may be at risk I will advise you on how you can get help concerning this with the help of the consultant hepatologist (Dr. Norris). However the results from this interview shall be in an anonymous format and your name will never be used in relation to the data gathered from this interview. Some questions may seem fairly personal and if you really don’t want to answer them then please just let me know.

I would appreciate it if you could answer all questions as truthfully as possible.

Can you describe your experience of being on Interferon to me?

Do you feel that your health is benefiting from taking Interferon?

1. Yes □
2. No □
3. Unsure □

Why do you feel that Interferon is affecting your health in that way?

Do you feel that you are benefiting in general from being on Interferon?

What is the best or most positive aspect of being on the treatment Interferon?

What is the worst aspect of being on Interferon alpha?

Would you say that your overall experience of being on Interferon alpha is a positive or negative one?

1. Positive □
2. Negative □

Why have you rated your experience of Interferon alpha in that way?

Do you feel that your experience of taking this treatment is the same as what you thought it would be?
1. Yes □
2. No □

Why do you feel that is?

The next few questions I am going to ask you concern your health.

How has your health been for the last month?

1. Excellent □
2. Very good □
3. Good □
4. Fair □
5. Poor □

Can you explain your reasons for describing your health in this way?

Does your state of health limit the physical activities that you can do?

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Can you list some activities that are affected?

Vigorous activities (Running, lifting heavy objects, strenuous sports)

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Moderate activities (Moving table, pushing vacuum cleaner, playing golf)

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

In the last month how much physical activity have you be doing per week in hours? This includes things like walking, or if you have a job that is physically demanding.

What type of activities do you do?
In the last month how much exercise did you get per week in hours? This includes things such as running or going to the gym.

What type of exercise do you get?

Has being on Interferon affected your relationships with others?

1. No □
2. A bit □
3. Moderately □
4. Quite a bit □
5. Extremely □

**THE FOLLOWING QUESTION SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.**

If you answered yes why do you think this is?

How supportive would you say your friends and family have been to you during the last 8 weeks?

1. Excellent □
2. Good □
3. Fair □
4. Poor □
5. Have had no support □

Why have you given that answer?

How much bodily pain have you had in the last month?

1. None □
2. Very mild □
3. Mild □
4. Moderate □
5. Severe □
6. Very severe □

Do you agree with any of these statements in relation to how you feel about your state of health? You can answer

1. My health makes me worried □
2. My health makes me upset □
3. My health makes me angry □
4. My health makes me happy □
5. My health doesn’t bother me □

What other words describe the way that you feel?

Why does that word/those words remind you of your health?
How much do you agree with the following statement?

"I expect my health to get worse over the next year"

1. Definitely yes □
2. Possibly yes □
3. Unsure □
4. Possibly not □
5. Definitely not □

Why do you think that is?

How would you rate how your health has been since going on Interferon?

1. Much better □
2. Slightly better □
3. Same as before □
4. Slightly worse □
5. Much worse □

Why do you think that Interferon has affected your health in that way?

Have you been experiencing difficulties with tiredness above and beyond what you were experiencing prior to being on Interferon-alpha?

1. Yes □
2. No □
3. Much the same as before □

**THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.**

If you are having difficulties with tiredness (if you answered yes) how long have you been like this?

1. During the last week □
2. During the last month □
3. During the last 8 weeks □
4. Before going onto Interferon-alpha □

How long exactly have you been feeling tired for?

Why do you think you have been experiencing problems with tiredness?

Have you been sleeping well over the last month?

1. Yes □
2. No □

How many nights per week on average do you have difficulty sleeping?
Do you agree with any of these statements in relation to how you normally sleep?

1. I have difficulty falling asleep  □
2. I wake up during the night □
3. I wake up early and I can’t go back to sleep □
4. I sleep fine and have no problems □

What time do you normally go to bed at?

How long after getting into bed does it take you to fall asleep?

What time do you normally wake up at?

How long after waking up does it take you to get out of bed?

Has anything about your day to day life changed since going onto Interferon?

1. Yes □
2. No □

The following questions should be asked only if the respondent said yes.

What do you feel has changed about your life since going onto Interferon?

The next portion of the experiment has questions in it which shall ask you about your mood and personality.

How would you rate how happy you have been over the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

The following questions should be asked only if the respondent said yes or normally feels sad.
If it is different what has happened to make you feel this way?

OR

If you are sad and usually feel sad why do you think you normally feel this way?

How long have you felt this way?

What caused you to feel this way?

Since you started taking Interferon which of the following statements most closely describes the way that you feel?

1. Much more sad
2. Slightly more sad
3. Much the same as before
4. Slightly happier
5. Much happier

Why do you think you feel that way?

How would you rate how worried you have been over the last month?

1. Extremely (all the time)
2. Quite a lot (most of the time)
3. A fair amount (half the time)
4. Not that much (a couple of days)
5. Not at all

Is this different from usual for you?

1. Yes
2. No

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS ANXIOUS.

If it is different what has happened to make you feel this way?

OR

If you normally feel anxious anyway why do you think this is?

How long have you felt this way?

What caused you to feel this way?

Would you say that you have been feeling more worried, less worried or much the same since going onto Interferon?
Appendix III: Interviews

1. Much more worried □
2. Slightly more worried □
3. Much the same as before □
4. Slightly calmer □
5. Much calmer □

Why do you think that you feel that way?

How irritated would you say you have been for the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS ANXIOUS.

If it is different what has happened to make you feel this way?

OR

If you normally feel irritable anyway why do you think this is?

How long have you felt this way?

What caused you to feel this way?

Would you say that you have been feeling more irritable, less irritable or much the same since going onto Interferon?

1. Much more irritable □
2. Slightly more irritable □
3. Much the same as before □
4. Slightly less irritable □
5. Much less irritable □

Why do you think that you feel that way?

How angry would you say you have been for the last month?

1. Extremely (all the time) □
Is this different from usual for you?

1. Yes ☐
2. No ☐

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES OR NORMALLY FEELS ANXIOUS.

If it is different what has happened to make you feel this way?

OR

If you normally feel angry anyway why do you think this is?

How long have you felt this way?

What caused you to feel this way?

Would you say that you have been feeling more angry, less angry or much the same since going onto Interferon?

1. Much more angry ☐
2. Slightly more angry ☐
3. Much the same as before ☐
4. Slightly calmer ☐
5. Much calmer ☐

Why do you think that you feel that way?

If you had to say that one of the following statements would sum up how you have been feeling over the last month, which one would most closely represent you?

1. I have felt happy ☐
2. I have felt quiet ☐
3. I have felt sad ☐
4. I have felt worried ☐
5. I have felt angry ☐
6. Other, please specify? ☐

Explain why this is to me?

The next few questions are going to ask you about your memory and attention.

How would you rate how your memory has being over the last month?
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?
1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If it is different what sorts of things have been happening recently that didn’t happen before?
OR
If it is normally bad anyway why would you say this is?

How long has your memory been this way?
What do you think caused your memory to get this way?

During the last month have you been at all forgetful, misplacing things and forgetting names?
1. Yes □
2. No □

THE FOLLOWING QUESTION SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If yes can you give me some specific examples?

Would you say that you have been feeling more forgetful, less forgetful or much the same since going onto IFN?
1. Much more forgetful □
2. Slightly more forgetful □
3. Much the same as before □
4. Slightly less forgetful □
5. Much less forgetful □

Why do you think that the Interferon has affected your memory in that way?

How would you rate how your ability to concentrate has being over the last month?
Appendix III: Interviews

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □

THE FOLLOWING QUESTIONS SHOULD BE ASKED ONLY IF THE RESPONDANT SAID YES.

If it is different what sorts of things have been happening recently that didn’t happen before?

How long has your concentration being this way?

What do you think caused your concentration to get this way?

Now I am going to give you a few examples of activities that involve concentration, could you rate how easily you find it to concentrate when doing the following things?

a. Reading a book or magazine
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (Have to keep re-reading passages) □

b. Watching a film or TV show with a complicated plotline
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (get easily lost, cannot remember any of the character names) □

c. Doing something you consider boring
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (Just cannot concentrate at all) □

Would you say that your ability to concentrate has been over the last month?

1. Much more difficult □
2. Slightly more difficult □
3. Much the same as before □
4. Slightly easier □
5. Much more easy □

Why do you think that the Interferon has affected your concentration in that way?

Is there anything that you feel is important regarding your treatment that you feel you should tell me that I have not covered?

Thank you for taking the time to answer these questions for me.
Post-treatment interview

Patient number: 

Group number: 

This interview is designed so that I may try and understand how you feel the treatment Interferon alpha affected you.
In general anything you tell me will be in complete confidence, however if during the course of this interview something is said which may be a cause for concern and means that you own health and wellbeing or that of some-one else may be at risk I will advise you on how you can get help concerning this with the help of the consultant hepatologist (Dr. Norris). However the results from this interview shall be in an anonymous format and your name will never be used in relation to the data gathered from this interview. Some questions may seem fairly personal and if you really don't want to answer them then please just let me know.
I would appreciate it if you could answer all questions as truthfully as possible.

I would like to ask you a few questions about your overall experience of being on Interferon. These questions are not limited to any one aspect of how treatment affected you, anything that you can remember as being particularly 'different' from what you would consider normal for yourself is of interest to me, whether that be something that was bad or good!

Can you describe your experience of being on Interferon to me?

Would you be able to label your experience of being on Interferon?

Was your experience of being on Interferon alpha mainly a positive or a negative one?

1. Positive □  
2. Negative □

Why do you feel that way about your experience of being on Interferon?

What was the best or most positive aspect of being on the treatment Interferon?

What was the worst aspect of being on Interferon alpha?

How was your health while on Interferon?

Do you feel your health has gotten worse or better having being on IFN?

1. Much better □
2. Slightly better □
3. Much the same as before □
4. Slightly worse □
5. Much worse □
Appendix III: Interviews

Why do you feel that way?

Do you feel that you benefited in general from being on Interferon?

If you had to sum up how you felt now that you have stopped treatment, how would you do this?

Which statement best sums up your feelings now that you have stopped the treatment?

1. I feel relieved
2. I feel grateful/thankful
3. I feel disappointed with the result
4. I am pleased with result
5. I feel angry
6. I have no feelings associated with this
7. Other, please specify?

Why does that word/those words best describe how you feel about your experience of Interferon?

Do you feel that you have benefited from taking Interferon?

1. Yes
2. No

Why do you feel that way?

If you knew someone who was unsure about whether they should start treatment with Interferon for Hepatitis C would you advise them to start treatment?

1. Yes, I would strongly recommend it
2. Yes, I would recommend it
3. Yes, I would recommend it but with caution
4. No, I would not recommend it
5. No, I would strongly recommend against it

Why did you give that answer?

How is your health since you finished treatment?

1. Excellent
2. Very good
3. Good
4. Fair
5. Poor
Can you explain your reasons for describing your health in this way?

Does your current state of health limit the physical activities that you can do?

1. Yes, limited a lot □
2. Yes, limited a little □
3. Sometimes, limited a lot □
4. Sometimes, limited a little □
5. No, not limited at all □

Is this different to when you were on Interferon?

If so in what way?

Has being on Interferon affected your relationships with others?

1. No □
2. A bit □
3. Moderately □
4. Quite a bit □
5. Extremely □

If so, why do you think this is?

How were your relationships with other people while on treatment?

How supportive would you say your friends and family were during your treatment?

1. Excellent □
2. Good □
3. Fair □
4. Poor □
5. Have had no support □

Why have you given that answer?

How much bodily pain have you had in the last month?

1. None □
2. Very mild □
3. Mild □
4. Moderate □
5. Severe □
6. Very severe □

Is this different to while you were on Interferon?

If so, in what way?

How have you been sleeping for the last month?

How did you sleep while you were on Interferon?
Was this different to normal for you?

1. Yes □
2. No □

In what way?

Could you describe a typical night’s sleep while on treatment to me?

Has anything about your day to day life changed since going onto Interferon?

1. Yes □
2. No □

What do you feel has changed about your life since going onto Interferon?

How would you rate how happy you have been over the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

If it is different what has happened to make you feel this way?

OR

If you are sad and usually feel sad why do you think you normally feel this way?

How long have you felt this way?

What caused you to feel this way?

Since you stopped taking Interferon which of the following statements most closely describes the way that you feel?
Appendix III: Interviews

1. Much more sad □
2. Slightly more sad □
3. Much the same as before □
4. Slightly happier □
5. Much happier □

Why do you think you feel that way?

How was your mood while you were on treatment?

Was it different to normal for you?

1. Yes □
2. No □

Why?

How would you rate how worried you have been over the last month?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

Is this different from usual for you?

1. Yes □
2. No □

If it is different what has happened to make you feel this way?

OR

If you normally feel anxious anyway why do you think this is?

How long have you felt this way?

What caused you to feel this way?

Would you say that you have been feeling more worried, less worried or much the same since coming off Interferon?

1. Much more worried □
2. Slightly more worried □
3. Much the same as before □
4. Slightly calmer □
5. Much calmer □
Appendix III: Interviews

Why do you think you feel that way?

How were your ‘anxiety levels’ while you were on treatment?

Was it different to normal for you?

1. Yes □
2. No □

How irritated would you say you were on the treatment?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

What sort of things would irritate you?

Is this different to normal for you?

1. Yes □
2. No □

If you had to rate how irritated you have been for the last month using the same scale how would you rate this?

How angry would you say you were on treatment?

1. Extremely (all the time) □
2. Quite a lot (most of the time) □
3. A fair amount (half the time) □
4. Not that much (a couple of days) □
5. Not at all □

What sort of things would irritate you?

Was this different to normal for you?

1. Yes □
2. No □

If you had to rate how irritated you have been for the last month using the same scale how would you rate this?

Do you feel like any aspect of your personality has changed while on treatment?

1. Yes □
2. No □
If so, can you describe how you feel your personality changed?

Does your partner or closest family member feel that any aspect of your personality has changed since stopping Interferon treatment?

1. Yes □
2. No □

If so, have they described this to you?

How would you rate how your memory has been for the last month?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □

If so, in what way and why?

How was your memory while on treatment?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Is this different from usual for you?

1. Yes □
2. No □

If so, in what way was it different?

Could you give me some examples?

How would you rate how your ability to concentrate has being over the last month?

1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □
Appendix III: Interviews

Is this different from usual for you?
1. Yes □
2. No □

If so why do you think this is?

Could you give me some examples?

How was your concentration while on treatment?
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad □

Was this different from usual for you?
1. Yes □
2. No □

If so, in what way was it different?

Could you give me some examples?

Now I am going to give you a few examples of activities that involve concentration, could you rate how easy you found it to concentrate when doing the following things while on treatment and then tell me if that has changed now?

a. Reading a book or magazine
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (Have to keep re-reading passages) □

b. Watching a film or TV show with a complicated plotline
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (get easily lost, cannot remember any of the character names) □

c. Doing something you consider boring
1. Excellent □
2. Good □
3. Neither good nor bad □
4. Not so good □
5. Very bad (Just cannot concentrate at all) □

Is there anything else that you may feel it is important to talk about that I have not covered in this interview?

Thank you for taking the time to answer these questions for me.
APPENDIX IV

Ethical approval and Consent forms
F.A.O. Kimberley Smith

School of Psychology Research Ethics Committee

17 November 2006

Dear Kimberley

The above met recently, and considered your application entitled “Interferon alpha action on the central nervous system: Neurobiological outcomes and functional brain imaging.” I am pleased to inform you that your application was approved subject to the following information being supplied to myself.

Please confirm in writing whether or not participants will be tested in TCIN (section 5 of the ethics application form).

Please confirm in writing that participants will be allowed to take at least one break in the 80-minute study testing session.

Please provide documentation concerning the TCIN fMRI scanning protocol (e.g., potential risks, health condition exclusions, etc.), which participants will be presented with prior to testing so that they have the necessary information about the scanning procedure before providing written informed consent to undergo it.

Please provide written confirmation of approval granted to the study by the medical research ethics committee at St. James’s Hospital.

Please confirm in writing that a suitably-qualified person will be taking blood samples from participants and analysing the blood samples.

Please confirm in writing the study’s procedure for dealing with any psychological distress that participants might experience as a consequence of answering questions about their current depressive and anxiogenic states. To this end, please supply an amended de-briefing sheet that at least contains contact details of professional support services and/or personnel that participants can access should they experience any such distress.

In order to provide participants with a point of contact for questions about the study, please amend the de-briefing, information and informed consent sheets to include

continuad overleaf

http://www.psychology.tcd.ie
Appendix IV: Ethics

contact details of yourself, your supervisor and any other relevant member(s) of the research team.

Please confirm in writing the method for dealing with the disparity between control group and experimental group participants in terms of monetary reward for taking part in the study.

Please supply an information sheet, which specifies the nature of the study, that participants will read before giving their written consent to take part in the study.

Once this information has been received by myself, you will be notified that your application has been granted unconditional ethics approval.

Yours sincerely,

Kevin Thomas
Chair,
School of Psychology Research Ethics Committee
To Whom It May Concern:

Re: Ethics Committee Application on behalf of Kimberly Smith
Project Title: Interferon Alpha Action on the CNS: Neurobiological Outcomes and Functional Brain Imaging

I hereby confirm that I am agreeing to research by Ms. Smith and Dr. Shane O’Meara on the interaction of Interferon with psychological function. I would anticipate that HCV infected individuals proceeding to antiviral therapy will be asked for informal consent to agree to this study that these patients will come from my Hepatitis C focused clinics. It is a very important study as the significant proportion of patients receiving Interferon have varying psychological ill health during treatment such that treatment may be withdrawn. Research which explores and helps our understanding of the biological mechanisms add play in this instance is of critical importance and I believe that Ms. Smith and Dr. O’Meara have planned an extremely worthwhile project.

Yours sincerely,

[Signature]

Dr Suzanne Norris FRCPI PhD
Consultant Hepatologist/Gastroenterologist
Appendix IV: Ethics

Dear Kimberly,

The Committee, at its meeting on November 29th 2006, has given a favorable ethical opinion on the study referenced above based on the application for review by the SJH/AMNCH Research Ethics Committee subject to the following:

• The Committee asks that it be clarified whether the signature on the Site Specific Assessment Form is that of Dr. Anne Marie O’Dwyer.

It is your responsibility to notify the Chief Investigator and the Investigator at each site in Ireland of the outcome of the review.

Yours sincerely,

[Signature]

Prof. Colm O’Morain, Chair of Committee.

E-mail: Dan.Lynch@amnch.ie
Ursula.ryan@amnch.ie

December 7th 2006

REC reference: 2006/11/02

(Please quote REC reference and EudraCT numbers on all correspondence)

Title of clinical trial: Interferon Alpha Action on the Central Nervous System: Neurobiological Outcomes and Functional Brain Imaging

List of documents (including version number and dates which have been reviewed by the Committee):

• Application Form
• Site Specific Assessment Form
• Administrative Application 2006 edition
• Participant Information Sheet & Consent Form
• Letter of Invitation to Control Participant
• Letter of Invitation to Patient
• Summary CV for Chief Investigator.

Ms. Kimberly Smith
Trinity College Institute of Neurosciences
Lloyd Building
Trinity College
Dublin 2

SJH/AMNCH
Research Ethics Committee
THE ADELAIDE & MEATH
HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN’S HOSPITAL
TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000
To Whom It May Concern:

Re: Ethics Committee Application on behalf of Kimberley Smith

Project title: Interferon Alpha Action on the CNS, Neurobiological Outcomes and Functional Brain Imaging

I hereby confirm that I am agreeing to support the above research project performed in collaboration with Kimberley Smith and Professor Shane O’Mara, investigating aspects of mood, cognition and cytokine production in patients with depression here at St. Patrick’s Hospital.

The work done in this hospital shall be used in order to compare patients with a primary depressive disorder to those who have a secondary depressive disorder induced by the drug Interferon-alpha. This research is important as it will inform us about the biological nature of depression, and will be useful both in those patients receiving Interferon-alpha therapy and those patients who have depression.

I also confirm that the number of patients (30) shall be forthcoming and agree to the research taking place on site here at St. Patrick’s Hospital subject to approval by the St Patrick’s Hospital Research Ethics Committee.

Prof Declan McLoughlin

October 4, 2007
CONFIDENTIAL

Professor Shane O’Mara
Professor Declan McLoughlin
Kimberley Smith
C/- Professor Declan McLoughlin
St Patrick’s Hospital

22nd May 2008

Re: Research Ethics Committee Form 02/08
Study protocol titled:
Primary and interferon-alpha induced depression: Neurobiological outcomes and functional brain imaging.

Dear Professor McLoughlin,

Thank you for submitting your study to the Research Ethics Committee of St Patrick’s Hospital which met today the 19th of May 2008 at St Patrick’s Hospital. The Research Ethics Committee agreed to approve this study.

The approval is subject to the following conditions:

• That within one year of the approval, feedback is given to the committee as to the outcome of the study/publication or otherwise.
• That any recorded material that needs to be stored or destroyed is done so according to agreed practices.

Thank you for submitting this study.

With best wishes

Yours sincerely,

JAMES V. LUCEY MD, Ph.D., FRCPI, FRCPsych,
MEDICAL DIRECTOR/ RESEARCH ETHICS COMMITTEE SECRETARY
Informed consent form

**Project title:** Interferon alpha action on the central nervous system: neurobiological outcomes and functional brain imaging

**Principal Investigators:** Kimberley Smith (Trinity College Dublin), Dr Anne Marie O'Dwyer (Consultant Psychiatrist, St. James’s Hospital), Dr. John Cooney (Consultant Psychiatrist, St. James’s Hospital), Dr. Suzanne Norris (Consultant Hepatologist, St. James’s Hospital) and Professor Shane O’Mara (Trinity College Dublin).

**Declaration of participant:**

- I have read or have had the information sheet read to me and I understand the contents
- I have been given the opportunity to ask questions and am satisfied with answers
- I consent to take part in this study
- I understand that participation in this study is voluntary and that I can withdraw at any time
- I understand that withdrawal from the study will not affect my access to services or legal rights
- I consent to the possible publication of results
- I understand that all results will be anonymous and only the principal investigators will have access to my personal details
- I understand that in the future the data obtained in this study may be used but that my personal details will remain confidential

**Participant name..........................................................................................................................**

**Participant signature.....................................................................................................................**

**Date: ....../....../....**

*Optional: I consent to parts of my interview being used by the experimenter for presentations and in papers, and understand that my name will never be used in relation to those quotes.*
Appendix IV: Ethics

Participant name.............................................................................................................

Participant signature....................................................................................................... 

Date: ....../...../.....

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

Name of first Witness: 

Signature:

Name of second Witness: 

Signature:

Declaration of researcher:

- I have explained the study and what is involved
- I have answered any questions
- I believe that the participant understands and is freely giving his or her consent

Researcher name...........................................................................................................

Researcher Signature......................................................................................................

Date: ....../...../.....
CONSENT FORM

Primary and Interferon-alpha induced depression: neurobiological outcomes and functional brain imaging

The participant must complete this form herself/himself

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet ................................................................. Yes No
- I have had the opportunity to ask questions and discuss the study ................................................................. Yes No
- I have received satisfactory answers to all my questions ................................................................. Yes No
- I have received enough information about this study ................................................................. Yes No
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care ... Yes No
- I agree to take part in this study without prejudice to my legal or ethical rights ................................................................. Yes No

Participant’s Signature: _________________________  Date:

Participant’s Name in Print: _________________________  Date:

Witness Signature: * _________________________  Date:

Witness’ Name in Print: _________________________  Date:

Investigator’s Signature: _________________________  Date:

Investigator’s Name in Print: _________________________  Date:

If the participant is under 18 years of age the consent of a parent or guardian must also be obtained.

I have received, read and understood the Patient Information Leaflet for the above study.

Participant Signature: _________________________  Date:

Participant named above has expressed a written willingness to participate in this research study and I hereby give my consent for this participation:

Parent/Guardian Signature: _________________________  Date:
Appendix IV: Ethics

Please attach the Participant Information Sheet to this Consent Form, ask the participant to sign and date it and, where appropriate, place a copy of both in the participant’s case notes. Witness must be someone other than the Investigator.
APPENDIX V

Ethical considerations for development of interview
Ethical considerations in administration of semi-structured interview

The following issues were considered in the design and administration of the semi-structured interview for Control participants, HCV patients and patients taking or who had taken IFN-α. Where appropriate those procedures that were instigated following the occurrence of a specified incident shall be discussed in more detail.

1. Disclosure of sensitive information

Where patients disclosed information of a sensitive nature that could affect their treatment, or had implications for their own well-being or that of some-one else there were procedures set in place in conjunction with both the Hepatology and Psychological Medicine departments at St. James’s Hospital. All participants were informed of these procedures prior to commencement of the interview;

“This interview is designed so that I may try and understand how your illness makes you feel and how you feel about the fact that you have to use the treatment Interferon alpha.

In general anything you tell me will be in complete confidence, however if during the course of this interview something is said which may be a cause for concern and means that you own health and wellbeing or that of some-one else may be at risk I will advise you on how you can get help concerning this with the help of the consultant hepatologist (Dr. Norris). However the results from this interview shall be in an anonymous format and your name will never be used in relation to the data gathered from this interview.

Some questions may seem fairly personal and if you really don’t want to answer them then please just let me know.

I would appreciate it if you could answer all questions as truthfully as possible.”

Where patients were currently taking the treatment IFN-α, should any issue arise that was a cause for concern, and the well-being of that patient or someone else was felt to be at risk, the researcher informed the nurse in charge of that patients...
treatment, who went on to implement whatever intervention they felt was most appropriate in conjunction with the Consultant Hepatologist.

Where patients were not taking IFN-α the counselling nurse at the Hepatology Department was instead approached directly.

Where Control participants were tested they were instead informed of counselling services at Trinity College Dublin and the researcher offered to help them in contacting and availing of the help of this service.

2. Similarity of research interview environment to therapeutic environment

There is a similarity in the environment that the research interview took place in to a environment where an individual may seek counselling. This issue was of particular importance given the nature of much of the interview, where participants were asked to talk about a number of sensitive issues.

Where it was felt by the researcher that a patient saw the interview as a form of counselling rather than an interview to be used for research, they were excluded from the study.

Where in the session participants would talk about issues that were affecting them rather than answering the questions associated with the research, care was taken by the interviewer not to upset them, but to inform them that as they were ill-equipped to deal with such issues and that if they felt that these were issues causing them distress that they could be referred on to the counselling nurse in the Hepatology department who would be able to speak to them about these more personal matters and help them in any way she could.

3. Debriefing of all participants

All participants and patients were fully debriefed at the end of each interview. They were informed that had they felt any of the issues spoken about during the course of the interview had caused them distress, or they felt that any issues had arisen that they wished to speak about in more detail that they could contact the Psychological Medicine department at St. James’s Hospital, speak to the counselling nurse in the Hepatology centre or where recruited through Trinity
College, they were informed of the number and contact information for the counselling service.

An example of the de-briefing sheet handed to participants is included below;

"The purpose of this study was to look at the effect that the drug interferon-alpha has on people who have Hepatitis C and their ability to do tests that look at memory and attention. We decided to test people before, during and after their treatment so we could see how this drug affected the individual. We then compared those people on interferon-alpha with people who also have Hepatitis C and healthy control participants at the same time-points so that we could see what effects were due to the drug and what were due to Hepatitis C. The brain imaging portion of the experiment allowed us to see what parts of the brain ‘light-up’ when people do memory tasks, and the effect that the drug has on this. Finally, the levels of blood proteins known as ‘cytokines’ which are involved in inflammation were looked at so that we could see how this related to performance.

Should you feel that taking part in this experiment has in any way caused you distress then please do not hesitate to contact the lead consultant psychiatrist for this study Dr. Anne-Marie O’Dwyer at (01) 410 3457.

Should you have any further questions about the study then please contact Kimberley Smith at (01) 896 8411 or kismith@tcd.ie".

4. Storage of interview recordings

All recordings were stored in accordance with procedures laid out in the ethics application in accordance with the Data Protection Act (2003):

The interview shall be taped in order for it to be transcribed at a later stage so that the content may be analysed efficiently and data entered into the computer. The taping shall take place on a digital voice recorder. The recording is then stored onto a computer which is password protected and deleted from the recorder.

Any data stored electronically will be password protected and accessible only by the lead investigator."
5. Maintaining patient anonymity

Patient anonymity was ensured through the use of participant numbers. Once allocated participants were only referred to using that particular number. If at any point during the interview participants referred to a name, this was changed to initials at the stage of transcription.

6. Use of patient quotations

Where patients spoke of issues that were of particular interest to the researcher, and there was potential for those quotes to be used in future dissemination of research permission was sought from the participant through an additional question on the consent form;

"Optional: I consent to parts of my interview being used by the experimenter for presentations and in papers, and understand that my name will never be used in relation to those quotes.

Participant name........................................................................................................

Participant signature....................................................................................................

Date: ...../...../....."

APPENDIX VI

Analysis of sleep question
Appendix VI: Sleep question

Sleep questions analysed to ascertain sleep quality

12a: What time do you normally go to bed at?
12b: How long after getting into bed does it take you to fall asleep?
12c: What time do you normally wake up at?
12d: How long after waking up does it take you to get out of bed?

Analysis of sleep quality

Component 1: Time to fall asleep
For question 12b, time taken to fall asleep, the answer was broken down in order to obtain a score from 0-3; \( \leq 15 \) minutes to sleep (0), 16-30 minutes to sleep (1), 31-60 minutes to sleep (2), > 60 minutes to sleep (3).

Component 2: Number of hours slept
For questions 12a, 12b and 12c, it was possible to ascertain how long the patient had been asleep for. The time was calculated by taking the time the patient went to bed at (12a) and calculating the number of hours till they woke up (12d), then taking away from this number however long it may have taken the patient to fall asleep (12c). A score was obtained for total n of hours asleep as such; > 7 hours asleep (0), 6-7 hours asleep (1), 5-6 hours asleep (2), < 5 hours asleep (3).

Component 3: Time in bed spent sleeping
For this component, the score from component 2 (total n of hours asleep), was divided by the total n of hours in bed and then multiplied by 100 in order to give a percentage of the time spent in bed sleeping. In order to calculate the total n of hours in bed, the number from component 2 was added to the answer from question 12b and 12d. Once this score was obtained, and the calculation to get the answer to component 3 performed, the percentage of time spent in bed sleeping was scored as such; > 85% time
spent sleeping (0), 75-84% time spent sleeping (1), 65-74% time spent sleeping (2), < 65% time spent sleeping (3).

Total sleep quality.

Once the 3 component scores were obtained, they were summed to give a total score out of a maximum of 9, which indicated the maximum impact on sleep quality. All component scores as well as the total score were reported.
APPENDIX VII

Normality of interview data
Normality of data for Control sample

<table>
<thead>
<tr>
<th>Question</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>Shapiro-Wilks test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health</strong></td>
<td><strong>-0.216 ± 0.717</strong></td>
<td><strong>-1.041 ± 1.4</strong></td>
<td>Statistic = 0.838, P = .055</td>
</tr>
<tr>
<td>Health limits activities</td>
<td>3.033 ± 1.4</td>
<td>0.723 ± 1.4</td>
<td>Statistic = 0.536, p &lt; 0.01</td>
</tr>
<tr>
<td>Health limits vigorous activities</td>
<td>1.771 ± 0.717</td>
<td>3.033 ± 1.4</td>
<td>Statistic = 0.73, p &lt; 0.01</td>
</tr>
<tr>
<td>Health limits moderate activities</td>
<td>2.888 ± 0.512</td>
<td>7.037 ± 0.992</td>
<td>Statistic = 0.351, p &lt; 0.01</td>
</tr>
<tr>
<td>Hrs physical activity per week</td>
<td>2.795 ± 0.717</td>
<td>-0.88 ± 1.4</td>
<td>Statistic = 0.561, p &lt; 0.01</td>
</tr>
<tr>
<td><strong>Hrs exercise per week</strong></td>
<td><strong>0.69 ± 0.717</strong></td>
<td><strong>-0.8 ± 1.4</strong></td>
<td>Statistic = 0.844, p = 0.65</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-0.655 ± 0.717</td>
<td>-0.425 ± 1.4</td>
<td>Statistic = 0.83, p &lt; 0.05</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 ± 0.717</td>
<td>9 ± 1.4</td>
<td>Statistic = 0.39, p &lt; 0.01</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>2.86 ± 0.717</td>
<td>8.082 ± 1.4</td>
<td>Statistic = 0.513, p &lt; 0.01</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>2.121 ± 0.717</td>
<td>4.647 ± 1.4</td>
<td>Statistic = 0.637, p &lt; 0.01</td>
</tr>
<tr>
<td>Hours slept</td>
<td>2.121 ± 0.717</td>
<td>4 ± 1.4</td>
<td>Statistic = 0.564, p &lt; 0.01</td>
</tr>
<tr>
<td>Hours in bed asleep</td>
<td>1.62 ± 0.717</td>
<td>0.735 ± 1.4</td>
<td>Statistic = 0.536, p &lt; 0.01</td>
</tr>
<tr>
<td>Overall sleep quality</td>
<td>1.772 ± 0.717</td>
<td>3.203 ± 1.4</td>
<td>Statistic = 0.728, p &lt; 0.01</td>
</tr>
<tr>
<td>Happiness</td>
<td>-0.606 ± 0.717</td>
<td>-0.286 ± 1.4</td>
<td>Statistic = 0.805, p &lt; 0.05</td>
</tr>
<tr>
<td>Worry</td>
<td>1.014 ± 0.717</td>
<td>0.185 ± 1.4</td>
<td>Statistic = 0.763, p &lt; 0.01</td>
</tr>
<tr>
<td>Irritation</td>
<td>-0.818 ± 0.717</td>
<td>1.126 ± 1.4</td>
<td>Statistic = 0.781, p &lt; 0.05</td>
</tr>
<tr>
<td>Anger</td>
<td>-0.271 ± 0.717</td>
<td>-2.571 ± 1.4</td>
<td>Statistic = 0.655, p &lt; 0.01</td>
</tr>
<tr>
<td>Memory</td>
<td>0.825 ± 0.717</td>
<td>-1.079 ± 1.4</td>
<td>Statistic = 0.748, p &lt; 0.01</td>
</tr>
<tr>
<td>Concentration</td>
<td>0 ± 0.717</td>
<td>4 ± 1.4</td>
<td>Statistic = 0.693, p &lt; 0.01</td>
</tr>
<tr>
<td>Concentration (book/magazine)</td>
<td>-0.018 ± 0.717</td>
<td>1.126 ± 1.4</td>
<td>Statistic = 0.781, p &lt; 0.05</td>
</tr>
<tr>
<td>Concentration (film)</td>
<td>-0.271 ± 0.717</td>
<td>-2.571 ± 1.4</td>
<td>Statistic = 0.655, p &lt; 0.01</td>
</tr>
<tr>
<td>Concentration (Boring task)</td>
<td>-0.825 ± 0.717</td>
<td>-1.079 ± 1.4</td>
<td>Statistic = 0.748, p &lt; 0.01</td>
</tr>
</tbody>
</table>

Table showing results for the normality of each dataset examined. The only sets of data that yielded normally distributed results were the health and hours of exercise per week questions, indicated by a non-significant variability within the group (in bold).
Normality of data for HCV sample

<table>
<thead>
<tr>
<th>Question</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>Shapiro-Wilk test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>0.107 ± 0.717</td>
<td>-0.643 ± 1.4</td>
<td>Statistic=0.917, P=0.36</td>
</tr>
<tr>
<td>Health limits activities</td>
<td>-0.188 ± 0.717</td>
<td>-1.232 ± 1.4</td>
<td>Statistic=0.884, P=0.17</td>
</tr>
<tr>
<td>Health limits vigorous activities</td>
<td>-0.159 ± 0.717</td>
<td>-1.432 ± 1.4</td>
<td>Statistic=0.897, P=0.23</td>
</tr>
<tr>
<td>Health limits moderate activities</td>
<td>0.501 ± 0.717</td>
<td>-1.275 ± 1.4</td>
<td>Statistic=0.808, p&lt;0.05</td>
</tr>
<tr>
<td>Hrs physical activity per week</td>
<td>2.256 ± 0.717</td>
<td>5.246± 1.4</td>
<td>Statistic=0.696, p&lt;0.01</td>
</tr>
<tr>
<td>Hrs activity per week</td>
<td>1.501 ± 0.717</td>
<td>1.467 ± 1.4</td>
<td>Statistic=0.696, p&lt;0.01</td>
</tr>
<tr>
<td>Hrs exercise per week</td>
<td>0.69 ± 0.717</td>
<td>-0.8 ± 1.4</td>
<td>Statistic=0.684, p&lt;0.01</td>
</tr>
<tr>
<td>Physical health interfered social</td>
<td>-0.152 ± 0.717</td>
<td>-1.961 ± 1.4</td>
<td>Statistic=0.826, p&lt;0.05</td>
</tr>
<tr>
<td>Social support</td>
<td>0.159 ± 0.717</td>
<td>-1.432 ± 1.4</td>
<td>Statistic=0.897, P=0.23</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-1.114 ± 0.717</td>
<td>0.757 ± 1.4</td>
<td>Statistic=0.839, P=0.56</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.857 ± 0.717</td>
<td>-1.714 ± 1.4</td>
<td>Statistic=0.617, p&lt;0.01</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>0.574 ± 0.717</td>
<td>-1.099 ± 1.4</td>
<td>Statistic=0.851, P=0.8</td>
</tr>
<tr>
<td>Time to fall asleep</td>
<td>0.501 ± 0.717</td>
<td>-1.275 ± 1.4</td>
<td>Statistic=0.808, p&lt;0.05</td>
</tr>
<tr>
<td>Hours slept</td>
<td>Not computed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours in bed asleep</td>
<td>Not computed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall sleep quality</td>
<td>0.501 ± 0.717</td>
<td>-1.275 ± 1.4</td>
<td>Statistic=0.808, p&lt;0.05</td>
</tr>
<tr>
<td>Happiness</td>
<td>0.214 ± 0.717</td>
<td>0.144 ± 1.4</td>
<td>Statistic=0.913, P=0.34</td>
</tr>
<tr>
<td>Worry</td>
<td>0.520 ± 0.717</td>
<td>-0.811 ± 1.4</td>
<td>Statistic=0.763, p&lt;0.01</td>
</tr>
<tr>
<td>Irritation</td>
<td>3 ± 0.717</td>
<td>9 ± 1.4</td>
<td>Statistic=0.901, p&lt;0.01</td>
</tr>
<tr>
<td>Anger</td>
<td>0.501 ± 0.717</td>
<td>-1.275 ± 1.4</td>
<td>Statistic=0.808, p&lt;0.05</td>
</tr>
<tr>
<td>Memory</td>
<td>0 ± 0.717</td>
<td>-1.714 ± 1.4</td>
<td>Statistic=0.748, p&lt;0.01</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.520 ± 0.717</td>
<td>-0.811 ± 1.4</td>
<td>Statistic=0.901, P=0.26</td>
</tr>
<tr>
<td>Concentration (book/magazine)</td>
<td>1.485 ± 0.717</td>
<td>4 ± 1.4</td>
<td>Statistic=0.728, p&lt;0.01</td>
</tr>
<tr>
<td>Concentration (film)</td>
<td>0.660 ± 0.717</td>
<td>0.825 ± 1.4</td>
<td>Statistic=0.873, P=0.13</td>
</tr>
<tr>
<td>Concentration (Boring task)</td>
<td>-0.092 ± 0.717</td>
<td>-1.692 ± 1.4</td>
<td>Statistic=0.854, P=0.08</td>
</tr>
</tbody>
</table>

Table showing results for the normality of each dataset examined. Those sets of data that yielded normally distributed results are indicated in bold.
### Normality data for IFN-α sample

<table>
<thead>
<tr>
<th>Question</th>
<th>Skewness (week 8)</th>
<th>Kurtosis (week 8)</th>
<th>Shapiro-Wilk test (week 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.207 ± 0.845</td>
<td>-0.459 ± 1.741</td>
<td>Statistic = 0.702, p&lt;0.01</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.668 ± 0.845</td>
<td>-0.446 ± 1.741</td>
<td>Statistic = 0.915, P=0.4</td>
</tr>
<tr>
<td><strong>Health limits activities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.666 ± 0.845</td>
<td>0.586 ± 1.741</td>
<td>Statistic = 0.915, P=0.5</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.075 ± 0.845</td>
<td>-1.550 ± 1.741</td>
<td>Statistic = 0.907, P=0.4</td>
</tr>
<tr>
<td><strong>Health limits vigorous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activities</td>
<td>0 ± 0.845</td>
<td>-1.875 ± 1.741</td>
<td>Statistic = 0.913, P=0.5</td>
</tr>
<tr>
<td></td>
<td>-1.537 ± 0.845</td>
<td>1.429 ± 1.741</td>
<td>Statistic = 0.701, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Health limits moderate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activities</td>
<td>0 ± 0.845</td>
<td>-3.33 ± 1.741</td>
<td>Statistic = 0.683, p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>0 ± 0.845</td>
<td>-1.041 ± 1.42</td>
<td>Statistic = 0.833, P=0.1</td>
</tr>
<tr>
<td><strong>Hrs physical activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per week</td>
<td>2.161 ± 0.845</td>
<td>4.933 ± 1.741</td>
<td>Statistic = 0.707, p&lt;0.01</td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.216 ± 0.717</td>
<td>-2.685 ± 1.4</td>
<td>Statistic = 0.656, p&lt;0.01</td>
</tr>
<tr>
<td>Week 8</td>
<td>1.783 ± 0.845</td>
<td>2.774 ± 1.741</td>
<td>Statistic = 0.684, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Hrs exercise per week</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.537 ± 0.845</td>
<td>1.429 ± 1.741</td>
<td>Statistic = 0.701, p&lt;0.01</td>
</tr>
<tr>
<td>Week 8</td>
<td>0 ± 0.845</td>
<td>1.429 ± 1.741</td>
<td>Statistic = 0.701, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Physical health</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interfered social</td>
<td>1.354 ± 0.845</td>
<td>1.240 ± 1.741</td>
<td>Statistic = 0.809, P=0.07</td>
</tr>
<tr>
<td></td>
<td>0.889 ± 0.845</td>
<td>-0.781 ± 1.741</td>
<td>Statistic = 0.831, P=0.1</td>
</tr>
<tr>
<td><strong>Social support</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.968 ± 0.845</td>
<td>-1.875 ± 1.741</td>
<td>Statistic = 0.640, p&lt;0.01</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.968 ± 0.845</td>
<td>-0.3 ± 1.741</td>
<td>Statistic = 0.640, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Bodily pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.668 ± 0.845</td>
<td>-0.446 ± 1.741</td>
<td>Statistic = 0.908, P=0.4</td>
</tr>
<tr>
<td>Week 8</td>
<td>0 ± 0.845</td>
<td>-0.3 ± 1.741</td>
<td>Statistic = 0.982, P=1</td>
</tr>
<tr>
<td><strong>Expect health get worse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.523 ± 0.845</td>
<td>-0.1875 ± 1.741</td>
<td>Statistic = 0.823, P=0.09</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.440 ± 0.845</td>
<td>1.335 ± 1.741</td>
<td>Statistic = 0.921, P=0.5</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.889 ± 0.845</td>
<td>-781 ± 1.741</td>
<td>Statistic = 0.831, P=0.1</td>
</tr>
<tr>
<td>Week 8</td>
<td>0 ± 0.845</td>
<td>-3.333 ± 1.741</td>
<td>Statistic = 0.683, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Difficulty sleeping</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.270 ± 0.845</td>
<td>1.531 ± 1.741</td>
<td>Statistic = 0.886, P=0.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.668 ± 0.845</td>
<td>-0.446 ± 1.741</td>
<td>Statistic = 0.908, P=0.4</td>
</tr>
<tr>
<td><strong>Time to fall asleep</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.313 ± 0.845</td>
<td>-0.104 ± 1.741</td>
<td>Statistic = 0.822, P=0.09</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.668 ± 0.845</td>
<td>-0.446 ± 1.741</td>
<td>Statistic = 0.908, P=0.4</td>
</tr>
<tr>
<td><strong>Hours slept</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.586 ± 0.845</td>
<td>2.552 ± 1.741</td>
<td>Statistic = 0.773, p&lt;0.05</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.968 ± 0.845</td>
<td>-1.875 ± 1.741</td>
<td>Statistic = 0.640, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Hours in bed asleep</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.857 ± 0.845</td>
<td>-0.3 ± 1.741</td>
<td>Statistic = 0.822, P=0.09</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.668 ± 0.845</td>
<td>-0.446 ± 1.741</td>
<td>Statistic = 0.908, P=0.4</td>
</tr>
</tbody>
</table>
### Appendix VII: Normality data

<table>
<thead>
<tr>
<th>Question</th>
<th>Skewness (week 8)</th>
<th>Kurtosis (week 8)</th>
<th>Shaprio-Wilks test (week 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall sleep quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.265 ± 0.845</td>
<td>-2.214 ± 1.741</td>
<td>Statistic=0.867, P=0.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.046 ± 0.845</td>
<td>-2.13 ± 1.741</td>
<td>Statistic=0.901, P=0.4</td>
</tr>
<tr>
<td>Happiness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.968 ± 0.845</td>
<td>-1.875 ± 1.741</td>
<td>Statistic=0.640, p&lt;0.01</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.968 ± 0.845</td>
<td>-1.875 ± 1.741</td>
<td>Statistic = 0.640, p&lt;0.01</td>
</tr>
<tr>
<td>Worry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.313 ± 0.845</td>
<td>-0.104 ± 1.741</td>
<td>Statistic=0.866, P=0.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>0 ± 0.845</td>
<td>-3.333 ± 1.741</td>
<td>Statistic = 0.683, p&lt;0.01</td>
</tr>
<tr>
<td>Irritation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>Not analysed</td>
<td>2.5 ± 1.741</td>
<td>Statistic=0.827, P=0.1</td>
</tr>
<tr>
<td>Week 8</td>
<td>0 ± 0.845</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.313 ± 0.845</td>
<td>-0.104 ± 1.741</td>
<td>Statistic=0.866, P=0.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>1.369 ± 0.845</td>
<td>2.5 ± 1.741</td>
<td>Statistic=0.814, P=0.08</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.857 ± 0.845</td>
<td>-0.3 ± 1.741</td>
<td>Statistic=0.822, P=0.09</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.383 ± 0.717</td>
<td>-1.481 ± 1.741</td>
<td>Statistic=0.920, P=0.5</td>
</tr>
<tr>
<td>Concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0 ± 0.845</td>
<td>-2.48 ± 1.741</td>
<td>Statistic=0.960, P=0.8</td>
</tr>
<tr>
<td>Week 8</td>
<td>-1.586 ± 0.845</td>
<td>2.552 ± 1.741</td>
<td>Statistic = 0.773, p&lt;0.05</td>
</tr>
<tr>
<td>Concentration (book/magazine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0 ± 0.845</td>
<td>-3.333 ± 1.741</td>
<td>Statistic=0.683, p&lt;0.05</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.326 ± 0.845</td>
<td>-2.253 ± 1.741</td>
<td>Statistic=0.805, P=0.07</td>
</tr>
<tr>
<td>Concentration (film)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.326 ± 0.845</td>
<td>-2.253 ± 1.741</td>
<td>Statistic=0.805, P=0.07</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.857 ± 0.845</td>
<td>-0.3 ± 1.741</td>
<td>Statistic=0.822, P=0.09</td>
</tr>
<tr>
<td>Concentration (Boring task)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.668 ± 0.845</td>
<td>-0.446 ± 1.741</td>
<td>Statistic=0.908, P=0.4</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.313 ± 0.845</td>
<td>-0.104 ± 1.741</td>
<td>Statistic=0.866, P=0.212</td>
</tr>
</tbody>
</table>

Table showing the normality of data for week 0 and week 8 of the scale data from the interview. Where there is normality of data this is indicated in bold, where only one of the two sessions yielded normal data the week is in bold, however, where both weeks showed normality of data this in indicated by the question also appearing in bold.
APPENDIX VIII

Cytokine data
Cytokine results

To assess a wide variety of cytokines it was decided to use the Randox biochip assay array in order to screen for potential cytokines and growth factors of interest in 28 patients from Week 0 to 8 of treatment (Randox laboratories Ltd, UK). Serum blood sample were analysed using the Randox Evidence Investigator™ (Randox Laboratories Ltd, UK). The evidence investigator uses biochip array technology to analyse multiple analytes in a single sample. The biochip used for this experiment was the cytokine and growth factors array (Cat. No. EV 3513), which measured levels of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, Vascular Endothelial Growth Factor (VEGF), IFN-γ, Endothelial Growth Factor (EGF), MCP-1 and TNF-α, meaning it was possible to analyse for all these cytokines using one 100μl sample per patient.

Table i.i: Patient characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>Gender</th>
<th>Genotype</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23</td>
<td>38.3 ± 2.6</td>
<td>Male: (15) 65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female: (8) 35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-α</td>
<td>28</td>
<td>39.36 ± 1.6</td>
<td>Male: (20) 71%</td>
<td>Genotype 46%</td>
<td>IVDU: (25) 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female: (8) 29%</td>
<td>Genotype 54%</td>
<td>Unknown: (3) 11%</td>
</tr>
<tr>
<td>Depressed</td>
<td>17</td>
<td>39.88 ± 3.1</td>
<td>Male: (14) 82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female: (3) 18%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure showing demographic data for all participants that were included in the cytokine analysis.

However, when results were analysed there was only a significant difference for IFN-α patients from Week 0 to Week 8 of IFN-α treatment in the chemokines MCP-1, (t(27)=5.96, p<0.01) (see Table i.ii). With additional significant results with Control participants at Week 0 for IL-10 (t(29.2)=2.95, p<0.01; Control: 0.26 ± 0.1; IFN-α: 2.44 ± 0.7) and TNF-α (t(49)=2.06, p<0.05; Control: 1.57 ± 0.3; Week 0: 3.62 ± 2.1).

When the control group was then compared to Week 8, there was a significant difference between the control and IFN-α group for IL-10 (t(32.5)=2.84, p<0.01; Control: 0.26 ± 0.1; IFN-α: 1.61 ± 0.5), TNF-α (t(49)=4.61, p<0.01; Control: 1.57 ± 0.3; IFN-α: 4.33 ± 0.5) and MCP-1 (t(43.1)=2.71, p<0.01; Control: 242.74 ± 14.5; IFN-α: 319.07 ± 24.2).

When cytokine levels were then correlated with mood there was found to be no significant relationship (see Table i.iii), and numbers of depressed patients were inferred as being too low to draw any reliable relationships from. Also when those patients who
became depressed on treatment were compared to those who did not, there was no significant difference between the two groups (see Table i.iv).

When 17 medically-healthy patients with a primary depression were then compared to Controls they exhibited more significant increases relative to the Controls than the IFN-α group did (see Table i.v). This unexpected difference led to the conclusion that the analysis run may have also been flawed. Also there was no significance for much of the IFN-α data examined, and there was no impact on mood for patients taking IFN-α. The additive effect of these two issues was the decision not to include this analysis in the thesis, and it did not add anything to the rest of the work conducted, and methodological issues meant the data could not be used to support any conclusions.

Table iJi: Table showing cytokine levels from Week 0 to 8 of treatment

<table>
<thead>
<tr>
<th>Cytokine/Growth factor</th>
<th>Mean ± SEM</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>Week 0: 5.49 ± 2.2</td>
<td>0.721</td>
<td>P=0.5</td>
</tr>
<tr>
<td></td>
<td>Week 8: 4.41 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-4</td>
<td>Week 0: 3.55 ± 0.7</td>
<td>0.538</td>
<td>P=0.6</td>
</tr>
<tr>
<td></td>
<td>Week 8: 3.32 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Week 0: 4.35 ± 1.7</td>
<td>1.519</td>
<td>P=0.1</td>
</tr>
<tr>
<td></td>
<td>Week 8: 3.16 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>Week 0: 16.15 ± 4.8</td>
<td>0.29</td>
<td>P=0.8</td>
</tr>
<tr>
<td></td>
<td>Week 8: 15.24 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>Week 0: 2.44 ± 0.7</td>
<td>0.44</td>
<td>P=0.2</td>
</tr>
<tr>
<td></td>
<td>Week 8: 1.61 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>Week 0: 151.2 ± 20.9</td>
<td>1.282</td>
<td>P=0.2</td>
</tr>
<tr>
<td></td>
<td>Week 8: 135.62 ± 16.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Week 0: 1.04 ± 0.4</td>
<td>0.16</td>
<td>P=0.9</td>
</tr>
<tr>
<td></td>
<td>Week 8: 1 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>Week 0: 3.62 ± 0.7</td>
<td>-1.318</td>
<td>P=0.2</td>
</tr>
<tr>
<td></td>
<td>Week 8: 4.33 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1α</td>
<td>Week 0: 0.44 ± 0.2</td>
<td>1.725</td>
<td>P=0.1</td>
</tr>
<tr>
<td></td>
<td>Week 8: 0.27 ± 0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>Week 0: 1.17 ± 0.5</td>
<td>1.491</td>
<td>P=0.1</td>
</tr>
<tr>
<td></td>
<td>Week 8: 0.7 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>Week 0: 219.83 ± 13.3</td>
<td>-5.961</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Week 8: 319.07 ± 24.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF</td>
<td>Week 0: 15.87 ± 4.8</td>
<td>0.964</td>
<td>P=0.3</td>
</tr>
<tr>
<td></td>
<td>Week 8: 12.11 ± 4.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table showing the difference in cytokine, growth factor and chemokine levels from week 0 to week 8 of treatment with IFN-α. The only cytokine that increased significantly was MCP-1 (indicated in bold).
Table i.iii: Relationship between cytokines and HAM-D in patients taking IFN-α

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Mean ± SEM</th>
<th>Pearson correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>5.6 ± 2.2</td>
<td>0.177</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Week 8</td>
<td>4.57 ± 1.5</td>
<td>-0.173</td>
<td>P=0.4</td>
</tr>
<tr>
<td>IL-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>3.52 ± 0.7</td>
<td>0.106</td>
<td>P=0.6</td>
</tr>
<tr>
<td>Week 8</td>
<td>3.32 ± 0.5</td>
<td>0.026</td>
<td>P=0.9</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>4.48 ± 1.8</td>
<td>0.156</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Week 8</td>
<td>3.17 ± 1.1</td>
<td>0.137</td>
<td>P=0.5</td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>16.31 ± 5</td>
<td>0.134</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Week 8</td>
<td>14.8 ± 2.2</td>
<td>-0.254</td>
<td>P=0.2</td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>2.49 ± 0.8</td>
<td>0.204</td>
<td>P=0.3</td>
</tr>
<tr>
<td>Week 8</td>
<td>1.62 ± 0.5</td>
<td>-0.165</td>
<td>P=0.4</td>
</tr>
<tr>
<td>VEGF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>153.05 ± 21.6</td>
<td>-0.004</td>
<td>P=1</td>
</tr>
<tr>
<td>Week 8</td>
<td>137.17 ± 16.7</td>
<td>-0.289</td>
<td>P=0.1</td>
</tr>
<tr>
<td>IFN-γ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.08 ± 0.4</td>
<td>0.023</td>
<td>P=0.9</td>
</tr>
<tr>
<td>Week 8</td>
<td>1 ± 0.3</td>
<td>-0.066</td>
<td>P=0.7</td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>3.64 ± 0.8</td>
<td>0.240</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>4.31 ± 0.5</td>
<td>-0.3</td>
<td>P=0.1</td>
</tr>
<tr>
<td>IL-1α</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>0.46 ± 0.2</td>
<td>0.065</td>
<td>P=0.7</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.27 ± 0.08</td>
<td>-0.124</td>
<td>P=0.5</td>
</tr>
<tr>
<td>IL-1β</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.21 ± 0.5</td>
<td>0.16</td>
<td>P=0.4</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.72 ± 0.3</td>
<td>-0.144</td>
<td>P=0.5</td>
</tr>
<tr>
<td>MCP-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>215.98 ± 13.2</td>
<td>-0.0285</td>
<td>P=0.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>306 ± 21.1</td>
<td>0.116</td>
<td>P=0.6</td>
</tr>
<tr>
<td>EGF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>16.46 ± 5</td>
<td>0.336</td>
<td>P=0.09</td>
</tr>
<tr>
<td>Week 8</td>
<td>12.23 ± 4.3</td>
<td>-0.158</td>
<td>P=0.4</td>
</tr>
</tbody>
</table>

Table showing the relationship between HAM-D scores at Week 0 (mean: 3.2 ± 0.5) and Week 8 (mean: 14.93 ± 1.3) with cytokine levels. There was no significant relationship for any cytokines at any time-point.
### Table i.iv: Difference in cytokine levels at Week 0 and Week 8 for those patients who did and did not become Depressed

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Nondepressed Mean ± SEM (n=18)</th>
<th>Depressed Mean ± SEM (n=7)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>4.42 ± 2.1</td>
<td>10.59 ± 6.6</td>
<td>-1.17</td>
<td>P=0.3</td>
</tr>
<tr>
<td></td>
<td>4.24 ± 8.9</td>
<td>6.73 ± 2.7</td>
<td>-0.662</td>
<td>P=0.5</td>
</tr>
<tr>
<td>IL-4</td>
<td>2.97 ± 0.7</td>
<td>4.64 ± 1.9</td>
<td>-1</td>
<td>P=0.3</td>
</tr>
<tr>
<td></td>
<td>3.26 ± 0.6</td>
<td>3.29 ± 1.1</td>
<td>-0.26</td>
<td>P=1</td>
</tr>
<tr>
<td>IL-6</td>
<td>2.46 ± 0.6</td>
<td>10.14 ± 6.6</td>
<td>-1.166</td>
<td>P=0.3</td>
</tr>
<tr>
<td></td>
<td>2.13 ± 0.6</td>
<td>6.38 ± 3.8</td>
<td>-1.105</td>
<td>P=0.3</td>
</tr>
<tr>
<td>IL-8</td>
<td>18.94 ± 7.2</td>
<td>12.59 ± 5.1</td>
<td>0.523</td>
<td>P=0.6</td>
</tr>
<tr>
<td></td>
<td>16.52 ± 3</td>
<td>12.07 ± 3.3</td>
<td>0.859</td>
<td>P=0.4</td>
</tr>
<tr>
<td>IL-10</td>
<td>2.1 ± 0.8</td>
<td>3.89 ± 2</td>
<td>-0.974</td>
<td>P=0.3</td>
</tr>
<tr>
<td></td>
<td>1.49 ± 0.6</td>
<td>1.9 ± 0.9</td>
<td>-0.361</td>
<td>P=0.7</td>
</tr>
<tr>
<td>VEGF</td>
<td>173.3 ± 29.7</td>
<td>95.13 ± 11.7</td>
<td>1.605</td>
<td>P=0.1</td>
</tr>
<tr>
<td></td>
<td>155.45 ± 21.4</td>
<td>91.49 ± 18.9</td>
<td>1.747</td>
<td>P=0.09</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0.96 ± 0.5</td>
<td>1.69 ± 0.9</td>
<td>-0.771</td>
<td>P=0.5</td>
</tr>
<tr>
<td></td>
<td>0.8 ± 0.3</td>
<td>1.54 ± 0.6</td>
<td>-1.152</td>
<td>P=0.3</td>
</tr>
<tr>
<td>TNF-α</td>
<td>3.96 ± 0.9</td>
<td>3.4 ± 1.8</td>
<td>0.307</td>
<td>P=0.7</td>
</tr>
<tr>
<td></td>
<td>4.57 ± 0.6</td>
<td>4.45 ± 0.9</td>
<td>0.097</td>
<td>P=0.9</td>
</tr>
<tr>
<td>IL-1α</td>
<td>0.38 ± 0.1</td>
<td>0.75 ± 0.6</td>
<td>-0.628</td>
<td>P=0.4</td>
</tr>
<tr>
<td></td>
<td>0.25 ± 0.1</td>
<td>0.42 ± 0.2</td>
<td>-0.834</td>
<td>P=0.4</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.75 ± 0.4</td>
<td>2.75 ± 1.6</td>
<td>-1.228</td>
<td>P=0.3</td>
</tr>
<tr>
<td></td>
<td>0.51 ± 0.3</td>
<td>1.49 ± 0.6</td>
<td>-1.509</td>
<td>P=0.1</td>
</tr>
<tr>
<td>MCP-1</td>
<td>220.44 ± 17.5</td>
<td>209.32 ± 25.4</td>
<td>0.361</td>
<td>P=0.7</td>
</tr>
<tr>
<td></td>
<td>311 ± 29.3</td>
<td>311.85 ± 26</td>
<td>-0.017</td>
<td>P=1</td>
</tr>
<tr>
<td>EGF</td>
<td>17.38 ± 7</td>
<td>15.48 ± 7</td>
<td>0.156</td>
<td>P=0.9</td>
</tr>
<tr>
<td></td>
<td>14.54 ± 6.2</td>
<td>9 ± 4.8</td>
<td>0.527</td>
<td>P=0.6</td>
</tr>
</tbody>
</table>

Table showing the difference in cytokine levels for those patients who were and were not depressed at Week 8 of treatment, assessed using criteria set out in Chapter 4. There was no significant difference between both groups at either Week 0 or Week 8, despite depressed patients showing higher levels of many cytokines at week 0. When split into their median components into ‘high’ and ‘low’ baseline groups for cytokines, there was no significant difference between groups for incidence of depression.
### Table i.v: Difference in cytokine levels for Depressed patients and age-and-sex-matched Control participants

<table>
<thead>
<tr>
<th>Cytokine/Growth factor</th>
<th>Control Mean ± SEM</th>
<th>Depressed Mean ± SEM</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>3.22 ± 1.5</td>
<td>2.6 ± 1.5</td>
<td>0.294</td>
<td>P=0.7</td>
</tr>
<tr>
<td>IL-4</td>
<td>4.55 ± 2</td>
<td>1.56 ± 0.7</td>
<td>1.399</td>
<td>P=0.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.44 ± 0.7</td>
<td>0.63 ± 0.5</td>
<td>0.95</td>
<td>P=0.4</td>
</tr>
<tr>
<td>IL-8</td>
<td>19.69 ± 12.6</td>
<td>3.97 ± 3.3</td>
<td>1.207</td>
<td>P=0.2</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.26 ± 0.2</td>
<td>3.26 ± 0.9</td>
<td>-3.173</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VEGF</td>
<td>143.8 ± 17.5</td>
<td>106.65 ± 14.9</td>
<td>1.615</td>
<td>P=0.1</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.52 ± 0.2</td>
<td>2.44 ± 0.9</td>
<td>-2.041</td>
<td>P=0.06</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.51 ± 0.4</td>
<td>2.44 ± 0.6</td>
<td>-0.918</td>
<td>P=0.4</td>
</tr>
<tr>
<td>IL-1α</td>
<td>0.25 ± 0.1</td>
<td>0.69 ± 0.1</td>
<td>-2.505</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.63 ± 0.4</td>
<td>2.55 ± 0.7</td>
<td>-2.329</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MCP-1</td>
<td>249.09 ± 19.2</td>
<td>178.17 ± 13.4</td>
<td>3.030</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EGF</td>
<td>12.14 ± 3.5</td>
<td>25.24 ± 5.3</td>
<td>-2.063</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table showing the difference in cytokine levels for Depressed patients, currently in a major depressive episode and age-and-sex-matched Control participants. Depressed patients showed significantly higher levels of IL-10, IL-1α, IL-1β and EGF, and significantly lower levels of MCP-1.