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INTERPERSONAL PSYCHOTHERAPY AND MIRTAZAPINE VERSUS MIRTAZAPINE ALONE IN TREATMENT RESISTANT DEPRESSED PATIENTS WITH SEQUENTIAL FUNCTIONAL BRAIN SCANS OF DOPAMINE D2 RECEPTORS WITH IBZM SPECT

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Doctor of Philosophy

07 JUN 2007

UNIVERSITY OF DURHAM

School for Health

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Research, like any piece of hard work can be all consuming and overwhelming; in addition to specific research skills I'm sure a sense of humour is invaluable. Just to show I've still got mine!

X-RAYS

In November 1895, Dr. William Roentgen, a German physicist, discovered X-rays and announced his findings, and within a year more than a thousand papers on this new diagnostic technique were published throughout the world. One English newspaper even ran an ad for special underwear that guaranteed to "keep the private parts private" during an X-ray examination.

(from Neuroanatomy Made easy and understandable. By Michael Lieberman. Third Edition, 1986, p 122)

INTERPERSONAL PSYCHOTHERAPY, MIRTAZAPINE AND DOPAMINE D2 RECEPTORS IN TREATMENT RESISTANT MAJOR DEPRESSION

ELIZABETH ROBINSON

Twenty DSM-IV major depressed patients who had not responded to at least one previous trial of antidepressant therapy at an adequate dose and duration agreed to participate in this study. They were randomly assigned to receive either mirtazapine (30-45mg) alone or in combination with 16 sessions of weekly Interpersonal psychotherapy (IPT). The patients were followed up naturalistically for one year, during this time the psychotherapy sessions were delivered monthly. Blinded clinician ratings and self ratings were obtained for depression (Hamilton Depression Scale (HamD), Beck Depression Inventory (BDI)), anxiety (Hamilton Anxiety Scale (HAS)), and social functioning (Social Adaptation Scale) at baseline, 6, 16, 26 and 52 weeks.

1123 Iodobenzamide Single Photon Computed Emission Tomography (IBZM SPECT) scans measured striatal dopamine D2 receptor activity at baseline and after 6 weeks of treatment.

A two way repeated measures analysis of variance (ANOVA) detected significant effects measured by the HamD and HAS for time ($p=0.001$; $p=0.001$ respectively), treatment ($p=0.007$; $p=0.033$) and the interaction between the two ($p=0.007$; $p=0.044$). Significant differences emerged between the two groups by six months and continued to one year follow up favouring the IPT group (HamD, $p=0.033$; HAS, $p=0.003$). The only significant effects for the BDI were for time ($p=0.001$). There were no statistically significant effects measured by the SAS.

A 3-way repeated measures ANOVA on the IBZM SPECT data detected a significant interaction between Time X Hemisphere, demonstrated by a higher IBZM uptake in the striatum in non-responders ($p=0.013$), agitated patients ($p=0.045$) and women ($p=0.012$). The same interaction effects were noted in patients with a high level of resistant depression ($p=0.001$).

This preliminary study shows promising initial results for IPT in resistant depression. There is some evidence to support a role for dopamine in treatment resistant depression.

Chapter One - Introduction	7
Treatment resistant depression (TRD).....	7
The impact of Treatment resistant depression	8
Brain imaging in treatment resistant depression	9
Treatment options in treatment resistant depression	9
Interpersonal Psychotherapy	11
Dopamine hypothesis of depression.....	12
Thesis study 1: Interpersonal Psychotherapy for treatment resistant depression a parallel trial.....	13
Participants.....	13
Clinical measurements.....	14
Demographic details	14
Depression.....	14
Interpersonal psychotherapy	15
Mirtazapine	15
Thesis study 2: Sequential dopamine D2 receptor mapping in treatment resistant depression	16
Design	16
Method	17
SPECT procedure - Quality control and performance tests	17
Scanning method	17
Results	18
Discussion	18
Chapter two - Treatment Resistant Depression (TRD).....	20
Definitions of treatment resistant depression	20
The concept of treatment resistant depression	23
Problems associated with a lack of an agreed definition for resistant depression.....	25
Epidemiology and course of resistant depression.....	26
Economic costs of TRD.....	28
Suicide risk	30
Psychosocial factors which affect treatment resistant depression	31
Work and social impairment	32
Gender.....	33
Aetiology of treatment resistant depression	34
Risk factors contributing to Treatment Resistant Depression	34
Type of depression and the number of episodes.....	34
Comorbid psychiatric disorders	35
Comorbid personality disorder.....	36
Comorbid medical conditions	39
Thyroid abnormalities in treatment resistant depression	39
Neuroimaging in treatment resistant depression	41
Management of treatment resistant depression	44
Initial assessment of treatment resistant depression	44
Clinician's role in achieving compliance	45
Treatment options in resistant depression	47
Switching antidepressants	48
Pharmacological action of antidepressants	48
Treatment approaches in resistant depression	49
SSRI to SSRI.....	49
SSRI to tricyclic antidepressant	50
SSRI to Venlafaxine.....	50
SSRI to Bupropion	51
SSRI to Mirtazapine	51
Combination strategies	52
SSRIs and TCA's	53



SSRIs and SSRIs	53
SSRIs and alpha agonists (Mirtazapine/ Mianserin)	54
Augmentation strategies	55
<i>Lithium augmentation studies</i>	55
SSRI and lamotrigine	56
Thyroid hormone augmentation	57
Antipsychotic medication augmentation.....	57
Pindolol Augmentation.....	59
Riluzole	60
Psychotherapy	60
Psychotherapy treatment in non responders	62
<i>Cognitive behavioural therapy</i>	62
<i>Other psychotherapies</i>	63
Psychotherapy treatment in partial responders	64
<i>Interpersonal Psychotherapy</i>	64
<i>Cognitive behaviour therapy</i>	65
Chronic depression	67
<i>Interpersonal Psychotherapy</i>	67
<i>Cognitive behaviour therapy</i>	71
<i>Other psychotherapies</i>	72
Electroconvulsive therapy (ECT)	75
Vagus Nerve Stimulation (VNS)	76
Transcranial Magnetic Stimulation (TMS)	77
Studies in progress	78
Future directions in treatment resistant depression studies.....	79
 Chapter three – Interpersonal Psychotherapy (IPT) for depression.....	 80
History and origins of IPT.....	80
Structure of a course of IPT.....	82
The Initial Phase	82
The Middle Phase.....	83
<i>Complicated bereavement</i>	84
<i>Role dispute</i>	84
<i>Role transition</i>	84
Interpersonal deficit.....	84
The End Phase.....	85
IPT for varying phases of treatment	86
Clinical trials of IPT as an acute treatment for adults.....	86
Clinical trials of IPT as an acute treatment in the elderly.....	90
Clinical trials of IPT as an acute treatment for adolescents.....	91
Clinical trials of IPT as a maintenance treatment in adults.....	94
Maintenance Therapies in Recurrent Depression Study (MTRD)	95
Clinical trials of IPT during continuation/maintenance phases in the elderly	99
<i>Overview of Maintenance Treatment Late Life Depression Study</i>	99
<i>Preliminary results reported during the acute and continuation phase</i>	100
<i>Findings from the MTLLD study</i>	102
<i>MTLLD 2 study</i>	106
<i>Treatment resistant depression - a single study reported</i>	107
Summary of acute and maintenance trials of IPT across all age groups	108
 Interpersonal Psychotherapy for various types of depression.....	 110
Recurrent depression	110
Dysthymia	112
Medical conditions and depression	114
IPT for ante partum/postpartum depression.....	116
Summary of IPT for chronic, recurrent, postpartum, antepartum depression and depression with concurrent medical conditions	119
 Delivery of Interpersonal Psychotherapy	 121
Interpersonal Psychotherapy by telephone.....	121
IPT in groups.....	122

Biological correlates of response to IPT	123
Brain functional imaging studies	123
Sleep studies.....	124
Summary of biological correlates of IPT	127
Effects on social adjustment.....	128
Therapist adherence in IPT	129
A case for IPT in Treatment resistant depression.....	131
Chapter four - The dopamine hypothesis of depression.....	139
The monoamine hypothesis of depression.....	139
Dopamine system	139
Diagram of basal ganglia.....	141
Dopaminergic pathways in the brain	141
The role of dopamine in depression.....	142
Animal studies	142
Human studies of depression.....	144
Post mortem studies	145
IBZM SPECT studies	145
Positron Emission Computed Tomography (PET) study of bipolar patients.....	145
Reduction of D2/3 in right striatum after total sleep deprivation (TSD)	146
High D2/D3 density characteristics depressed in patients.....	147
Decreased IBZM binding in treatment responders.....	148
Progressive increase in D2/D3 with treatment response.....	148
A suggestion of high D2/D3 in depression.....	151
Dopamine Transporter System (DAT) in depression	152
Dopamine Transporter System (DAT) in depression in Parkinson's disease	152
Brain Reward System	154
Growth hormone response to apomorphine stimulation test.....	155
Antidepressant effects of dopaminergic agents	156
Electroconvulsive therapy (ECT)	158
Summary.....	158
Chapter Five - The effects of Interpersonal Psychotherapy augmented to mirtazapine in treatment resistant depressed subjects.....	160
Design.....	160
Method	160
Depression.....	161
<i>Table C5-1 shows the participant characteristics of depression</i>	162
Number of previous depressive episodes.....	162
Duration of the current (index) depressive episode	163
The total number of months depressed	163
Number of different antidepressant treatments	163
<i>Table C5-2 shows the participant's antidepressant treatment prior to study entry</i>	164
Assessment of treatment resistant depression	166
<i>Table C5-3 shows the participant's severity of treatment resistant depression</i> ...	167
Patients diagnosis and comorbidity	168
<i>Table C5-4 shows the participant's diagnosis including comorbid anxiety disorders</i>	169
<i>Table C5-5 demonstrates a summary of the types of diagnosis of participant's in each group</i>	169
<i>Table C5-6 shows the number of additional DSM IV diagnoses in each treatment group</i>	170
Demographic data	170
Handedness	170
Age	170
Gender.....	170
<i>Table C5-7 shows the educational background of participant's in each group</i> ..	170
<i>Table C5-8 shows the occupation of participant's in each group</i>	171
<i>Table C5-9 shows the social contacts of participant's in each group</i>	171

<i>Table C5-10 shows the marital status of participant's in each group</i>	171
<i>Table C5-11 shows the alcohol and drug use of participant's in each group</i>	172
Interventions	172
Sample selection	172
Interpersonal Psychotherapy	172
IPT therapists	172
IPT therapy raters	173
Mirtazapine	174
Clinical ratings	174
Safety issues	175
Results	175
Clinical ratings	176
<i>Table C5-12 shows the total scores of the participants Hamilton depression scores at baseline and after week 6, week 16, week 26 and week 52</i>	177
<i>Table C5-13 shows the mean scores (SD) for the Hamilton depression scale at Week 0, week 6, week 16, week 26 and week 52</i>	178
<i>Table C5-14 shows a graph of the Hamilton depression scores at baseline and weeks 6, 16, 26 and 52</i>	179
<i>Table C5- 15 shows the total scores of the participants Beck Depression Inventory depression scores at baseline and after week 6, week 16, week 26 and week 52.</i>	180
<i>Table C5-16 shows the mean scores (SD) for the Beck Depression Inventory at Week 0, week 6, week 16, week 26 and week 52</i>	181
<i>Table C5- 17 shows a graph of the Beck Depression Inventory scores at baseline and weeks 6, 16, 26 and 52</i>	182
<i>Table C5-18 shows the total scores of the participants Hamilton Anxiety scores (HAS) at baseline and after week 6, week 16, week 26 and week 52</i>	183
<i>Table C5- 19 shows the mean scores (SD) for the Hamilton anxiety scale at baseline and after week 6, week 16, week 26 and week 52. Plus percent changes in reductions in HAS scores from baseline measurements (brackets)</i>	184
<i>Table C5-20 shows a graph of the Hamilton anxiety scores at baseline and weeks 6, 16, 26 and 52</i>	185
<i>Table C5-21 shows the total scores of the participants Social Adaption scores at baseline and after week 6, week 16, week 26 and week 52</i>	186
<i>Table C5-22 shows the mean scores (SD) for the Social Adaption Scores at baseline and after week 6, week 16, week 26 and week 52</i>	186
<i>Table C5-23 shows a graph of the Social Adaptation scores at baseline and weeks 6, 16, 26 and 52</i>	187
Interpersonal Psychotherapy	187
Dose of Interpersonal Psychotherapy treatment	188
<i>Table C5-24 shows the number of IPT sessions the participant received during the first six weeks, and acute and maintenance phases</i>	189
<i>Table C5-25 shows the mean number of IPT each completer received by week 6, during acute and maintenance treatment phases and after one year (Optimum dose in brackets)</i>	189
<i>Table C5-26 shows the mean number of IPT sessions delivered (total IPT group) and the total time (months) of therapy</i>	190
Interpersonal Psychotherapy problem areas.....	190
<i>Table C5-27 demonstrates the problem area which was the focus of treatment</i> .	190
IPT therapist adherence monitoring	191
Initial phase of IPT - adherence monitoring.....	191
<i>Table C5-28 shows the tasks of the initial sessions on the NIMH adherence rating form</i>	192
<i>Table C5-29 shows the results of the therapist adherence monitoring for the initial sessions</i>	192
Middle phase of IPT - adherence monitoring.....	193
Role disputes - therapist adherence monitoring.....	193
<i>Table C5-30 shows the goal directed activity for role disputes on the NIMH adherence rating form</i>	193

<i>Table C5-31 shows the results of the therapist adherence monitoring for role disputes</i>	193
Role transitions - therapist adherence monitoring	194
<i>Table C5-32 shows the goal directed activity for role transitions on the NIMH adherence rating form</i>	195
<i>Table C5-33 shows the results of the therapist adherence monitoring for role transitions</i>	195
Therapist strategy in IPT	196
<i>Table C5-34 shows the therapist strategy for goal directed activity (interpersonal focus) the on the NIMH adherence rating form</i>	196
<i>Table C5-35 shows the results for the therapist adherence monitoring for therapist strategy</i>	197
Therapist overall competence	198
<i>Table C5-36 shows the scores for the therapist overall competence ratings</i>	199
Mirtazapine	200
<i>The table C5-37 lists the dose of mirtazapine prescribed for each participant and includes the compliance to the antidepressant medication</i>	200
<i>Table C5-38 shows the mean dose of mirtazapine in milligrams taken for each participant</i>	201
<i>Table C5-39 shows the mean dose of mirtazapine (allowing for non compliance) for the total group and each treatment group at each time period</i>	202
Adverse events	203
<i>Table C5-40 shows the adverse events reported for each participant</i>	203
Concomitant medication	204
<i>Table C5-41 shows the use of concomitant medication used for each participant</i>	204

Chapter Six - Sequential dopamine D2 receptor mapping in treatment resistant depression..... **205**

Introduction	205
Design	206
Method	206
SPECT procedure	207
<i>Quality control and performance tests</i>	207
<i>Scanning method</i>	207
<i>Reconstructions</i>	208
Analysis of Regions of Interest (ROI) using BRASS to obtain IBZM uptake values	208
Results	209
<i>Treatment groups</i>	210
<i>Table C6-1 demonstrating mean uptake ratios for treatment group in the striatum using the cerebellum as a reference region</i>	210
<i>Responders / nonresponders</i>	210
<i>Table C6-2 demonstrating mean uptake ratios in the striatum for responders and non-responders using the cerebellum as a reference region</i>	211
<i>Table C6-3 shows the percent change scores in the Hamilton depression scale</i>	211
<i>Level of treatment resistant depression</i>	212
<i>Table C6-4 demonstrates the definition of the levels of treatment resistant depression for this study</i>	214
<i>Table C6-5 demonstrates the levels of treatment resistant depression for all the participants in the study</i>	215
<i>Impact of the levels of treatment resistant depression (TRD)</i>	215
<i>Table C6-6 demonstrating mean uptake ratios for TRD level in the striatum using the cerebellum as a reference region</i>	215
<i>Graph C6-7 showing IBZM uptake for week 0 and week 6 for low TRD participants</i>	216
<i>Graph C6-8 showing IBZM uptake for week 0 and week 6 for moderate TRD participants</i>	217
<i>Graph C6-8 showing IBZM uptake for week 0 and week 6 for high TRD participants</i>	218

<i>Graph C6-10 showing IBZM uptake for week 0 and week 6 for high TRD responding participants</i>	219
<i>Graph C6-11 showing IBZM uptake for week 0 and week 6 for high TRD non-responding participants</i>	219
Agitation.....	220
<i>Table C6-12 demonstrates significant symptoms of agitation at weeks 0 and 6 in each treatment group</i>	220
<i>Table C6-13 demonstrating mean uptake ratios for agitated participants in the striatum using the cerebellum as a reference region</i>	220
Gender.....	221
<i>Table C6-14 demonstrating sex differences in the mean uptake ratios in the striatum using the cerebellum as a reference region</i>	221
Chapter seven - Patterns of change	223
Reliable Change Index.....	223
<i>Table C7-1 demonstrating Hamilton Depression scores taken from clinical population in previous TRD studies</i>	225
<i>Table C7-2 demonstrating results of Hamilton Depression scores taken from non-clinical population studies</i>	226
<i>Table C7-3 demonstrating Beck Depression Inventory scores taken from clinical population in previous TRD studies</i>	226
<i>Table C7-4 demonstrating results of Beck Depression Inventory scores taken from non-clinical population studies</i>	227
Results section for the reliable change index (RCI) scores.....	228
<i>Table C7-5 demonstrating reliable change in Hamd and BDI scores</i>	228
<i>Table C7-6 demonstrating clinically significant and reliable change response and treatment effects over time – Hamilton depression score of 12 or below</i>	229
<i>Table C7-7 demonstrating clinically significant response and reliable change and treatment effects over time – Beck Depression Inventory scores of 16 or below</i>	230
Chapter eight - Discussion	233
Thesis study 1: Interpersonal Psychotherapy for treatment resistant depression, a parallel trial.....	233
Characteristics of depression of the participants	234
Defining TRD for this study	237
Demographics.....	239
IPT therapists.....	240
Format and delivery of IPT.....	242
Dose of IPT	243
Quality of IPT.....	244
Research unit.....	247
Conclusion	249
Thesis study 2: Sequential dopamine D2 receptor scanning with the use of IBZM SPECT.....	252
Cerebellum as a reference region	252
Treatment groups.....	253
Responders versus nonresponders.....	254
Gender.....	257
Agitation	259
Levels of TRD.....	259
Conclusion	262
References	264

Chapter One - Introduction

This chapter provides a summary of all of the chapters covered in this thesis. A review of current literature on treatment resistant depression (TRD), interpersonal psychotherapy (IPT) for depression and the role of dopamine in depression, including an overview of functional brain imaging of dopamine receptors will be presented. This will lead on to a description of two parts of a clinical research trial. Firstly, the effects of IPT combined to the antidepressant mirtazapine are compared to mirtazapine alone in participants with treatment resistant depression. Secondly, there are functional brain imaging scans of the dopamine D2 receptors in the above group pre-treatment and 6 weeks post-treatment.

Treatment resistant depression (TRD)

Depression is a debilitating illness and has a lifetime prevalence of around 17% (Kessler et al, 1994). Although many patients respond to antidepressant treatment there is a range of about 17% (Robbins et al, 1991) to 50% (Hirshfield et al, 2002) of patients who do not respond to initial antidepressant treatment. This lack of response to treatment, or *treatment resistance* accounts for approximately one third of patients with major depressive disorder (Dinan, 1993; Burrows et al, 1994; Kleine et al, 2004). Despite a growing interest regarding treatment resistant depression in the scientific community, there is a lack of consensus in the literature regarding how best resistant depression should be defined. Numerous definitions have been suggested, most of which generally focus on antidepressant treatment and duration of therapy (Souery et al, 1999). Literature reviewed in this chapter regarding treatment resistant depression includes patients who do not respond to treatment, partial responders or patients with chronic depression. Providing these patients are receiving antidepressant treatment at a therapeutic dose for an appropriate period of time and yet still remain symptomatic, they are to be considered resistant to treatment. As some patients require multiple antidepressant medications or combinations with neuroleptic medication

while others respond after just two or three different antidepressants indicates a spectrum of non response or treatment resistance. The lack of an agreed definition regarding treatment resistant depression makes interpretation of research in this area difficult and reduces the generalisability of the findings.

The impact of Treatment resistant depression

The economics of treatment resistant depression will be considered. Major depression has been found to be associated with increasing health and social care costs, however, costs for the employer of patients with treatment resistant depression have been found to be 3.5 times that of normal comparison employees, and double that of major depression (Greenberg et al, 2004). Furthermore, costs increase with increasing resistance to treatment (Russell et al, 2004).

The personal impact on an individual suffering from major depression cannot be underestimated. For example, suicide is a serious concern in major depression as around 15% of patients with major depression commit suicide (APA, 2004). Within the context of resistant depression, there is an increased preoccupation with suicidal ideation compared to patients with major depression (Papakostas et al, 2003a). Furthermore, there is an increased risk of suicide reported in partial responders (Fawcett, 1990) and an increased incidence of suicide and hospitalisations reported in chronic depression (Van Vulkenberg et al, 1984; Coryell et al, 1988; Klein et al, 1988; 1998).

Patients with treatment resistant depression have been found to have more problems relating to psychosocial adjustment (Petersen et al, 2004), additionally, chronic depression is reported to be more psychosocially disabling than some medical conditions including arthritis, diabetes and hypertension (Hays et al, 1995). Indeed mild or moderate depression has been associated with work impairment (Petersen et al, 2004).

Risk factors which contribute or increase the risk of resistant depression will be reviewed including family history (Nelsen and Dunner, 1995), psychotic depression (Lee and Murray, 1988; Aronson, 1988) initial slow responders to treatment, and poor or non responders (Boyer and Feigner, 1994; Neirneberg et al, 1995). Comorbid psychiatric disorders including anxiety and panic attacks (Dubovsky et al, 2005; Rosenbaum et al, 2001), double depression, that is major depression alongside dysthymic disorder (Keller and Shapiro, 1982) and personality disorders (DeBattista and Muella, 2001; Black et al, 1991; Papakostas et al, 2003b) will be presented. Comorbid medical conditions are also reviewed including thyroid abnormalities (Prange et al, 1996), heart disease (Carney et al, 1993; Harnett, 1994), and urea and electrolyte imbalances (Franco-Bronson, 1996).

Brain imaging in treatment resistant depression

There are a small number of studies evaluating the functioning and structure of the brain in patients with treatment resistant depression. Three studies which used Single Photon Emission Computed Tomography (SPECT) found increased hippocampal amygdala activity (Hornig et al, 1997), increased blood flow in the left dorsolateral prefrontal cortex post treatment (Zheng et al, 2000), and reduced blood flow bilaterally in the frontal regions of the brain (Conca et al, 2002). Structural changes as measured by Magnetic Resonance Imaging (MRI) scans demonstrate right striatal atrophy (Shah et al, 2002), changes in frontal lobe volumes (Coffey et al, 1993) and white (Steffens et al, 2001) and grey matter hyperintensities (Hickie et al, 1995).

Treatment options in treatment resistant depression

Treatment options which have been suggested and reviewed in the literature will be presented. There are a greater number of pharmacological approaches for treatment resistant depression reviewed in the literature than psychotherapy. Pharmacotherapy options include switching or combining antidepressant medications; alternatively another approach is to augment the antidepressant with a different agent

including the mood stabilisers lithium (Bauer, 2003) and lamotrigine (Barbosa et al, 2003), low dose atypical antipsychotic medication (Thase et al, 2004), thyroid hormone augmentation (Aronson et al, 1996), or pindolol (Artigas et al, 1994; Perez et al, 1997). There are also a small number of studies which evaluate the efficacy of biological treatments such as electroconvulsive therapy (ECT) (Sackheim et al, 1993), transcranial magnetic stimulation (TMS) (George et al, 1999) and vagus nerve stimulation (VNS) (Rush et al, 2000).

The literature reviewing psychotherapy in treatment resistant depression is sparse. The use of a psychoeducational group (Antonuccio et al, 1984) and cognitive behaviour therapy (CBT) has been useful in non responders (Fava et al, 1996; 1998; Barker et al, 1998). Positive results have been obtained in partial responders with Interpersonal Psychotherapy (IPT) (Scocco and Frank, 2002; Frank, 2000) and CBT (Fava et al, 1996; Paykel et al, 1999). Most of the literature published concerns psychotherapeutic approaches used in the management of chronic depression. The majority of the evidence suggests either IPT (Markowitz, 2003; Feijo de Mello, 2001; Browne et al, 2002); CBT (Thase et al 1997; Moore and Blackburn, 1997; Ravidran, 1999) or a more recently devised psychotherapy called Cognitive Behavioural Analysis System of Psychotherapy (CBASP) (Keller et al 2000) for this treatment group. Other psychotherapies including group psychotherapy (Hellerstein, 2001), Problem Solving Therapy (PST) and counselling are evaluated. A significant number of psychotherapy studies have involved open trials and been hampered by small numbers, a lack of a control condition, or a placebo. IPT has not been tested for tolerability, feasibility or efficacy in treatment resistant depression.

There are limited data evaluating treatment approaches in resistant depression. Although there is a growing body of literature reviewing a pharmacological approach, there is a paucity of information relating to the use of a psychotherapeutic approach in resistant depression. The efficacy of IPT in treatment resistant depression has not been evaluated.

The burden of resistant depression is great and has an impact on the sufferers' personal, work and social relations. Moreover, the risk of suicide, the economic implications and potential course of the disorder if untreated or inadequately treated cannot be ignored. Further research is needed to establish which treatments work for whom, taking into account the spectrum of treatment resistant depression.

Interpersonal Psychotherapy

Interpersonal Psychotherapy (IPT) is a manualised brief psychotherapy treatment which was developed initially to treat major depression (Klerman et al, 1984). In this chapter the author will provide an overview of IPT, describing the three phases of treatment; the initial, middle and the end phase and will provide an overview of the goals and strategies of treatment. The literature detailing the efficacy of IPT in depression during acute, continuation and maintenance therapy across all age groups (DiMascio et al, 1979; Weissman et al, 1979; Elkin et al, 1989; Sloane et al, 1985; Rothrum et al, 1982; Mufson et al, 1999) will be reviewed. The use of IPT in patients with highly recurrent depressive episodes (Frank et al, 1989) and combined IPT and antidepressant medication (Klerman et al, 1974; Weissman et al, 1974; Reynolds et al, 1994) will also be evaluated.

Adaptations of IPT will be presented including IPT as maintenance therapy (Frank et al, 1989), treatment for dysthymia (Markowitz, 1998a); depression and concurrent medical conditions including heart disease (Miller, 2002; Stuart and Cole, 1996) and HIV positive patients (Markowitz et al, 1995) and IPT for post partum (O'Hara et al, 2000) and antepartum depression (Spinelli, 1997; Spinelli and Endicott, 2003). Additionally, the delivery of IPT either by telephone (Miller and Weissman, 2002) or as a group (MacKenzie and Grabovac, 2001; Levkovitz et al, 2001) will be outlined. Data from a small number of studies which have evaluated biological correlates of treatment with IPT in depression, involving functional neuroimaging studies (Martin et al,

2001; Brody et al, 1999; 2001) and sleep studies (Reynolds et al, 1997) will be reviewed.

Dopamine hypothesis of depression

The monoamines are chemical neurotransmitters which include serotonin, noradrenaline and dopamine, all of which have been implicated in at least subtending if not causing depression. A review of the evidence which supports the dopamine hypothesis of depression will be presented, including areas of concentrations of dopamine in the brain and the three dopaminergic pathways by which dopamine is transmitted; the *nigrostriatal pathway*, the *mesolimbic* (*mesocortical* or *mesocorticolimbic*) pathway and the *tubero-infundibular* pathway. This chapter will then focus on various lines of evidence supporting the role of dopamine in depression; this includes changes in dopamine levels (Birkmayer and Riederer, 1975; Manji et al, 2001; Rajkowska, 2000) or its metabolite, homovanillic acid (HVA) (Traskman-Bandz et al, 1984) as well as alterations in the dopamine transporter system (DAT) (Weintraub et al, 2005) in the brain and in the cerebral spinal fluid of depressed patients compared to controls.

Additionally, further evidence for the role of dopamine in depression is outlined in terms of identifying the mechanism of action and alterations in dopamine function following treatment with either antidepressant medication (Arbuthnott, In Johnson et al, 1998; Johnson, In Fiegner and Boyer, 1991) or electroconvulsive therapy (ECT) (Puri and Hall, 2004).

The introduction of Single Photon Emission Computed Tomography (SPECT) brain functional imaging scanning procedures using radiopharmaceuticals is a technological advance which allows in vivo assessment of brain neurotransmitters, blood flow and glucose metabolism. A brief introduction to the techniques of SPECT and a review of the literature of dopamine in depression will be presented. Dopamine function is assessed with the use of the radioligand ¹²³Iodobenzamide (IBZM) which binds to the dopamine D2 / D3 receptors reflecting dopaminergic functioning. Although there is a paucity of

literature in this area, dopamine abnormalities demonstrated by increased (Shah et al, 1997; D'haenen and Bosnyak, 1994) or decreased IBZM binding (Klimke et al, 1999) have been identified in depression. Only two studies have assessed the sequential effects of antidepressant treatment either with an SSRI (Klimke et al, 1999) or total sleep deprivation (Ebert et al, 1994), reduced initial IBZM uptake has been reported in treatment responders when compared to controls and nonresponders (Klimke et al, 1999). The author will discuss limitations of previous studies including heterogeneity of patients studied, different scanning methods, different treatments and varying methods of interpreting the results.

Thesis study 1: Interpersonal Psychotherapy for treatment resistant depression a parallel trial

IPT has proven efficacy for major depression in all age groups (Elkin et al, 1989; Reynolds et al, 1996; Mufson and Fairbanks, 1996) and in dysthymic adults (Markowitz et al, 1998; Browne et al, 2002). There have been no clinical trials to date which have reviewed the efficacy of IPT in a resistant depressed population. This parallel group trial aimed to evaluate the effects of IPT combined with the antidepressant mirtazapine versus mirtazapine alone.

Participants

Following informed consent, twenty major depressed participants according to DSM IV criteria (American Psychiatric Association, 1994) who had not responded to at least six weeks of antidepressant therapy at an adequate dose were randomised to mirtazapine (30-45mg daily) alone or combined with 16 sessions of weekly IPT. They were then followed up naturalistically for one year; participants who were randomised to receive IPT continued to do so for one year at a monthly maintenance dose.

Participants came from the Sunderland area and were recruited from GP's and psychiatrists from March 2000 to June 2001. Participants with

a concurrent diagnosis of dysthymia or anxiety disorders were included in the trial. However, participants with psychotic depression, or current alcohol/ drug abuse were excluded from the trial.

Clinical measurements

A blinded clinical rater obtained baseline measurements of depression and anxiety using the 21 item Hamilton Depression Scale (Hamilton, 1960) and 14 item Hamilton Anxiety Scale (Hamilton, 1969); the rater also asked the participants to complete the Beck Depression Inventory (Beck, 1987) and Social Adaptation Scale (Weissman, 1976). These measurements were repeated at week 6, 16, 26 and 52. At baseline the author completed the Structured Clinical Interview (DSM-IV) and recorded details of previous depressive episodes including antidepressant treatment and response.

Demographic details

An equal number of males and females were recruited and were aged 28-52 (mean 39.5, SD 7.24). Most of the participants had left school without any qualifications, and a large proportion of this group were randomly allocated to the IPT and mirtazapine group (9 vs. 5). There were only a minority of participants who had professional (n=2), or further education (n=2) qualifications; all of these participants were all assigned the mirtazapine only group.

Nearly all (n=9/10) of the combined IPT and mirtazapine group were out of work, the remaining participant was employed in unskilled work; whereas only half of the mirtazapine only group were not working and most of the remaining participants (4/5) were in skilled employment. There were more divorcees in the combined group compared to the mirtazapine only group (4 vs. 1).

Depression

The duration of the current major depressive episode in the total group ranged from 2.5-42 months (mean 17.05, SD 12.05). The medication

only group had experienced eight months longer symptoms of depression during their current index episode (mean 21.05, SD 10.06 vs. mean 12.93, SD 12.05). The total number of months of depression over a lifetime in the total group ranged from 12 to more than 300 months and was 26 months longer in the combined IPT and mirtazapine group (mean 67.8, SD 88.3 vs. mean 41.4, SD 21.62). From the total sample, fourteen participants had a concurrent diagnosis of dysthymic disorder which was more heavily distributed in the combined group (8 vs. 4). The numbers of previously failed antidepressant treatments were similar in both groups (combined treatment, mean 2.6, SD 2.6 vs. monotherapy, mean 2.3, SD 1.15). Depression scores at baseline were similar in both groups with the Hamilton Depression Scale (mirtazapine plus IPT 29.7, SD 5.69 vs. mirtazapine 29.4, SD 4.03); and were slightly lower with the self rated Beck Depression Inventory with the mirtazapine only group (39.6, SD 8.57 vs. 33.2, SD 3.22)

Interpersonal psychotherapy

IPT was delivered as per manual for acute (Klerman et al, 1984) and maintenance treatment (Frank et al, 1989) by two research trained IPT therapists. Sixteen sessions of IPT (mean 11.3, range 7-17) were provided for the acute phase, followed by monthly IPT sessions (mean 5.8, range 3-12) for remainder of the year. IPT sessions were audiotaped and monitored for adherence by two raters. There were only two out of a possible four problems areas addressed during either acute or maintenance sessions; role transition and role dispute, both of which are the most common areas of focus in IPT. There were no participants requiring therapy for interpersonal deficit or complicated bereavement.

Mirtazapine

Mirtazapine is a "new" generation antidepressant which is classified as a noradrenergic and serotonergic antidepressant (NaSSA). Its principle action is to block the presynaptic alpha 2 receptors resulting in an increase in noradrenaline in synaptic clefts through the inhibition of the reuptake of noradrenaline. This also leads to an increase in stimulation

and release of serotonin (DeBoer et al, 1996). Additionally, animal studies show that mirtazapine increases extracellular dopamine and noradrenaline in the medial prefrontal cortex (Devoto et al, 2004; Nakayama et al, 2004; Millan et al, 2000).

Participants were prescribed a daily dose of 30-45mg of mirtazapine. Compliance was monitored using the pharmacy returns. Taking into account the prescribed dose and medication returns the mean dose of both groups were 31.3mg in the mirtazapine and IPT group versus 34.7mg in the mirtazapine only group. By today's standards these are relatively low/ moderate doses of mirtazapine, however this study took place in 2000/2001. Dosing schedules of the present day may be higher for patients who are resistant to treatment. 30mg of mirtazapine is efficacious for most depressed patients and we were not aiming to do a dose ranging study.

Thesis study 2: Sequential dopamine D2 receptor mapping in treatment resistant depression

I123- Iodobenzamide (IBZM) is a radioligand which has a strong affinity for the neurotransmitter dopamine, specifically the subtype dopamine D2 receptor. Following intravenous administration, the radioligand increasingly binds to the dopamine D2 receptor sites and emits a single photon of gamma radiation. This is detected using Single Photon Emission Computed Tomography (SPECT) imaging. These in vivo functional brain scans can give us some insight into the functional dopaminergic activity in depressed participants; this may be correlated to specific symptoms of depression or indeed response to antidepressant treatment.

Design

This design involves a parallel group study comparing IBZM SPECT before and after 6 weeks of treatment with mirtazapine alone or

mirtazapine plus Interpersonal Psychotherapy in treatment resistant depressed participants.

Method

The 20 participants in this study have already been described in the IPT trial. A further three participants had originally consented to the trial withdrew consent before the start of the trial for “personal reasons”.

This clinical trial comprising thesis studies 1 and 2 received ethical approval from Sunderland Ethics Committee in advance of the start of study. In addition, as per UK requirements, Professor David Williams, Chief Medical Physicist obtained the necessary consent from Administration of Radioactive Substances Committee (ARSAC) for the use of the IBZM SPECT scans at the same time. Dr Terry Featherstone, Consultant Neuroradiologist, was the ARSAC certificate holder.

A thyroid blocking agent was given to the participant the day before each SPECT scan in order to protect the thyroid gland during the scanning procedure.

Following a three day antidepressant washout phase, IBZM SPECT scans took place at week 0, before either treatment had started and after 6 weeks of treatment with either mirtazapine alone or combined with IPT. Clinical ratings, as detailed in the psychotherapy trial (HamD, BDI, SAS, HAS) took place on the same day as scan one and within one day of the second scan.

SPECT procedure - Quality control and performance tests

A quality control programme was carried out by the medical physicists before any participants had entered the trial to establish sensitivity and uniformity of the scans.

Scanning method

Having received an intravenous injection of the IBZM radioligand the participants had to wait for two hours before the IBZM SPECT scan

could be acquired. The results of the scans were analysed at the end of the trial.

Results

The results report any changes between the two groups in IBZM uptake. Additionally, functional dopaminergic changes were examined in relation to a number of clinical areas including: the level of treatment resistant depression, responders versus non responders, agitated participants versus non agitated participants and men versus women.

Discussion

Of the twenty three participants who agreed to participate in this trial only three withdrew their consent prior to the start of treatment. There were a further two participants, one in each group, who were not available for week 16 clinical assessments. For the statistical analysis this was identified as an intention to treat sample and the last observation was carried forward. Attrition to IPT was highest; there were no drop outs from either group although three participants switched from mirtazapine to an alternative antidepressant medication due to intolerable side effects, after the second IBZM scan.

There are certain limitations which restrict the generalisability of this study. The treatment provided during this trial took place at one research site. All of the participants came from the same area in the North East of England. Moreover, most of the participants studied came from a low socioeconomic class; particularly those participants randomised to IPT, most were out of work and had left school without any qualifications.

There was no placebo or normal control comparison used in this study, although both mirtazapine and IPT have been shown to be effective in the treatment of depression. Additionally, a UK Ethics Committee would not grant approval for a placebo study of this treatment population or application of the treatments to normal controls. In addition, by UK standards it is unethical to irradiate the brains of normal subjects, for which an ARSAC certificate would not have been granted.

This study breaks boundaries in a number of ways: firstly, IPT has never been tested in treatment resistant depressed patients before; secondly, no researchers have previously examined the role of dopamine D2 receptors in selected resistant depression nor is there any such work with particular regard to increasing levels of treatment resistance. Finally, it is very rare to see research which spans psychotherapy, medication and brain imaging to investigate the potential biological correlates of psychotherapy in such a difficult to treat patient group.

Future research is needed to identify the treatment options which may be effective to accommodate the potential variability of treatment resistant depression. The use of IPT alongside a sequential pharmacological approach to increase potency of antidepressant medication after a given period of time is needed. This may provide critical information about which particular treatments benefit which particular patients at varying stages of resistant depression. Longer term treatment and follow up studies are also needed. Comparisons to an alternative psychotherapy, such as CBT combined with medication are an area for future work.

Chapter two - Treatment Resistant Depression (TRD)

Definitions of treatment resistant depression

Treatment resistant depression has captured the attention of researchers for two decades. However, despite 20 years of research and investigation, there is still no widely accepted definition which can be used for clinical and research purposes. Currently, neither the International Classification of Diseases 10 (ICD 10, 2003) or the Diagnostic and Statistical Manual for Mental Disorders IV Text Revision (DSM IV TR, 2000) have a distinct classification of resistant depression.

Fawcett and Kravitz (1985) were the first to conceptualise treatment resistant depression, and did so on the basis of the duration of the depressive illness, extent of the antidepressant treatment, and the use of augmentation strategies in order to improve depressive symptoms.

Despite continued references over the next few years in the literature to "resistant depression" there was no consensus on how best to describe it (Nelson and Dunner, 1993), and no internationally agreed definition of either treatment resistance or non-response to treatment (Dinan et al, 1993). Nelson and Dunner (1993) recognised this problem and suggested that a definition would help make future research more generalisable and verifiable.

Having conducted a meta-analysis Fava and Davidson (1996) suggested the most simple definition of treatment resistance was a failure to achieve euthymia (that is a normal mood) with adequate antidepressant treatment and proposed a definition: *"Treatment resistant depressed patients may be identified as those who fail to respond to a standard dose of antidepressants administered continuously for a minimum duration of 6 weeks."* Researchers over the next few years became interested in defining resistant depression; this prompted a review by

Sourey et al (1999) who highlighted that more than 15 definitions had been proposed. Fawcett and Kravitz (1985) conceptualised treatment resistant depression based on the duration of the illness, extent of treatment and the use of augmentation strategies. Nierenberg et al (1990) suggests a model in which treatment resistant depression is an episode of major depression that persists despite any number of adequate antidepressant treatment within the current episode and in which the number of failed treatments is used as a measure of the degree of resistance. Sourey et al (1999) proposed a model which took into account the various stages, or levels of severity of treatment resistant depression, incorporating classifications at different levels of resistance. This started with a "*non responder*" (to one single class of antidepressants for 6-8 weeks), the next level of severity would be classified as "*treatment resistant depression*" where 2 or more antidepressant trials have been tried, and the longer the period of time not responding the greater the level of treatment resistance. Finally, the authors suggested the term "*chronic refractory depression*" should be applied to those patients who have had several trials of antidepressants including augmentation strategies.

The scientific community became increasingly aware of other areas for clarification; response, partial response and non-response were also necessary within the context of researching resistant depression (Nierenberg and DeCecco, 2001). For example, Thase and Rush (1995) argued that there is a spectrum of patients' responses to antidepressant treatment. They proposed distinguishing between relative treatment resistance and refractoriness and classified antidepressant responders along a continuum of five stages; Stage 1 involves one adequate trial of a single antidepressant. The Stages that follow involve more complex treatment incorporating different classes of antidepressant medications culminating in Stage V which would involve multiple classes of antidepressants in addition to bilateral ECT (see table below for details of Stage I-V). This staged approach has more recently been cited in some of the literature regarding identifying the degree of treatment resistance.

However, there are limitations in this conceptualisation as it excludes augmentation with mood stabilisers, antipsychotic medications, thyroxin, transcranial magnetic stimulation, vagus nerve stimulation and antidepressant psychotherapy. This may be due in part to the lack of substantial clinical trials supporting the efficacy of these treatments in TRD at this moment in time. Indeed, Pridmore and Turnier-Shea (2003) argued that the Thase – Rush guidelines are useful for research purposes but have less routine clinical utility.

	<i>An updated system for staging antidepressant resistance</i>
Stage I	Failure of an adequate trial of one class of major antidepressant
Stage II	Failure of adequate trials of two distinctly different classes of antidepressants
Stage III	Stage III plus failure of a third class of antidepressant including a TCA
Stage IV	Stage III plus failure of an adequate trial of an MAOI
Stage V	Stage IV plus failure of an adequate course of ECT

From: Thase ME. CNS Spectr. Vol 9, No 11.2004

Despite these advances, at this moment there is no clear definition of resistant depression which is widely accepted in both a clinical and a research setting. As recently as 2004, Kleine reiterated this problem when identifying that despite 30% of patients being treatment resistant there was still no general consensus or definition in use.

Although the most common approach has been to define resistance primarily by degrees of non response in order to detect levels of treatment resistance, Fagiolini and Kupfer in 2003 were interested in assessing if treatment resistant depression was a unique subtype of depression. They carried out a review addressing issues such as the clinical characteristics and course of the disorder, the neurobiological profile and the context and environment in which resistant depression develops. The authors concluded that although patients with resistant depression share a number of clinical, biological and environmental characteristics there is still a lack of available data, and the clinical

heterogeneity of the condition does not allow a classification of treatment resistant depression as a unique subtype.

The concept of treatment resistant depression

Researchers and clinicians alike agree with the concept of treatment resistant depression despite no universally accepted definition. There are common themes which emerge from suggested definitions which appear fundamental to the conceptualisation of resistant depression. These include potency of antidepressant medication, response to treatment and the overall time taken to achieve a remission or response.

It is essential that the antidepressant treatment prescribed to the patient is carefully assessed; dose and duration of pharmacotherapy is frequently highlighted as a starting point, this usually forms the focus of the first or second pharmacological intervention. Additionally, the number of strategies used to achieve remission of symptoms must have some relevance in determining the level of patients' resistance to treatment. If the treatment approaches have become more complex, such as the use of antidepressant and mood stabiliser combinations or electroconvulsive therapy (ECT), which is usually used in severe major depression, the patient may well be considered to be more resistant to treatment than those patients who may eventually respond after just 2 or 3 less complex antidepressant switching strategies. Following treatment algorithms that involve staged systematic approaches may give us some indication that patients may well be entering into the spectrum of resistant depression.

When considering a response to treatment, there are a number of factors which need to be addressed. For instance, chronic depression, non responders, partial responders (Fawcett, 1994), and responders who immediately relapse without a sustained period of remission (Little et al 1998) all fall short of a distinct period of wellness and therefore are not considered "healthy". However, all of these patients can, to some degree be placed within a continuum of treatment resistance; they may not have responded, or indeed poorly responded to a given treatment regime.

Furthermore, the issue of how and what is measured in relation to a “response” needs to be addressed. Hamilton depression scores and Beck Depression scores are routinely used in depression studies; response is usually accepted as a 40 - 50% reduction in scores. This may be misleading as “responders” may have demonstrated significant improvements in terms of a reduction in total depression scores, but may still actually be very symptomatic (Dyck, 1994). There have been similar concerns raised regarding the use of the Clinical Global Impression scales (Greenberg et al, 2004). Souery et al (1999) argued that measurements of social functioning should also be taken when considering a response to treatment.

Some, but not all of the literature suggests that resistant depression needs to be graded based on the time taken to achieve a response or remission of symptoms. Clearly, all three factors contribute in some way to our understanding of how a patient will respond to treatment; and the level of non response. It is unclear if a certain number of patients with depression will follow a chronic refractory course, and be truly “resistant” to any treatment. Evidently, there are distinct levels of response to treatment ranging from immediate positive and prolonged responders, poor or partial responders eventually leading to increasing levels or degrees of limited or no response. The range of the lack of response is currently given a general term of “treatment resistance”. For the purposes of this thesis I will conceptualise treatment resistant depression as varying levels of treatment response (or non response) to treatment. Clearly, there is a spectrum of response on which patients can be placed when considering the potency of antidepressant treatment, including the number of trials used, the level of response and the time taken to achieve any clinically significant progress.

Although the literature has included all patients across the difficult to treat spectrum it is hard to establish the true extent of the problem. Factors such as numerous definitions of treatment resistant depression,

the study of heterogeneous samples and the lack of prospective studies confound the situation further. Despite the growing literature relating to resistant depression, there is a need for longer term studies, reviewing different treatment approaches, using consistent definition and classification of the varying levels of resistant depression.

As these mechanisms for classifying, measuring and monitoring response in the difficult to treat depressed population improve, we will begin to gain further insight into this debilitating condition including the prevalence rates for poor and partial responders and the efficacy of treatment options for all levels of treatment resistant depression. We may also demonstrate a number of patients who do not respond favourably to the current treatment approaches available.

Some of the papers reviewed for this thesis have included a mix of patients who were either poor or non responders, or intolerant of antidepressant medication. Whilst the poor and non responders are to some degree treatment resistant; those patients who are "intolerant" cannot be considered resistant to treatment. It is reasonable to assume that patients intolerant of medication would not have continued with pharmacotherapy at an adequate dose and duration; a fundamental criterion of resistant depression.

Problems associated with a lack of an agreed definition for resistant depression

Although there is an agreement amongst the scientific population that resistant depression exists, the lack of an agreed definition to date makes research in this area difficult to interpret. One study may view a particular patient population as "resistant" whereas another study may use an altogether different definition. Research to date is clearly not generalisable. Further questions are raised when considering not just whether a patient is resistant to treatment, but also the potential extent of lack of response, (i.e. levels of resistance) as recently suggested by Thase and Rush (1995) stages I-V.

As a result of multiple definitions of treatment resistant depression, clinical trials have used different criteria for the number and type of previously failed trials needed to establish a diagnosis of treatment resistant depression; thus systematic and meaningful interpretation of the results of the trials is extremely difficult (Fagiolini and Kupfer, 2003).

Other factors which may confound the situation include patients who have been inappropriately diagnosed as "resistant to treatment" who may in fact have a "psuedoresistance" in that they might have been inadequately treated or misdiagnosed (Kornstein and Schneider, 2001). Fava and Davidson (1996) also argued that a diagnosis of resistant depression might actually reflect the expectations or assumptions of a clinician regarding a patient's response rather than the true clinical picture. A systematic and structured method of evaluating treatment in addition to a definition of treatment resistant depression may help ease the problems identified, such as misdiagnosis or pessimistic clinicians' assumptions and expectations. Clinical outcome measures such as the Hamilton Depression Scale can be a critical part of monitoring objectively a response to treatment and aid appropriately timed interventions.

Epidemiology and course of resistant depression

Kessler et al (1994) identified major depressive disorder as the most prevalent psychiatric condition over the course of a lifetime (17.1%) as well as over a 12 month period. Although, no study has systematically assessed the epidemiology of treatment resistant depression, there are estimates of levels of treatment resistance and response cited in the literature. Robbins et al (1991) identified that only 19%-37% of those who suffer from depression ever seek treatment; and at least 50% of those people who do begin treatment with an antidepressant do not respond (Hirschfield et al, 2002). Furthermore, as many as 30% of patients suffering from major depression are resistant to antidepressant treatment (Dinan et al, 1993; Brodaty et al, 1993; Burrows et al, 1994; Kleine et al, 2004).

It has been argued that partial responders and chronic depression should be conceptualised as a form of resistant depression (Fawcett, 1994). Fawcett (1994) suggests the definition of a partial responder should be symptomatic improvement between 25-50%, as measured by a depression rating scale. This could mean that if a patient's BDI score was 40 at the start of treatment and dropped by 50% to 20, although defined as a "partial responder", the participant is still moderately depressed, according to conventional interpretation of BDI scores.

Estimates of the incidence of partial response to antidepressant treatment vary in the literature. In a review Fawcett (1994) identified between 40-60% of patients with only a partial response to treatment. Fava, (1994) however, increased this figure having identified that 50-60% of patients seen in clinical practice receiving adequate dose of antidepressants at an appropriate duration do not demonstrate an adequate response to treatment. Bellas et al (2002) estimated partial response as high as 60-75%.

According to data from the Mental Health Collaborative Depression Study, about 20% of patients with a depressive disorder will develop a chronic course of illness (Keller and Hanks, 1984). A later review carried out by the same author found that 25% of patients follow a chronic course and 21% had still not recovered after 2 years (Keller et al, 1994). In the same year Burrows et al (1994) reviewed 36 randomised controlled trials involving 3,679 patients identified that 28% of patients followed a chronic course. Elderly depressed patients were a particular risk as half of this group followed a chronic course. Nearly half, (46%) of the total subjects studied failed to respond to an antidepressant treatment of an adequate dose and duration. Of the 46%, 12-15% were partial responders and 19-34% were treatment resistant. It is reasonable to hypothesise that this is a significant underestimation as most depression trials exclude previous non responders from entering the trial at baseline. A more recent review conducted by Michalakam in 2002 identified that one third of all cases become chronic.

Partial responders do not reach acceptable levels of well-being and continue to experience suicide risk, work impairment and distress (Thase, 2003). It may be more appropriate when evaluating a patient's response to treatment, that depressive measures should consider the severity of the depression, i.e. mild, moderate or severe, rather than baseline scores and the percentage reduction after treatment. In addition, assessment of social functioning using the Social Assessment of Functioning Scale (SAS) for example, which takes into account social, work and leisure activities could help us appreciate more fully the clinical significance of response to treatment.

Factors which may contribute to chronic depression and partial response are: inadequate treatment, persistent stress, neurotic personality and dysfunctional attitudes (Fawcett 1997).

Economic costs of TRD

The social, economic and personal burdens caused by depression are tremendous. Pharmacoeconomic studies of depression have demonstrated that increased treatment effectiveness is positively correlated with significant reductions in treatment costs (Simon et al, 2000; Mitchell et al, 1997; Thompson et al, 1996) Those individuals with treatment resistant depression (TRD) have been found to be frequent users of health care services incurring significantly greater costs than those without resistant depression. (Simon et al, 2000). Greenberg and colleagues 2004 were keen to explore the economic implications of treatment resistant depression among employees and carried out a data claims analysis of employees of a large national US employer. This consisted of medical, pharmaceutical and disability forms from 1996-1998, inclusive involving more than 100,000 enrolled beneficiaries. Having identified 1692 employees who had a medical or disability claim, 180 employees were then identified as treatment resistant depressives after the authors applied a treatment algorithm. Direct and indirect costs to the employer were then compared with three groups: the TRD group, a depressed non-treatment resistant major depression group and a

random 10% sample with other types of claim used as a control. The results demonstrated substantial differences in average annual costs to the employer for each group. The annual direct and indirect costs of the control group were \$4000. These costs increased by 50% in the depressed non-treatment resistant group. However, the treatment resistant group was by far the most expensive group with annual direct and indirect costs over 3.5 times that of the control condition. Not surprisingly the authors concluded that TRD produces a significant burden on an employer; they also identified that TRD employees are more likely to be treated for co-morbid conditions and have higher medical and work costs across all conditions. Although this paper raises interesting findings, there are limitations to this research. Retrospective data gathered from medical, pharmaceutical and disability forms have restricted value; only a small piece of the jigsaw, which may in itself be out of context. Psychosocial factors, family history, compliance with medication and sub clinical or unidentified medical illness such as thyroid disease were not considered, all of which could have a significant effect on treatment resistant depression. Additionally, it is not clear what the relationship is between the treatment resistant depression and co-morbid medical disorders. Have the medical disorders made the depression more difficult to treat, or vice versa? These questions have not been considered in this paper and warrant further study.

Russell et al in 2004 wished to assess healthcare costs of patients with treatment resistant depression in terms of pharmaceutical and medical expenditures. The authors used a medical and prescription claims database covering 3.5 million enrollees from 1995-2000. 7,737 patients who were identified to have had 2 or more unsuccessful trials of antidepressants were identified as treatment resistant. In addition the number of antidepressant medication changes was used as a guideline that the TRD was increasing in severity. The results demonstrated that depression-related and general medical health care increased significantly as TRD increased in severity. There was greater health care cost associated with each additional antidepressant change. The authors

reported a maximum of eight changes in the medication regimes. The mean total health care expenditure increased by 104% from \$571/month to \$1165/month when patients had moved from the second to their eighth antidepressant change. The total depression related healthcare costs increased by 176% from the second (\$139/month) to the eighth medication regime change ($P < 0.05$).

Suicide risk

Long term studies demonstrate the risk of suicide in depression is 15% and several symptoms including moderate alcohol abuse, anhedonia, psychic anxiety, panic attacks, diminished concentration and global insomnia are found to be significant predictors of suicide (Fawcett et al 1990). Partial responders have been identified as a greater risk of suicide, in addition to a 50% chance of work impairment and a 65% chance of subjective stress associated with their interpersonal and family lives. (Fawcett, 1994). Several studies have shown that patients with chronic depression carry out a greater number of suicide attempts and hospitalisations (Van Vulkenberg, 1984; Coryell et al, 1988; Klein et al, 1998).

Papakostas et al, (2003a) were the first group to prospectively study the prevalence and impact of hopelessness and suicidal ideation in 89 patients with treatment resistant depression. Having identified suicidal ideation and hopelessness as a risk factor for suicide, the authors assessed these symptoms using items 3 and 30 of the 31 item Hamilton Depression Rating Scale at baseline and follow up. The patients then entered a six week trial of nortriptyline. More than half of the patients reported thoughts and wishes of death to self and significant hopelessness and one third reported significant suicidal ideas or gestures. The authors concluded that patients with TRD are more likely than not to report prominent suicidal ideation and hopelessness. Thase (2004) in a review supported the findings that resistant depressed patients are more likely to attempt suicide, and added they were more

likely to suffer greater morbidity and mortality from general medical conditions (Thase 2004).

Psychosocial factors which affect treatment resistant depression

Several environmental factors have been related to both a positive and negative treatment outcome in depression. Psychosocial factors which have been found to be detrimental to a positive recovery include chronic stressors (Joyce and Paykel, 1989; Thase and Rush 1995), multiple loss events (Akistal, 1982), low socioeconomic status (Downing and Rickels, 1973; Thase and Kupfer 1987), low levels of education (Keller et al 1986; Scott et al 1994), a non-supportive social environment (Miller et al 1992; Akistal, 1982) or high levels of psychosocial impairment (Alpert and Lagomasino, 2001; Thase, 2003b). In addition, explicit family conflicts or even the absence of family support can also have a negative effect (Keitner, 1992; Moos, 1990). Fava (1994) has suggested that mild or moderate use of alcohol can have a negative effect on antidepressant use and lead to treatment resistance. It is difficult to ascertain if these psychosocial factors cause or maintain the depression, or develop as a result of the depression.

Corey-Lisle et al in 2004 were interested in factors which related to a poorer outcome when treating depression and prospectively studied 601 depressed patients in a naturalistic trial comparing SSRI treatment in Primary care. Significant predictors of non response included older age, diagnosis, worse physical functioning and lower energy level.

Positive psychosocial factors have demonstrated a protective effect in resistant depression; living with a partner, higher education and a higher quality of life (Hirshfield et al, 1998), better family functioning (Keitner et al, 1992), lower family conflict, and adequate family support predicts a more favourable outcome (Moos et al, 1990). Better social adjustment at baseline predicted less severe depression in a three year naturalistic study at the Sydney Mood Disorders Unit (Brodaty et al, 1993). Marital status (i.e. being married) and contrary to an earlier study, (Akistal, 1999)

an early onset of depression favoured a positive response to treatment in resistant patients (Perlis et al, 2003). Moreover, positive life events have also been found to predict a better outcome (Paykel, 1992; Scott et al, 1988) and higher satisfaction scores (Koivumma-Honkanen et al, 2001).

Work and social impairment

It is without doubt that resistant depression has a major impact on the sufferer's life which stretches beyond purely physical symptoms of depression. Chronic depression has been found to be associated with severe and pervasive functional impairment, to a greater degree than that seen in major depressive disorder; and has been found to be more psychosocially disabling than major depressive disorder (Hays et al, 1995). In fact, chronic depression has been found to be more severe than in many chronic medical conditions such as arthritis, hypertension and diabetes (Hays et al, 1995). Patients who have a Hamilton depression score between 10-16, can be classified as having mild to moderate depressive symptoms. This is the average Hamilton depression score at end point to most antidepressant studies, and unfortunately these patients have been found to have a 45-50% probability of work impairment. (Petersen et al, 2004; Mintz et al, 1992; Fawcett, 1994). Impairment of work function can be demonstrated by absenteeism, poor work performance and/or significant interpersonal conflict, and has been shown to have a 65% probability of patients reporting subjective distress associated with their interpersonal and family lives (Fawcett, 1994). In addition, impairment of work function has been found to continue even after remission of depressive symptoms in about a third of patients (Mintz et al, 1992). Finally, Lim and colleagues (2000) identified that depression and generalised anxiety disorder were both predictive of work impairment, which increases when the two conditions coexist. Furthermore, Lim and colleagues (2000) found that mental health sufferers exhibited extremely low treatment seeking behaviour which is an important predictor of poor work productivity.

The Global Burden of Disease Study was launched in 1992 with the aim to develop measures of the burden of disease. This resulted in two measures becoming widely accepted: disability adjusted life years (DALY's), which assesses the years of life lost to the disease, or the years lived with the disability due to the disease (YLD). These two measures were compared worldwide for 100 disorders and revealed a high burden of disease for depression. Neuropsychiatric conditions were found to be the world leaders in YLD, accounting for almost 30%. Moreover, unipolar major depression alone accounted for 11% of the global YLD's. Whilst the authors acknowledged that no separate disability assessments were compiled for resistant depression, they argued that these patients are the most severely disabled depressed patients. The key reasons given for providing the high burden in this treatment group were the depressive recurrences, cycle acceleration and increasing severity of treatment resistant depression (Greden, 2001).

Petersen et al (2004) were the first group to prospectively evaluate psychosocial functioning in 92 patients with resistant depression using the Longitudinal Interval Follow up Evaluation (LIFE) scale. This group of patients demonstrated poor social adjustment, a poor level of involvement in recreational activities, mild impairment to enjoy sexual activities and mild to moderate impairment in work activities. Interestingly, the authors noted that in their sample there was a tendency for both the patients and the clinicians to assign more severe global impaired ratings than when comparing ratings for specific functional areas. The authors suggested this may be due to accumulative effects of depressive, social, interpersonal and work related symptoms affecting the global ratings.

Gender

In older literature, female gender is sometimes mentioned as a risk factor for treatment resistant depression; however there is little evidence to support this. As depression is more common in women than men, any sample of treatment resistant cases would naturally demonstrate a

preponderance of women because of the gender differences in the depression prevalence rates (Kessler et al 1993). Gender has not been found to have a positive correlation with poor response in initial treatment (Sotsky et al, 1991). Two studies have recently been published which have analysed different gender responses to the SSRI Sertraline and the TCA Imipramine. Women were found to respond better to Sertraline, and men to Imipramine. Pre-menopausal women responded better to the SSRI than post-menopausal women (Kornstein et al, 2000).

Aetiology of treatment resistant depression

Risk factors contributing to Treatment Resistant Depression

There are many factors which increase the risk of developing a resistant depression which include the severity and type of depression, the number of previous episodes, chronic depression and being partial responders. Concomitant co-morbid medical and psychiatric disorders can also increase resistance. Furthermore, psychosocial and environmental factors can be instrumental in contributing and maintaining treatment resistant depression.

Type of depression and the number of episodes

Nelsen and Dunner (1995) found that patients with treatment resistant depression are more likely to have a history of affective disorder; moreover, there have been suggestions that a family history of affective disorder increases the risk of resistant depression (Akistal et al, 1981; Scott, 1988). However, these findings have not been confirmed in large well designed prospective studies (Kornstein and Schneider, 2001). Although patients cannot be identified as resistant to treatment when prescribed inadequate doses of antidepressant medication; they do however, increase the risk of developing a resistant depression the longer the duration of the depressive episode. Additionally, there is good evidence that the greater the number of depressive episodes the higher the risk of developing a resistant depression (Keller et al, 1986; Scott, 1988; Akistal, 1981). Scott et al (1988) found that the number of previous

psychiatric hospital admissions contributes to chronic or resistant depression however; this has not been confirmed by any other studies (Judd, 1997; Black et al, 1991). In addition, patients who are severely depressed on the Hamilton depression scale have been found to be more likely to be treatment-resistant (Kornstein and Shneider, 2001). Psychotic depression which is often associated with severe depression has been found to worsen outcome in terms of response to treatment and subsequent resistance (Lee and Murray, 1988). As few as 17% of patients recover with antipsychotic treatment and remain well for 12 months (Parker et al, 1991). Aronson (1998) found that a subgroup of late onset delusional depressed patients were more likely to become treatment resistant. Relapse or recurrence has been reported in 50-92% of psychotic depressed patients (Nelson and Bowers, 1978; Aronson et al, 1987; Aronson et al, 1988). The speed of response to antidepressant treatment in depressed patients can also provide an indication of future resistance. Non response or a poor response to treatment within the first 2-6 weeks has been found in a number of studies to predict poor outcome (Boyer and Feigner, 1994; Neirenberg et al, 1995; Gasperini et al, 1992). A meta- analysis carried out by Boyner and Feigner (1994) found that those patients who had not responded by at least a 20% reduction in Hamilton depression scores in the first two weeks had only a 33.7% chance of being a responder as determined by the 50% reduction in the Hamilton depression scores.

Comorbid psychiatric disorders

Both early onset and late onset of depression have been identified as risk factors for resistant depression (Akistal et al, 1981; 1998; Aronson et al 1988).

Early onset depression, before the age of 21 is correlated with higher rates of comorbid personality disorders, substance abuse and a greater family history of affective disorder; and has been associated with a chronic course, lower response rates and incomplete remission of symptoms (Akistal et al, 1981; 1999). In addition, late onset depression,

after 60 years has been associated with several factors which contribute to treatment resistance, including the increased likelihood of psychotic depression, comorbid medical conditions and dementia (Brown et al, 1983; Brodaty et al, 1991).

Comorbid psychiatric conditions have been linked with an increase in treatment resistance. Keller and Shapiro (1982) used the term “double depression” to describe where an episode of major depression is superimposed on dysthymic disorder. In a study of 101 subjects, 26% had double depression. Relapse rates were higher in this group as well as slower rates of recovery compared to the single diagnosis of major depressive disorder (Keller and Shapiro, 1982). In a further study, Keller et al (1986) found that patients who have double depression can recover from major depression but take much longer to recover from the dysthymia.

Anxious patients have a poorer prognosis (Fawcett, 1994) in terms of delayed or poor response to antidepressants, and greater severity of both the anxiety and impairment associated with depressive symptoms, makes the depression more refractory to treatment (Dubovsky et al, 2005; Rudd et al, 1993, Rosenbaum et al, 2001). Additionally, those patients who have panic attacks alongside depression have a much worse outcome compared to a diagnosis of depression alone; both in terms of treatment outcome and the severity of the depression (Van Vulkenberg, 1984; Coryell et al, 1988). In addition there have been reports of higher rates of suicide, higher risk of recurrence and greater psychological and psychosocial impairment in patients with concomitant anxiety disorders (Alpert and Lagomasino, 2001; Thase 2003).

Comorbid personality disorder

There is a wealth of literature reviewing the effects of concomitant personality disorder in addition to depression. The DSM IV TR (APA, 2000) lists 10 specific personality disorder diagnosis as well as residual “not otherwise specified” category. It defines personality disorders in

terms of habitual and enduring patterns of perception, cognition and behaviour that are relatively inflexible and maladaptive and lead to significant functional impairment and distress. The disorder must manifest itself by late adolescence or early adulthood and is not due to the consequence of another mental disorder, chronic intoxication, or a general medical condition such as a head injury.

Most surveys indicate that depressed people have an increased rate of personality disorder and more pathological traits when compared with healthy controls (Farmer and Nelson-Gray, 1990; Charney et al, 1981). In fact, Fava (1994) has suggested that personality disorders are frequent in depression. In depressed outpatients the prevalence of personality disorder is 30%-70% (Alnaes and Torgersen, 1990; Black et al, 1988; Charney et al, 1981; Davidson et al, 1985; Frank and Kupfer, 1990; Kaye et al, 1994; Koenigsberg et al, 1985; Reich et al, 1987; Sanderson et al, 1992; Shea et al, 1990). In-patient samples have yielded the same prevalence rates with the most predominant diagnosis of borderline personality disorder (DeBattista and Mueller, 2001).

A retrospective study carried out by Black et al (1991) studied 1471 depressed patients and found that a comorbid personality disorder was associated with a worse outcome. In a more recent prospective study Ezquiga et al (1998) found a significant relationship between the presence of a comorbid personality disorder and non-response or a partial response. These findings have not been reproduced in subsequent studies (Fava 1994, 1996; Perry et al 1999).

Shea et al (1990) found that patients diagnosed with personality disorder had a poorer response to tricyclic antidepressants than those without a personality disorder. This was reinforced by Papakostas et al (2003b) who prospectively examined 92 outpatients with treatment resistant depression and found that a presence of avoidant personality disorder predicted a poorer response to nortriptyline.

Despite the references to personality disorder and depression in the literature, the issue of concomitant personality disorder in depression is controversial. Some researchers and clinicians believe that depressive symptoms can frequently be confused with those of a personality disorder, and often as the patient recovers from their depression the apparent "personality disorder" also remits. Furthermore, research on the relationship between depression and personality disorder is compromised by a number of methodological factors (Akistal, 1983; Farmer and Nelsen-Gray, 1990). For example, personality disorder is a longitudinal construct which is developmental in origin and typically manifest by late adolescence. Patients however typically are assessed at one point in time; that is cross-sectionally. They can usually provide an accurate portrayal of their depressive symptoms; however descriptions of their habitual patterns and tendencies are often biased by a negative cognitive set. Their depressive state biases recall of past memories and experiences in a negative way, as well as increasing the probability of negative recollections (Cohen et al, 1988). They are more likely to view themselves as weak, ineffective, lazy, unintelligent, undependable and unlovable (Thase, 1996). Under these conditions this can make the diagnosis of personality disorder extremely difficult. These problems were reinforced when in one study, Thase (2000), deferred formal assessment of personality until the depressed person had responded to successful antidepressant treatment. The number of comorbid personality disorders was reduced by 50%, indicating a very large misdiagnosis of affective disorder as personality disorder.

From a scientific perspective, there are pitfalls in the relatively reliability of diagnoses many Axis II disorders (Loranger et al, 1991). Lower reliability represents a particular problem because it imposes an upper limit or constraint on the validity of the diagnosis. Furthermore, research sampling presents a concern: Many depression trials exclude patients with a serious Axis II comorbidity such as antisocial personality disorder or borderline personality disorder. Thus when investigators report the relationship of personality disorder and outcome using data from a

clinical trial, the study group may not be generalisable to the broader range of patients seen in clinical practice (Thase, 1996).

Comorbid medical conditions

Medical comorbidity represents another major factor of treatment resistance and can play a major role in inducing and maintaining treatment resistant depression, especially when the medical illness is irreversible (MacEwan and Renwick, 1988; Akistal, 1982). Undiagnosed medical illness has been found to lead to a non response, for example (Guscott and Goff, 1991; Wehr et al, 1988), only 40% of patients with a comorbid medical illness respond to treatment with antidepressant medication (Popkin et al, 1985). Most of the studies published are nearly 20 years old and therefore have involved less choice of antidepressants. The antidepressants may not have been less efficacious but attrition rates may be higher due to intolerable side effects or drug interactions. Additionally, the tricyclic antidepressants have considerably cardiotoxic effects which may restrict clinical use in the medically depressed patient. Fava (1994) suggested that concomitant medical illness, even when treated, can lead to poor response and treatment resistance. This, however, was not supported by further work carried out by Perlis et al (2004) among 386 fluoxetine non-responders, and Papakostas et al (2003c) with 89 nonresponders. Perhaps newer forms of antidepressant treatment may have contributed to the different findings.

Thyroid abnormalities in treatment resistant depression

It has been found that 5-10% of depressed patients present with thyroid dysfunctions (Prange, 1996). In addition to frank hypothyroidism, resistant depression is associated with two other abnormal thyroid profiles: elevated basal thyrotropin (TSH) levels alongside normal L-triiodothyronine (T3) and thyroxine (T4) levels, or a normal basal TSH level with an exaggerated response to thyroid releasing hormone stimulation (Prange, 1996). Thyroid abnormalities including hypothyroidism, abnormal TSH, T3 and T4 can be detected by a simple

blood test. Howland (1993) carried out a review of studies involving depression and thyroid disease and found that 52% of refractory depressed patients show evidence of sub-clinical hypothyroidism (range 29%-100%). This estimate compares with a prevalence of 8% to 17% in unselected populations of depressed patients, demonstrating a 3-6 fold increase in prevalence rates. Howland et al (1993) in a review summarising research into resistant depression reported that nearly half of the patients who do not respond initially to treatment for depression have sub-clinical hypothyroidism. Exaggerated thyroid stimulating hormone (TSH) response to thyroid releasing hormone (TRH) has been found in cases of refractory depression (Targum et al, 1984). In fact, Baruch et al (1985) found this response to be higher in treatment resistant depressed patients than responders to antidepressant treatment. A history of thyroid dysfunction was found to worsen outcome in treatment resistance in a number of studies (Scott et al, 1988; Hatterer et al, 1993; Phillips and Neirenberg, 1994), although there is one contradictory study (Fava et al, 1988).

Myocardial infarction, ventricular arrhythmias and congestive heart failures have all been associated with the development of major depression (Carney et al, 1993; Harnett, 1994; Kuttner et al, 1990). Depression may inhibit recovery or even increase the risk of mortality from myocardial infarction (Fraser-Smith et al, 1993). Conversely, physical problems associated with heart disease may also cause a deterioration of depressive symptoms.

Papakostas et al (2004a) identified an association between treatment resistance and low serum folate and low vitamin B12 levels. The same group demonstrated that high serum cholesterol at baseline would be more likely to lead to a poor response to treatment. A second study confirmed the relationship between hypercholesterolaemia and poor outcome in the treatment of resistant depression (Papakostas et al, 2003d; Sonawalla et al, 2002).

Pies (1994) found that uraemia (excess urea in the blood), hyponatraemia (low sodium concentrations in the blood), hypokalaemia (low potassium concentrations in the blood) are commonly associated with depression (Franco- Bronson, 1996). Some patients who do not respond to antidepressant medication may on occasion have an occult malignancy (Franco-Bronson, 1996). Until this is identified and excised the medication for depression may not work (Pomara and Gershon, 1984).

Even assuming a medical diagnosis is correctly established, any medication subsequently used to treat general medical conditions may significantly confound the evaluation and management of treatment resistant depression: for example, glucocorticosteroids are associated with depression mania and delirium; antihypertensives at high levels in high use can also increase the risks of depression (Kornstein and Schneider, 2001).

Finally, it is important to note that any chronic illness regardless of whether it is medical or psychiatric in origin is a considerable psychosocial stressor which can also increase and maintain the severity and duration of depressive symptoms or in fact delay response to treatment.

Neuroimaging in treatment resistant depression

Neuroimaging has only recently provided evidence regarding changes or abnormalities in the brain structure and function of depressed patients. Most of the published data focuses on major depressive disorder with a paucity of studies reviewing treatment resistant depression.

There are only three functional studies assessing treatment resistant depressed patients reviewing the changes in regional cerebral blood flow as measured by 99m Technetium-hexamethylpropalineamineoxime (HMPAO) Single Photon Emission Computed Tomography (SPECT).

Hornig and colleagues (1997) compared 8 resistant depressed patients with 13 major depressed patients and 16 controls. The TRD patients demonstrated significant increases in the hippocampus-amygdala activity compared to major depressed patients and the healthy controls. There were no differences in the HMPAO activity in any other brain region, or right/ left symmetry between the groups.

Five patients with treatment resistant depression were studied with HMPAO SPECT before and after treatment with Transcranial Magnetic Stimulation (TMS). Increases in the regional cerebral blood flow in the left dorsolateralprefrontal cortex were found post treatment (Zheng et al, 2000).

Recently, a group of four resistant depressed patients were evaluated using HMPAO and simultaneous (18) F-fluorodeoxyglucose (to measure cerebral metabolism) following 10 sessions of repetitive Transcranial Magnetic Stimulation augmented to antidepressant medication. There were increased uptake of both radioisotopes bilaterally in the frontal regions and a decreased uptake in the left orbitofrontal cortex compared to controls (Conca et al, 2002).

Structural imaging studies using Magnetic Resonance Imaging (MRI) have suggested a relationship between resistant depression and right frontostriatal atrophy (Shah et al, 2002), changes in the left hippocampus (Mervaala et al 2000; Shah et al, 2002), changes in the frontal lobe volumes (Coffey et al 1993), and the presence of subcortical gray matter hyperintensities (Steffens et al, 2001) and white matter hyperintensities which are found to increase the more severely resistant the patient becomes (Hickie et al, 1995).

Several studies involving mainly elderly depressed patients have suggested that pathologic vascular changes involving gray or white matter hyperintensities may play an important role in treatment non-response (Steffens and Krishnan, 1998). Indeed, several authors

propose that vascular depression may be classified as a specific subtype of depression (Alexopoulos et al, 1997; Simpson et al, 1998; Soares and Mann, 1997; Steffens et al, 2001; Steffens and Krishnan, 1998).

Some brain imaging studies have used picture caption pairs to manipulate a depressed subjects mood prior to and during brain scans. During one such study, Kumari and colleagues (2003) investigated neural abnormalities using functional magnetic resonance imaging (fMRI) in resistant depressed patients. Picture caption pairs were shown during the fMRI procedure to elucidate neural correlates of cognitive generations of affect in treatment resistant depression. The authors found differences between patients and controls; participants demonstrated a relative decrease response in the anterior cingulate (rostral and right) with both negative and positive picture caption pairs and in the medial frontal gyrus and hippocampal (left) with positive picture pairs. An increase response was found in the inferior (right) and middle temporal gyri (left) with negative picture caption pairs and in the parahippocampal gyrus (right). Increased response was also found in the Inferior frontal gyrus subgenual cingulates (right) striatum (right) and brain stem (left) with positive picture caption pairs. The authors concluded that different brain regions appeared to activate during positive and negative affect disturbances in treatment resistant depression; reduced medial-middle prefrontal and hippocampal activity may have accounted for the positive affect disturbances, and temporal lobe hyperactivity for negative affect disturbances.

It is important to note that neuroimaging results are not always replicated, for which there may be several reasons. This may often reflect lack of homogeneity of clinical features, especially medication and organic factors of the study samples and there are often small sample sizes. In addition, biological variables may be found in the same brain area but in extreme variation. This may be erroneous or due to pathoplasticity. As methodological and technical aspects of brain imaging research is refined and improved the possibility of identifying

neuroanatomical, functional or biochemical substrates of treatment resistance is not unrealistic.

Management of treatment resistant depression

Initial assessment of treatment resistant depression

Despite a lack of consensus in defining treatment resistant depression, there is agreement amongst clinicians and researchers regarding what an initial assessment should entail. The first step is simply to check the diagnosis and use of antidepressant medication in relation to compliance, therapeutic dose and duration of treatment (Flint, 2002; Thase, 2003b; Davidson et al, 1996; Nelson and Dunner, 1993). Although there are discrepancies in the literature regarding what an adequate dose or duration is, six weeks is thought to be a reasonable trial at therapeutic antidepressant levels (Nelson and Dunner, 1993). It is a concern that the most common cause for initial failure is not in fact resistance but under-treatment due to inadequate therapeutic doses being prescribed from the outset (Thase 2003).

The NICE guidelines (2004) define resistant depression as that which fails to respond to at least two antidepressants given sequentially for an adequate time. Furthermore the guideline suggests that a combination of pharmacological and psychological treatment may be effective in the case of chronic depression; a hint that chronic depression may be considered part of the spectrum of resistant depression.

If present, the issue of non-compliance needs to be evaluated and clinically managed. Intolerable side-effects have often led to non-compliance (Nelsen and Dunner, 1995). It is imperative that education about the depressive disorder, treating symptoms without side-effects and close monitoring during early weeks of treatment is maintained during the initial weeks of recovery. Researchers in some older scientific papers have suggested that plasma level monitoring may enhance compliance to antidepressant treatment (Davidson et al, 1996) and

improve response rates (Glassman et al, 1977). Whilst plasma monitoring may have provided some clinical value with the older tricyclic antidepressants, it has been found to have little value with the modern antidepressants such as the serotonin specific reuptake inhibitors or serotonin and noradrenaline reuptake inhibitors (Thase, 2003). Assessing clinical effects and possible side effects of antidepressant medication to maintain compliance and aid recovery is an important part of treatment. It is important that the clinicians address any concerns the patient may have.

Clinician's role in achieving compliance

Despite the fact that there is broad agreement in scientific publications which outline compliance to medication as an important issue in managing resistant depression; surprisingly only one paper reflects specifically on the clinician's role in achieving compliance. Fawcett (1995) argued that compliance cannot be defined simply as the patient physically taking prescribed medication, but has proposed the term "adherence" which encompasses a broader clinical and behavioural context. Fawcett argues that responsibility should be placed on the clinician to form a therapeutic alliance using educational techniques to increase behavioural compliance to medication. Fawcett identified factors which may affect patient compliance to treatment. These include *patient characteristics* encompassing specific symptoms such as guilt, suspiciousness, or additional comorbid symptoms such as panic attacks, severe anxiety symptoms, and alcohol or drug abuse. These symptoms can confound the treatment progress both in terms of compliance and clinical outcome. *Medication characteristics* can be assessed by a clinician proactively by providing psychoeducation regarding the patients' illness, the need for medication to aid recovery as well as dealing with any fears or concerns they may have regarding treatment. Finally, the *expertise of the clinician* is an area often overlooked, but is a crucial component in helping the patient achieve compliance leading to subsequent recovery. Fawcett argues that the interpersonal processes of the patient-doctor relationship are often down-played as medication

algorithms become the focus. Fawcett recommends that psychotherapeutic and psychopharmacological approaches need to be integrated in order to reduce the problems which lead to non-compliance.

It has also been found that side-effects and lack of therapeutic response are not always the cause of non-compliance in depressed patients (Blackwell et al, 1982). The landmark NIMH study compared 16 weeks of Imipramine, Interpersonal Psychotherapy and Cognitive Behaviour Therapy to placebo. The project designers anticipated many problems with compliance particularly with regard to the placebo group. In order to maximise compliance they provided the clinicians with training and a manual (Elkin et al, 1985). The drop-out rates were 27% for the placebo group, 23% for Imipramine and 25% and 27% for the two psychotherapies respectively after eight weeks of treatment. The authors found that systematic attention to the clinical process may have contributed to the retention and treatment outcomes.

The clinicians have a role to ask the patient about their medication and deal with any concerns they may have regarding their medication. Many authors have agreed that an accurate assessment of resistant depression would be helpful both in the clinical and research setting (Fava and Davidson, 1996; Burrows et al, 1994; Nelson, 2003; Thase, 2004). Systematic reviews using the Hamilton Depression scale for example would provide additional help (Davidson et al 1996). In addition, a stepped care and systematic treatment approach will help clinicians achieve remission in resistant patients (NICE, 2004, Flint, 2002).

In addition to monitoring and managing the patients' response to antidepressant medication the clinician needs to consider factors such as thyroid problems (Thase, 2003; Howland, 1993; Franco-Bronson, 1996), substance abuse (Linoila, 1990), endocrine disturbances (Nelson and Dunner, 1993; Kornstein and Schneider, 2001), and mild head injury (Dinan and Mobayed, 1991). These factors can all confound effective antidepressant treatment. Furthermore, the clinician should assess

alcohol and illicit drug use (Thase 2003b; Linoila, 1990) and psychosocial stressors which may maintain both alcohol intake and depressive symptoms (Pridmore and Turnier-Shea, 2003; Linoila, 1990).

Treatment options in resistant depression

There are many different treatment options in resistant depression which comprise of pharmacological methods such as switching to another single antidepressant, combining two or more antidepressants, or augmenting another agent such as low dose antipsychotic or a mood stabiliser. Additionally, non-pharmacological approaches can be used and include both psychological treatments such as Interpersonal Psychotherapy, Cognitive Behavioural Therapy, and other biological or physical interventions such as Electroconvulsive therapy, Transcranialmagnetic Stimulation, and Vagus Nerve Stimulation (Kleine et al, 2004; Nelson, 2003; Trivedi, 2003.) The latter two treatments have largely been used in a research setting. Indeed, transcranialmagnetic stimulation is only licensed as a treatment in Canada and Israel. However, there is little empirical evidence as yet to support any of these treatment strategies and a paucity of controlled studies to support their efficacy (Nelson 2003; Thase, 2004).

Following a review of resistant depression, Kennedy and Lam (2003) recommended that a combination or augmentation strategy early in the treatment increases the likelihood of remission. Similarly, Blier and Ward (2002) suggested that combination therapy may provide a more time efficient approach to relieve depression rather than drug substitution. It has frequently been suggested in the literature that the development of a treatment algorithm would be a positive step to effectively manage resistant depression (Aldie et al, 2003; Thase, 2004). There is clearly a need for more research needed to help us understand both the efficacy of particular treatment approach as well as gaining an understanding of which treatment will work for which patient.

Switching antidepressants

Pharmacological action of antidepressants

There are a range of pharmacological approaches used in treating depression; all of the current antidepressant medications target the neurotransmitter monoamine system which includes serotonin, noradrenaline and dopamine. The antidepressant drugs produce their effects by interacting with the drug receptors. Drugs that bind to receptors to initiate a response are called agonists. Drugs with no intrinsic pharmacological activity which produce effects by preventing an agonist initiating a response are called antagonists (Arbuthnott, 1990).

The first two groups of antidepressants, the tricyclic antidepressants (TCA's) and the monoamine oxidase inhibitors (MAOI's) were developed in the late 1950's and are often referred to as the "classical antidepressants". The selective serotonin reuptake inhibitors (SSRI's) followed in the late 1980's and grew out of a greater need for increased selectivity. More recently compounds with actions on both noradrenergic and serotonergic systems are being used to treat depression (Stahl, 1999).

The tricyclics are so called because of their three ringed structure. The therapeutic effects of the TCA's are due to the blockade of the reuptake of noradrenaline and serotonin, and to a lesser extent dopamine. The monoamine oxidase inhibitors (MAOI's) are defined by their ability to inhibit monoamine oxidase, an enzyme which usually acts to destroy noradrenaline, serotonin and dopamine. Selective serotonin reuptake inhibitors (SSRI's) were introduced in the late 1980's and have become popular due to their better tolerance and side effect profile. The SSRI's rapidly block presynaptic serotonin (5HT) reuptake, this causes the presynaptic autoreceptors to down regulate and results in an increase in the net serotonin transmission (DeMontigny et al, 1981). The next group of antidepressants are known as atypical or novel antidepressants due to their unique pharmacology and mechanism of action. As they are quite diverse they need to be considered individually. Bupropion is a reuptake

inhibitor of noradrenaline and dopamine. Although widely available in the United States it does not currently have a licence in the United Kingdom. Trazodone acts as an antagonist at histaminergic and alpha 1-adrenergic receptors which results in the inhibition of serotonin. Nefazodone is a potent serotonin 5HT₂ receptor agonist which inhibits both serotonin and noradrenalin. Mirtazapine is an agonist at several receptors (5HT₂, 5HT₃, H₁ and presynaptic alpha-2) thus enhancing serotonin and noradrenaline release (DeBoer, 1996). Venlafaxine is a reuptake inhibitor of both noradrenaline and serotonin, at lower dosages serotonin reuptake inhibition is prominent, at moderate to high doses noradrenaline reuptake becomes more significant and at higher doses dopamine reuptake occurs (Ellingrod and Perry, 1994).

Treatment approaches in resistant depression

First line approaches to non or partial responders to antidepressant treatment are often to increase the dose or switch antidepressant medication. Thase and Rush (1997) suggested that a switch to antidepressants in the same class is less likely to be effective than a switch to a different antidepressant class. Although clinicians tend to switch to a different class of antidepressant, some would argue that there are sufficient differences in the pharmacokinetics and secondary neurochemical effects to justify switching within the same antidepressant class (Gilmore et al, 2002).

SSRI to SSRI

Thase and colleagues (1997b) studied 106 out patients with major depression who had a history of intolerance or non response to sertraline. Treatment was switched to fluoxetine (mean dose 37.2mg/day) and evaluated with the 28 item Hamilton Depression Scale throughout the 6 week trial. 63% (n=67) of the 106 patients demonstrated a 50% reduction in their initial Hamilton depression scores. A limitation of this study is the inclusion of patients who were intolerant to medication; clearly this group cannot be considered resistant to treatment as they were unlikely to have received an adequate trial of antidepressant medication. Another study

conducted by Zarate and colleagues (1996) examined the response to sertraline after failure or intolerance to fluoxetine in 31 hospitalised patients with major depressive disorder. Uniquely this study carried out longer term evaluations of the efficacy of treatment. At discharge 42% (n=13) of the patients were responders. Seven months later at follow up only a disappointing 26% (n=8) were still to be judged responders. An open study evaluating the efficacy of a switch to another SSRI in 55 depressed patients who had failed to respond to prior treatment was undertaken by Joffe and colleagues (1996). This is the only study to have purely evaluated non-responders and excluded intolerance to the current treatment. After 5 weeks 51% (n=28) of patients had a marked or complete antidepressant response.

SSRI to tricyclic antidepressant

There are limited data in the use tricyclic antidepressants following SSRI failure. The first small study (n=15) was a double blind cross over study switching patients who had failed on paroxetine to imipramine. Eleven (73%) of the patients responded (Peselow et al, 1989). Thase and colleagues (2002) carried out a larger study comparing imipramine and sertraline in chronic depression. After 12 weeks of treatment, 117 patients who failed initial treatment with sertraline crossed over, double blind to imipramine. In the intent to treat sample 44% (n=52) of the patients responded to treatment. Although the switch to tricyclic antidepressants can be clinically effective, there are serious risks of cardiotoxic side-effects, death after overdose and high levels of TCA toxicity when switching from fluoxetine or paroxetine which may restrict their use.

SSRI to Venlafaxine

Neurenberg et al (1994) reported on a sample of 84 resistant depressed patients who were given 12 weeks of treatment with venlafaxine (a serotonin and noradrenalin reuptake inhibitor (SNRI) which blocks the serotonin and noradrenalin reuptake pumps resulting in an antidepressant effect similar to that of the tricyclic antidepressants). About one third of the patients responded. In a later open label study in Canada, deMontigny

and colleagues (1999) studied 152 patients who had previously failed at least 1 previous antidepressant and switched treatment to venlafaxine. 58% demonstrated at least 50% reduction in the Hamilton depression scores. More recently Kaplan (2002) reported an uncontrolled study of 73 patients who had not responded to SSRI treatment and were switched to venlafaxine. 87% (n=60) patients achieved full remission assessed by the Hamilton depression scale after 6-8 weeks of treatment with venlafaxine. In the same year Poirer and Boyer (1999) described a double blind open label study comparing venlafaxine and paroxetine in 122 patients who had failed two previous antidepressant trials. Venlafaxine was provided at 200-300mg daily and paroxetine 30-40mg daily. The response rate was 52% (venlafaxine) versus 33% (paroxetine) ($P<0.04$) and remission was achieved in 42% of the venlafaxine patients versus 20% of the paroxetine patients ($p<0.01$).

SSRI to Bupropion

Fava and colleagues (2003) carried out an open switch study for patients who were unresponsive to 20mg of fluoxetine. 29 patients who were refractory to 8-12 weeks of fluoxetine were prescribed bupropion SR (an antidepressant noradrenalin and dopamine reuptake inhibitor (NDRI) which is only available in the United States) for an 8 week trial. Completer (n=20) and intention to treat analysis (n=26) were carried out yielding 35% (n=7) responders and 40% (n=8) partial responders and 48.8% (n=9) non-responders.

SSRI to Mirtazapine

Thase (2000a) reported a double blind study involving a switch to mirtazapine (mean dose 30mg/day) or sertraline (mean dose 120mg/day) in 243 patients who had reported failure to citalopram, fluoxetine or paroxetine. Although reduction in depression scores were significantly better in the mirtazapine groups at weeks 3 and 4, there were no significant differences (remission rates 37% versus 29%) by the end of the 8 week trial.

In an open pilot study 69 patients having failed a prospective double blind study using either sertraline, fluoxetine or paroxetine were switched to mirtazapine; 48% (n=33) responded to mirtazapine (Fava et al 2001).

Combination strategies

There are some patients who do not respond or respond poorly to a staged approach of switching antidepressant medications resulting in a pharmacological blockade of the different monoamine systems. The next step to increase the potency of the antidepressant treatment is to combine antidepressant pharmacotherapy. The rationale is to broaden the central nervous system effects by combining agents affecting different neurotransmitter systems. This can be done in various ways; the contemporary standard is to combine the relatively selective yet dissimilar antidepressants such as bupropion, a dopamine and noradrenaline reuptake inhibitor, venlafaxine, a noradrenaline and serotonin reuptake inhibitor or the 5HT₂, 5HT₃ and Histaminergic₁ and alpha 2-autoreceptor mirtazapine which enhances serotonin and noradrenaline to create a broader spectrum (Fredman et al, 2000).

Pharmacokinetics describes the way the concentration of a drug is reached within the tissues in the body and includes absorption, distribution, biotransformation and excretion. Pharmacodynamics describes the way the drug acts on the body; this includes the mechanism of action of the drugs and receptor sensitivity. Receptor sensitivity is influenced by complex regulatory homeostatic factors. Changes in receptor sensitivity mean that the same concentration of drug will produce a greater or lesser physiological response. Desensitisation or down regulation occurs for example after prolonged stimulation of cells by agonists. Thus the cell becomes refractory to further stimulation. There is a rationale for a combination of two SSRI's to be used in treatment resistant depression due to the different pharmacokinetic and pharmacodynamic properties of the antidepressants (Fava, 2001; Bondolfi et al, 1996).

SSRIs and TCA's

The most extensively studied strategy is the combination of a TCA and SSRI. Nelson et al (2004) recently published a double blind replication study of 39 depressed in patients in which the combination of fluoxetine and desipramine was significantly more likely to result in remission of depressive symptoms than either drug alone (combination 58% vs. fluoxetine 7.1% or desipramine 0% (P.0.001). Combining two antidepressants are not always found to be more clinically efficacious than monotherapy; in 2 published studies Fava et al (1994, 2002) found that increasing the single dose of fluoxetine was more effective than a combination of fluoxetine 20mg/day and desipramine 25-50mg/day. However, as the patients in the combined therapy group had a mean desipramine blood plasma level of 100ng/ml, it is likely that the dose of tricyclic antidepressant used in this study was too small (Nelson and Price, 1995). Taylor and Prather (2003) examined the efficacy of nefazodone augmentation in resistant depression where the patients had marked anxiety symptoms. Eleven outpatients received nefazodone 50mg/day increased until an optimal dose was achieved. This was added to ongoing antidepressant treatment. Seven of the 11 patients achieved complete remission of their depressive symptoms and 9/11 patients demonstrated complete remission of their anxiety symptoms.

SSRIs and SSRIs

SSRIs vary in potency and specificity of serotonin reuptake inhibition in vitro, this provides the rationale for trying this option in resistant depressed patients; augmenting another SSRI may increase the antidepressant potency without adding to the side effect burden (Lam et al 2002). However, there is more anecdotal evidence rather than well researched clinical trials reviewing the efficacy of this treatment (Fava, 2001). Bondolfi et al (1996) carried out an open trial of seven patients who had not responded to 40mg/day citalopram. 50-100mg of fluvoxamine was added which resulted in an 85.7% (N=6) response rate. The combination of medication was well tolerated with few side effects reported (nausea and slight tremor).

SSRIs and alpha agonists (Mirtazapine/ Mianserin)

Mirtazapine antagonises presynaptic alpha adrenoceptor activity which in turn enhances noradrenalin (via autoreceptor antagonism) and serotonin (via heteroreceptor antagonism) neurotransmission. It has been postulated that its action may complement the action of SSRI and SNRI antidepressants (Kent, 2000). Positive antidepressant responses have been demonstrated in five studies combining an SSRI with either mianserin or mirtazapine. A pilot study of open label mirtazapine (30mg/day) combination to SSRIs of 20 resistant depressed outpatients yielded a 55% response rate at week 4. (Carpenter et al, 1999). This finding was replicated in a double blind study carried out by the same researchers using 26 depressed patients who were randomised to either mirtazapine or placebo in addition to their primary antidepressant medication. A positive response was categorised as a 50% reduction in the Hamilton scores and was demonstrated by 64% of the mirtazapine group versus 20% in the placebo group. 45.4% of the mirtazapine group achieved remission versus 13.3% of the placebo group (Carpenter et al, 2002).

An open label study of mirtazapine augmented antidepressant treatment was conducted in Vancouver with 24 non-responding or partial responding depressed patients (Wan et al, 2003). Eight of the patients had previously been treated with ECT; there was a mean of 7 previous antidepressant trials and 1.5 augmentation strategies. The patients were receiving concomitant antidepressant medication. Symptomatic improvement (CGI $\geq$ 2) was observed in 38% (n=9), and partial response observed in 38% (n=9) of the 24 patients who received an average of 14.1 months of mirtazapine treatment at a mean dose of 36.7mg/day. This study is limited by a number of factors including the small number of subjects, the open retrospective and uncontrolled design.

Maes et al (1999) recruited 31 patients who were unresponsive to a prior

adequate trial of an antidepressant and randomly assigned them to treatment with either fluoxetine 20mg daily, fluoxetine 20mg plus pindolol 7.5 mg/day or fluoxetine 20mg plus mianserin 60mg/day. Sixty percent of patients responded to fluoxetine plus mianserin compared to only 9% of the fluoxetine only group.

A higher dose of mianserin (60mg) was assessed in a double blind randomised controlled trial involving 104 depressed patients who had not responded to 6 weeks of fluoxetine (Ferreri et al, 2001). The patients were switched to mianserin alone, mianserin plus fluoxetine, or continued on the fluoxetine. The combined group had significantly greater reductions in the Hamilton depression scores compared to the monotherapy groups. Additionally, response rates were greater in the combination groups (combined 63%, mianserin alone 49%, fluoxetine 37%).

Augmentation strategies

Augmentation strategies can be distinguished from combination strategies as they typically involve the addition of a drug which is not primarily an antidepressant. The addition of the new medication does however have pharmacological properties which enhance the potency of the antidepressant. Improvement following antidepressant augmentation tends to occur after 3-4 weeks. Most studies which review the efficacy of treatment tend to focus on short term strategies with very little data available for longer term effects, including when the augmenting agent should be stopped (Fava, 2001).

Lithium augmentation studies

Although lithium is not as popular now as it was in the 1980's, it is the most extensively studied augmentation strategy (Bschor et al, 2003). Its therapeutic effects are thought to be due to serotonergic and noradrenergic mechanisms. This has been supported by animal models which demonstrate that lithium increases serotonin (5HT) transmission by reducing the activity of post synaptic serotonin. In contrast to the usual decrease in hypothalamo-pituitary adrenocortical (HPA) axis with tricyclic

antidepressants, lithium augmentation appears to demonstrate a marked increase in the adrenocorticotrophic hormone (ACTH) cortisol response (Bschor et al, 2003).

As early as 1981 DeMontigny found dramatic early response within 38 hours when adding lithium to tricyclic antidepressants compared to placebo. When lithium was compared to ECT, both groups improved; however the lithium augmentation group demonstrated the quickest improvement.

Bauer (2003) reviewed the literature from January 1966-February 2003 addressing the clinical evidence for lithium augmentation. 27 trials were reviewed: 13 open labelled trials, 10 double blind placebo controlled trials and 4 randomised comparative trials. The authors summarising the data from the open and controlled trials demonstrated approximately 50% of the patients responded to lithium augmentation within 2-6 weeks.

The risk of toxicity, weight gain, and the need for blood monitoring may contribute to its current low rate of clinical use (Fava, 2001; Salama and Shafey, 1989). At present, it remains unclear whether the antidepressant response to lithium augmentation is a result of synergistic effects or whether it is simply due to the antidepressant properties of the lithium itself. Randomised double blind studies controlling for the effect of lithium alone compared with combined lithium and antidepressant medication are still needed.

SSRI and lamotrigine

Negative findings were reported by Barbosa et al (2003) who compared the anticonvulsant/mood stabiliser lamotrigine versus placebo augmentation to the antidepressant fluoxetine in 23 depressed patients. Eight were diagnosed with bipolar II disorder and 15 suffered major depressive disorder. The effect of lamotrigine was found to be statistically greater than placebo on the clinical global impression scale at end point. However, lamotrigine failed to distinguish from placebo on both the

clinician rated scales Hamilton depression scale and Montgomery and Asberg Depression Scale. The small sample size reduces the power of the study and increases the likelihood of an artefact accounting for the results.

Thyroid hormone augmentation

Thyroid hormones may enhance antidepressant response by two principle mechanisms: correcting suboptimal thyroid function and "priming" noradrenergic function (Joffe and Sokolov, 2000). Joffe et al (1993a) in a comparative study found that triiodothyronine (T3) to be as effective as lithium augmentation and better than placebo. A meta-analysis carried out by Aronson et al (1996) demonstrated that T3 25-50mcg augmentation has significant effects in approximately one half of the studies.

Pfeffier and colleagues (2004) looked at the efficacy of high dose Lthyroxin treatment in 28 depressed patients who were resistant to at least 6 antidepressant strategies. Nearly 40% demonstrated a good outcome and 21% showed a very good outcome as measured on the Hamilton depression scale and the Clinical Global Impression scale.

Antipsychotic medication augmentation

Imipramine, the first tricyclic antidepressant was discovered during the search for alternatives to the antipsychotic chlorpromazine. This led to early clinical trials reviewing the efficacy of phenothiazines in the treatment of depression (Thase 2002a). 17 double blind trials of chlorpromazine or thioridazine were undertaken between 1960-1976 involving nearly 17000 depressed patients. The phenothiazines were found to be better than placebo and as effective as tricyclic antidepressant medication but had significant increases in extra-pyramidal side-effects which prevented their clinical use (Robertson and Trimble 1982). As the newer atypical antipsychotic medications have reduced side-effects, investigators have turned their attention to examine their use in mood disorders. Zhang and colleagues (2000) suggested

that antidepressant effects of antipsychotic medication augmentation may be as a result of increased release of monoamines in the prefrontal cortex. The antidepressant response is enhanced by direct effects on agitation, insomnia and anxiety via blockade of the post synaptic 5-HT₂ receptor (Thase, 2002).

Ostroff and Nelson (1999) reported on 8 depressed patients who had failed to respond to an SSRI alone. Every patient improved within one week of the addition of risperidone. A prospective open study of 36 non responsive depressed patients who received risperidone in addition to fluvoxamine was reported by Hirose and Ashby (2002). Thirty two of the 36 (89%) patients responded (50% improvement) within 4 weeks. It is worthy of note that only 5 of the patients used in this study had not responded to a previous trial of an antidepressant.

Shelton et al (2003) conducted an 8 week double blind study with 28 patients with recurrent unipolar depression who had failed to respond to an initial course of fluoxetine treatment. Patients were randomly assigned fluoxetine (52mg/day) and placebo, olanzapine (12.5mg/day) and placebo or a combination of fluoxetine and olanzapine (52mg/day and 13.5mg/day respectively). Results consistently favoured the group receiving the combined therapy, demonstrating a differential response as early as one week.

Barbee et al (2004) carried out a retrospective chart review of 79 medication trials in 49 patients to determine the effectiveness of olanzapine, risperidone, quetiapine and ziprasidone as augmentation agents in treatment resistant major depression. The authors again assessed the patients Global Assessment of Functioning (GAF) in addition to Clinical Global Impression (CGI) at baseline and following treatment. The individual response rates were 57% for olanzapine, 50% risperidone, 33% quetiapine and 10% ziprasidone. Of all the antipsychotics studied, only the olanzapine was found to be statistically significant.

Papakostas and colleagues (2004) used ziprasidone with its strong 5HT (1A) agonist activity augmented to SSRI antidepressants in 20 unresponsive patients. Of the 13 patients who completed the 8 week trial, 8 patients responded. The authors carried out an Intention to treat analysis and showed 50% responders as demonstrated by $\geq 50\%$ reduction in Hamilton depression scores.

In summary, there is little good quality evidence base for antipsychotic augmentation. Clinical experience and research suggest fairly good tolerability and safety and good coverage of hyper-arousal symptoms of depression including irritability, agitation and insomnia. The agent with the most proven efficacy is olanzapine (Thase, 2004), however there are currently trials underway and are close to completion which will inform the literature further.

Pindolol Augmentation

Pindolol augmentation is rarely used in the United States although is more popular in Europe and Canada. Pindolol is a beta-blocker which is also a potent antagonist of post-synaptic 5-HT autoreceptors. This blockade of the autoreceptors enhances the initial cellular effects of the SSRI's and thus may facilitate the antidepressant response (Artigas et al 1994).

Pindolol has been shown to quicken response to SSRI treatment in five studies (Perez et al, 1997; Tome et al, 1997; Zanardi et al, 1997; Bordet et al, 1998; Blier and Bergeron, 1998). Three further negative studies found no response (Moreno et al 1997) or difference to placebo (Perez et al, 1999; Berman et al, 1999).

At present there has been little evidence (Thase 2004) to show its benefits in resistant depression or else negative results have been demonstrated (Maes et al, 1999; Berman et al, 1999).

Riluzole

Glutamate is the most widely distributed excitatory transmitter in the central nervous system and has been implicated in depression (Tzshentke and Grunenthal, 2002; Sancora et al, 2003; Zarate et al, 2004). Riluzole is a glutamate modulating agent which results in an antidepressant effect.

Zarate et al in 2004 carried out an open labelled trial of riluzole (a glutamate modulating agent) in 19 patients with treatment resistant depression in order to determine the efficacy and safety of patients with recurrent major depression. 53% of all patients were classified as having stage two treatment resistance (failure of 2 adequate trials of two distinctly different antidepressant classes). After an average dose of 169mg daily a significant improvement in the depressive symptoms were noted. The authors concluded that riluzole may have some antidepressant properties in some patients.

Sancora and colleagues (2004) reported case studies of two women with long standing treatment resistant major depression. Following the augmentation of riluzole, both women demonstrated a significant reduction in their Hamilton Depression scores after one week (21-5, 34-22 respectively). After six weeks the scores reduced further to 1 and 7. This small data yields promising results regarding the efficacy of riluzole in highly resistant depressed women. Further studies are needed to confirm this initial data.

Psychotherapy

Although there is considerable evidence for short term psychotherapies such as IPT and CBT in acute phase treatment of major depression (Segal et al, 2001), there is a paucity of information published regarding the efficacy of psychotherapy in resistant depression. Currently there is no literature which demonstrates any specific study of psychotherapy in treatment resistant depression; however, there are a small number of studies assessing psychotherapy in partial responders and chronic

depression. Past reviews of the literature have found that although psychotherapy does appear to ameliorate symptoms of chronic depression, the majority of previous trials are hampered by small, idiosyncratic samples, open designs, different outcome measures and other methodological limitations making any general conclusions difficult (Mason et al, 1993; Markowitz, 1996). Until recently, no large systematic clinical trials of psychotherapy have been performed.

With regard to treatment resistant depression, there is one case study of a depressed patient who had not experienced a remission despite numerous trials of antidepressant medications in addition to ECT (Cooper and Hedges, 1994). Intensive CBT was provided (39 sessions over 8 months). Improvements in the depression was noted by a drop in the BDI score to 10 from 46 at the start of treatment, which was maintained at 12 month follow up (Cooper and Hedges, 1994).

In the absence of studies for treatment resistant depression, the available studies on non and partial responders, dysthymia alone or in addition to major depression will now be reviewed. Although these cannot directly address the efficacy of psychotherapy in treatment resistant depression; these studies address samples of patients that may overlap with treatment resistant depression as defined earlier in this chapter. Non and partial responders and chronic depression all remain symptomatic to some degree despite adequate treatment. As previously discussed this falls into the spectrum of resistant depression. We know from the literature available these patients at a particular point in time lie at the mild end of the spectrum of difficult to treat depression. What is not known however, is the course of these particular patients' depression over time. Some of the patients, following a depression trial may not continue to respond or only partially respond to increasing trials of potent antidepressants, this then would lead to a progression further into the spectrum of increasing treatment resistance.

Psychotherapy treatment in non responders

Cognitive behavioural therapy

Five depressed patients who had not responded to an "adequate trial" of antidepressant medication were provided 20 sessions of CBT, by a trained and experienced therapist over 16 weeks. 20% of the patients demonstrated a complete improvement and the mean Hamilton depression scores fell from 22.8 to 7.4. There were no statistical tests published in this paper (Fennel and Teasdale, 1982).

A small study of 12 patients who were "unresponsive to antidepressant medication" was carried out by Harpin et al (1982). Patients were equally assigned to CBT (26-36 sessions) or to a waiting list control condition. There was a statistically significant difference in the depression scores in favour of the CBT group ($P=0.05$), and 30% of the group were considered responders. The Hamilton depression scores fell from 26 to 16.3 in the CBT group versus 24.7 to 23.3 in the control condition. The CBT in this study was carried out by a single therapist, a 5th year undergraduate psychology student, not the best design for a treatment resistant depression study.

A slightly larger open study of non responsive (3 months of antidepressant medication at an adequate dose) was carried out by Mirabel-Sarron et al (1993). Twenty one of the 25 patients recruited to the study completed the 3 months CBT. The Hamilton depression scores demonstrated an improvement in depressive symptoms from moderate (21) to mild (10.3). Although the patients did not experience a total remission of symptoms the depressive symptoms remained mild (10.3) at 12 month follow up.

Five patients who received group CBT were compared to the same number using a self help management programme. (Bristow and Bright, 1995) 16-20 sessions were provided over 16-20 weeks and Hamilton depression scores were taken at baseline, post treatment and at 6 and 12 month follow up. There was an improvement in depression scores

following treatment with no differences between groups. Improvements gained during treatment were maintained at 6 and 12 months. Although some patients in this study were non responders, the authors also included subjects who had refused antidepressant treatment, or were intolerant. This limits the findings of this small study.

Twenty patients who had not responded to 6 weeks of an adequate dose of an antidepressant were randomly assigned to CBT plus antidepressant medication or medication alone. Fifteen sessions of CBT was provided. There were similar reductions in the Hamilton depression scores post treatment with no significant differences between groups (Barker et al, 1998).

Fava et al (1997) reported an open trial of CBT in 19 patients who had not responded to at least two trials of antidepressant medication at an adequate dose. Sixteen patients completed the trial. The CBT was provided by a trained and experienced CBT therapist for 15 sessions, antidepressant medication was stopped in 8 out of 12 of the patients who were responding to CBT treatment. The Clinical Interview for Depression measured depressive symptoms pre and post treatment. The mean scores fell to 31.4 from 54.1 and were clinically significant ($P < 0.001$). Twelve of the patients were in remission by the end of the trial and only one of these had relapsed at 2 year follow up.

Other psychotherapies

Ten patients who had not responded to a 6 week trial of a therapeutic dose of an antidepressant were given an open trial of a psychoeducational group treatment. 12 two hour sessions were administered over eight weeks by an experienced therapist. The improvements in the BDI scores after treatment were statistically significant ($p < 0.005$) and improvement in depressive symptoms was maintained at 9 month follow evaluations ($p < 0.05$) (Antonuccio et al, 1984).

The literature on psychotherapy treatment in patients non responsive to antidepressant treatment is sparse. There are just six CBT studies involving 91 patients. There are three open studies, two comparative studies and one waiting list controlled trial. There has been no difference in CBT compared to the comparison treatment (Bristow and Bright, 1995). The CBT sessions have ranged from 15-36. Most of the studies have evaluated CBT in the short term and demonstrate improvements in depressive symptoms which have been maintained at one year (Bristow and Bright, 1995; Mirabel-Sarron, 2003) and two year follow up (Fava et al, 2003).

A single open study of a psychoeducational group yielded a significant reduction in the Beck Depression Inventory scores which was maintained after 9 months, however a lack of control group or comparator therapy limit these findings.

There have been no studies evaluating the efficacy of IPT in patients who have not responded to antidepressant medication.

Psychotherapy treatment in partial responders

Interpersonal Psychotherapy

A single report of a case series of 5 elderly depressed patients who received IPT augmented to SSRI treatment was reported by Scocco and Frank 2002. The authors were unable to establish the adequacy of previous pharmacological treatments received before the trial, therefore patients were prescribed either citalopram (20mg) or sertraline (50mg); both medications were doubled after 3 weeks as the Hamilton scores taken at baseline were not reduced by 50%. After 6 weeks the patients started 16-20 sessions of IPT. The mean pre-treatment Hamilton depression scores had dropped from 21 to 15 after medication, and to 4 at the end of combined IPT and pharmacotherapy treatment. All patients were in remission post treatment. The lack of control and small number of patients limit this study. Furthermore, every patient was in fact

responding, although slowly in some cases, to their current moderate dose of a single antidepressant.

Two separate but methodologically similar studies were compared by Frank and colleagues (2000) in order to ascertain the sequential effects of treatment in highly recurrent depressed women. In one study the women were assigned treatment with IPT combined with the antidepressant imipramine (n=180); in the second study women were treated with IPT initially and if not responding adequately received either fluoxetine or sertraline in addition (n=159). Response rates of the combined group were similar to that of other studies (66%); interestingly, of the women who needed antidepressant medication following a poor or non-response, 79% responded, which was statistically significant ($P<0.02$).

Cognitive behaviour therapy

Fava and colleagues (1996) wished to examine the usefulness of CBT in treating residual symptoms of depression in patients who did not fully respond to antidepressant medication. In this study 40 patients were randomly assigned to CBT or clinical management. Antidepressant medication was gradually tapered by 25mg amitriptyline each week and stopped. After 2 years there was a lower rate of relapse in the CBT group (15% vs. 35%); at four years the relapse rates between the 2 groups became statistically significant (35% vs. 70%) in favour of the CBT group (Fava, 1996). The follow up assessment at 6 years did not yield significant differences in the relapse rates between the 2 groups (CBT, 50% relapse; CM 75%).

Paykel and colleagues (1999) observed a significant relapse prevention effects in a 2 centre study of incompletely remitted patients (n=158) who were randomly assigned to clinical management (CM) alone or combined with CBT. This study differed from Fava's study (1994) in that both groups continued to receive antidepressant medication, (mean dose equivalent to 125mg amitriptyline/33mg fluoxetine), additionally 15% of

the subjects were receiving lithium augmentation (there was no difference in lithium patients in both groups). Patients were very mildly depressed at baseline, the mean Hamilton depression scores were 12.2 (SD2.9) for the control group and 12.1 (SD2.7) for the CBT group. Furthermore, the symptoms of depression had been experienced for a limited period of time (2-18 months duration). The cumulative relapse rate (residual symptoms for 2 months plus Hamilton ≥ 14) at 68 weeks was reduced significantly from 47% in the CM group to 29% in the CBT group. In addition CBT also increased full remission rates at 20 weeks (24% vs. 11%), but this effect was relatively small and not associated with significant improvement in depression symptom ratings.

In a later paper, reporting the same study the authors suggest that CBT, although more costly, was more effective than intensive treatment alone (Scott et al, 2003). They also report the use of CBT in chronic depression despite the mean duration of the depressive episode being 13/14 months for each treatment group. This diagnosis however, falls short of the DSM IV or ICD 10 criteria for chronic depression.

In summary, there have been four studies evaluating IPT and CBT which have included 542 partially responding depressed patients. A small case series of elderly partial responders who received 16-20 sessions of IPT augmented to their antidepressant medication demonstrated improvements in all patients. The small sample size, lack of comparison groups and non blind ratings limit these findings. Nevertheless, this does provide an indication of the feasibility and tolerability of IPT in this patient group. The efficacy of the sequential effects of medication added to IPT was assessed in a comparison of two clinical trials (Frank et al, 2000). Superior response rates were obtained with patients who received IPT initially followed by antidepressant medication only if patients were not responding. It was surprising that during this study the initial lower dose of sequential treatment provided better response rates than the higher dose of combined IPT and medication from the start of treatment. Patients who had not reduced Hamilton depression scores by at least

33% during the sequential treatment approach, had the dose of IPT doubled to twice weekly; if, after a further 4 weeks the Hamilton scores had not fallen by 50% either fluoxetine or sertraline was added. As patients were promptly treated with potent antidepressant therapy quickly during this trial, this may have contributed to the positive outcome. Further, the use of different antidepressant medication may have also led to superior results.

Currently there are no other published data which review sequential effects of psychotherapy treatment in resistant depression; although there is one trial involving CBT is currently underway (Fava et al, 2003).

The two CBT randomised trials compare CBT to clinical management; one of the studies involved the concomitant use of an antidepressant (Paykel et al, 1999). Relapse rates for the CBT were found to be lower than the clinical management condition post treatment and at 68 week follow up (Paykel et al, 1999) and 2 and 4 year follow up (Fava et al, 1996).

Chronic depression

Interpersonal Psychotherapy

IPT has been specifically adapted as a treatment for dysthymia (IPT-D) and has been manualised (Markowitz 1998). A fifth problem area has been introduced whereby the therapy itself becomes an iatrogenic role transition; that is a transition from chronic illness to a healthy state. The IPT therapist works with the patient to help mourn the loss of the old role (dysthymia) and gain mastery of the new (healthy) role. During this phase the therapist may spend also of time detoxifying and normalising feelings. There are a limited number of studies of IPT in chronic depression; not all studies have used the modified version of the therapy.

One of the first published reviews of IPT in dysthymia was the analysis of a subgroup of 65 patients who were diagnosed with early onset chronic depression from the NIMH Treatment of Depression Collaborative

Research Programme (Agosti and Ocepek-Welikson, 1997). This study, which recruited 239 patients, had four treatment cells which provided 16 weeks of IPT, CBT, imipramine plus clinical management and placebo plus clinical management. The authors found that post treatment scores of depression were not found to be any different between groups to the placebo and clinical management condition.

Cornell University Medical College reported pilot data on three small series of subjects totalling 17 patients, who were treated with an open trial of up to 16 sessions of IPT-D, (without medication). All of the patients met the DSM criteria for early onset dysthymic disorder and nearly half had double depression (i.e. major depression superimposed on dysthymia; Keller and Shapiro, 1982). Seven of the patients had been non responsive to antidepressant treatment. None of the patients deteriorated and 11 (65%) remitted (final Hamilton depression score >8), the average Hamilton depression scores fell from 21.5 (SD4.4) to 7.4 (SD4.7) (Markowitz, 1994). Of the sample reported above, 7 patients had previously failed a trial of treatment with the tricyclic antidepressant desipramine (Mason et al 1993).

Following on from the pilot data, the same researchers at Cornell have conducted 3 further controlled trials; the final results have not yet been published. The first study addressed early onset dysthymic patients and compared 16 weeks of IPT-D, sertraline, a Brief Supportive Psychotherapy (BSP, used as an active control) and combined sertraline and IPT-D. Improved patients are entered into a continuation phase where IPT patients are seen for biweekly or bimonthly sessions. Non responders are crossed over to alternative treatment cells. A second study included patients with double depression who were randomly assigned IPT-D or BSP for 16 weeks. There is a 6 month continuation phase although there is no cross over design to this study. The third study recruited dysthymic patients with comorbid alcohol abuse. This study involves random assignment to 16 weeks of IPT-D or BSP both in addition to attending Alcoholics Anonymous. All three studies are now

complete and data analyses are underway. Preliminary results suggest no statistical difference between groups; IPT-D appears to be equally effective to pharmacotherapy and to a relatively active control condition (Markowitz, 2003). There is no published data available on these three studies regarding the numbers of subjects recruited and the trial design.

Feijo de Mello and colleagues (2001) wished to assess the applicability of IPT augmented to antidepressant medication in Brazilian dysthymic patients of a lower socioeconomic background. Thirty five dysthymic patients were randomly assigned to IPT and moclobemide (n=16) or moclobemide alone (n=19). This study included an acute and maintenance phase totalling 48 weeks. Moclobemide was provided at 300-600mg daily and IPT was provided acutely as 16 weekly sessions, followed by monthly maintenance sessions. Blinded ratings of depression (HamD, Montgomery and Asberg Depression Rating Scale (MADRS)), quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire) and global functioning (Global Assessment of Functioning) were performed at baseline, 12, 24, and 48 weeks. Six patients (37.5%) dropped out of the IPT and eleven (57.9%) dropped out of the medication only group. Both treatment groups improved on all measures over time, particularly between baseline and 12 weeks ($p<0.0001$); there was a non significant trend for the combined IPT and medication group. One single therapist provided the modified version of IPT-D for this study. The small sample size limits the generalisability of the findings.

A large study was undertaken in Canada (Browne et al, 2002) comparing IPT and sertraline alone or in combination with 707 dysthymic primary care patients. Ethical restrictions prevented the use of a placebo condition. Sertraline (50-200mg) and IPT (up to 12 sessions, mean 10) were provided within the first 6 months of acute treatment followed by an 18 month naturalistic follow up. Blinded assessments of depression and social functioning (MADRS, SAS) were performed at baseline, 6, 18 and 24 month follow up. Costs of treatment including the counsellors time,

antidepressant medication and health and social care use was collected at the same time. 586 subjects (83%) were available for the six month assessments and demonstrated significant difference in response (40% reduction in MADRS scores) rates: 59.7% in sertraline alone, 57.5% in sertraline and IPT and 46.6% in IPT group ($P<0.025$). At 2 years, 525 (74%) were available for follow up and no differences in the depressive symptom reductions were found in sertraline alone (13.2 ± 11.0) or combined group (13.6 ± 10.9). However, both of these treatments were more effective than IPT alone (10.2 ± 11.0) in symptom reduction ($p<0.02$). At six months, there was no statistically significant difference in health and social service costs between groups; however, compared to sertraline alone both IPT groups used less of the other health and social care costs. After 2 years, there was a statistically significant difference among the groups in the total per person 2 year costs (\$7866 sertraline, \$7386 sertraline and IPT, \$5657 IPT; $p<0.001$).

As the focus of this study was to assess the effects of augmenting sertraline with IPT, patients were not prohibited from receiving alternate treatments during the 18 month follow up phase which included antidepressant medication, the numbers of patients who received alternate treatments were small ($n=3$ sertraline group, $n=6$ combined group, $n=9$ IPT group). It is worthy to note that the IPT used in this study was not the adapted IPT-D for dysthymia; additionally the number of sessions fell below the recommended number for acute treatment of major depressive disorder, or indeed the recommended dose of up to 18 sessions for dysthymia (Markowitz, 1998). There is a great deal of evidence in the literature which supports the use of more potent antidepressant treatment in chronic depression. Providing IPT at such a low dose (10 sessions for acute treatment and no maintenance sessions) when sertraline was continued at a higher dose and continued throughout maintenance phase may not have provided a fair comparison.

Cognitive behaviour therapy

A small open study of 6 female inpatients was carried out by Miller and colleagues (1985). All patients were deemed as drug resistant (to a 3 week trial of antidepressants) and four of the group were also dysthymic. Treatment involved hospital intervention, pharmacotherapy (based on clinical need) and either CBT (n=3) or social skills training (SST, n=3). Both psychotherapies provided an intensive programme; the patients were seen 5/7 days for the first week and then sessions were reduced to weekly for 16 weeks. The mean BDI scores fell from 25.7 in the CBT group to 9.3 ($P=0.07$) and 22 to 8 in the SST group ($p=0.08$). Four of the women were in remission at the end of the treatment and 2 were partial responders ($BDI \leq 17$).

Thase and colleagues (1994b) were interested in differential response to CBT in 84 patients who were diagnosed with either major depressive disorder or double depression. The authors found that after a time limited course of CBT remission rates were greater in the major depressed group (55% vs. 27%) and concluded that more intensive CBT or alternate treatment methods may be necessary in patients with double depression.

Moore and Blackburn (1997) compared CBT (n=7) to antidepressant medication (n=6) in chronically depressed outpatients. 15-30 sessions of CBT were provided over a 12 month period. Four of the CBT and 5 of the medication group completed treatment and were available for follow up evaluations. There was a statistically significant difference of the CBT group compared to the medication only group ($P<0.01$) as measured by the pre and post treatment Hamilton depression scores.

Ninety seven patients diagnosed with primary dysthymia were compared with group CBT, sertraline, or both active treatments combined against a placebo for 12 weeks (Ravindran et al, 1999). The response rates were significantly higher for the combined group (71%) and sertraline group (55%) compared with the CBT alone or the placebo. The group CBT

alone was no different to the placebo. Although the addition of CBT to medication did not have a statistically significant effect in relation to response rates, it was found to augment the effects of the sertraline with regard to functional changes.

Other psychotherapies

Waring and collaborators (1988) reported preliminary data from a randomised study reviewing the effectiveness of combined marital therapy and antidepressant medication (doxepin) in the treatment of dysthymic women. After 10 weeks of combined treatment, the dysthymic women showed statistically significant improvement on all depression measurements and intimacy scale compared to placebo.

A 36 week randomised pilot study reviewed the effects of combining group psychotherapy and fluoxetine in 40 patients with dysthymia versus fluoxetine alone. All patients who had received 8 weeks of fluoxetine and had shown more than 40% decrease in their baseline Hamilton depression scores were randomly assigned to medication alone or medication plus 16 weeks of group psychotherapy. After 24 weeks at termination 89% (16/19) of the combined group responded to treatment (Hamilton depression score <50%) versus 76% (13/17) of the fluoxetine only patients. Remission was defined as no longer meeting the DSM IV criteria for dysthymia plus a "0" score on item 1 of the Hamilton depression scale. At termination 82% (14/16) and 63% (10/16) of medication only subjects were in remission, and at follow up, 31% (4/13) and 50% (6/12), respectively, were in remission. There were no statistically significant differences between groups (Hellerstein et al, 2001).

Keller and colleagues (2000) designed a psychotherapy which is incorporates techniques and strategies from IPT and CBT, Cognitive Behavioural Analysis System of Psychotherapy (CBASP) specifically as a treatment for dysthymia (McCullough 2000). A pilot study of 10 early and late onset dysthymic patients (McCullough, 1991) demonstrated the

feasibility and efficacy of the CBASP therapy. After treatment all patients met the termination criteria and 9 out of 10 achieved remission which was sustained at 2 year follow up. This led to a large randomised controlled trial. This multi-centre study recruited a total of 681 patients with chronic major depressive disorder, double depression that is major depression superimposed on dysthymic disorder or recurrent depression with incomplete remission. They were randomised to 12 weeks of CBASP monotherapy (16-20 sessions, patients were seen twice a week for the first 4 weeks which could be extended to 8 weeks if the patient was not adequately performing a learned social problem-solving procedure), nefazodone therapy (maximum dose of 600mg daily) or combination treatment. The study also included a 4 month continuation/maintenance phase. Results from the acute study indicated that nefazodone produced quicker results initially and was more efficacious than CBASP alone during the first 4 weeks of treatment. By the end of the 12 weeks however, both appeared to be equally effective, completer analysis of the 519 subjects demonstrated response rates of 52% for CBASP and 55% for the nefazodone and 85% combined nefazodone and CBASP ($p < 0.001$ for both comparisons). Remission rates showed similar trends (CBASP, 33%; nefazodone, 29%; combined treatment, 48%) and psychosocial outcome was significantly superior in the combined group (Hirschfield et al 2000).

Barrett and colleagues (2001) examined the effects of 11 weeks of treatment with paroxetine, Problem Solving Treatment (PST) or placebo (pill plus clinical management) in 241 primary care patients with either dysthymia ($n=127$) or mild depression ($n=114$). 191 (73%) of subjects completed all treatment visits. For the dysthymia, remission rates, defined by the authors as a Hamilton depression score of 6 or below, were significantly higher for the paroxetine (80%) and PST groups (57%) compared to placebo (44%) ($p < 0.008$). The remission rates were high for the mild depression group (64%) with no statistical difference between treatment groups (60.7% paroxetine group, 65.5% PST group, 65.6 placebo group).

A parallel study was conducted in patients over the age of 60 ($n=415$) by Williams and colleagues (2000). The subjects included 211 dysthymic patients and 204 patients with minor depression. 311 (74.9%) of patients completed all visits. After 11 weeks of treatment the paroxetine group demonstrated the greatest improvement in depressive symptoms compared to placebo ($p<0.004$); although no differences were found between the PST and placebo the psychotherapy group demonstrated the more rapid symptoms improvement during the latter weeks compared to placebo ($p<0.001$). Mental health functioning was found to improve with paroxetine in the dysthymic group ($p<0.03$) but not the PST group compared to placebo. Both the medication and PST groups improved mental health functioning in patients with minor depression as measured by the Medical Outcomes Study Short-Form (SF-36).

A UK study carried out by Simpson and colleagues (2000) examined the effects of counselling added to usual GP care in 181 primary care patients with chronic depression and/or anxiety. Patients in the experimental condition were compared to a treatment as usual (TAU) control group. Beck depression Inventory scores were taken at baseline, 6 months and 12 months follow up. Comprehensive cost measurements were taken. There was an improvement in the BDI scores over time, although there were no significant differences between the groups. Fewer of the experimental group were still "cases" on the BDI (>14) than controls at 6 and 12 months; this difference disappeared at 36 months (Corney and Simpson, 2005). The cost burden to GP practices was significantly higher in the counselling group. One key limiting factor of this study is the authors idiosyncratic definition of chronic depression; a BDI score of ≥ 14 alongside symptoms of mild depression for at least 6 months. This does not fulfil the ICD 10 or DSM IV criteria for chronic depression.

Despite the limited literature available there are promising data emerging which suggest a role for psychotherapy in treatment resistant depression (Thase 1997b, 1997c). The most effective treatment appears to suggest

a combination of pharmacotherapy and psychotherapy, including IPT, which may be beneficial in chronic or severe depression as well as preventing a relapse (Hollon et al, 2005; Hegerl et al, 2004). Clearly, there is a gap in the evidence base in this difficult to treat population; it has been argued that more trials of psychological treatments in resistant depression are needed (McPherson et al, 2005; NICE guidelines, 2004).

Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) was introduced in 1938 by Cerletti and Bini and has been used ever since. However, with the development of antidepressant medication its use has become less frequent. It does form an essential treatment of severe or treatment resistant depression (Husain et al, 2004). Many comparisons of the two forms of therapy have been carried out in order to define better their relative clinical indications and our understanding of the mechanisms of action (Brandon et al, 1984; Gregory et al, 1985; Greenblatt et al, 1964; Sackheim et al, 1987).

ECT involves the application of electrical stimulation of the brain by passing a current through two electrodes placed in contact with the scalp. This can be administered bilaterally, on one side of the head, or unilaterally, on both sides of the head. ECT does not produce any structural changes of brain matter as assessed by sophisticated neuroimaging (Scott, 1995) and does not lead to neuronal death (Devand et al, 1994). Unilateral ECT has been found to cause less short term cognitive impairment (Sackheim et al, 1993). ECT is commonly used for a treatment for depression after antidepressants have been tried unsuccessfully. A study of 100 medication resistant depressed patients conducted by Prudic et al (1996) found the response rates after one week of treatment was 63.1% which decreased to 47.7% after cessation of the ECT. Although the response rates were found to be lower in medication resistant depressed patients in the United States, this has not been supported in other areas where similar responses are reported in medication-resistant patients and non medication-resistant patients (van de Broek et al, 2004; Husain et al, 2004; Pluijms et al, 2002).

Vagus Nerve Stimulation (VNS)

Vagus Nerve Stimulation (VNS) involves the implantation of a generator that stimulates the vagus nerve which is effective in reducing seizure activity. Vagus nerve stimulation is known to affect a variety of neurotransmitters including noradrenalin, serotonin, GABA and glutamate, and is thought to affect multiple areas of the brain which are implicated in mood disorders (George et al 2000). A recent pilot study of 30 patients with treatment resistant depression reported a 40% response rate after 10 weeks of vagus nerve stimulation (Rush et al 2000). Several tests of neurological function showed improvements in this group (Sackheim et al, 2001a). After an additional 9 months of vagus nerve stimulation, response rate was sustained and the remission rate significantly increased (Marangell et al, 2001).

An open pilot study of 60 treatment resistant patients was reported by Sackheim and collaborators (2001b). Patients had not responded to at least 2 trials of antidepressant treatments. Concomitant antidepressant medication was permitted throughout the trial (at the same dose or decreased dose). After 10 weeks of VNS treatment 59 patients completed the ratings. There was a 30.5% response rate on the Hamilton depression scale and 37.5% for the Clinical Global Impression –Improvement score. The authors found that patients who had not previously received ECT were 3.5 times more likely to respond. Furthermore, none of the 13 patients who had not previously responded to 7 trials of antidepressant medication responded compared to 39.1% the remaining patients ($p<0.005$) suggesting increasing levels of treatment resistance are less likely to respond to VNS. A one year naturalistic study of treatment resistant depressed patients was conducted by George et al (2005). Patients received VNS plus treatment as usual (TAU, which could include increasing doses of antidepressant medication and ECT if needed) ($n=205$) and were compared with TAU alone ($n=124$). The combined group was associated with a greater improvement each month as measured by the 30 Item Inventory of Symptomatology – Self Report (IDS-SR (30)) ($P<0.001$). There was a

significantly superior response rate in favour of the VNS as compared to the TAU group (27% vs. 13%; $P < 0.01$). Twelve months of VNS was well tolerated and the authors suggested a role for VNS in longer treatment of resistant depression (Rush et al, 2005).

Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a brain stimulation device which delivers a time varying current through a coil close the head in order to stimulate the brain of a conscious patient. It stimulates the cortex by creating a time varying magnetic field over the surface of the head, depolarising the underlying superficial neurons which induces electrical currents in the brain (George et al, 1999). It is hypothesized that TMS produces behavioural effects solely through the production of electrical currents in the cortex of the brain (Wassermann, 1996).

There have only been a handful of studies reviewing the efficacy of TMS in resistant depression which have involved mostly open trials and only a small number have compared the active TMS to a sham (placebo) condition. Fitzgerald and colleagues (2003) in Australia compared high frequency left TMS (HFL-TMS) with low frequency right TMS (LFR-TMS) against a sham condition in 60 treatment resistant depressed patients. There was no distinction between HFL-TMS and LFR-TMS treatments and both were significantly better than the sham group ($p < 0.005$).

An open trial of 10 medication resistant patients received repetitive TMS (rTMS) augmented to antidepressant therapy (Huang et al, 2005). After two weeks there were significant reductions in the Hamilton depression and Beck Depression Inventory scores (48% and 28% respectively). Although three patients did not improve, 5 were considered responders (decrease of at least 50% in Hamilton depression scores) and were in remission (Hamilton < 8).

A randomised controlled trial compared 15 sessions of TMS to the same number of sham treatments (Avery et al, 2005). Of the 68 medication

resistant depressed patients a superior response was obtained in favour of the TMS group (11/35; 30.6%) versus 6.1% (2/33) which was clinically significant ($P=0.008$). Furthermore, 7/35 (20%) achieved a remission with the active treatment compared to the 3% (1/33) of the sham group.

A comparison of rTMS to ECT in 40 severe and resistant depressed patients was conducted in Israel by Grunhaus and collaborators (2003). Patients were randomly assigned treatment with ECT or rTMS for 4 weeks. Overall, 58% (23/40) of the patients improved (Hamilton depression score reductions $> 50\%$) with no significant differences between treatment groups (response rate ECT, 12/20; rTMS 11/20). Whilst there have been positive results regarding the efficacy of TMS in resistant depression (Kaufman et al, 2004), there have been a small number of negative findings where active TMS at both high and low dose (Minuissi et al, 2005) have been no different to the sham condition (Loo et al, 2003).

TMS is a relatively newcomer to treatment and is largely still only used as a research intervention. It is only available as a clinical option in Canada and Israel.

Studies in progress

Although there are data supporting certain approaches, efficacy of a broad range of clinical treatments tend to rely on anecdotal evidence and we have yet to achieve a firm scientific foundation from which to base our clinical practice. Researchers in the United States have started to address this concern and have developed a large clinical trial with the aim to evaluate a staged treatment approach for varying levels of treatment resistance (Tamminga, 2003; Wisniewski et al, 2003).

Recruitment has started for a multi-site, prospective randomised clinical trial of 4000 depressed out patients. There are four levels of treatment options being evaluated, entailing various randomised treatment options at each level. This will be the first and only study of its kind to

systematically evaluate a staged approach to manage treatment resistant depression. Patients who continue to demonstrate an unsatisfactory response at each stage progress on to the next level. The first level is treatment with citalopram. The second level treatments involve a switch or an augmentation category (Switch options: sertraline, bupropion, venlafaxine and cognitive therapy. Augmentation options: bupropion, buspirone and cognitive therapy). At this stage the cognitive therapy poor responders can be given venlafaxine or bupropion in addition. The third level also has a switch or augment option (switch to mirtazapine or nortriptyline; or augment lithium or thyroid hormone to the primary antidepressant). The final level involves one of two switch options (1) tranylcypromine or 2) venlafaxine and mirtazapine). The patients will be followed up for a twelve month naturalistic study. Although complex, the unique design of the study will allow generalisability to a large set of patients (Rush et al 2004; Fava, 2003b).

Future directions in treatment resistant depression studies

Clearly, resistant depression is a common problem which has only recently attracted scientific investigation; we are just beginning to understand clinically relevant and meaningful information. Yet, we still need to gain further insight into the spectrum of resistant depression, the efficacy of specific treatment approaches and which treatment approaches suit which particular patients. Moreover, there are limited data on the efficacy of any psychotherapy as a treatment for resistant depression, and no research has been conducted evaluating IPT in this treatment group. Indeed, the National Institute for Clinical Excellence (NICE, 2004) recommend that adequately powered randomised controlled trials are carried out to compare true efficacy of different psychological models including IPT, CBT and behaviour therapy in resistant depression.

Chapter three – Interpersonal Psychotherapy (IPT) for depression

History and origins of IPT

The interpersonal approach has a long history dating back from the work of Adolf Meyer (1957) and Harry Stack Sullivan (1965). Meyer argued that mental disorders developed as a result of an individual's attempt to adapt to his or her environment. He was the first psychiatrist to introduce a psychobiological approach where he recommended that psychiatric evaluation included consideration of social and cultural factors. Sullivan extended this theory further, suggesting that interpersonal relationships could be connected to psychiatric disorders. Rather than focusing exclusively on the mind, the brain or indeed society, he proposed that psychiatric assessment should involve the scientific study of people and the processes between people, that is, "interpersonal relations". Sullivans' approach has been applied to therapeutics within psychiatry; for example an interpersonal modification of intensive psychodynamic psychotherapy was proposed for schizophrenia (From-Reichmenn et al 1960) and for manic depressive young people (Cohen et al 1954).

In a related approach, Bowlby's attachment theory (1969) proposed that humans have an innate tendency to seek attachments which lead to individual satisfaction and thus contribute to survival of the species. Humans generally develop attachment bonds with few people such as a spouse, friend or member of the family (Henderson 1978). Bowlby argues that individuals are happiest when there are clear attachments; conversely, they are vulnerable to develop a depression when there is a disruption in attachments.

The consideration and assessment of interpersonal and social factors in understanding and treating depression has developed from work carried out by founders of the interpersonal approach. Mabel Cohen and colleagues (1954) led the first group in applying the interpersonal ideas

specifically to depression. A group of 12 manic depressive patients were studied, all of whom had experienced disrupted interpersonal relationships during childhood. Early family experiences were found to be reflected in their adult life, demonstrated by interpersonal and dependency problems.

Using an interpersonal approach the focus of observation and therapeutic intervention is the primary social group; particularly the individual's closest relationship such as the spouse or partner, family members, friends, work and wider community relationships. The relationship between psychopathology and social roles can be viewed in 2 ways: disturbances in social roles can contribute to clinical pathology, and mental illness can lead to a reduced capacity to perform a social role.

There is empirical evidence which supports the focal areas of treatment in IPT. Complicated bereavement has been shown to lead to depression (Walker et al, 1977; Maddison and Walker, 1967; Maddison, 1968). In addition, marital disputes (Paykel et al, 1969; Pearlin and Liberman, 1977) and the life changes encompassed by interpersonal role transitions (Overholser and Adams, 1977) are stressors which can also contribute to a depressive illness. This is especially the case when there is an absence of social supports. In contrast, intimate relationships, and/or having someone to talk to as a confidant have been shown to have a positive and protective effect against depression (Henderson, 1977; 1978; 1980; Brown-Harris and Copeland, 1977). Frank (1973) stressed that helping that patient achieve a mastery of current interpersonal situations is an important component of psychotherapy.

A group of researchers from the New Haven Boston Collaborative Depression Research Project drew on these theoretical approaches and tested variants of Interpersonal Psychotherapy in several clinical trials (Klerman et al, 1974; Weissman et al, 1974, Weissman et al, 1979; DiMascio et al, 1979). It took over 15 years for the above group to

develop IPT in its current form. A manual of IPT originally developed for research purposes to train therapists in the concepts and techniques of IPT was published to aid application of IPT in a clinical and research setting (Klerman et al, 1984).

Structure of a course of IPT

Interpersonal Psychotherapy is a brief psychotherapy which can be provided as acute treatment for major depressive disorder. The 50 minute sessions are provided weekly for up to 16 weeks and involve three phases of treatment: an *initial*, *middle* and an *end phase*.

The Initial Phase

The *initial phase* of Interpersonal Psychotherapy (IPT) has a dual focus, to reduce depressive symptoms and to deal with the social and interpersonal problems associated with the depression. It takes up to three sessions; during this time the therapist provides an overview of the therapy and thus sets a framework for treatment. The IPT therapist starts with a comprehensive psychiatric history and a diagnosis of depression is made using the standard DSM IV TR criteria (APA 2000). Once confirmed, the patient is explicitly told that they have a diagnosis of depression; the therapist reinforces they suffer from a treatable medical illness. This "sick role" (Parsons, 1951) excuses the patient from overwhelming social obligations, helps to ease guilt often associated with depression and reinforces what treatment is needed to help the patient get better. The sick role is used as a therapeutic rather than regressive mechanism. The therapist outlines that although the patient does not have full control over their illness, they can take full control over what they can do to bring about a remission. This helps to provide hope for the future that things will improve. At the start of treatment the therapist obtains a baseline measurement of the severity of the patients' depression by using the Hamilton depression rating scale. Suicidal intention is assessed, as is the need for concomitant antidepressant medication. The therapist regularly evaluates the depressive symptoms using this scale throughout treatment to monitor progress.

As part of the history, the IPT therapist gathers an Interpersonal Inventory. This is a review of the patients social and interpersonal functioning and comprises of an in-depth assessment of the quality of relationships in the patient's life, both past and present. Details of significant relationships are explored, including frequency of contact, expectations of both parties in the relationship and whether their expectations are realised, any changes the patient feels they would like to make, levels of satisfaction or dissatisfaction with the relationship, benefits and drawbacks including any overt or covert disagreements. Changes which have occurred in the relationships or interpersonal situation are examined in relation to the onset of the depressive episode. This could include significant events such as bereavement, promotion, demotion, children leaving home or increased marital disharmony.

At the end of the initial phase the therapist offers an interpersonal formulation (Markowitz and Swartz, 1997). Here a link is made between the onset and maintenance of the current depressive episode and the patient's social and interpersonal situation. This framework includes four potential problem areas: bereavement, role-transitions, role-disputes and interpersonal deficits. The therapist seeks to reach an agreement with the patient regarding this potential problem area. Once established, a treatment contract is set for both therapist and the patient; hence the focus for the middle phase is agreed.

The Middle Phase

The *middle phase* of IPT, which usually lasts between sessions 3-14, forms the main focus treatment. Here one or two of potentially four problems areas are identified with the patient and clearly-defined treatment strategies as outlined in the treatment manual are used (Klerman et al, 1984). The aim is for the therapist to work with the patient to reduce depressive symptoms caused and maintained by interpersonal problems. The four interpersonal problem areas are as follows:

Complicated bereavement

The patient has experienced a death of a loved one and for various reasons may not have grieved appropriately which leads to ongoing symptoms of depression.

Role dispute

The patient may be in open dispute or disagreement with an individual or group of individuals which could include friends, family or employee/employer relationships. This conflict may be contributing to current symptoms of depression.

Role transition

This is a broad area and could involve a change in role such as a promotion, demotion, having a baby, leaving home, moving house, separation or divorce or even receiving a diagnosis of a medical illness. The new role could cause or maintain depressive symptoms.

Interpersonal deficit

There are some individuals who have very few, if any, interpersonal relationships. The lack of fulfilling or rewarding social relationships in itself may be a contributing factor to continuing depressive symptoms

Once the IPT therapist has identified the problem area, he or she will work through the strategies highlighted in the manual in order to reduce depressive symptoms. In the case of a complicated bereavement following the death of a loved one, the therapist focuses the sessions on the facilitation of mourning and gradually helps the patient move forward, encouraging the patient to find new activities and relationships in order to help compensate their loss.

Strategies which the IPT therapist employs in the case of a role dispute include helping the patient to explore the relationship, particularly the nature of the dispute and options to resolve it. In the cases where the

dispute cannot be resolved the patient may conclude that the relationship has reached an impasse and seek to end the relationship and replace it.

When dealing with a role transition, the IPT therapist encourages the patient to mourn the loss of the old role; exploring with the patient the strengths and weaknesses. The therapist then helps a patient adapt to the new role by recognising both positive aspects of this role.

The residual fourth problem area identifies the patient as significantly lacking in social skills resulting in problems initiating or sustaining relationships. The IPT therapist encourages the patient to build relationships with others and reflects to the patient improvement in social skills.

Every depressed patient will meet the criteria for at least one of the four problem areas and the problem area may in fact change in the course of the treatment. This most notably occurs when Interpersonal Psychotherapy is provided as a maintenance treatment. The patient may have several related problem areas and may work on more than one, or select the most salient area.

The End Phase

The final phase of IPT typically is provided over last 2-3 weeks of treatment. During this time the therapist encourages the patient to recognise and consolidate therapeutic gains, and to develop ways of identifying and countering depressive symptoms should they arise in the future. The use of prophylactic antidepressant treatment, which could include psychotherapy and/or antidepressant medication, is also discussed.

IPT sessions focus on “here and now” problems rather than childhood or developmental issues. Sessions typically start with the question, “How have things been since we last met?” This allows the patient and therapist to focus on recent interpersonal events and its impact on the

patient's current mood. The IPT therapist takes an active, non neutral, supportive and hopeful stance.

As in the case of other psychotherapies, IPT employs similar techniques including the use of a supportive encouraging therapeutic stance and a non-judgemental positive regard. However, there are distinct differences unique to IPT such as the use of strategies used to deal with specific problem areas.

IPT for varying phases of treatment

Researchers have become increasingly aware of the importance of distinguishing between varying stages of treatment. Phases of treatment have been split into acute, continuation and maintenance therapy which has helped us to gain more insight into optimal dose and duration of antidepressant treatment at a given point in an individuals treatment programme. Nevertheless, this is a relatively new area and there are limited data available incorporating this approach. There are some more recent IPT studies which address the efficacy of IPT at varying stages of treatment which are reported below. In addition, the application of IPT has also been assessed for different aged populations in depressive disorder. The findings are presented below.

Clinical trials of IPT as an acute treatment for adults

The efficacy of IPT was first reviewed during a 16 week randomised control trial which compared IPT and amitriptyline alone or in combination against a non-scheduled control treatment in 81 depressed out patients (DiMascio et al, 1997; Weissman et al, 1979). IPT was administered weekly by a trained therapist who was encouraged to adhere to a treatment manual. Amitriptyline was provided at a daily dose of 100-200mg. The therapeutic dose recommended in the British National Formulary (2003) is 75-200mg per day. The patients in the non-scheduled treatment condition were allocated a psychiatrist. Although there were no scheduled treatment sessions routinely arranged, patients

were told they could telephone to arrange a 50 minute session if they were in distress. This was limited to a maximum of one session per month.

Although the antidepressant effects of IPT were slower to start than in the case of the amitriptyline (2 weeks versus 4 weeks) by the end of the 16 week trial both active treatment groups were found to be equally effective. Interestingly, combined IPT and amitriptyline was more effective than both monotherapies; this may be due in part to the preferential effects of each single treatment. IPT was found to target mood, suicidal ideation, apathy and reduced interest; whereas the initial effects of amitriptyline was on neurovegetative symptoms of depression including somatic symptoms, sleep and appetite disturbances. (DiMascio et al, 1979). Improvements in social functioning were the same in each treatment group after 16 weeks. The non scheduled treatment group had a worse overall outcome.

The National Institute for Mental Health Treatment of Depression Collaborative Research Program (NIMH TDCRP) which started in May 1982 (Elkin et al, 1985) carried out an enterprising and original study involving 250 depressed out patients. There were a number of innovative and unique aspects to this study; it was the first head to head comparison of IPT and CBT, and was the first multisite psychotherapy trial where both psychotherapies were tested in a neutral setting (Pittsburgh, Washington and Oklahoma). In addition, it was the first time both psychotherapies were tested outside of their original area of development.

The study involved 4 randomly allocated treatment groups: IPT (n=61), CBT (n=59), Imipramine plus Clinical Management (IMI-CM) (n=57), Placebo plus Clinical Management (PLA-CM) (n=62). Each treatment group during this trial had a detailed manual which described the theoretical rationale to each approach, an outline of the techniques to be employed and suggestions for how to deal with specific problems. IPT

and CBT sessions were audiotaped and monitored by independent raters using a specifically developed psychotherapy rating scale (Collaborative Study Psychotherapy Rating Scale, Hollon et al, 1987). Pharmacotherapy sessions were 45-50 minutes duration at baseline and 20-30 minutes for each subsequent session. The average dose for imipramine treatment was 185mg; (the British National Formulary recommended dose is 75-200mg each day). "Clinical Management" was added to imipramine and placebo and was also manualised in an attempt to prevent the pharmacotherapists from administering psychotherapy. During this trial the pharmacotherapists were allowed to review depressive symptoms, monitor side effects and provide a biochemical explanation for the patients' progress. This could be done in a warm supportive manner. These treatment sessions were taped and monitored for treatment adherence (Hill et al, 1992). Depression was measured using the Beck Depression Inventory (BDI) and blinded ratings using the 17 Item Hamilton Depression Scale. Additionally, the general level of functioning was rated using the Global Assessment of Functioning.

Treatment lasted 16 weeks and most subjects completed at least 12 treatment sessions over 15 weeks. Eleven patients dropped out of the study before treatment started. About a further third (32%) cohort were withdrawn or dropped out before the end of the trial, having completed less than 15 weeks of treatment or 12 sessions). 25% of this cohort was due to "negative reasons" such as non-compliance, side effects, or dissatisfaction with treatment. Surprisingly, only 9% of the sample were symptomatic failures. There were positive results in all treatment groups yielding a significant reduction in depressive symptoms at the end of the 16 week treatment ($P < 0.001$). Primary analysis of the data included subjects with a range of mild to severe depression; there were no differences in the pre-treatment scores of all of the groups. The results demonstrated that imipramine had the best response, placebo the worst and the psychotherapies were in the middle. Of the 239 patients who completed the treatment, imipramine and clinical management was found to be statistically significant to placebo ($p < 0.01$) with a trend in

favour of IPT ($p < 0.018$) and CBT ($p < 0.019$). There were no significant differences in recovery rates (Hamilton depression score < 7) between the active treatments (IMI-CM 57%, IPT 55%, CBT 51% and PLA-CM 21%).

Secondary analysis separated patients who had severe depressive symptoms (44%) at baseline (Hamilton depression score ≥ 20) from those who were mildly depressed (Hamilton depression scores ≤ 19); this produced superior recovery rates for IPT and imipramine in the more severe depressed and functionally impaired group ($P = 0.017$; Brunden corrected, $p = 0.1$; $p = 0.017$, Brunden corrected $p = 0.1$ respectively). Imipramine plus CM produced the most rapid response to treatment with a superior efficacy compared to placebo. IPT was comparable to imipramine plus CM in several areas and showed a mean outcome superior to placebo plus CM.

The efficacy data from this study was reanalysed by Klein and Ross (1993). Similar results were found with imipramine being superior to psychotherapy and the psychotherapies somewhat superior to placebo. When the patient group having a cut off score of 30 on the Beck Depression Inventory (moderate to severe depression), CBT was found to be relatively inferior to IPT.

On first examination it is disappointing that neither psychotherapy treatments were found to be more effective than placebo in the primary analysis. However, it must be stressed that during this trial the placebo with the added clinical management arm was neither "inactive" nor a "no treatment" condition. Patients' in this condition were seen initially for 50 minutes for the first session, followed by 20-30 minutes each week by an experienced psychiatrist who reviewed depressive symptoms, side-effects and social functioning. They could be supportive and encouraging. This amount of contact provided to the patient in addition to supportive and sympathetic attention to reviewing depressive symptoms and side effects must be acknowledged as something more than a

placebo, which may have provided enhanced antidepressant effects. A waiting list control may have provided a more suitable placebo control for this study. Twenty-eight therapists were taped and monitored using a Collaborative Study Psychotherapy Rating Scale (Hollon et al, 1987) and were found to be adherent.

A naturalistic follow up study was carried out by Shea et al (1992) who studied the course of depressive symptoms following the 16 weeks of treatment using IPT, CBT, imipramine plus clinical management (CM), or placebo plus Clinical Management (PLA-CM). Ratings were completed at 6, 12 and 18 months after completion of the trial. The patients who participated in this study demonstrated the same percent recovery rates as shown at the end of the 16 week period of acute treatment (30%, 14/46, CBT; 26%, 14/53, IPT; 19%, 9/48, IMI-CM; 20%, 10/51, CM). Relapse rates at the end of the 18 month follow up period were 36% for the CBT, 33% for the IPT, 50% for imipramine plus clinical management and 33% for the placebo plus clinical management. This was an early indication that active antidepressant treatment is needed to manage depressive symptoms in the longer term.

Clinical trials of IPT as an acute treatment in the elderly

IPT was first used with elderly patients in the early 1980's as an addition to a 6 week medication trial. The initial aim was to increase compliance as well as provide some active treatment in the placebo group (Rothbrum et al, 1982; Sholomskas et al, 1983). Eighteen patients aged 68-85 were randomised to 6 weeks of weekly 30-50 minute IPT sessions augmented to imipramine, alprazolam or placebo. Eleven patients (61%) completed the trial and demonstrated a positive response to treatment, which was evident from week 2 of the trial and continued for the duration of the protocol. One patient (6%) deteriorated and 6 (33%) dropped out of the study due to side-effects, treatment refusal or illness. The mean Hamilton depression scores fell from 20.9 at baseline to 7.2 post treatment. The authors reported that the patients showed good

compliance with medication and tolerated the combined treatment very well.

The first clinical trial of IPT alone compared to antidepressant medication was performed by Sloane et al (1985). Fifty-five elderly depressed patients were randomised to receive IPT, nortriptyline (NT) or placebo for 6 weeks. All three groups demonstrated significant improvements in mood as measured on the BDI and Hamilton depression scale ($p=0.005$). IPT was found to be as effective as nortriptyline. There was a significant difference in attrition rates between the groups ($p<0.005$); none of the IPT patients failed to complete the first 6 weeks, whereas 8/18 of the NT group and 4/18 of the placebo dropped out of the study by this time.

Reynolds has adapted IPT to deal with both uncomplicated bereavement as well as complicated bereavement which is an area most commonly experienced by elderly patients. The authors carried out a randomised study to establish the efficacy of IPT and nortriptyline as a monotherapy or combined compared to placebo in 80 subjects over the age of 50 who had bereavement related depressive illness. The combined group achieved the highest rates of remission (69%) (Hamilton depression score of 7 or below.) Nortriptyline alone achieved remission (56%), IPT and placebo (29%) and placebo and medication clinic (45%). Additionally, the combined group was associated with the highest rate of treatment completion and the lowest attrition rates. The authors failed to detect an effect of IPT which may be due to a small treatment size or due to the research protocol restrictions which meant that the researchers had to break the blind treatment if patients had not responded after 8 weeks. In addition, the supportive medication clinic may have had an antidepressant effect on the placebo group (Reynolds et al, 1999a).

Clinical trials of IPT as an acute treatment for adolescents

Interpersonal Psychotherapy has been modified to treat adolescent depression (IPT-A) (Moreau et al, 1991) and addresses common

developmental issues such as separation from parents, peer pressure, development of interpersonal relationships and the initial experience of death of a loved one. Because of its frequent occurrence, a fifth problem area addressing issues around single parent families was added as a focus during the intermediate stage (Mufson et al, 1993). There is a published manual available for IPT for adolescents (Mufson et al, 1993).

IPT was first tested as a monotherapy with adolescents in a 12 week open feasibility study involving 14 depressed adolescents. At the end of the treatment all patients had significantly reduced depression scores and none met the DSM III R criteria for major depression. In addition, social functioning had significantly improved (Mufson et al, 1994). Ten of the 14 patients agreed to clinical assessments as part of a naturalistic 1 year follow up study. Only one of the ten patients reported a second major depressive episode (this subject had dropped out of the original study after 4 weeks). The remaining subjects demonstrated that improvements in social functioning ($p<0.001$) and few depressive symptoms ($p<0.001$) during the following year compared to baseline scores. There had been a significant number of negative life events occurred throughout the year in a number of cases there had been no reported hospitalisations, suicide attempts or pregnancies. Additionally, all patients had been attending school regularly (Mufson and Fairbanks, 1996).

Rossello and Bernal (1999) were the first to publish results on a randomised controlled trial comparing IPT and CBT to a waiting list control (WL). 71 patients with major depression, dysthymia or both aged 13-18 were randomly allocated IPT ($n=22$), CBT ($n=25$) or WL ($n=24$). Most of the patients met the criteria for double depression (IPT $n=21$, CBT $n=16$, WL $n=17$) Self-rated measures of depression, social adjustment, self esteem and family involvement were recorded at baseline, post treatment and 3 month follow up. The IPT used in this trial was based on the original manual (Klerman et al 1984) and not the specifically adapted IPT-A (Mufson et al, 1993). IPT ($p<0.002$) and CBT

($p < 0.015$) significantly reduced depressive symptoms compared to the control condition. Furthermore IPT was more effective than CBT compared to placebo in increasing self esteem ($p < 0.001$) and social adaption ($p < 0.003$).

Mufson and colleagues (1999) reported the efficacy of IPT-A in a 12 week clinical trial of 48 depressed adolescents (ages 12-18) randomly assigned to either IPT-A ($n=24$) or to a Clinical Monitoring (CM) condition ($n=24$) which involved monthly 30 minute sessions reviewing symptoms and functioning with an option for further sessions. A blinded clinical rater assessed symptoms of depression, global functioning, social functioning and problem solving skills every two weeks until the end of the trial. Self ratings by the patients of depression and social functioning were completed at the same time. 32 of the 48 patients completed the protocol. Significant decreases in the Hamilton depression scores became apparent after week 12 and continued to termination for the IPT-A group ($p < 0.01$). However, no differences were noted in the Beck depression scores between groups. 75% of the IPT-A group met the recovery Criteria ($\text{HamD} < 7$) compared to 46% of the control group. At termination 13 (27%) of patients still met the criteria for major depressive episodes, of these patients 10 were in the CM group and only 3 in the IPT-A group. At the end of the study the IPT-A group were significantly less depressed ($p < 0.001$) demonstrated significant improvements in functioning overall ($p < 0.02$), with friends ($p < 0.02$), dating ($p < 0.02$) and problem solving ($p < 0.05$) compared to the clinical management group. There was a high attrition of the CM group (56% vs. 12% IPT-A group). Similar to the NIMH Elkin study (1989), the CM in this study was more than a placebo condition which was deemed by the authors to be an ethically acceptable treatment. The adolescents who participated in this study were largely female, Latin American and "older" (mean age 15.7 and 15.9 for each treatment group). Psychotic illness, obsessive compulsive disorder, substance abuse all excluded entry into the trial and therefore would reduce generalisability of the findings.

Santor and Kusumakar (2001) carried out a 12 week open trial of IPT for 25 adolescents with moderate to severe mood disorders which had lasted several months (mean 8 months). Uniquely, not all of the therapists in this trial had used IPT previously, however they were well supervised. The majority of patients showed improvement on the Hamilton Depression Scale, the Montgomery and Asberg Rating Scale, The Beck Depression Inventory, the Children's Global Assessment of Functioning. Eighty percent met the remission criteria on the BDI and 84% remitted on the Hamilton Depression Scale. The authors noted in addition to confirming the efficacy of IPT for adolescents in this small group, IPT also demonstrated that limited training alongside careful supervision in this cohort had been an effective approach.

Clinical trials of IPT as a maintenance treatment in adults

Psychotherapy can be a useful alternative for patients who may not wish to take or indeed tolerate antidepressant medication including pregnant or nursing mothers, or those awaiting major surgery, for example. Maintenance Interpersonal Psychotherapy (IPT-M) has a role when dealing with social or interpersonal consequences or triggers of depression (Weissman 1994). Frank and others (1989; 1990b; 1991a) were the first to research and demonstrate the efficacy of any antidepressant maintenance psychotherapy. However, Klerman and collaborators reported a maintenance phase of IPT in an early study (Klerman et al, 1974).

Although in 1974 IPT had not been clearly developed to its current form, Klerman and colleagues were the first to study psychotherapy alone or combined with amitriptyline in 150 patients aged 25-60 following an acute phase of treatment of 4-6 weeks of 100-200mg amitriptyline. Responders progressed to what the authors called a maintenance phase although today this would be considered a continuation phase. The patients were allocated to one of six possible options: amitriptyline, placebo or no pill, all of these treatments were augmented to either high interpersonal contact (one hour per week session with experienced

social worker focusing on the patients' current problems and interpersonal relations) or low interpersonal contact (maximum of 15 minutes a month with a psychiatrist reviewing symptoms, side effects and rating depression).

The amitriptyline group (high and low interpersonal contact) yielded the lowest relapse rates; 12.5% and 12% respectively. This was closely followed by the no pill and weekly psychotherapy group (16.7%). The placebo group in the high and low interpersonal contact conditions showed higher relapse rates (28%, 30.8%) and the no pill and monthly 15 minute interpersonal contact (virtually no treatment) had the highest relapse rates (36%). Blinded raters used the Social Adjustment Scale (SAS) one month after maintenance treatment started and after 2, 4 and 8 months. There were 106 patients available at follow up. Although no treatment effects were noted after four months, numerous differences were noted between the high contact and low contact groups at month eight. High contact psychotherapy (44%) was found to improve the patients' social adjustment, family relations, work performance, improve communication, and reduce friction compared to the low contact group (28%). There were no drug treatment effects on the patients' social adjustment. Combined IPT and amitriptyline demonstrated the greatest efficacy in preventing relapse and improving social functioning (Klerman et al, 1974, Weissman et al, 1974). Although the effects of psychotherapy in preventing relapse were suggested, it was not found to be statistically significant.

Maintenance Therapies in Recurrent Depression Study (MTRD)

Researchers led by Ellen Frank in Pittsburgh were interested to see if IPT could be adapted as a maintenance treatment and used successfully with prophylactic benefits in highly recurrent major depressed patients. A sophisticated study known as The Maintenance Therapies in Recurrent Depression Study (MTRD) (Frank et al, 1989) recruited 128 patients aged between 21-65 who had had at least three previous major depressive episodes (the last episode not exceeding 2.5 years before

index episode). Patients with major depression who had a Hamilton Score of at least 15 and minimum Raskin Score of 7 met the inclusion criteria of the trial.

Patients with double depression (co-morbid dysthymic disorder) were excluded from the trial. At the start of treatment patients underwent a 2 week drug washout period and received biological (sleep and neuroendocrine) and psychosocial (social adjustments and social supports) assessments. Patients were then treated during the acute phase with a combination of IPT (weekly for 12 weeks reduced to fortnightly for 8 weeks) and imipramine (150-300mg). When depression scores dropped to below 7 on the Hamilton Scale and below 5 on the Raskin Scale for three consecutive weeks the patients entered 17 weeks of a continuation phase. This prolonged and maintained the patients' recovery from depression, and ensured a clear remission of depressive symptoms. At the end of the 17 weeks the patients were randomised to one of five treatment cells for the maintenance phase of treatment lasting three years: Monthly maintenance IPT (IPT-M); Imipramine and monthly IPT (IMI-IPT-M), monthly IPT and placebo (IPT-M-PLA); IMI and Medication Clinic (IMI-MC); and placebo and medication clinic (PLA-MC). Biological and psychological assessments were carried out at baseline, at the end of the acute and continuation phase. Depression was measured by an experienced blinded rater throughout the trial.

A variant of IPT was developed specifically for this study. Sessions were planned monthly and therapists were encouraged to employ interpersonal strategies in order to prevent a relapse. A longer time frame would allow the patient and therapist to shift focus among the four problem areas. There was no work done to establish a reasonable "dose" of IPT-M, and it must be noted that monthly IPT is significantly less than the weekly acute dose. Imipramine however, was administered at high acute doses, at a mean dose of 210mg/day.

The course of the illness and early recurrences were reported (Frank et al, 1989) in 74 patients who had been randomised to no active medication during the maintenance phase. It is not surprising in this high risk group that 44 of 74 patients relapsed during the three year period, 8 dropped out or were noncompliant and only 22 of 74 remained well. 50% of the medication clinic group had relapsed by 21 weeks in contrast to 61 weeks for the IPT-M group. Only IPT-M was found to significantly extend survival time ($p < 0.02$). Interestingly the authors found no correlation between initial severity of depression and treatment outcome; this was thought to be due in part to the 20 weeks continuation phase where patients remained on high doses of imipramine and frequent IPT-M psychotherapy sessions. Gender, age of onset, length of depressive episode all did not predict survival time.

In 1990 Frank and collaborators reported the results of the study in total. 230 patients had entered the study, 73 of whom failed to reach continuation treatment, and 128 out of 157 patients completed the continuation phase. Dropouts were due to relapse, intolerable side effects, non-compliance or a secondary diagnosis of psychotic disorder. The patients were randomly assigned to the treatment cells as follows: IPT-M, $n=26$; IPT-M + PLA, $n=26$; IPT-M + IMI, $n=25$; IMI-MC, $n=28$; MC-PLA, $n=23$. There were no significant differences in the treatment groups regarding age, gender, number of previous depressive episodes or illness duration. Although the entry criterion was a minimum of 3 major depressive episodes the mean number of episodes was 7, suggesting an extremely high risk for a future relapse. Only 22 (17%) failed to complete the 3 year study. Survival analysis revealed that high dose Imipramine (average dose 215mg) was found to effectively provide protection against a recurrence and IPT-M greatly extended survival time ($p < 0.05$); the overall effect of the IPT-M occurred regardless of whether it was combined with medication or not. The mean survival time starting with the best treatment group and ending with the worst were as follows: IPT-M + IMI 131 weeks (sd10); IMI + MC 124 weeks (sd13); IPT-M 82 (sd13); IPT-M + PLA 74 (sd12); PLA + MC 45 weeks (sd11). The groups

were ranked in the same order with respect to survivors after one year (IPT-M +IMI 84%; IMI+MC 60.7%; IPT-M 46.2%; IPT-M+PLA 46.2% and finally PLA + MC 21.7%) and maintained their positions after 3 years (IMI 60%; IMI+MC 46.4%; IPT-M 30.8%; IPT-M+PLA 19.2%; PLA+MC 8.7%).

Twenty of 28 patients who had completed the 3 year study and remained well on active medication agreed to an additional 2 years comparison of imipramine versus placebo (Kupfer et al, 1992). Patients who were receiving maintenance IPT-M would continue to do so (n=13). Twelve patients completed the 2 years, 7 of which had a depressive recurrence. 1 patient was withdrawn. The high dose imipramine group yielded the best survival results (82%, $p<0.001$) and not surprisingly the recurrence rates for the placebo group was 11 times greater than that of the imipramine group. It is worthy of note that 78% of the placebo survivors had continued to receive IPT-M and 11% of the placebo survivors did not; promising results for the antidepressant potency of IPT in this high risk group of patients.

Researchers of the MTRD study were eager to evaluate the quality of the therapy provided during the trial (Frank et al 1991). Blinded raters reviewed 7-minute segments at the beginning of each session using a 27 item Psychotherapy Rating Scale which was designed to ascertain interpersonal interventions (the focus of IPT-M) or somatic interventions (which would be a primary focus during medication visits). Blind raters using psychometrically sound instruments were found to discriminate between the two maintenance conditions ($p<0.0001$). Furthermore, subjects receiving IPT-M could be divided into groups providing a high and a low interpersonal focus. Interestingly, there were significant differences in the survival rates of these two groups. Low interpersonal focus during psychotherapy sessions resulted in a median of 18.1 weeks to recurrence, whereas the high interpersonal focus (i.e. more specific interpersonal approach) demonstrated 101.7 weeks to a recurrence ($p<0.0001$). Given the history of response and duration of being well between episodes, the lower interpersonal focus group survived for the

same period of time as previously. In sharp contrast, the higher specificity group survived more than four times longer than expected.

Clinical trials of IPT during continuation/maintenance phases in the elderly

Psychotherapy research for depression in late life was identified a priority by a National Institute of Mental Health conference, U.S. in 1990 (Reynolds et al, 1992). This led to a sophisticated long term study led by Reynolds and collaborators similar in design to the Maintenance of Recurrent Depression Study which was conducted at the same research centre, the Depression Prevention Clinic, Pittsburgh. This group carried out a rigorous study with a large sample size evaluating the efficacy of IPT in old age depression. (Reynolds et al, 1992; 1994; 1996a; 1996b; 1997; 1999a; 1999b) Although primarily a maintenance study this encompassed treatment during acute and continuation phases.

Overview of Maintenance Treatment Late Life Depression Study

The Maintenance of Therapies in Late Life Depression (MTLLD) study was designed to compare 4 treatment maintenance therapies in prolonging recovery and preventing a recurrence of major depression in recurrent elderly depressives. Acute, continuation and maintenance phases of treatment were studied; outcome measures included depressive symptoms, global functioning and social functioning. The study recruited 187 depressed elderly subjects. During the acute phase of the trial patients received an open trial of nortriptyline (titrated to achieve blood levels of 80-120ng/ml) and at least 12 weekly IPT sessions. Patients who did not demonstrate a minimum of 50% reduction in the Hamilton depression scores by 8 weeks were provided additional antidepressant, mood stabilising or tranquilising medication until remission of depressive symptoms. Concomitant medication administered at the acute phase was then withdrawn for the continuation phase. Patients who were in remission (3 weeks of a Hamilton Depression Score of 10 or below), progressed to the 16 week continuation phase. IPT was then reduced to fortnightly for the first 8

weeks and then to 3-weekly for the remaining period. Sustained remitters at this point were then randomly assigned to one of four treatment conditions and followed up for 3 years: Combined IPT and nortriptyline (IPT-NT); IPT and placebo (IPT-PLA); nortriptyline and medication clinic (NT-MC) (medication clinic was a 15 minutes review by a psychiatrist of symptoms and side effects); placebo and medication clinic (PLA-MC).

Preliminary results reported during the acute and continuation phase

After two years of the study Reynolds and colleagues (1992) reported preliminary results an open trial of weekly IPT and nortriptyline during acute and continuation phase.

73 patients aged 60-80 (mean 67.5) were initially enrolled in the study. Twelve patients (16.4%) withdrew consent or dropped out before the treatment started. One patient died and another withdrew consent during the continuation phase. 61 subjects of the original cohort completed the acute phase; and 59 (80.8%) of the subjects who entered the study completed both the acute and continuation phases. 48 (78.7%) subjects responded fully to combined IPT and nortriptyline, three patients showed a partial response (Hamilton depression score 11-14) and 10 patients were found to be nonresponders. There were no differences detected in response when comparing early onset (≥ 60) major depressive disorder to late (< 60) onset (70% vs. 64.2% respectively). There were low attrition rates from the trial (16.4%). During the 16 week continuation phase the clinic/psychotherapy visits were decreased to fortnightly for half of the phase, and then to 3 weekly for the remaining period. Five of the 51 (9.8%) patients who had responded to the acute phase relapsed but were successfully restabilised. It is not surprising that the 10 nonresponders during the acute phase remained as depressed during the continuation phase. Six out of 25 patients (24%) of patients assigned to placebo-maintenance condition relapsed during the double blind discontinuation of nortriptyline. None of the patients assigned to continue nortriptyline relapsed during the 4-6 week transition period. Additionally, global functioning as measured on the Global Assessment

of Functioning (GAF) Scale demonstrated a steady improvement from a baseline GAF score of 76.6 at the start and 82.3 at end of continuation phase of treatment. It is debatable whether this is a meaningful difference on a semi-objective scale.

In the next paper, Reynolds and collaborators (1994) reported 32 patients (mean age 66.8) who had relapsed following treatment with placebo during the maintenance phase of the study. They had a pre-trial median of four major depressive episodes and were re-treated with an open trial of nortriptyline and IPT within 2 weeks of the onset of the subsequent episode. Two patients withdrew from treatment and 27/30 (90%) achieved remission; however 3/30 failed to remit and required further treatment intervention. The protocol required that the subjects were monitored closely, thus an early diagnosis of the subsequent major depressive episode was made alongside prompt antidepressant intervention; as a result this group of 27 responders to IPT and nortriptyline were not as depressed or as functionally impaired at the start of the subsequent episode compared to the index episode. This prompt intervention for the subsequent episode demonstrated significantly reduced time to remission (8.1 weeks versus 13.3 weeks respectively; $p < 0.01$). Twenty-two of 27 (81%) subjects demonstrated a shorter time to remission during treatment of the subsequent episode; whereas only 5/27 (19%) took longer. Furthermore, there was a significant difference in total episode length between the index episode (41.5 weeks) and subsequent episode (9.9 weeks) ($p < 0.0001$). The remission rates and time to remission in this study were comparable to non geriatric patients studied from the same site (Kupfer et al, 1989). Clearly, this is promising data supporting the efficacy for a combination of IPT and nortriptyline in recurrent depression, particularly as an early intervention.

Opdyke and colleagues (1996) found in that in 105 patients who received combined nortriptyline and IPT, situational depression at baseline was associated with higher levels of residual depressive symptoms; whereas



the level of chronic medical burden, personality and social support were not.

The pattern of response in depression and functioning during the continuation phase in the same subjects by the same authors was reported (Odyke et al, 1996/7). Fourteen subjects were excluded from the analysis, 11 subjects had suffered a major depressive relapse during the initial continuation phase (Reynolds et al 1996b) and three had entered the continuation phase as a partial responder. Ten patients (19.5%) received concomitant adjunctive pharmacotherapy which was stopped when remission was achieved in order to progress to the maintenance phase. Due to a positive response to acute phase treatment, symptoms of depression at the start of the continuation phase were low (mean Hamilton score 7, SD=2.3), and patients continued to demonstrate moderate improvements in depression scores by the end of the continuation phase (mean Hamilton score 5, SD=3; $P>0.04$). The authors were interested to identify which depressive symptoms which were present and persistent throughout the continuation phase. The greatest variability was observed with depressed mood, apathy, anxiety and anergia. Moderate resolution of symptoms was evident with insomnia, guilt and reduced libido. An excellent resolution of retardation, agitation, hypochondriasis, and suicidality, loss of insight, reduced appetite and weight loss was seen during the continuation phase. Additionally, the GAF scores demonstrated a significant improvement in the scores from the start to the end of the continuation phase ($p=0.001$). The mean GAF score at the end of treatment was 81.8 which indicated only a mildly impaired level of functioning.

Findings from the MTLLD study

180 patients were successfully recruited to the MTLLD, study of whom 140 (78%) responded (Hamilton score ≥ 10) to a combination of IPT and nortriptyline during the acute phase therapy. Nineteen patients were nonresponders and a further 21 dropped out of the study mainly due to side effects and non-compliance; two subjects reported finding the IPT

too traumatic. By the end of the continuation phase 124 / 140 patients had maintained a remission of their depressive symptoms. Recurrence rates over the three year maintenance study were as follows: nortriptyline plus IPT 20% (95%CI, 4%-36%), nortriptyline plus medication clinic 43% (95% CI, 25%-61%), IPT plus placebo 63% (95% CI, 45%-83%), and medication clinic plus placebo 90% (95% CI, 79%-100%). Combined treatment with IPT and nortriptyline was superior to IPT and placebo ($p<0.01$) and showed a trend for superiority over nortriptyline monotherapy ($p<0.06$).

Having completed the acute and continuation phase, the researchers found they could split the patients ($n=140$) into 4 different categories of response: delayed responders; sustained responders; mixed responders without a sustained improvement and prolonged non-responders. The groups were then randomised to three years of maintenance therapy with IPT and nortriptyline alone or in combination against a placebo. Each group was compared on subsequent recovery rates and time to a depressive recurrence. The authors found that the initial response profile predicted ultimate recovery rates: Rapid initial responders, within 4-5 weeks, showed significant maintenance treatment effects ($p<0.001$) and lower recurrence risk with either combined or monotherapy relative to placebo. Either IPT or nortriptyline alone as a maintenance treatment appeared equally effective in the rapid responder group. Combined therapy, which was marginally better than monotherapy, was the only treatment which was superior to placebo with initial mixed responders ($p<0.006$). For delayed responders (more than 6 weeks), combined therapy was the only treatment superior to placebo ($p<0.024$). Prolonged non-responders did not benefit from maintenance treatment (Dew et al, 2001).

The effects of age was evaluated in two sets of analyses; firstly, the effects of treatment with increasing age, and secondly, the age of onset of the first depressive episode and treatment outcome. The speed of response, remission and recurrence was reviewed in the two subgroups

of elders, 60-69 (n=113) and 70+ (n=67). Although no differences in time to remission, relapse or recovery was evident between the two subgroups, the "older" group (70+) showed significantly higher recurrence rates during the first year of maintenance treatment ($p>0.0005$). This was statistically detectable at 70 years and could predict poorer outcome at the age of 75 ($p<0.007$). The older group reported greater impaired subjective sleep quality and a higher incidence of medical comorbidity as well as a more frequent focus on bereavement, loss and role transition (Reynolds et al, 1997) which are all factors likely to increase the risk of depression.

The data of 187 subjects was analysed in order to examine the effects of age at onset of first depressive episode in relation to treatment outcome and course. Early onset depressives (n=129, aged 59 or younger) were compared to late onset (n=58, age 60+) depressed subjects. Although there were no differences in absolute rates of remission, recovery and relapses were found between the groups; the early onset group took significantly longer to achieve remission (12.9 weeks) compared to the late onset group (7.3 weeks). In addition, a higher proportion of early onset 22.5%, (n=29) versus 1.7% (n=1) reported a history of suicide attempts which was statistically significant ($p<0.0006$) (Reynolds et al, 1998).

Analysis of clinical variables which correlated with depression free symptoms during the maintenance phase was conducted by Taylor and colleagues (1999). Patients with baseline Hamilton Scores of ≤ 19 (n=6/9) were found to benefit most from IPT-M; conversely, Hamilton scores of over 19 (n=14/16) demonstrated greater relapse rates ($p<0.01$). In addition, the number of previous depressive episodes, chronic medical burden, time to remission and social support measures were not associated with an increased risk of a recurrence. However, these results should be viewed with caution due to the small sample size of highly selected patients during this study.

Ageing populations bring about similar common problems; conjugal bereavement being one of the most frequent. The incidence of major depressive disorder is higher than the general population, at around 15-30% following the death of a spouse within the first year of the loss (Zisook, 1991). Reynolds and collaborators (1999) were keen to examine the effects of nortriptyline and IPT alone or combined compared to placebo in 80 patients who had bereavement related major depression. Depression was measured using the Hamilton Depression scale and grief symptoms were measured using the Texas Revised Inventory of Grief. The combined IPT and nortriptyline group demonstrated the best remission rates (69%, n=11) followed by the nortriptyline only group (56%, n=14); then medication visits and placebo (29%, n=10) and finally IPT-PLA (29%, n=5). Additionally, the combined group showed the lowest attrition rates. As the authors suspected there was a significant effect of combined IPT and NT over placebo, however, no differences were found between IPT and PLA-MC. The authors concluded that this may be due to a number of factors: the small sample size may not have provided sufficient statistical power. Furthermore, the protocol dictated that the blind treatment is broken for patients who have not demonstrated 50% reduction in the Hamilton scores after 8 weeks; this may have discriminated against the IPT group. Furthermore, as was the case of the clinical management treatment used in the Elkin trial (1989) the supportive medication visit may also be considered a treatment with beneficial effects.

There were no differential effects of the four treatment conditions on bereavement as assessed by the Texas Revised Inventory for Grief. This in itself may reflect the need for more time for the patient to resolve the grief, as bereavement alone is not a pathological condition but a normal response.

Miller and colleagues (2003) examined the recurrence rates of depression in elderly depressed patients who were treated up to 3 years with pill placebo and either monthly IPT, or monthly clinical management

in addition. The authors were specifically interested to see if a different focal area in IPT would have a significant clinical effect. The authors found that patients with a focus on role conflict who were treated with maintenance-IPT survived for 3 years without a recurrence compared to the placebo/ clinical management group. The median time to recurrence was 68.3 weeks for the IPT patients versus 16.3 weeks for the patients receiving clinical management. The authors found no differential for subjects with an IPT focus on role transition or complicated bereavement.

MTLLD 2 study

Extending further the MTLLD study the same researchers have started to attempt to ascertain how the “old-old” (by which they meant patients over 70 years) will respond to IPT, paroxetine alone (mean 22.4mg/day), or in combination when compared to placebo. Patients over the age of 70 are being recruited to the MTLLD 2 study, which differs slightly from the original study in that subjects are not required to have had a previous episode of depression, and also may suffer from mild to moderate cognitive impairment (mini mental state scores of 18 or above). Miller and colleagues (2001) reported the preliminary findings on 70 subjects who have entered the trial and completed at least 10 sessions of IPT. At baseline, the researchers have noted there are no differences in the depressive severity between groups. Not surprisingly, the older patients (70+) have generally shown the greatest cognitive dysfunction and demonstrated worse physical activities of daily living compared to the 60-70 age group. IPT therapists report a progressive decline in their ability to engage ($p<0.003$), allow the patient to focus ($p<0.001$), and recall ($p<0.0001$) as patients demonstrate increasing cognitive impairment. Despite these findings, there have been no differences identified between the cognitively impaired and unimpaired group in the rates of remission and time to remission for the combined group. The IPT therapists for this group have adapted IPT to regularly involve and include family members and caregivers in reviewing symptoms and reinforcing options and strategies for change in between sessions. This

is an ambitious study which clearly breaks new ground into helping us understand the value of the efficacy of IPT in an older population. It also allows further evaluation of the adaptability and versatility of IPT with two main areas: the application of IPT in depressed patients with mild cognitive impairment, and the involvement of family and carers with IPT in this challenging group.

Treatment resistant depression - a single study reported

Scocco and Frank (2002) reported progress of a group of five depressed elderly patients who received IPT augmented to SSRI antidepressant treatment (sertraline or citalopram) having responded poorly to 6 weeks of an SSRI alone. All patients received 16-20 IPT sessions and achieved remission. All of the patients of this open study were classified as "difficult" cases and were referred to the author as the treating psychiatrist. Every patient had failed to respond to at least one previous adequate trial of an antidepressant, although the documentation of other antidepressant trials was not available in the notes, hence the level of treatment resistance was not established. Further restrictions of this open trial meant that patients could only start treatment subject to the psychiatrist availability to provide IPT sessions. As a result all participants were asked to sign a contract to agree to attend the sessions. It also appears that the author, who was the treating psychiatrist, and IPT therapist carried out the Hamilton Depression ratings. All of these factors may have seriously biased the results of this small case series.

Evidently, IPT is a well tolerated and efficacious intervention for the elderly depressed population, and has been found to be readily adaptable to their needs without major modifications (Miller et al, 1998). Furthermore, elderly patients have demonstrated they can work as partners in psychotherapy, learn from psychoeducational components of IPT as well as modify interpersonal interactions with others (Miller, 1998). Hartman and Lazurus (1992) support this approach arguing that elderly patients do benefit from a structured therapeutic relationship

where a therapist allows the patient to recognise and master problems which contribute to their depression.

Moreover, during combined treatment IPT, through encouragement and extensive psychoeducation has supported good compliance with the pharmacotherapy resulting in increased potency of the antidepressant intervention (Wolfson et al, 1997; Miller et al, 2001). This phenomenon can readily be applied to the rationale for using IPT in the resistant depressed population; clearly an area which needs more potent treatment and intervention.

Although both IPT and CBT have the largest evidence base for their clinical use in old age depression (Arean and Cook, 2002), more research is needed, notably in the frail elderly population (Karel and Hinrichsen (2000). It is interesting that only one study has attempted to assess the value of IPT in the treatment of a small number of poor responders (Scocco and Frank, 2002). The data from this open trial is limited: there is no available information on the number of previous episodes of depression, or indeed previous antidepressant therapy or response. Furthermore, the clinical ratings were not blind and were conducted by the IPT therapist/author. Despite these limitations, this study does still provide initial preliminary data on the tolerability and feasibility of IPT in poor responders. There have been no published reports on the efficacy of IPT in resistant depression in any other age group.

Summary of acute and maintenance trials of IPT across all age groups

1200 depressed patients, including adolescents, adults the elderly patients have been studied in 15 trials, 9 of which were randomised controlled trials. Most of the studies have focused on treatment outcome, with IPT demonstrating efficacy in acutely reducing depressive symptoms across all age groups (Elkin et al, 1989; Sloane et al, 1985; Reynolds et al, 1996; Mufson et al, 1999). IPT can be used as an effective

treatment in severe depression (Thase, 1997b; Sotsky et al, 1991) although combined IPT and antidepressant medication is the better option for severely depressed adult patients (Klerman et al, 1974) and in delayed responder elderly patients (Reynolds et al, 1999). Continuation and maintenance studies have also demonstrated the efficacy of IPT (Klerman et al, 1974; Frank et al, 1989). IPT alone or in combination has been shown to significantly increase the survival time of highly recurrent depressed elderly (Miller et al, 2003), and adult patients (Kupfer et al, 1992), and with adults has been correlated to the therapist maintaining a specific a focus on interpersonal issues during treatment (Frank et al, 1991). Miller and colleagues (2003) found that depressed elderly patients with the focus of role disputes increased the survival time to a recurrence four-fold compared to placebo. Furthermore, the earlier the antidepressant interventions during a depressive relapse, the quicker the response (Kupfer et al, 1989; Reynolds et al, 1994). Feske et al (1998) found that the longer the duration of the index episode of depression, the less likely an early response is seen with IPT alone. There have been no studies to specifically address the dosage of IPT when delivered at the acute, or continuation phases of treatment. Benefits of improved social functioning following treatment in addition to reducing depressive symptoms is reported in the literature (Mufson et al, 1994; Klerman et al, 1974) which have been sustained after one year of follow up (Mufson and Fairbanks, 1996).

Clinical management, clinical monitoring (Elkin et al, 1989; Mufson et al, 1999) and supportive medication visit (Reynolds et al, 1994; 1996) have been used as a placebo in studies which have been noted by the researchers to be more effective than a placebo control. The numbers involved in each study have varied greatly ranging from an open study of 5 to a randomised controlled trial of 187 patients. The larger studies have included a number of different treatment cells with about 16-26 patients in each cell.

The attrition to IPT is generally lower than antidepressant medication (Sloane et al, 1985; Reynolds et al, 1999); furthermore, researchers from previous trials have argued that IPT has been found to improve compliance to pharmacotherapy (Wolfson et al, 1997; Miller et al 2001), both of these factors may be important in the role of IPT in treatment resistant depression. It is possible that the results of IPT trials have more power than medication with less attrition taking into account Intention-to-Treat analysis. This warrants thorough meta-analysis beyond the scope of this study.

Interpersonal Psychotherapy for various types of depression

Recurrent depression

The efficacy of IPT as a maintenance treatment (IPT-M) was established and initially reported in a group of adult major depressives (Kupfer, 1989; Frank et al, 1991). Frank and colleagues (2000) were interested to see if a sequential treatment approach using IPT followed by an antidepressant in poorly responding patients would have a different impact on treatment than if IPT and antidepressant medication was provided from the outset. In two separate but methodologically similar studies involving women with DSM IV recurrent major depressive disorder, Frank and colleagues (2000) compared IPT alone as an initial treatment and only non-remitting patients received pharmacotherapy in addition (fluoxetine or sertraline) (Buysse et al, 1997; 1998; 1999) to IPT and pharmacotherapy (imipramine) provided at the outset (Frank et al, 1990). Patients who started in the IPT group alone who had not demonstrated a minimum Hamilton depression symptom reduction of 33% after 4 weeks had the dose of IPT increased to twice weekly for a further 4 weeks. If this did not yield a 50% reduction in scores, treatment with fluoxetine or sertraline prescribed according to clinical need was initiated. The group which had combined treatment at the outset (n=180) had a remission rate of 66%, whereas the women in the second cohort who were treated with IPT alone, and if there was no improvement received pharmacotherapy in

addition (n=159) demonstrated a remission rate of 79%. This was significantly greater than the initial combined group ($p=0.02$). The IPT only group was found to be slower in its onset of action. There were differences in the studies which may have contributed to the discrepant results; there were slightly higher doses of IPT used in the sequential treatment group. Additionally, there were different classes of antidepressant medication used in both studies. However, similar remission rates (78%) have been reported in a separate study using a mixed sex cohort treated with IPT followed by fluoxetine or imipramine (Thase et al, 1997). A sequential treatment approach may be interesting strategy which is attractive to women particularly in the child bearing and breast feeding years.

Although the studies reported below are maintenance studies reported earlier, one common factor not previously explored was that both studies provided treatment for highly recurrent depressed patients. Reynolds and colleagues (1996) were eager to compare the temporal course, remission and response rates in the elderly group (n=148, mean age 67.9) against the midlife (n=214, mean age 38.5) recurrent depressives. They analysed the data from the Maintenance Treatments for Recurrent Depression Study (Frank et al 1991) and the Maintenance Treatment in Late Life Depression study (Reynolds 1996). Patients were treated acutely and during the continuation phase with an open trial of IPT and tricyclic antidepressants (imipramine for the midlife patients and nortriptyline for the elderly patients). 78.4% (n=116) of the elderly and 69.6% (n=149) midlife patients remitted during the acute phase. There were similar low attrition rates for both groups (12.2%, n=18 elderly, 11.2%, n=24 midlife patients). Although both groups demonstrated significant responses to treatment ($p<0.001$) the elderly patients were slower to show a reduction in Hamilton depression scores. Furthermore a greater proportion of elderly subjects (15.5%, n=18/116) relapsed during the continuation phase compared to midlife patients (6.7%, n=10/149). These relapses were seen earlier in the elderly patients

compared to their younger counterparts (7.4 weeks versus 16.6 weeks). Despite the slower response to treatment, and earlier relapse rates there were no significant differences in recovery rates (elderly=66.2% versus 57% midlife patients). Although there were many similarities in both trials there were also notable differences: IPT had been adapted slightly for use in the elderly population. Two different tricyclic antidepressants were used, imipramine for midlife patients and nortriptyline for the elderly patients, each with its unique proportion of serotonergic and noradrenergic mechanisms. Elderly patients had a greater number of comorbid medical conditions compared to the midlife patients.

Dysthymia

Dysthymic disorder, or chronic depression is a prevalent disorder, 6% of the population develop dysthymia during their lifetime (American Psychiatric Association, 2005). Markowitz (1995) identified a need for a psychotherapeutic treatment for the disorder for those patients unable or unwilling to take medications; hence Interpersonal Psychotherapy was adapted as a treatment for dysthymic disorder (Markowitz, 1998). Initial pilot data was obtained through three small series of subjects at Cornell University Hospital, New York. Mason and colleagues (1993) treated 9 dysthymic subjects with an open trial of IPT; 5 of whom had not responded to the antidepressant desipramine and the remaining 4 had refused antidepressant medication. All of the subjects were long term dysthymia sufferers with the mean duration of the disorder of 22.4 years. Twelve sessions of IPT were provided and the Hamilton depression scores fell from 19.4 pre treatment to 7.4 post treatment. This response equalled that of the desipramine only subjects. Markowitz (1992b) treated 2 dysthymic patients with 12 and 16 sessions of IPT. The Hamilton scores fell from 20.5 to 5 post treatment. In order to test the applicability of IPT in dysthymia a further 2 therapists provided IPT treatment to 6 more patients resulting in a drop of the Hamilton scores to 8.5 from 20.8 at the start of treatment.

Browne et al (2002) explored the long term effects of IPT for dysthymic disorder on depressive symptoms, social and medical costs in primary care patients in Canada. They randomised 707 adults aged 18-74 years who were diagnosed with DSM IV dysthymic disorder with or without past and/or current major depressive disorder to receive either sertraline (50-100mg), IPT alone (10 sessions) or both treatments combined. All patients received 6 months acute phase treatment and were followed up with an 18 months longitudinal study. Depression was assessed by a rater, blind to the treatment condition using the Montgomery and Asberg Rating Scale (MADRS) at six months and twice during the 18 month follow up period. Treatment costs and subjects' use of other health and social services were also investigated. At six months 586 subjects completed the MADRS. Responders were identified by the authors as those who demonstrated a 40% reduction in the depression scores. 60.2% of the sertraline group, 46.6% IPT alone and 57.7% of the combined group responded. There was no statistically significant difference between the sertraline alone or combined group in depressive symptoms reduction. There was however a significant difference between groups in the costs for health and social service use, with the IPT group having the lowest costs (total costs per person: sertraline only, \$7866; sertraline and IPT, \$7386; IPT only, \$5657. $p = 0.001$). Over the long term all three treatments were effective in treating dysthymia, the most efficacious treatment was either sertraline alone or in combination with IPT. The combined group also demonstrated \$480 per person less per year on health and social care costs compared to the sertraline group.

DeMello et al in Brazil (2001) compared outcomes of 35 outpatients with dysthymic disorder who received either moclobemide antidepressant, a reversible monoamine oxidase inhibitor, with routine clinical management ($n=19$) or in combination with IPT ($n=16$). Depression scores were assessed at baseline and week 12, 24 and 48 by trained raters. Despite the low numbers of patients, both treatment groups showed a significant improvement at each measurement ($p=0.047$ vs.

$p=0.043$ respectively). There was a non-significant trend towards lower scores on the Hamilton depression scores and Montgomery and Asberg Rating Scale for the moclobemide and IPT group, which provides interesting pilot data. A larger study with greater power may provide substantial evidence of differential treatment outcomes.

Medical conditions and depression

The prevalence of depression in medically ill patients is around 6-8% (Reiger et al 1993). The subsequent economic burden, increased social and vocational disabilities is well established (Greenberg et al, 1990; Wells et al, 1989; Weissman et al, 1997). There have been a number of studies evaluating IPT for depressed patients with concurrent medical conditions.

Although there have not been any epidemiological studies demonstrating the prevalence rates for depression in those patients who are HIV positive; there is some evidence which demonstrates depression can occur (Markowitz et al 1994). Colleagues at Cornell University, including Gerald Klerman carried out the first efficacy study during the late 1980's. During this pilot open trial, 23 depressed HIV positive patients received 16 weeks of IPT. Twenty (87%) subjects responded with a remission of depressive symptoms by the end of treatment. The authors reported that specific aspects of IPT worked particularly well with HIV positive depressed patients, including: the here and now framework, an interpersonal focus, grief, role transitions and an option for change. Patients benefited from learning to act out their reasonable fantasies to regain a quality of life. The structure of IPT was helpful for the therapist (Markowitz et al, 1992).

A National Institute of Mental Health (NIMH) funded study; based on the NIMH Treatment of Depression Collaborative Research Programme (Elkin et al, 1989) was undertaken by the same researchers at Cornell.

This was the first controlled study of psychotherapy for 32 depressed HIV positive patients. 101 depressed HIV positive patients were randomly assigned to receive either IPT (n=24), CBT (n=27), supportive psychotherapy (SP) (n=24), or imipramine plus supportive psychotherapy (IMI-SP) (n=26). Each treatment was manualised and monitored for adherence using audio or video tapes (Markowitz et al, 1994b).

Preliminary data from the IPT (n=16) and supportive psychotherapy group (N=16) demonstrated that patients who were randomised to IPT yielded clinically and significantly superior results which was evident from week 8 and maintained to week 16. Mean Hamilton scores fell from 19.5 at baseline to 5.8 post treatment for the IPT group versus 20.7 to 11.9 for the SP group. This suggested increased antidepressant potency of IPT for this cohort of patients (Markowitz et al, 1995). The final results presented data on all four treatment groups; IPT (n=24), supportive psychotherapy with imipramine (n=26), supportive psychotherapy (n=24) and CBT (n=27) showed similar reductions in Hamilton depression scores for each treatment. Pre to post treatment completer analysis mean Hamilton depression scores fell from 19.6 to 6.5 in the IPT group and 20.8-9.6 in the supportive psychotherapy with imipramine group. The supportive psychotherapy and CBT performed less well with a reduction in Hamilton scores of 20.3-11.7 and 20.4-12.9 respectively. Intention to treat analysis demonstrated that Imipramine and supportive psychotherapy and IPT were both superior to CBT ($p<0.05$). Although supportive psychotherapy had the third best results they were not significantly different.

A direct association between post myocardial infarction (MI) and social isolation and life stress has been found (Case et al 1992). 27% of patients who have suffered an MI develop major depression (Scheifer et al, 1989). There have been two reported case studies of IPT in heart disease. Miller (2002) reported a case of a 67 year old man who

developed major depression following a cardiac transplant. IPT was added to paroxetine to help the patient address his preconceived expectations of the transplant, reintroduce his social contact and reduce his depressive symptoms. Stuart and Cole (1996) in Iowa report a case history of a depressed 57 year old man following his myocardial infarction. He was successfully treated with paroxetine and Interpersonal Psychotherapy. IPT using the strategies suggested in the manual for role dispute and role transition was found specifically to target interpersonal conflicts and grief and loss associated with his MI in addition to reducing his depressive symptoms. The depression scores fell from HamD 20, Beck Depression Inventory 29 at the start of treatment to 3 and 2 respectively at termination.

IPT for ante partum/postpartum depression

10-12% of pregnant women develop a major or a minor depression (Spinelli, 1997); with similar prevalence rates reported for post partum women (O'Hara and Swain, 1996). This causes great personal suffering, additionally; there is good evidence to suggest that mother-infant bonding is impaired by maternal depression (Downey et al, 1990). Furthermore, subsequent development of infants has negative consequences during social relationships. Women during pregnancy and breast feeding may express natural concerns about the effects of pharmacological treatments for depression for their developing foetus or baby.

A treatment manual has been developed for ante partum depression (Spinelli, 1997); the basic approach of IPT is the same, although the content relates to the pregnancy. This role transition allows the mother to evaluate her feelings regarding parenthood, her relationship with her spouse and physical changes in her body. A fifth area of "complicated pregnancy" has been added.

Spinelli (1997) reported on an open pilot study using IPT to treat 13 depressed pregnant women. At the end of 16 weeks of treatment, all of

the patients had responded positively as measured by a clinician rated and patient rated depression scales. The mean depression scores dropped from 22.1 to 3.9 on the Hamilton depression scale and 21.8 to 8.9 on the Beck depression Inventory. All subjects met the criteria for recovery post treatment and none of the ten women available for review at 3 months post partum reported any depressive symptoms. Based on this study the authors carried out a randomised controlled trial whereby 50 subjects were entered into a 16 trial assigned to receive either IPT or a didactic parenting education programme (Spinelli and Endicott, 2003). Depression was measured with the Hamilton depression scale, Beck Depression Inventory and Edinburgh Postnatal Depression scale (EPDS). IPT demonstrated a statistically significant advantage over the parenting education programme demonstrated by reductions on all mood scores; (EPDS 11.8% vs. 33.3%; BDI 52.4% vs. 23.5%; HamD 52.4% vs. 29.4% ($p<0.001$)). The authors reported a significant correlation of the mother's improved mood with her ability to interact with the infant.

Zlotnick and colleagues (2001) reported on an open pilot study which attempted to use IPT provided in a group format for four sessions compared to treatment as usual in 37 pregnant women who had at least one risk factor for depression. Of the 35 women who completed the study within 3 months of the birth 6 (33%) of the treatment as usual group had developed post partum depression compared with none of the 17 women in the IPT group.

Swartz (1997) report the case of a depressed HIV positive woman who received four months of IPT. The areas of dispute (with the baby's father) and transition, regarding both pregnancy and HIV infection were the prime focus of IPT. Her Hamilton Depression Scores fell from 18 at the start of treatment to 2 as she worked through therapy and regained mastery over a difficult situation.

An unpublished treatment manual is available for post partum depression which was used in the following study. The researchers reviewed the

efficacy of IPT compared to a waiting list condition in 120 women with DSM IV post partum depression. The average duration of major depression in this study was 7 months (apart from 3 chronic depressed women with a mean duration of over 2.5 years). Subjects were randomly assigned to 12 weeks of Interpersonal Psychotherapy or to a waiting list condition (WLC). Depression was measured by an unblinded clinician using the Hamilton Depression Scale (HDS) or self rated by the patients using the Beck Depression Inventory (BDI) at baseline and 4 weekly. Additionally, social functioning and post partum adjustment were also assessed. 99 subjects completed the study; dropout rates (20% for IPT and 15% for the WLC group respectively were not statistically significant.) Significantly greater improvements in depression scores, social functioning and post partum adjustment were noted in the IPT group both on the HDS and the BDI compared to the waiting list control group. A significantly greater proportion of women (37%) versus (13.7%) who received IPT recovered from their depressive episode with a Hamilton score of 6 or lower. Furthermore, social adjustment revealed significant differences favouring the IPT group ($p < 0.009$). Post partum adjustment demonstrated significant effects of IPT group at week 8 which continued to the end of the trial ($p < 0.001$). Although Hamilton scores are usually blind for a study of this type, the authors gave practical reasons for this not being the case. They believed this would help women in the WLC develop a relationship with the rater which would allow compliance with the trial. It is significant that there was a strong significant correlation found between the results of the Hamilton Depression scores and the Beck Depression Inventory (O'Hara et al, 2000).

Klier and colleagues (2001) in Austria also carried out group IPT for 17 women diagnosed with post partum depressive disorder. There were significant reductions in mean scores on the Hamilton depression scale which fell from 19.7 at baseline to 8 post treatment. Six month follow up evaluation revealed continuation of the positive treatment effect.

IPT demonstrates promising results as a treatment for ante partum and post partum depression. The areas of role transition and role dispute are the most common focal areas for attention during therapy. Clearly, an advantage of antidepressant treatment without the use of medication is of tremendous value to pregnant or breast feeding women. Although women studied to date have not been resistant to treatment, there have been a small number of patients from the studies who were chronically depressed (O'Hara et al, 2000); it has been suggested that chronic depression is a form of treatment resistance (Fawcett 1994) and falls within the spectrum of "difficult to treat" category. Based on this limited data it is reasonable to test the efficacy of IPT for resistant depression with the general population. If successful, further work is warranted with this treatment population, which may help to reduce the risk of developing a treatment resistance and increasing the quality of relationship between the mother and baby at a critical period of time.

Summary of IPT for chronic, recurrent, postpartum, antepartum depression and depression with concurrent medical conditions

The efficacy of IPT in 1413 patients with either recurrent depression or dysthymia has been reviewed. This has involved 8 studies, 3 of which were randomised controlled trials (Frank et al, 1991; Reynolds et al, 1996; Browne et al, 2001), and 2 were parallel group studies (Frank et al 2000, De Mello et al, 2001). IPT has been shown to be effective in recurrent depression. Despite the fact that recovery rates are the same in adult and elderly patients, the latter group tend to demonstrate a slower response to treatment and relapse earlier (Reynolds et al, 1996). One interesting study starts to demonstrate how a staged approach to treatment has had positive benefits for depressed women with recurrent depression. During this study, Frank and colleagues (2000) initially compared IPT as a monotherapy, with imipramine added later to poor responders, to IPT combined with antidepressant medication. It was not surprising that initially, combination therapy yielded superior results. However, when an antidepressant medication was added to IPT at a

later date for the poor responders in the group, this resulted in higher recovery rates (79% vs. 66%) compared to those who received combination therapy from the start. Although IPT as a monotherapy is less potent and slower to demonstrate its antidepressant effects; augmentation of an antidepressant at a later date led to greater recovery rates. Clearly, more research is needed to explore the value of a sequential approach when treating depression, and whether it would benefit patients to start with either psychotherapy or pharmacotherapy.

IPT is an effective treatment for dysthymic disorder (Markowitz, 1998; DeMello et al 2001; Browne et al, 2002). Although combined IPT and sertraline was as effective as sertraline alone in the large dysthymia study (Browne et al, 2002) when treating depressive symptoms; low dose IPT alone or combined with sertraline led to a significant reduction in the use of health care costs. This has been the only study to report the economic effects of IPT. There have not been any studies reviewing the efficacy of IPT in treatment resistant depression.

There are less data available on the efficacy of IPT as a treatment for depression in the medically ill. Eight trials including just one randomised controlled trial and 3 case studies have been presented involving 396 patients. Most of the literature concerns the treatment of depressed HIV positive patients. IPT has been shown to be an effective antidepressant treatment and the specific goals and strategies have been reported to fit well for this group of patients. For example, as part of a role transition, a common focal area in this group of patients, therapists would encourage the patients to "live out their fantasy", which helped to frame their situation in a more positive way and improved depressive symptoms. In contrast, however, the treatment approach of challenging negative cognitions in CBT was more difficult, particularly when patients had just received a diagnosis of HIV positive. The model of CBT appears to be disadvantaged with this treatment group. Additionally, the authors also

acknowledged the time limit of IPT worked well with HIV positive patients (Markowitz et al, 1992; Markowitz et al, 1995).

For postpartum and antepartum depression IPT has demonstrated efficacy as an antidepressant and has been well tolerated (Spinelli et al, 1997; Spinelli and Endicott, 2003; O'Hara et al, 2001). Furthermore, it has also been found to improve social adjustment (O'Hara et al, 2001) and has helped to improve mother and infant interaction in postpartum women (Spinelli and Endicott, 2003). Group IPT has been evaluated in 2 open trials involving antepartum and postpartum depression (Zlotnick et al, 2001; Klier et al, 2001). During these small trials it has been effective and has been shown to prevent a depressive recurrence in the short term (Zlotnick et al, 2001).

Delivery of Interpersonal Psychotherapy

Interpersonal Psychotherapy by telephone

Accessibility of treatment for individuals who have depression may become problematic; time constraints, financial limitations and demands for childcare (Miranda et al 1996) can prevent a patient obtaining appropriate treatment which may increase the risk and incidence of treatment resistant depression. With this in mind, Miller and Weissman (2002) developed the concept that IPT could be delivered over the telephone. They conducted a 12 week study of IPT which was delivered over the telephone (IPT-T). 30 women with a life time history of recurrent major depression were randomly assigned to equal groups of either IPT-T or no treatment. A blind rater carried out assessments of the depression and social functioning scores at baseline and after 12 weeks. The IPT-T group showed significant improvement in depression scores ($p<0.02$), global functioning scores ($p<0.02$) and social adjustment ($p<0.02$). Although a small study, this demonstrates the versatility and adaptability of IPT. This may help us manage major depression more effectively, preventing the incidence of treatment resistant depression by adding IPT to the antidepressant therapy armamentarium.

IPT in groups

Group psychotherapy is a popular type of treatment which may have the added benefits of being cost-effective and also provides an ideal forum for social support and an opportunity to develop and practise social skills. There have been minor adaptations for IPT to be used in a group setting (IPT-G) and there is a published treatment manual, (Wilfey et al 2000). The group members have separate individual interviews where the therapist assesses and confirms the diagnosis, completes the interpersonal inventory and agrees a treatment contract. The group therapy sessions are 50% longer, 90 minutes in duration.

MacKenzie and Grabovac (2001) reported on a case study of IPT delivered in a group setting in Vancouver. Eight depressed patients who had received extensive adequate trials of antidepressant pharmacotherapy attended 14 ninety minute group session of IPT. The Beck Depression Inventory was completed by the patients at the start of treatment, during the middle phase and at the end of treatment, followed by 4 month after the end of therapy. Most (6/8) of the patients were severely depressed and had a comorbid diagnosis of dysthymic disorder. Five of the patients demonstrated a marked reduction in their depression scores, which was maintained at 4 month follow up. The authors found IPT-G to be helpful in its broad application to clinical practice.

Levovitz and colleagues (2001) in Tel Aviv evaluated the effectiveness of IPT in groups for patients who had suffered moderate to severe depressive disorder and responded to acute treatment with antidepressant medication. After acute treatment the patients were split into two groups: IPT-G (n=7) and a continuation of the standard treatment (n=7). The group IPT comprised of 18 weekly sessions lasting 90 minutes. The depression was assessed five times (HamD and Clinical Global impression scale) during treatment, and 6 months after termination. In addition to the rater being blind to the treatment condition, the author reported that the group therapists and the patients were also

blind to the fact the study was being completed. Although an interesting finding, consent and ethical approval are required from most research studies. The IPT-G demonstrated significant improvements in recovery rates by 6 months (86% vs. 29%; $p < 0.01$).

Biological correlates of response to IPT

Brain functional imaging studies

Our understanding of the biology of depression has increased dramatically over the past 4-5 decades. We have gained awareness into the effectiveness of IPT in depression for various age groups and types of illness. Furthermore, we have started to understand specific potent effects of the treatment, including purity of IPT important for standardising intervention for biological investigation (Frank et al, 1991) and combined pharmacotherapy and IPT (Klerman et al 1984; Frank et al, 1991, Reynolds et al 1996). Technological advances have allowed scientists to study brains *in vivo* during depressed states and following recovery with treatment. There is evidence that there are functional brain changes in depressed patients compared to controls. Abnormalities, usually demonstrated as areas of hypoperfusion have been shown in depressed patients compared to controls, including: frontal and temporal cortices (Sackheim et al, 1990; Mayberg et al, 1992, Austin et al, 1992), the left dorsolateral prefrontal cortex (Dolan et al 1992, Martin 1995), and the cluster of cingulate gyrus, anterior parietal regions and the caudate in the basal ganglia (Mayberg et al, 1994). There are 2 recent studies which have extended our understanding of IPT to include the physiological response of the brain to treatment which correlated with an improvement in clinical symptoms of depression.

In a Single Photon Emission Computed Tomography (SPECT) study Martin and colleagues (2001) reported functional changes in blood flow scans in 28 depressed outpatients who were randomly treated with either venlafaxine or IPT. Brain scans were performed at baseline and after 6 weeks; depression was measured using the Hamilton depression scale

on the same day of the scan. Both treatment groups demonstrated significant improvements in depression scores. There were functional brain changes with both treatment groups. The venlafaxine group showed right posterior temporal and right basal ganglia activation ($p < 0.01$) while the IPT group had limbic right central cingulate and right basal ganglia activation ($p < 0.01$).

In a similar study, Brody and colleagues (2001) conducted a brain metabolism study which used Positron Emission Tomography (PET) to measure glucose uptake to compare 24 depressed outpatients who selected treatment with either weekly IPT or paroxetine and 16 normal control subjects. Brain scans were taken at baseline and after 12 weeks of treatment. At baseline patients with major depression demonstrated higher normalised metabolism in the prefrontal cortex, caudate and thalamus and lower metabolism in the temporal lobe. Both treatment groups demonstrated an improvement in the clinical scores as measured by the Hamilton depression scale (61.4% reduction for paroxetine and 38% IPT group). Both groups showed decreases in the prefrontal cortex (bilaterally in the paroxetine treated group and on the right in IPT treated patient), left anterior cingulate gyrus metabolism and increases in normalised left temporal lobe metabolism. The results from this study should be viewed with caution as only one patient had IPT and two scans in sequence though.

Sleep studies

A number of studies have been undertaken to understand the relationship between neurobiological correlates of depression and subsequent response to treatment. Abnormalities in all night sleep electroencephalogram (EEG) studies have been found to be more common among depressed patients compared to controls (Benca et al, 1992, Knowles and MacLean 1990). Specific abnormalities such as delta wave proportion (Kupfer et al, 1990) and rapid eye movement (REM) latency around dream sleep (Giles et al 1987) have been associated with a recurrence of a major depressive episode. Some studies have shown

that specific patterns of change in sleep EEGs during early drug treatment correlate with ultimate clinical response (Kupfer et al, 1981, Reynolds et al 1991). It has been argued that antidepressant medication has helped to “normalise” some of the depressive sleep changes (Buysse et al, 1996). Furthermore, patients with reduced REM latency have responded poorly to placebo and favourably to antidepressant medication in both uncontrolled (Akistal et al, 1980; Svenson et al, 1981) and controlled studies (Rush et al, 1985; Rush et al, 1989; Zammit et al, 1988). We know that serotonin has a major involvement in depression aetiology; it is also crucial in sleep neurochemistry.

Correlates of psychotherapy response help us to understand better the biological underpinnings and effects of psychological treatments. Moreover, if differential predictors of response can be established, the most clinically appropriate and cost effective treatment can be planned.

Thase and collaborators (1997d) wished to establish the relationship between abnormal sleep profiles and response to IPT. They classified 91 depressed patients into those with a normal sleep profile (n=50) and those with an abnormal sleep profile (n=41) after monitoring sleep for 2 nights for sleep efficiency, REM latency and REM density. Patients who did not respond to IPT alone received antidepressant medication as an augmentation to psychotherapy. These responders were also compared in the analysis. The patients with abnormal sleep profiles had significantly poorer outcomes in depression, poorer attrition rates and less remission compared to patients who had normal sleep profiles.

Reynolds and colleagues (1997) examined the outcomes of 47 elderly patients who had recovered from a major depressive episode and remained well with monthly IPT, after discontinuation of antidepressant medication. Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index. Of the patients who reported good subjective sleep quality, 90% IPT group remained well after one year. Whereas five (31%) of the patients assigned to medication clinic had remained well for this

period. Impaired subjective sleep quality yielded less favourable results; 33% of the IPT-M group and 17% of the medication clinic group were well after one year.

Buysse et al (1992) examined the longitudinal EEG sleep studies in 19 depressed patients who were treated with IPT. Sleep measurements were taken at baseline and shortly into recovery. The baseline assessments revealed no abnormal findings. Automated measures of delta-sleep and REM activity showed small state related changes, with delta activity increasing from baseline to remission and automated REM measures decreasing. Strong baseline-remission correlations were noted for most sleep measures including slow wave sleep, phasic REM activity and automated delta wave counts.

In the same study reported later Buysse and colleagues, (1999b) compared EEG sleep measures of patients who remitted with psychotherapy to those who did not remit. 111 women with recurrent major depression received weekly Interpersonal Psychotherapy; pre and post psychiatric measurements and sleep assessments were taken by a rater other than the patients' therapist. Clinical symptoms and sleep measures were compared between 62 remitters and 49 nonremitters. Treatment nonremitters had significantly elevated phasic REM. The authors could correctly identify 68.3% of nonremitters and 68.5% of remitters using linear discriminant function analysis of subjective sleep quality and REM activity.

Later the same group (Buysse et al, 2001) carried out sleep studies to examine the correlates of remission and recovery in depressed patients receiving IPT alone or combined with fluoxetine. The authors used sleep electroencephalogram (EEG) power spectra of NREM and REM sleep as well as observed phasic REM as quantitative measures of sleep at baseline and post treatment. 130 women were studied; 23 patients recovered with IPT alone and 23 recovered with the combination therapy. IPT nonremitters had increased phasic REM compared to

remitters, but no significant differences in EEG power spectra. IPT and fluoxetine recoverers but not IPT recoverers showed increases in phasic REM and REM percentage from baseline to recovery. In non-REM sleep, the combined group showed a decrease in the alpha power from baseline to recovery, while IPT alone showed a slight increase.

This study was limited as there was no control group. There was no proof of a specific EEG effect from IPT although the authors claimed IPT slightly increased EEG wave strength (alpha power). This happens anyway in recovery. The same team in 1992 with IPT alone showed a slight increase in slow delta wave power. The authors suggested that an abnormal sleep profile may reflect a more marked disturbance in the central nervous system arousal that warrants pharmacotherapy.

Summary of biological correlates of IPT

Research in depression has led to a greater understanding of its biological basis: disturbances in monoamine neurotransmitters serotonin, noradrenaline and dopamine are widely reported. Furthermore, functional and structural brain scans including MRI, SPECT, PET and fMRI have yielded abnormalities in depressed patients compared to controls. There is a paucity of literature which evaluates the biological correlates of IPT in depression. Only 2 functional brain studies have been reported, one SPECT and one PET study, and just three sleep studies. There have been no studies examining biological correlates of treatment resistant depression in IPT.

Both functional brain imaging studies assessed patients with a major depressive disorder. Abnormalities in depression pre-treatment were seen to normalise with IPT treatment in both studies (Martin et al, 2001; Brody et al, 2001), although one study reported data on a single patient (Brody et al, 2001). Interestingly, this included different brain areas (limbic right central cingulate) to those which changed with antidepressant medication.

There are sleep disturbances in depression (Benca et al, 1992) including an abnormal delta ratio (Kupfer et al, 1990) and abnormal REM latency around dream sleep (Giles et al, 1987). Early changes in sleep have been found to predict a good response to antidepressant medication (Kupfer et al, 1981; Reynolds et al, 1997). Good sleep at baseline appears to predict a positive outcome with IPT, whereas poor sleepers appear to do less well with IPT (Reynolds et al, 1997; Buysse et al, 2001). The dose of the IPT received by remitters versus nonremitters reported by Buysse et al (2001) is unclear. Low dose IPT (monthly sessions) was effective in preventing a recurrence in a maintenance study (Reynolds et al, 1997) for good sleepers, but not poor sleepers. The question which may need to be addressed is the potency of the antidepressant therapy, including pharmacotherapy or indeed a higher dose of IPT.

Effects on social adjustment

Depression has been found to have a significant negative effect on psychosocial functioning (Jarrett and Rush, 1994). To complicate matters further, depression often occurs within a psychosocial context which may in itself confound antidepressant treatment. Psychotherapy can play a crucial role to help address psychosocial contexts and provide treatment tailored to patients' individual needs, increase engagement and help make depression less difficult to treat.

Weissman and colleagues (1974) were the first to assess the treatment effects on the social functioning in depressed patients. 106 patients were treated acutely with amitriptyline and then randomly assigned amitriptyline, placebo or no medication with either high contact weekly psychotherapy treatment or low contact (basic symptom review). Social adjustment was measured using the Social Adjustment Scale (SAS) following one month of acute treatment, and then at 2, 4 and 8 month intervals. There were substantial differences in the percentage

improvements in the social functioning in the psychotherapy group (44%) compared to the low contact medication group (28%). The psychotherapy patients demonstrated significantly less impaired work performance, interpersonal friction and anxious rumination. However, these differences did not emerge until 8 months of treatment.

In a much later study, Lenze and colleagues (2002) studied depressed elders to assess the impact of IPT and nortriptyline (NT) in doses sufficient to produce a steady blood level of 80/120ng/ml together or alone against a placebo condition during maintenance treatment. Following successful acute and continuation treatment, patients were randomised to one of the four treatment conditions for 3 years. The authors were interested in assessing the social functioning of those subjects who remained in recovery with active treatments for one year of maintenance therapy (IPT and NT n=18; NT n=18; IPT n=13). The mean scores on the Social Adjustment Scale (SAS) improved with the combined group, but declined with both monotherapies ($P<0.01$). The authors found that a decline in social functioning during maintenance treatment predicted future recurrences. Only one (5.3%) of the 19 subjects who maintained the SAS scores during the first year had a depressive recurrence in the following 2 years; in contrast 5 of 19 (26.3%) subjects who had a decline in SAS scores during the initial year suffered a depressive relapse before the end of the trial.

Combined therapy was found to enhance the length and quality of recovery. In contrast to Weissman's (1974) study, gains in social adjustment were maintained rather than improved during maintenance therapy. O'Hara et al (2000) in his study of post partum depressed women found IPT led to improvements in social adjustment.

Therapist adherence in IPT

Psychotherapy research requires us to investigate differential psychological therapies, just as we would with different medicines in head to head pharmacotherapy studies. It is also helpful to establish and

identify what are the specific potent effects of the psychotherapy, just as with pharmacodynamics and dose ranging studies with medication trials. There are three studies outlining the adherence monitoring used in the NIMH TDCRP study (2 applied to the study itself and the scale used in a separate IPT trial). Two of the studies demonstrated adherence, another provides qualitative detail of the different psychotherapeutic approaches. There is one conflicting study.

Hill and collaborators (1992) used the Collaborative Study Psychotherapy Rating Scale (CSPRS) to monitor the adherence of therapists from the NIMH TDCRP. Four sessions from each of the 180 patients were rated. This included one from the initial and end phase of treatment, and 2 sessions from the middle phase of therapy. The authors found that cognitive behavioural therapists increased scores on the CBT scale after the first session and stayed at a high level and were more directive in the middle and than the initial or later sessions. Clinical management (CM) therapists had higher CM scores during the initial phase than any other phase. IPT therapists and CBT therapists scored higher CM scores for the first session than any other session. This was not inappropriate given there is an overlap of all therapies at the initial phase when obtaining a psychiatric history, depressive symptoms, suicidal ideation and general functioning. Therapists were found to exhibit more behaviour appropriate to their own respective treatment approaches than any other treatment approach. The CSPRS was found to discriminate between the three treatments. High interrater reliability and consistency was found during analysis of the psychometric properties.

Markowitz et al (2000) published results using the same adherence monitoring techniques from the NIMH study to assess level of therapist adherence in a randomised controlled trial of 56 HIV positive depressed patients treated with either IPT, CBT or supportive psychotherapy alone or with imipramine. The therapists were certified in the manualised treatments. Blind independent raters randomly selected taped sessions

and used an adaptation of the NIMH scale. Adherence scores were given for the individual therapies as well as for therapist interventions. All therapists were found to be adherent with high inter-rater reliability (0.89-0.99) and the scale discriminated each of the four treatments ($p < 0.0001$) with each therapy scoring highest in its own scale. Facilitative comments were found to vary by intervention but did not predict treatment outcome. This study shows that both therapists and adherence monitors can be trained to deliver specified treatments. This is an important approach to investigate consistency based effectiveness in psychotherapy.

Albon and Jones in 2002 in a later analysis examined the transcripts of the NIMH treatment of Depression Research Programme which compared IPT, CBT, imipramine and placebo plus clinical management in 239 depressed outpatients.

The authors hypothesised that the process and technique of IPT and CBT would overlap and be responsible for patient change. Prototypes of the ideal regimes of IPT and CBT were developed by expert therapists using the Psychotherapy Q-Set, an instrument designed to provide a standard language for describing treatment processes. Ratings of sessions ($n=35$, IPT, $n=29$, CBT) identified higher correlations with the CBT prototype than IPT in both treatment groups ($p < 0.001$) and a moderate correlation between Q-set ratings and the IPT prototype ($p < 0.001$). The authors suggested that in the NIMH trial there were no separate and distinct psychotherapy treatments provided, and that common characteristics, which were supportive in nature were associated with a positive outcome with both psychotherapies. The small numbers used in this study and others monitored limit these findings. The application of this rating instrument would be helpful, particularly in studies which identify high specificity and purity of the therapy provided.

A case for IPT in Treatment resistant depression

IPT has come a long way since Meyer's initial psychobiological approach, which accounts for social and cultural aspects of the

individuals' life. In addition, Sullivan's interpersonal approach brought further change to the way psychiatry has continued to work, encompassing a holistic approach which addresses physical, psychological, social and interpersonal factors. IPT is a useful treatment which provides psychoeducation about the patients' depression, which is regularly and systematically reviewed through the use of validated depression rating scales. Reassurance is a strong component of treatment and is provided regularly to the patient. These factors in combination may in fact help to increase compliance and subsequent response to potent antidepressant treatment and thus reduce the factors which are known to increase the likelihood of a resistant depression.

Meyer made the connection between a psychiatric illness and the environment; proposing that mental illness was the result of the patients' ability to adapt to a changing environment. IPT explicitly links environmental and interpersonal factors within the context of the patients depression, and through the use of problem areas with clearly defined strategies, the IPT therapist helps the patient resolve these issues which subsequently alleviates their depressive symptoms. In a recent study evaluating the specific components of IPT which were considered to have an antidepressant effect, the resolution of problem areas during IPT correlated significantly with reduced Hamilton depression scores (Markowitz et al, 2006). Although IPT deals with depression in the "here and now" the therapy also allows the patient to understand long term management of their depression; an important factor in treatment resistant depression. Psychoeducation in depression, duration of antidepressant treatment required for each episode and what steps to be taken in the event of a recurrence are dealt with during therapy. The strong interpersonal focus during treatment has been shown to have a protective effect against future episodes, even in those patients who have a high risk of a recurrence (Frank et al, 1989; 1991a; 1991b; Kupfer et al, 1992). Furthermore, the better the quality of even low dose IPT (monthly IPT, IPT-M), the longer the patient remains in remission, regardless of whether the patient is receiving antidepressant medication

in addition (Kupfer et al, 1992; Frank et al, 1991b). This study involved more complex patients who had had at least seven previous episodes of major depression. It is reasonable to assume the specific antidepressant components of IPT which involve maintaining a high interpersonal focus would have similar beneficial antidepressant effects in resistant depression.

Frank (1973) argued that mastery of interpersonal situations is important in psychotherapy and should be targeted. Social psychiatric research into the effects of reduced social contact or support on depression is well established (Brown and Harris, 1979; Paykel et al, 1971). One aim of IPT is to increase the social contact and support network available to the patient, using specific treatment strategies which support this. Again this may be considered a vital component of IPT which may help to have a protective effect on depression – both in terms of maintaining a euthymic mood, or preventing the development of a future recurrence (Frank et al 1991), or indeed a resistant depression.

Although there are limited data on the clinicians' role with respect to helping the patient achieve compliance, it is apparent that this is an ideal area which could help improve the potential treatment outcome; which is critical in a treatment resistant depressed population. IPT is one psychotherapy which sits comfortably with both the medical model of depression (i.e. that depression is a treatable medical illness), as well as utilising a psychological and interpersonal approach. Indeed, patients with treatment resistant depression are a difficult to treat group and would need treatment with medication in addition to antidepressant psychotherapy. The IPT therapist synthesises these approaches in a practical way to aid the patients understanding of the context of their depressive episode, and what steps can be taken to allow the patient to get better. The clear aim of therapy is to reduce depressive symptoms and increase social and interpersonal functioning. If patients do not respond or only partially respond to antidepressant treatment, as is the case in treatment resistant depression, the IPT therapist addresses

issues in a pragmatic way and from a holistic perspective. Medication, interpersonal and social issues are all evaluated. If medication changes are needed they are encouraged, additionally, interpersonal events occurring in the patients life which contribute to the current depression or which may lead to vulnerability to future episodes are addressed. This may help reduce the risk of a future recurrence (Frank et al, 1991). This practical and systematic approach ensures potent antidepressant treatment is provided and 'may reduce the likelihood of the patient becoming resistant to treatment. Many authors (Pridmore and Shea, 2003; Thase, 2003;), when reviewing treatment resistant depression report under-treatment of depression and have classified this as pseudoresistance rather than treatment resistance (Kornstein and Schneider, 2001). IPT in treatment resistance depression which uses a medical model of depression in addition to a psychological approach may help prevent the incidences of pseudoresistance and help with the practical management of treatment resistance.

As with any psychotherapeutic approach, extra time and support is given to the patient. Similarly, the psychotherapist obtains supervision which helps the IPT therapist adhere to the goals of treatment.

Throughout the course of Interpersonal Psychotherapy treatment, weekly reviews of the patient's depression take place. Formal assessments of the depression are done using the Hamilton Depression Scale, a well established measure, at baseline and regularly throughout treatment. This may have a number of substantial advantages. It can help the patient feel that their depression is being carefully assessed, managed and monitored throughout the course of treatment. This can instil confidence in both the therapist and the treatment. The rationale for the provision of a diagnosis of depression when assigning the sick role to the patient is not just to ease any guilt or blame they may feel; but also to provide hope to the patient that things will get better. The optimism provided in IPT during therapy in resistant depression may offer a key

component to help the patient understand their situation and continue to work in treatment to get better.

For example, one patient, who received IPT as part of this study, had received a number of antidepressant trials in complex cocktails prior to her entering the study. She was clearly resistant to treatment. Although her depression scores improved throughout treatment, she did not reach a sustained period of euthymic mood. At the end of treatment she told the therapist, "Thank you for being so supportive. I truly believe I could not have coped over this past year. I think I would have probably killed myself." There were many times that the therapist found resistant depression difficult to manage; it is difficult to maintain an optimistic approach when the gains obtained are so slow to arrive. However, one factor specific to IPT which may have helped this particular patient and others with a resistant depression is the approach where the therapist encourages the patient to blame their *illness* and not *themselves* through the course of recovery.

This has also been effective when using IPT in dysthymic patients. The structure of having this as part of the therapy prevents the therapist giving up, and allows them to provide realistic optimism that the patients' situation can improve. The therapist can reinforce to the patient that they cannot blame themselves for a reduced level of social or interpersonal functioning when they are suffering from a debilitating illness such as resistant depression. This can help prevent the patient from losing hope and continue to engage and comply with treatment. In dysthymia the IPT therapist encourages the patient to view the transition from dysthymia to euthymia as an iatrogenic role transition (Markowitz, 1998). As patients have suffered chronic periods of debilitating depression they often lack confidence in trying out new social or interpersonal roles and activities, which are often overwhelming. The IPT therapist is active in acknowledging these fears, and encouraging new activities thus reinforcing their potential antidepressant benefits.

Psychoeducation, a fundamental concept of IPT, should include a realistic overview of treatments offered for resistant depression. A diagnosis of treatment resistant depression brings the need for potent antidepressant therapy, which may involve high doses of antidepressant medication, or combination or augmentations strategies with additional pharmacological agents. Within the framework of IPT this is a significant role transition. Occasionally patients can complain that medication; either as a monotherapy or as part of a complex combination of antidepressants, mood stabilisers and low dose antipsychotics is overwhelming. Although this prospect is not the most desirable; it may be the most clinically appropriate option for the patient to consider. These issues can be addressed using the goals and strategies identified for role transition in IPT. Furthermore, psychoeducation allows the therapist to reinforce that the patient with resistant depression represents one third of depressed patients, reinforcing the medical classification of treatment resistant depression and preventing the patient from blaming themselves; this is a reasonable clinical approach and patients need the support to make this transition. Similarly the IPT therapist can draw similarities by comparing patients who have diabetes, heart disease or cancer for instance may need long term pharmacotherapy which is necessary to their recovery. Patients in these conditions all face a transition when accepting long term or life long prophylactic medication of any sort, and this is not an easy transition. There are however fundamental differences in that a cancer sufferer may be more willing to accept the need for treatment than a depressed patient. Accepting the sick role and a medical model in IPT is a fundamental component in resistant depression which may help to reinforce the rationale and need for medical treatment with the aim of optimising treatment outcome.

In addition to improvements in the patients' depression, the IPT therapist will also reflect and reinforce social and interpersonal gains throughout treatment. Frequently, patients who suffer from depression underestimate their achievements and this can help the patient to recognise some aspects of their progress.

It is essential that the IPT therapist should maintain an optimistic approach to treatment, particularly in the case of difficult to treat depression. This is very similar to using IPT in chronic depression, when there can be a limited or a slower response to treatment. The strategy of the therapist being encouraged to blame the illness rather than the individual in chronic depression (Markowitz, 1998) is transferable to dealing with patients with resistant depression, and provides the structure for the therapist to deal more confidently with the patient during sessions. For example, IPT therapists are encouraged to treat a number of patients with a major depressive disorder initially before attempting to use IPT as a treatment for dysthymia. This is because the therapist should gain confidence and competence in their skills in IPT before working with a more difficult and demanding illness such as dysthymia. Treating resistant depression would be likely to present very similar challenges to the therapist and it is reasonable to apply the same training restrictions.

Although IPT has never been evaluated for treatment resistant depression prior to this study, efficacy of IPT in major depression in adults, adolescents and old age has been well established (Klerman et al, 1974; Weissman et al, 1979; Mufson et al, 1999; Reynolds et al, 1996; 1997). Patients with increasing levels of complexity have also been successfully treated with IPT, including highly recurrent depression (Frank et al, 1991) and dysthymic disorder (Markowitz, 1998). Having originated from psychiatry and psychotherapy researchers, initial studies of IPT have predominantly consisted of efficacy studies. Despite this, a small amount of the literature has evaluated specific components of IPT which has been suggested to contribute its antidepressant effects. Studies involving highly recurrent depression have demonstrated that the greater quality of IPT i.e. the more specific an interpersonal focus, the longer the antidepressant effects (Frank et al, 1991; Kupfer et al, 1992); furthermore, these effects have been maintained at long term follow up (Spanier et al, 1996). Researchers at the same site having identified that

patients with abnormal sleep are vulnerable to further episodes, have also found that high quality IPT during monthly maintenance sessions extends the period of wellness in recurrent depressives for an extra year compared to patients who received lower quality of IPT according to objective ratings (Spanier et al, 1996), which suggests that a high treatment specificity of IPT is of significant prophylactic benefit. Using the data from the IPT training programme for the NIMH Treatment of Depression Collaborative Research Programme (TRDCP), high scores on therapist competence in conducting IPT have been positively correlated with treatment outcome (Rounsaville et al, 1987; O'Malley et al, 1988). Finally, in a recent study of dysthymic patients researchers in New York reported that clinicians and patients in separate ratings were both in agreement with the problem areas chosen during IPT sessions; and critically, resolution of these problem areas during therapy correlated significantly with a reduction in Hamilton depression scores ($p= 0.0001$).

Chapter four - The dopamine hypothesis of depression

The monoamine hypothesis of depression

The monoamine hypothesis of depression predicts that the underlying pathophysiological basis of depression is at least in part, depletion in the levels of the serotonin, noradrenaline and dopamine monoamines in the central nervous system (CNS). This hypothesized pathophysiology appears to be supported by the mechanism of action of antidepressant medications which mediate levels of neurotransmitters in the brain. These include serotonin, noradrenaline and dopamine, and all have been shown to be effective in the treatment of depressive symptoms. Intensive investigation has failed to find convincing evidence in at least some medicines affecting each of the neurotransmitters singularly for a primary dysfunction in the monoamine system. Since noradrenaline, dopamine and serotonin all have reciprocal interactions, it is virtually impossible to act on a specific neuronal element without affecting a cascade in the other two systems (Tremblay and Blier, 2006). The brain does not function on the basis of passive isolated pathways. The monoamine depletion paradigm reproduces the clinical syndrome of depression, thus allowing a more direct method using animal models for investigating the role of monoamines. Results from these studies have shown antidepressant responses being transiently reversed. Interestingly, monoamine depletion does not worsen symptoms in depressed patients not taking medication, or cause depression in healthy volunteers with no depressive illness. This strongly suggests a transmitter receptor interactional process in any pathology. It appears that antidepressants appear to require intact monoamine systems to reach a therapeutic effect (Delgado 2000).

Dopamine system

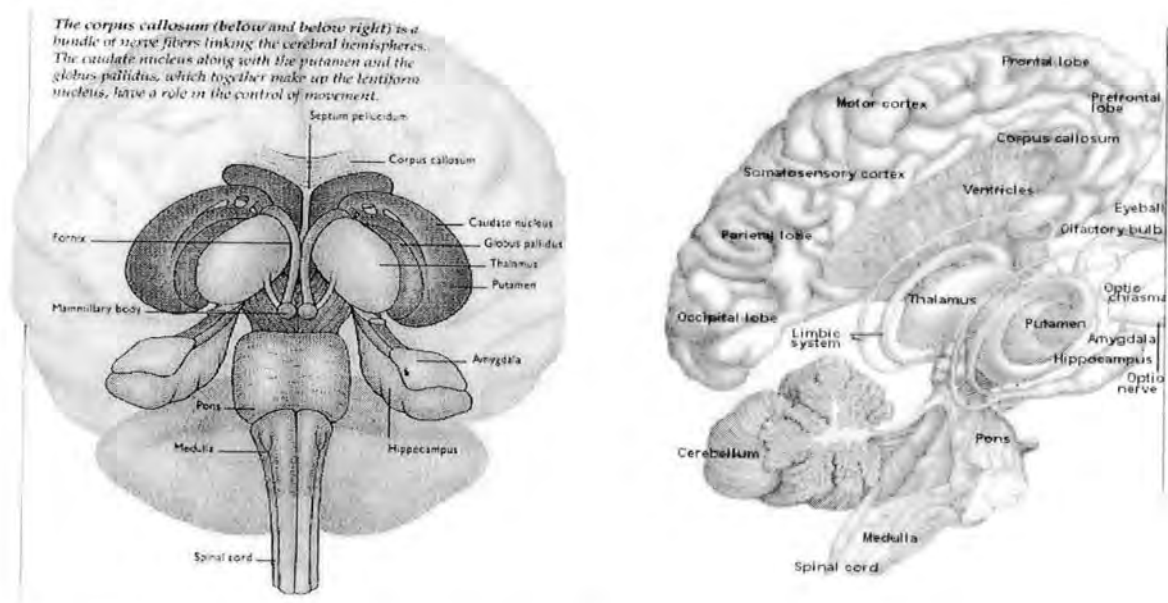
Since the initial dopamine hypothesis of depression was suggested by Randrup and colleagues (1975), multiple lines of investigation have explored the role of

the dopaminergic systems in depression. Dopamine dysfunction is now recognized as playing a major role in a wide range of psychiatric disorders.

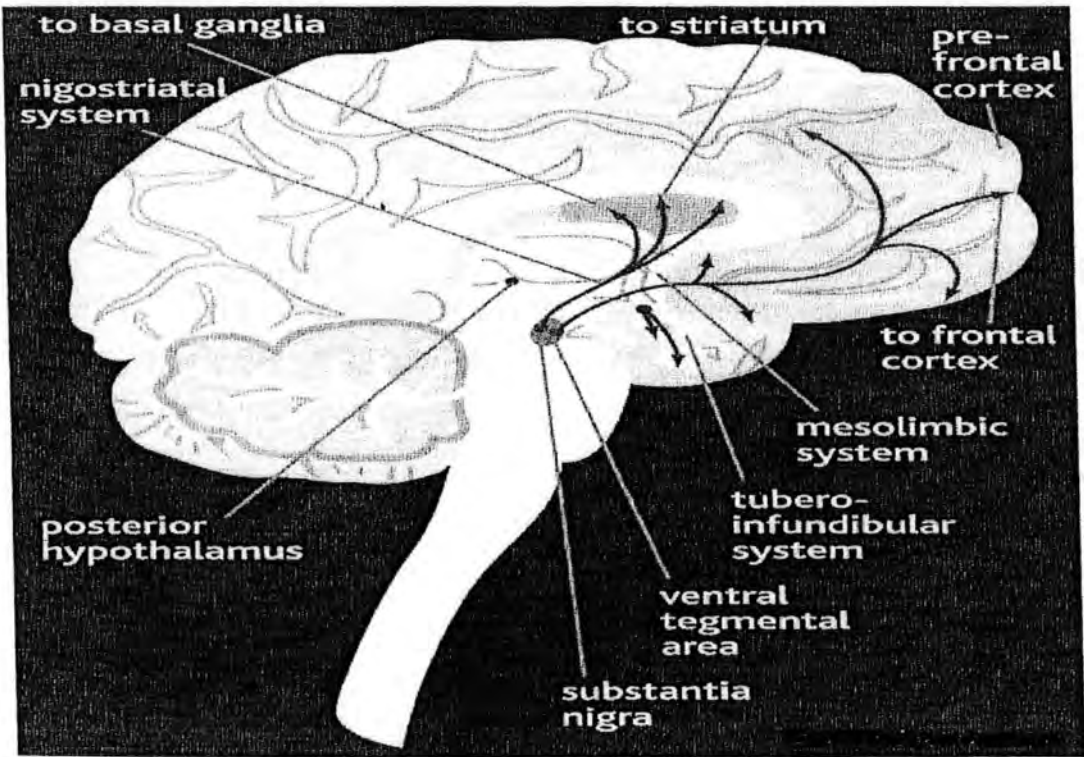
Dopamine is a neurotransmitter which acts in the brain and spinal cord. The effects of dopamine in the central nervous system (CNS) were initially considered to be mediated by 2 receptor subtypes, D1 and D2. The D2 receptors are localized both presynaptically and postsynaptically; the presynaptic receptors function as inhibitory autoreceptors (Andersen et al, 1990). D1 receptors are important in the prefrontal cortex subtending working memory, planning and sorting tasks (Abi Dargham, 1998). Developments in genetic cloning have assisted with the identification of a further 3 types of dopamine receptor subtypes; D3, D4 and D5, all of which are localized in the limbic system (Sokoleff et al, 1990; Sunahara et al, 1991; Van Tol et al, 1991). There are different membrane protein characteristics of D2/D3 and D1/D4/D5.

The dopaminergic systems in the brain arise from groups of cells in the midbrain and hypothalamus (van den Pol et al, 1996). Concentrations of dopamine producing cells which consist of a number of nuclear masses lying within the cerebral hemisphere are collectively known as the *basal ganglia*; the major components of which include the *caudate nucleus*, *putamen*, *nucleus acumbens*, *substantia nigra*, *sub thalamic nucleus* and *globus pallidus*. Groupings of the basal ganglia are as follows: *striatum* (caudate + putamen + nucleus acumbens), the *corpus striatum* (striatum + globus pallidus), and the *lentiform nucleus* (putamen and globus pallidus) (Crossman and Neary, 2002). Although large, the striatum is scarcely even visible to the naked eye at post mortem, with the appearance of its surrounding white matter.

Diagram of basal ganglia



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Dopaminergic pathways in the brain

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There are three pathways by which dopamine is transmitted; the *nigrostriatal pathway* extends from the substantia nigra to one of the basal ganglia called the caudate, these neurons contain 70% of brain dopamine and are involved with sensory stimulation and movement; the *mesolimbic* (*mesocortical* or *mesocorticolimbic*) pathway projects from the ventral tegmentum to the mesolimbic forebrain (anterior cingulate, amygdala, hippocampus) and is associated with cognitive, motivation, reward and emotional behaviour (Roth et al, 1987); the third *tubero-infundibular* pathway is concerned with the neuronal control of the hypothalamic-pituitary endocrine system (Kapur and Mann, 1992). The diagram above shows these three dopaminergic pathways.

The role of dopamine in depression

The role of dopamine in depression has been studied from various perspectives; a summary of the results from animal and human models will be presented. Studies using animal models of depression are correlated with dopamine dysfunction. Human studies involve depressed patients compared to healthy controls and include altered concentrations of the dopamine metabolite homovanillic acid (HVA) in cerebral spinal fluid, plasma or urine. There are abnormalities in the dopamine demonstrated by in vivo functional imaging studies, the dopamine transporter system and post-mortem studies. Further support is obtained from studies of Parkinson's disease which is associated with dopamine dysfunction as well as a higher incidence of depression (Carlton, 1997) not seen in other similarly debilitating illnesses. Finally, antidepressant therapies which have a direct effect on the dopaminergic system including medication and ECT have a therapeutic effect, which support the role of dopamine in depression.

Animal studies

Clinical symptoms of depression in humans including depressed mood and anhedonia make it difficult to establish the validity of animal models as a representation of human conditions (Willner et al, 1984). To help us link animal to human models, three approaches investigating the role of

dopamine in depression have been used: firstly, alterations in the dopamine system in animal models of depression are assessed; secondly, the role of dopamine in behaviours assumed to have relevance to human depression such as motivation and reward seeking are examined; finally the effects of drugs on the dopamine system in animal models of depression are evaluated (Willner, 1995; Porsolt, 2000; Lucki, 2001).

“Learned helplessness” is a commonly used animal model of depression wherein animals exposed to stressful, inescapable situations exhibit decreased spontaneous activity, decreased effort to escape and a variety of somatic changes. Treatment with antidepressants has been shown to reverse the occurrences of learned helplessness in these situations (Sherman et al, 1982). Dopamine depletion in the caudate nucleus and nucleus accumbens occurs in animals with “learned helplessness” (Anisman et al, 1979a; Anisman et al, 1979b). Furthermore, prior treatment with a dopamine agonist prevents the development of the learned helplessness state (Anisman et al, 1979a; Anisman et al, 1979b).

“Behavioural despair” or the “forced swim test” is another model in which rats are forced to swim in a confined space. After initial attempts to escape they assume an immobile posture. Antidepressants exert anti-immobility effects; dopamine agonists augment the anti-immobility effects and dopamine antagonists reverse it (Borsini and Meli, 1990). This has been found to be the most effective test for predicting the efficacy of new medications (Nestler et al, 2002). Healthy dopamine function in the striatum has been clearly shown to be central to learning new motor tasks progressively in primates.

Another approach is based on the assumption that depression involves a neurobiological alteration in the central reward seeking, motivation, and environmental responsivity mechanisms which leads to anhedonia, social isolation, and psychomotor retardation, all core symptoms of

depression (Wise, 1989; Willner, 1991). Studies have investigated the role of the mesolimbic dopaminergic system in the maintenance of the reward response. One method used by researchers involves the use of drug self administration paradigms. They have shown that self administration of drugs possesses reinforcing properties such as nicotine, cocaine and psychostimulants which are associated with an increase in firing of dopaminergic neurons in the mesolimbic pathway. There is considerable electrophysiological and biochemical data in animal studies whereby the serotonin receptor subtype 5HT-2C agonists decrease the 5HT-2C levels resulting in an enhanced mesolimbic dopaminergic function (DiMatteo et al, 2002). Recent animal studies carried out by Alex and colleagues (2005) support growing evidence which indicates the 5HT-2C receptors inhibit nigrostriatal dopaminergic transmission. Furthermore, chronic treatment with antidepressant drugs produces a variety of changes in dopaminergic neurotransmission including increased sensitization of D2 like receptors in the mesolimbic dopaminergic system (Willner et al, 2005), and receptors within the nucleus accumbens (Willner et al, 1997). Although these studies implicate the involvement of dopamine in specific behaviours, it is unclear what the exact role of dopamine in human depression is, and whether it is primary or secondary in causation (Willner, 1991; Wise, 1989; Dailly et al, 2004).

Human studies of depression

The most consistent finding in human studies is decreased turnover of dopamine in patients with depressive disorders. Lower levels of homovanillic acid (HVA), a major metabolite of dopamine has been found in the cerebral spinal fluid (CSF) of depressed patients. Most studies report this decrease in the CSF HVA of patients with depression (Lambert et al, 2000; Traskman-Bandz et al, 1984), which is more pronounced in a subgroup of patients with psychomotor retardation (Papeschi and McClure, 1971; van Praag and Korf, 1971; Randrup et al, 1975). However, two later studies have failed to replicate these findings or have found increased CSF HVA in depressed patients (Jimmerson, 1987; Vestergaard et al, 1978). Although there is considerable evidence that

CSF HVA may be lower in depression, again it is not clear whether this is a primary abnormality or whether it is secondary to psychomotor retardation (Kapur and Mann, 1992).

Post mortem studies

Biochemical human post mortem studies on depressed patients indicate an unspecified deficiency of neurotransmitters in several brain areas. Birkmayer and Riederer, (1975) reported decreased concentrations of striatal dopamine in depressed subjects which was correlated to a reported loss of drive shown in subjects before death.

More recently, post mortem studies use ligands to map dopamine receptors including D1, D2/D3 and the dopamine transport system which have yielded important results. Dopamine transporter enzymes have been consistently shown to be abnormal in Parkinson's disease, a condition with a very high incidence of depression. Klimek and colleagues (2002) compared the brains of depressed subjects to normal controls and found no differences in D1 receptor binding. However, depressed patients were noted to demonstrate higher D2/D3 binding in the basal, central, amygdaloid nuclei, additionally a reduced binding in the dopamine transport system was found in the basal and central amygdaloid nuclei compared to controls; providing further evidence that major depression may be associated with a deficiency of mesolimbic dopamine.

IBZM SPECT studies

I123-Iodobenzamide (IBZM) is a radioligand with a high affinity for dopamine D2 receptors (Kung et al, 1989; Kung et al, 1990; Brucke et al, 1991). There has been only a very small number of functional dopamine D2 neuroimaging studies attempted or published in depression, and none with psychotherapy

Positron Emission Computed Tomography (PET) study of bipolar patients

Suhara and colleagues (1992) used carbon labelled 11C-SCH23390 (a radio-labelled dopamine D1 drug) to measure dopamine D1 binding in a

PET study of 10 bipolar mood disorder patients, who were compared to 21 control subjects. Only three patients were depressed at the time of scanning (Hamilton depression scores were 34, 18 and 10), one patient was manic and the remaining 6 bipolar patients were euthymic. There were significantly lower binding of the ligand in the frontal cortex of the patients, regardless of their thymic state when compared to normal controls, and no significant differences in the binding potentials in the striatum were found between patients and controls. There were no differences in the binding potentials of patients with or without current symptoms. This study is seriously flawed for a number of reasons: The small sample size of 10 patients initially is further confounded by the fact that only 4/10 (40%) of the patients were clinically symptomatic. The 60% of the patients who were asymptomatic could have been considered a psychiatric control group. Furthermore, there was a significant heterogeneity in the remaining four patients; the depressed patients symptoms ranged from mild, moderate to severe and there was only one manic patient studied using PET. These data are wholly inadequate to provide any statistically significant or clinically meaningful data.

Reduction of D2/3 in right striatum after total sleep deprivation (TSD)

Ebert et al (1994) studied 10 patients and 5 controls, all of whom had past psychiatric histories. The patients all were male, and depressed, with a DSM III R (APA, 1987) diagnosis of melancholic type depression with bipolar II course. The patients were rated using the Hamilton Depression scale (HAM-D), in addition the Clinical Global Impression Scale (CGI) of the severity of depression was also completed at baseline. All patients underwent 2 185Mbq 123 I-(s)-2-Hydroxy-N-(11-Ethyl-2-pirrolidinylMethyl) Benzamide (1-123J IBZM) SPECT scans, before and after total sleep deprivation treatment (TSD), an old antidepressant treatment of proven efficacy, generally used in Europe now only for drug-free research to minimize pharmacodynamic confounding variables. The patients also continued to take 75mg twice daily of the antidepressant 'amitriptyline'. The authors found that after

sleep there were no difference between responders, non-responders and controls. However after total sleep deprivation the relative basal ganglia IBZM occupancy decreased in responders; this was significant on the right ($p < 0.02$) and with a trend towards significance on the left ($p < 0.06$).

The authors hypothesised that the positive total sleep deprivation response in the subgroup of patient responders is connected to an increase in the dopaminergic response. That is, the IBZM ligand is competing with endogenous dopamine for receptor occupancy; the lowered relative dopamine D2 occupancy in responders after total sleep deprivation may reflect a change in dopamine release with TSD responders compared to non-responders. An alternative explanation of these results is that there may be post synaptic changes such that TSD may reduce D2 receptor densities in responders owing to enhanced dopamine release. TSD may change the D2 receptor agonist binding from a low to a high affinity state in responders.

As all patients were medicated during this study, this may have increased the expected differences in the dopaminergic system between responders and non-responders. Furthermore, the fact that the controls had a past psychiatric history is also a confounding variable.

High D2/D3 density characteristics depressed in patients

A cross sectional analysis with IBZM in depression was conducted by D'haenen and Bosseyut (1994) in 21 DSM III R major depression cases (4 males, 17 females, aged 21-61, mean age 40.5), who were compared to 11 controls (3 males, 8 females, aged 30-56, mean age 41). The scans were done 90 minutes post injection, measuring striatocerebellar ratios. Depression scores were assessed using the Hamilton Depression Scale by the same rater within 5 days of the scan; although patients were moderately depressed (mean Hamilton score 21.7, SD 5.04), the range of the severity of depression was from 11 (mild) to 32 (severe). The drug washout period was from 7 to over 21 days. Both the left and the right basal ganglia/cerebellar IBZM uptake ratio was higher in patients than

controls (left 1.93 (0.30) vs. 1.75 (0.18); right 1.95 (0.26) vs. 1.73 (0.17) which was statistically significant ($p < 0.025$). The washout period did not affect the results. Retardation and Hamilton depression symptoms had no specific D2 correlates. Age had no D2 effect. The results suggest that patients either had more D2 receptors or a stronger affinity between receptor and ligand or both. Further, high receptor counts may reflect low dopamine turnover.

Decreased IBZM binding in treatment responders

Ebert and colleagues (1996) performed IBZM SPECT on 10 medicated and 10 unmedicated depressed patients and compared them to 10 controls. Ten patients who were initially unmedicated received a second IBZM SPECT scan following 3 weeks of antidepressant medication. Patients were severely depressed at baseline with mean Hamilton depression scores of 26 (SD 3.6). A regional activity index (RAI) (ratio of counts per voxel) of the basal ganglia was compared with all of the counts per voxel in 36 brain regions. There were no correlations in IBZM uptake with age. No differences were found in patients and controls in striatal IBZM uptake. Four patients with psychomotor retardation demonstrated statistically significant higher right basal ganglia IBZM uptake and showed a non significant increase in IBZM binding on the left side, when compared to non psychomotor-retarded depressed patients and normal controls. Of the ten patients who were scanned in sequence before and during antidepressant treatment, there were an equal number of responders and non responders (Hamilton 10.3 (SD 3) vs. 20.2 (SD 2.8)). IBZM uptake decreased in responders after antidepressant therapy and remained unchanged or increased in nonresponders ($p < 0.05$).

Progressive increase in D2/D3 with treatment response

Methodologically and in terms of clinical relevance to our study the project of Larisch et al (1997) is the most important study. Thirteen major depressed patients as per DSM IV (APA, 1994) who had not responded to tricyclic antidepressant treatment were scanned using

IBZM SPECT before and after treatment with SSRI therapy. All patients underwent a one week washout period before the first scan.

All subjects were given 2 x I-123 IBZM scans, before and after six weeks of antidepressant treatment with a serotonin specific reuptake inhibitor (SSRI) (30-50mg paroxetine or 60mg fluoxetine). The IBZM has an affinity for both the low and the high affinity states of the D2/D3 receptor. The data acquisitions after the SPECT scans were taken 90 minutes after injecting the radioligand. SPECT and MRI were co-registered with the Computerised Brain Atlas (CBA). Individual patients' striata were drawn on the individual SPECT slices; between patients there was high variability in terms of size and position of the striatum. The authors selected the cerebellum rather than the frontal cortex as a reference region because D2 and D3 are present in frontal cortex and the anterior cingulate gyrus. Responders were defined as showing a greater than 80% Hamilton depression score reduction and a CGI of "very much improved". This 80% improvement criterion is considered a stringent measure.

D2/D3 binding and depressive symptom changes were analysed with Spearman's rank order correlation. The mean Hamilton depression scores of all of the patients dropped from 28 (SD 5) at baseline to 11 (SD 10) after treatment, which was clinically significant ($p < 0.001$). The mean treatment duration was 40 (SD 9) days and ranged from 21-54 days of SSRI therapy between scans. The second scan was performed prematurely at week 3, 4 and 5 in three unresponsive patients. The control subjects and patients did not differ in age, gender or IBZM binding. Responders and non responders showed no differences in age, gender or severity of depression at the start of treatment. Four patients demonstrated an 80% reduction in their Hamilton depression scores, a further three patients demonstrated a partial response (60-80% drop in Hamilton depression scores) and 6 patients did not respond. The authors found a significant difference in IBZM binding between responders and nonresponders; IBZM binding increased in the SSRI responders in the

anterior cingulate gyrus and the striatum. Furthermore, there was a significant linear correlation between IBZM binding and clinical response as measured by the Hamilton depression scale in the left ($p<0.04$) and right ($p<0.05$) striatum

The same group reported an extension of this study in which 2 additional patients were recruited to the trial and were compared to 17 normal controls in order to establish if there were differences between the two groups in the baseline IBZM binding ratios (Klimke et al 1999).

IBZM striatal binding in the control group was significantly correlated to age ($p<0.01$); linear regression analysis revealed a decline of striatum/cerebellar ratio of 0.092/decade. In the depressed group the age dependant reduction of IBZM striatal binding was lower per decade (0.036/decade), but was not statistically significant. After age correction at baseline, responders had a lower IBZM binding compared to non-responders and controls ($p<0.05$). Furthermore, there was a significant correlation between change of IBZM binding values and the percent change of depressive symptomatology. The authors suggested that reduced dopamine densities in the striatum underlie depressive symptoms, which may indicate a good response to pharmacological modulation of the serotonergic system. This was further supported by correlations with the intra-individual change of striatal binding and improvements in depression as measured on the Hamilton depression scale.

Helpfully Klimke's group (1999) recorded that no patients had ever received neuroleptic medication, and their tricyclic prescriptions had tended to be over a long period (62-443 days of treatment). Although the authors identified that the patients had not responded to one previous trial of a tricyclic antidepressant, no further details were provided. Responders had lower baseline binding ratios than controls and non-responders. D2/D3 density did not reduce more in responders as per Ebert's findings. The authors suggested that these findings may be due

to reduced D2 receptor densities in the striatum and that this may underlie depressive symptoms.

This is a rigorous study involving a non-psychiatric control group (n=17) and a homogeneous group (n=15) of depressed patients who had failed at least one previous trial of tricyclic antidepressants. The patients studied during this trial were severely depressed (mean Hamilton Depression score 28.5). IBZM SPECT scans were conducted at baseline and after 6 weeks of treatment with an SSRI, although no differences were noted between patients and controls, increased IBZM binding was noted in patients who responded to SSRI treatment, and interestingly IBZM binding was found to correlate linearly with percentage improvements on the Hamilton Depression scale. The authors suggested that this may reflect an increase in density and/or affinity for the striatal dopamine D2 receptors. Changes in D2/3 densities in the striatum in responders have been reported (Ebert et al, 1994; Larisch et al, 1997; Klimke et al, 1999) and may reflect plasticity of receptors to increase or decrease in those who recover, and not to change or decrease in patients who remain resistant to treatment. Non-responders showed no change or a reduction in the IBZM binding in Klimke's work. Inter-study result variability due to camera type and region of interest method were discussed but the authors found the non-responder results unexpected and difficult to explain. Changes in the regional cerebral blood flow particularly in the striatum may have influenced the results.

A suggestion of high D2/D3 in depression

Shah et al (1997) studied 15 depressed patients 2 of whom were bipolar, 8 of whom were on antidepressants, 3 on benzodiazepines and 4 were drug free. They were compared to 15 healthy matched controls in a cross sectional study with a single scan using a whole slice of the brain as a reference region. It also included a neuropsychological battery of cognitive tests for memory, verbal fluency and motor function.

Depressed patients showed higher right striatal D2 density than controls. In both patients and controls, women had greater D2/D3 in the striatum. There were no significant differences between medicated and unmedicated patients, but there was a larger effect size in medicated patients for higher binding. There was no significant effect due to retardation as measured on the Hamilton depression score, or any measured depressive clinical subtype or severity group. These investigators had hoped to find neurotic/psychotic D2 correlates but did not. A strong negative correlation between D2/D3 density and suicidality was not explained by sex differences. The authors suggest it is possible that suicidal patients had experienced high dopamine release due to stress, then down regulated their receptors.

The small numbers of patients studied during this trial are further hampered by the homogeneity of the group; two patients were diagnosed with bipolar disorder and patients were studies with or without melancholic and/or psychotic features, which may seriously confound the results.

Dopamine Transporter System (DAT) in depression

Dopamine transporters (DAT) are monoamine transporters which are responsible for the homeostasis of dopamine pools at nerve endings (Iveston, 2006). Animal studies have shown that administration of antidepressants, irrespective of pharmacological class produce changes in the DAT binding affinity. This has led scientists to test the hypothesis that dopamine transporter function may play a crucial role in the pathophysiology of depression (Brunswick et al, 2003).

Functional imaging studies using PET and SPECT allow in vivo exploration of these transporters and have found higher binding of the radioligand to DAT in the basal ganglia in depressed patients compared to controls (Brunswick et al, 2003; Laassonen-Balk et al, 1999).

Dopamine Transporter System (DAT) in depression in Parkinson's

disease

Parkinson's disease is an idiopathic disorder characterized by rigidity, akinesia and tremor and is associated with degeneration of the nigrostriatal dopaminergic system, and loss of projections of the midbrain limbic and cortical projections (Cummings 1985). The role of dopamine in Parkinson's disease is clearly established. The incidence of depression in Parkinson's disease is more than ten times greater than that of healthy controls (40-50% vs. 3-4%), and as other similarly debilitating illnesses do not have an increased prevalence of depression, this cannot solely be attributed to the disabling effects of the illness. As depression often occurs before the motor symptoms of Parkinson's disease emerge (Mayeux, 1990), and there is no relationship between the severity of Parkinson's disease and depression (Cummings, 1985; Mayeux, 1990), a neurobiological contribution to the pathogenesis of depression in Parkinson's disease is likely (Carlton 1997). However, a direct relationship between dopamine and depression in Parkinson's disease has previously been harder to establish; depression in Parkinson's disease does not correlate with CSF HVA levels; antidepressants often improve mood without a change in the motor component of the disease, ECT however, improves both (Andersen et al, 1980; Cummings et al, 1985; Mayeux, 1990). This has led to a SPECT study of the dopamine transporters in Parkinson's disease.

A SPECT study imaging the dopamine transporter (DAT) with labelled beta-CIT (2beta-carbomethoxy-3-beta (4-iodophenyl)-tropane) was conducted on 76 patients with Parkinson's disease and compared with 46 age matched healthy volunteers. Specifically, the authors were interested in correlations between patients with symptoms of depression and anxiety and DAT availability. The presence of depression in Parkinson's disease was significantly associated with diminished left anterior putamen DAT availability reflecting lower dopamine turnover (Weintraub et al, 2005). Conversely, DAT density was found to be higher among Parkinson's disease patients compared to controls in both sides of the basal ganglia when imaged using 123I-labelled beta-CIT (2beta-carbomethoxy-3-beta

(4-iodophenyl-tropane) SPECT. The authors hypothesized that upregulation of the DAT in Parkinson's disease may be a primary alteration which leads to lower intrapsychic dopamine concentration and to lower neural transmission subtending depression in those Parkinson's disease patients who get it.

Thus it appears that although dopamine degeneration may be a link in the causal chain of depression, it may not solely be responsible for the mood alterations seen in Parkinson's disease.

Brain Reward System

Psychostimulants such as amphetamine cause euphoria in normal volunteers. Amphetamine promotes the release of noradrenaline and dopamine from nerve terminals and inhibits their reuptake. The behavioural effects of amphetamine have been shown to be mediated by the dopaminergic system (Randrup et al, 1975; Willner, 1983a).

Central dopaminergic neurotransmission has multiple actions at each level of the mesolimbic reward pathway. The role of dopamine in the reward process has long been believed to be associated with the ability to experience pleasure; dysfunction of the dopamine transmission in the reward circuit is associated with symptoms such as anhedonia, apathy and dysphoria, all common symptoms of depression (Bressen and Crippa, 2005). The state of the brain reward system can be assessed in major depression using dextroamphetamine, which provokes the release of dopamine within the mesolimbic system, and producing measurable behavioural changes, including rewarding effects of euphoria. Hypersensitive symptom responses have been found in depressed patients compared to controls which are positively correlated to the severity of the depression (Tremblay et al, 2002). Although outside the scope of Tremblay's study, patients who take amphetamine become more mentally ill as a rule in clinical experience. There is a large body of literature on psychotic deterioration with amphetamine with strong evidence for dendrite damage after dopamine release.

Following a single blind administration of dextroamphetamine to stimulate the brain reward system, subjects with major depression demonstrated a hypersensitive response to the reward system activating effects of dextroamphetamine compared to controls ($p=0.01$). Functional MRI showed altered brain activation in the ventrolateral prefrontal cortex, orbitofrontal cortex, the caudate and the putamen (Tremblay et al, 2005).

Parsey and colleagues in New York (2001) with the use of IBZM SPECT imaging, wished to assess the density of D2/D3 receptor availability in non-psychotic unmedicated unipolar patients during depression in relation to amphetamine induced dopamine release. 9 depressed subjects and 10 healthy matched controls were studied. There were no differences in the IBZM uptake ratios when comparing patients and controls. This study was seriously flawed by an absence of baseline symptom characterization and absence of analysis of any specific dopamine related symptoms e.g. a completely non agitated or psychomotor retarded group may putatively have shown no D2 pathology in any event. Amphetamine reduced D2/D3 similarly in both patients and controls. This suggested that stimulant induced dopamine release is not altered in depression. Whilst this could reflect a lack of baseline D2/D3 pathology in depression, it may be explained by the depressed state still remaining responsive to amphetamine, a very powerful drug which releases dopamine with clinical effects for anyone who takes it. This study would probably not have received ethical approval in Britain.

Growth hormone response to apomorphine stimulation test

The tuberoinfundibular dopaminergic system has neuroendocrine functions, stimulating the release of growth hormone (GH) and inhibiting the release of prolactin. Thus baseline levels of these hormones have been examined as potential markers of dopaminergic function in mood disorders, and their responses to dopamine agonists have been used to evaluate dopamine receptor responsiveness. The sensitivity of central

dopamine receptors can be assessed with growth hormone response to the dopamine agonist apomorphine. Depressed patients have demonstrated a reduced sensitivity of central dopamine receptors compared to control subjects. Affective flattening has been associated with both dopamine receptor sensitivity and psychomotor slowing (Healy and McKeon, 2000).

Studies with growth hormone have been inconclusive. Baseline levels of GH have been reported to be increased (Mendlewicz et al, 1985), normal, (Mitchell et al, 1991; Lechin et al, 1985) or decreased (Price et al, 1991) in depression. Additionally, blunted GH responses to apomorphine have reported a difference between major and minor depressives (Pitchot et al, 1992; Ansseau et al, 1987).

Abnormal prolactin levels have frequently been reported in depressed patients, but there is no consistency on the direction of change; low, normal and high levels have been reported in different studies (O'Keane and Dinan, 1991; Sher et al, 2003; Joyce et al, 1985). Studies have reported a decrease in prolactin levels in patients with seasonal affective disorder (SAD) which was present in winter when patients were depressed and summer during euthymia (Levitan et al, 1998; Depue et al, 1989; 1990).

Antidepressant effects of dopaminergic agents

Antidepressants whose primary mode of action is on the dopaminergic system provides further evidence for the role of dopamine in depression. The dopamine agonist bromocriptine which has been used in the treatment of Parkinson's disease has been shown to have antidepressant efficacy equivalent to that of tricyclic antidepressants (Theohar et al, 1981; Wells and Marken, 1989). Another dopamine agonist, pramipexole has been shown to have antidepressant qualities (Mouret et al, 1987). The antipsychotic medications olanzapine, sulpiride and amisulpride enhance dopamine function (Del Zombo et al, 1990; Standish-Barry et al, 1983; Dailly et al, 2004) and all have been shown to

have antidepressant properties. Furthermore, amisulpride the D2/D3 antagonist is licensed in France as an antidepressant medication in dysthymia. The D2 antagonist flupenthixol is licensed in the UK for depression.

Nomifensine a dopamine reuptake inhibitor, which in clinical trials has proven antidepressant efficacy equivalent to TCA'S (Forest et al, 1977; Grof et al, 1977; McClelland et al, 1977; Kinney et al, 1985). It has been shown to increase dopamine release in the striatum of rat brains (Butcher et al, 1991). It has a specific effect on patients with psychomotor retardation, and greater efficacy in patients with lower CSF HVA levels. This antidepressant is no longer marketed as it causes haemolytic anaemia, an unrelated effect of its dopaminergic actions.

Bupropion, a dopamine reuptake inhibitor has been studied extensively in clinical trials and found to be superior to placebo and as effective as standard antidepressants (Settle 1989; Zung, 1983). Rat studies have shown dopamine concentrations are found to rise in the striatum and the nucleus accumbens and no alterations to the noradrenaline or serotonin levels (Nomikos, 1989). Alpha-amineptine, an antidepressant recently introduced in Europe selectively inhibits the reuptake of dopamine (Ceci et al, 1986; Bonnet et al, 1980). Large scale double blind studies have demonstrated the antidepressant efficacy of alpha-amineptine (Kemali, 1989; Mendis et al, 1989) early results suggest a preferential response in patients with psychomotor-retarded depression (Rampello et al, 1991).

The antidepressant mirtazapine has been shown to increase extracellular noradrenaline and dopamine in the medial prefrontal cortex. This is thought to occur when the mirtazapine inhibits the alpha (2)-adrenoreceptors which produces a co-release of noradrenalin and dopamine (Devoto et al, 2004).

A research group in Wales (Willner et al, 2005) administered a low dose of sulpiride, a dopamine D2 antagonist to 8 depressed patients who had

responded to treatment with an SSRI (citalopram, fluoxetine or paroxetine) compared to 10 age matched normal controls (Willner et al, 2005). Mood and psychomotor effects were measured. The control group reported an increase in their general feelings of well-being and the depressed group demonstrated a reinstatement of their depressed state. This data is consistent with the hypothesis that sensitization of the D2 receptors may be central to the action of SSRI's.

Electroconvulsive therapy (ECT)

ECT is a powerful tool with which to investigate the biochemical effects that accompany antidepressant response. Animal models of depression show that chronic treatment with ECT increases dopaminergic activity in the nigrostriatal and mesolimbic pathways (Nomikos et al, 1991; Gulati et al, 1987; Willner, 1983).

The effect of dopaminergic activity was evaluated following treatment with ECT using prolactin and growth hormone responses. Of the studies of growth hormone release in response to an apomorphine challenge, only one, Costain et al, (1982) out of three found evidence of enhanced dopaminergic function after ECT (Balldin et al, 1982; Christie et al, 1982; Costain et al, 1982). One study (Zis et al, 1992) of prolactin release found evidence to suggest increased dopaminergic transmission after a clinically successful course of ECT whereas two did not (Balldin et al, 1982; Christie et al, 1982).

Summary

Animal and human studies have suggested there are abnormalities in dopamine in depression including: depleted levels of striatal dopamine as found in post mortem studies, functional neuroimaging studies, reductions in the dopamine transporter system and reduced levels of the dopamine metabolite, homovanillic acid (HVA). Additionally, the mechanism of action of antidepressant treatments including both pharmacotherapy and Electroconvulsive therapy has been found to enhance dopaminergic function. Pharmacological probes such as dextroamphetamine and

apomorphine which stimulate the release of dopamine have demonstrated increased sensitivity of dopamine receptors which have been correlated to a depressed state, in particular psychomotor slowing. Furthermore, antidepressant medication which acts specifically on the serotonergic system appears to have an indirect effect on the dopaminergic system.

Although not all of the evidence is consistent, there is an indication that abnormalities of dopamine in depression exist. There is a great need for further exploratory research in studies of improving methodological rigor to examine the role of dopamine in depression; this should include various types of depression, different treatment modalities and include various levels of response to treatment. Correlations of dopamine function to particular depressive symptoms should also be explored. Functional neuroimaging techniques are one mechanism which will allow us to the opportunity still to try to answer some of these questions.

Chapter Five - The effects of Interpersonal Psychotherapy augmented to mirtazapine in treatment resistant depressed participants

Design

The author wished to assess the effect of Interpersonal Psychotherapy augmented to the antidepressant mirtazapine in the treatment of resistant depression. This was a parallel group study where participants were randomly assigned to mirtazapine alone (30-45mg daily) or mirtazapine (30-45mg daily) plus 16 sessions of weekly Interpersonal Psychotherapy. The participants were then followed up naturalistically for one year; during this time those participants who had received weekly IPT continued to receive IPT administered as a monthly maintenance treatment. All participants could continue their antidepressant medication during this time.

Participants used self rating scales to measure their depression (Beck Depression Inventory, Beck 1961) and social functioning (Social Adaptation Scale, Weissman, 1976), and clinician rated measurements of depression (Hamilton Depression Scale, Hamilton, 1960) and anxiety (Hamilton Anxiety Scale, Hamilton, 1969) were administered by a blind rater at baseline, 6 weeks, 16 weeks, 6 months and after one year. The Annett scale (Annett, 1970) of handedness was also administered at baseline in order to establish if patients were left or right handed.

Method

Twenty three depressed participants who had not responded to at least six weeks of an antidepressant medication at an adequate dose were randomised using the sealed envelope technique to receive either mirtazapine alone (30-45mg daily) or combined with 16 weekly sessions of Interpersonal Psychotherapy (IPT). Three participants who had originally consented to the trial withdrew their consent following randomisation before treatment had started (2 participants were allocated to the IPT and mirtazapine group and one was allocated to the mirtazapine only group). As this study included functional brain scans of the dopamine D2 receptor using IBZM SPECT (and previous IBZM dopamine D2 receptor SPECT studies have found increased dopamine receptor binding in woman compared to men, (Shah et al 1997)); the author

controlled for this confounding variable by randomising an equal number of men and women into both treatment groups.

At baseline, comorbid conditions, demographic information and details of the depressive episodes were taken for each participant, which included the number of previous depressive episodes, the total number of months depressed during lifetime and the previous number of failed antidepressant treatments. This allowed an assessment of the level of treatment resistance for each particular participant. Information regarding the participants' depression history was retrospectively obtained from the medical notes and through verification with the participant. At times, however, there was limited clinical information in the medical notes and participants could not always remember details of timing, duration or treatments for depression. Where this was the case, the author has reported only the known facts (i.e. the period of time the participant had definitely been suffering from a depressive episode). Therefore, for this study, restraints of retrospective data collection led to an underestimation of the number of depressive episodes suffered and subsequent treatment received for each participant. Details of the participants' diagnosis and depression are listed in the table below. The shaded area of each table throughout this thesis represents the combined IPT and mirtazapine group, the clear area denotes the mirtazapine only group.

Depression

Details of the participants' depression, past and current episodes are presented below.

Table C5-1 shows the participant characteristics of depression

Participant ID number	Sex	Previous major depressive episodes	Total months depressed	Duration of current episode	Previous failed / poor treatments
001	F	3	40	4	6
005	F	3	>132	12	4
011	F	2	38	12	2
012	F	2	>24	3	1
021	F	0	48	36	2
004	M	3	18	5.3	3
006	M	>2	>300	21	1
015	M	3	24	6	1
016	M	2	>36	>12	3
023	M	0	>18	>18	3
003	F	1	>42	12	2
010	F	0	36	36	1
017	F	0	30	30	2
019	F	3	60	24	3
020	F	>2	84	12	5
008	M	2	>18	>12	1
007	M	5	>60	2.5	3
018	M	>2	12	12	2
022	M	0	42	42	2
024	M	0	30	30	2

** Note: Where > sign is shown the participant reported a greater number of depressive episodes, or months depressed, however specific dates could not be ascertained from the medical records.*

There were three participants who withdrew their consent post randomisation but before starting treatment in the study, the details of which are listed below.

ID number 009 –“Personal reasons”.

ID number 013 –“Personal reasons”.

ID number 014 – No reason given.

Number of previous depressive episodes

The number of previous major depressive episodes in the total group of 20 participants in the study ranged from 0-5 (mean=1.75; SD=1.4). The number of previous major depressive episodes in the combined IPT and mirtazapine group ranged from 0-3, with a mean number of 2 depressive episodes (SD=1.15). Two of the participants who were randomised to the combined treatment group had no previous episodes of depression and

were experiencing their first depressive episode. The range of previous episodes of major depression in the mirtazapine only group was 0-5 with the mean number of 1.5 (SD=1.65). Four participants of the mirtazapine group had not had a previous major depressive episode and were experiencing their first episode at trial entry. Small to moderate effect sizes (0.35, CI 0.14-0.84) were detected in relation to the group differences regarding the number of previous major depressive episodes.

Duration of the current (index) depressive episode

The author then examined the duration of the current depressive episode for which the participant sought help. The total group ranged from 2.5 to 42 months (mean=17.09; SD=12.05). The combined group had a range of 3-36 months (mean duration=12.93; SD=10.06). The mirtazapine only group had reported the duration of current depressive episodes for 2.5 to 42 months with a mean score of 21.05; SD= 12.05. The difference between the two treatment groups was demonstrated with medium to large effect sizes (0.73, CI 0.24-1.22)

The total number of months depressed

The total number of months depressed during the participant's lifetime ranged from 12 to more than 300 months (mean=54.6; SD=63.9) for the whole study sample. The medication only group had been depressed for 12 to 84 months (mean=41.4; SD=21.62). The combined IPT and mirtazapine group had experienced depressive symptoms over a longer period of time, this ranged from 18 to >300 months (mean=67.8; SD=88.13). The difference between the two groups was demonstrated with moderate effect sizes (0.44; CI 0.08-0.9).

There were no significant differences between the two groups at baseline regarding duration of total or current episode of depression, and the total number of previous depressive episodes, although the small sample sizes limit these findings.

Number of different antidepressant treatments

The number of previous antidepressant medications including mood stabilisers was retrospectively gathered from the medical notes and are listed in the table below.

Table C5-2 shows the participant's antidepressant treatment prior to study entry [n.b. this table occupies pages164-5]

Participants	Medication	Start date	End date	Response
F01	Seroxat ?dose	?03.94	?03.95	Poor
	Fluoxetine 20mg	?03.95	?04.95	Poor
	Fluoxetine 40mg	?4.95	12.07.95	Poor
	Nefazodone 200mg	12.0795	31.07.95	Poor
	Seroxat 20mg	31.07.95	21.09.95	Poor
	Seroxat 30mg	21.09.95	24.07.96	Poor
	Citalopram 20mg	24.07.96	09.08.96	Poor
	Citalopram 40mg	09.08.96	12.08.98	Fair
	Venlafaxine 75mg	12.08.98	?09.98	Poor
	Citalopram 20mg	22.12.99	28.01.99	Poor
	Mirtazapine 15mg	28.01.99	29.01.99	Not known
	Citalopram 40mg	17.03.00	29.04.00	Poor
F05	Imipramine ? dose	?	?	Poor
	Dothiepin ? dose	?	?94	Poor
	Fluoxetine 20mg	?	?07.94	Poor
	Seroxat 20mg	?07.94	?10.95	Fair
	Venlafaxine 37.5mg	?10.95	?03.96	Poor
	Seroxat ? dose	?2.97	?06.99	Poor
	Venlafaxine ? dose	?06.99	?12.99	Poor
F11	Citalopram 60mg	?12.99	?04.00	Poor
	Dothiepin ? dose	?10.98	?08.99	Poor
	Fluoxetine 20mg	?10.99	?09.00	Poor
F12	Venlafaxine 75mg	?09.00	?12.00	Poor
	Fluoxetine 40mg	?04.00	?01.01	Poor
F21	Unknown antidepressant x 2	unknown	unknown	Poor
F03	Fluoxetine 20mg	?11.00	31.01.01	Poor
	Venlafaxine 75mg	31.01.001	?05.01	Poor
M04	Citalopram 20mg	26.11.97	4.01.98	Poor
	Citalopram 40mg	04.01.98	15.09.98	Fair
	Mirtazapine 30mg	15.09.98	17.09.98	Not known
	Citalopram 60mg	15.12.99	09.02.99	Good
	Venlafaxine 225mg	09.02.99	24.03.99	Poor
	Mirtazapine 30mg	24.03.99	26.03.99	Not known
	Venlafaxine 225mg	25.06.99	02.04.00	Poor
M06	Sertraline 50mg	?02.98	?11.99	Poor
	Dothiepin 75mg	?11.99	?12.99	Poor
	Dothiepin 150mg	?12.99	?02.99	Fair
	Venlafaxine 150mg	?02.99	?03.00	Fair
M15	Paroxetine 50mg	?03.95	?09.95	Poor
	Lofepamine 210mg	?09.95	?02.97	Fair
M16	Amitriptyline 100mg	?02.99	?05.99	Poor
	Citalopram 20-60mg	?02.00	?06.00	Poor
	Citalopram 30mg	?09.00	?02.01	Poor
M23	Seroxat 20mg	15.09.99	?11.99	Poor
	Sertraline 150mg	07.04.00	?05.01	Fair
	Sertraline 100mg	11.02.00	07.04.00	Poor
	Sertraline 50mg	18.01.00	11.02.00	Poor
	Venlafaxine 75mg	15.12.99	18.01.00	Poor
F03	Venlafaxine 75mg	?12.98	?06.99	Poor
	Venlafaxine 150mg	?06.99	?02.00	Poor
F10	Seroxat 30mg	?05.98	?12.00	Poor
F17	Citalopram ?dose	?2.98	?98-3 months	No response
	Paroxetine ?dose	?2.98	?98-3 months	No response
	Dothiepin 75mg	?98	?98 18months	No response

F19 *	Clomipramine 100mg	?.01.97	?.07.97	Poor
	Clomipramine 150mg	?.07.97	?.10.97	Poor
	Citalopram 20mg	?.10.97	?.12.97	Poor
	Citalopram 40mg	?.12.97	?.03.98	Poor
	Paroxetine 40mg	?.03.98	?.11.00	Fair
	Venlafaxine 75mg	?.01.01	?.02.01	Poor
	Reboxetine 8mg	?.02.01	?.04.01	Fair
F20	Dothiepin ?dose	Unknown	.07.95	Unknown
	Trazodone 150mg	.07.95	.07.97	Poor
	Fluoxetine 20mg	.01.97	.03.97	Poor
	Dothiepin 150mg	.04.97	.05.97	Good
	Venlafaxine 75mg	.06.97	.07.97	Fair
	Venlafaxine 150mg	.06.97	.07.97	Fair
	Sertraline 50mg	.07.97	.05.98	Fair
	Sertraline 150mg	.02.99	.05.99	Poor
	Seroxat 20mg	.05.99	.11.99	Poor
	Venlafaxine 150mg	.11.99	.03.00	Poor
	Venlafaxine 225mg	.03.00	.04.01	Poor
M08	Dothiepin ? dose	.04.91	.05.91	Poor
	Paroxetine? dose	26.10.99	17.01.00	Poor
	Venlafaxine ?dose	18.01.00	14.02.00	Poor
	Citalopram ?dose	15.02.00	05.06.00	Poor
	Trazodone ? dose	06.06.00	04.07.00	Poor
M07	Fluoxetine 20mg	.06.95	.06.95	No response
	Fluoxetine 40mg	.06.95	.07.95	No response
	Clomipramine 150mg	.07.95	.06.96	Good
	Clomipramine 200mg	.02.96	.06.96	Good
	Lithium 400mg	.03.96	.03.96	Good
	Dutonin 200mg	.02.96	.04.96	Side effects
	Lithium 800mg	.06.96	.10.96	Poor
	Lithium 600mg	.10.96	.12.96	Fair
	Lithium 1000mg	.07.97	.02.99	Poor
	Venlafaxine 75mg	.02.99	.03.99	Side effects
	Mirtazapine 30mg	.03.99	.05.99	Non compliant
	Mirtazapine 45mg	.05.99	.06.99	Non compliant
	Lithium 1000mg	.05.99	.08.99	No response
	Lithium 800mg	.08.99	.11.99	Fair
	Citalopram 20mg	.06.99	.08.99	Fair
	Citalopram 60mg	.08.99	.10.99	Fair
	Epilim chrono 1000mg	.11.99	.03.00	Fair
	Reboxetine 8mg	.11.99	.03.00	Fair
	Fluoxetine 40mg	.11.99	.03.00	Fair
M18	Lofepramine 140mg	.05.00	.10.00	Fair
	Fluoxetine 20mg	.12.00	.02.01	Poor
	Venlafaxine 75mg	.02.01	.04.01	Poor
M22	Sertraline 50mg	05.06.00	27.06.00	Poor
	Reboxetine 8mg	27.06.00	29.09.00	Poor
	Venlafaxine 75mg	29.09.00	15.05.01	Poor
M24	Fluoxetine 20mg	?.12.00	?.06.01	Poor
	Venlafaxine 75 mg	?.02.00	?.12.00	Poor

* Participant ID number F19 comment recorded in notes pre 1997 "numerous antidepressants" however no specific medication was documented.

All of the known antidepressant treatments were recorded in the table above. In order to establish the number of previous *failed* antidepressant treatments the author excluded some of this data which identified responses to treatment as “good”, “fair” or “unknown”. Furthermore, participants who were non-compliant to a particular trial of medication, or had experienced side effects were also excluded. Although all data from the medical records were included in the above table, not all the data represented a *failed* antidepressant trial. All of the data excluded from the analysis, which could not be confidently identified as a failed trial were recorded on the above table in italics.

Antidepressant medication which was explicitly prescribed at a therapeutic dose for at least 6 weeks was included as a single treatment, increases in the dose of antidepressant medication within the first six weeks was recorded as a single treatment. Medication which was increased after 6 weeks, due to poor response was recorded as a separate treatment. This was because the increased dose was assumed to be a change in the management of non or poor responding depression. There were only four participants for which this was the case, one in the IPT and mirtazapine group (F01) and the remaining three in the mirtazapine only group (F03, F19 and F20). Lithium which was provided to augment the effects of the antidepressant was also included in the data as an antidepressant treatment.

Taking all of the above into account the range of failed antidepressant treatment for the total study sample ranged from 1-6 (mean 2.45; SD 1.35). The range of failed antidepressant treatment for the combined group was 1-6 (mean 2.6; SD 1.57). The range of failed antidepressant treatments in the mirtazapine only group was 1-5 with a similar mean score of 2.3 (SD 1.15).

As this data was gathered retrospectively, and factors which could not be confirmed were excluded, this represents an underestimation of the likely number of previous treatments for the sample of participants used in this study.

Assessment of treatment resistant depression

Treatment resistant depression (TRD) was first conceptualised over 2 decades ago by Fawcett and Kravitz, (1985) who took into account the length of the depressive episode, the number of antidepressant treatments and the use of augmentation strategies to help improve the depression. Although there have been as many as 15 alternate definitions of TRD proposed (Sourey et al, 1999),

none have been widely accepted and used in clinical or research settings (Kleine, 2004). For the purposes of this study the author accepted a minimum definition of treatment resistance; a lack of a clinical response to an antidepressant at an adequate dose and duration.

Clearly, participants recruited to this study demonstrate a spectrum of non response or poor response to treatment. In order to identify these participants and then to establish increasing levels of non-response or resistance to treatment, the author identified factors which may help with this process. The number of previous failed antidepressant treatments, the duration of the current episode as well as the chronicity of depressive symptoms in a lifetime were considered appropriate clinical markers of non-response and treatment resistance. This data is recorded in the table below.

Table C5-3 shows the participant's severity of treatment resistant depression

Participant ID	A Total no. of failed antidepressant treatments ≥3	B Duration of current episode ≥12	C Chronicity of depression ≥30	A B C	A B	A C
F01	6	-	40			X
F05	3	12	>132	X	X	X
F11	-	12	38			
F21	-	36	48			
M04	3	-	-			
M06	-	21	>300			
M16	3	12	>36	X	X	X
M23	3	18	-		X	
F03	-	12	>42			
F10	-	36	36			
F17	-	30	30			
F19	3	24	60	X	X	X
F20	5	12	84	X	X	X
M08	-	>12	>18			
M07	3	-	>60			X
M18	-	12	-			
M22	-	42	42			
M24	-	30	30			

The sample of participants recruited did demonstrate a spectrum of treatment resistance. Only 2 participants did not score highly on any of the above items (chronicity, duration or severity of the depression) and their level of TRD status could be considered as mild at that point in time. Both of these patients were randomised to the IPT and mirtazapine group (Pt ID: F12 and M15).

There were 5 participants who had only had one clear previous failed antidepressant treatment before the trial, three were in the IPT and mirtazapine group (F12, M06, M15) and two were in the mirtazapine only group (F10, M08). Four participants, two in the IPT and mirtazapine group (F05, M16) and two in the mirtazapine only group (F19, F20) scored highly in all three areas of chronicity of depression, long duration of current episode and more than two failed antidepressant treatments.

Patients diagnosis and comorbidity

The author conducted an assessment using the Diagnostic and Statistical Manual for Mental Disorders IV Structured Clinical Interview (DSM IV SCI) at baseline which formerly assessed psychiatric diagnosis at the start of the study. The participants' diagnosis including comorbid anxiety disorders are listed in the table below.

Key:

MDE	Major depressive episode
MDER	Major depressive episode – recurrent
DD	Dysthymic disorder (chronic longer term depression)
PA	Panic disorder <i>with</i> agoraphobia
P	Panic disorder <i>without</i> agoraphobia
GAD	Generalised anxiety disorder

Table C5-4 shows the participant's diagnosis including comorbid anxiety disorders

Participants	MDE	MDER	DD	PA	P	GAD
F01		X	X			
F05		X	X	X		
F11		X				
F12		X	X		X	
F21	X		X			X
M04		X	X			
M06		X	X		X	
M15		X				
M16		X	X	X		
M23	X		X			
F03		X	X			X
F10	X		X			
F17	X			X		
F19		X			X	
F20		X	X			X
M08		X			X	
M07		X				
M18		X				
M22	X		X			
M24	X					

There was twice the number of participants diagnosed with double depression, that is, dysthymia superimposed on major depressive disorder in the IPT and mirtazapine group. There was an equal distribution of anxiety disorders (panic disorder with or without agoraphobia and generalised anxiety disorder) throughout both treatment groups.

Table C5-5 demonstrates a summary of the types of diagnosis of participant's in each group

Diagnoses	IPT and mirtazapine	mirtazapine
Single diagnosis of depression	11, 15	07, 18, 24
Double depression – major depressive disorder and dysthymia	1, 4, 23	10, 22
Double depression and panic	05, 06, 12, 16	
Double depression and generalised anxiety disorder	21	03, 20
Major depression and panic		08, 17, 19

Table C5-6 shows the number of additional DSM IV diagnoses in each treatment group

Number of diagnosis	Combined group	Mirtazapine only
1 diagnosis	2	3
2 diagnoses	3	5
3 diagnoses	5	2

The author documented the number of additional psychiatric diagnoses for each participant. The tables (C5-5 and C5-6) below demonstrates that there were a greater number of participants in the combined IPT and mirtazapine group (n=5, n=2) who had major depression plus 2 additional comorbid diagnoses.

Demographic data

Demographic data was collected by the author at baseline and is detailed below.

Handedness

All of the subjects apart from one female in the psychotherapy group (F015) were right handed.

Age

The age range of the total patient group studied was 28-52 (mean= 39.5, SD=7.24). The age range of the combined group was 32-52 years (mean=40.7; SD=6.43) and the range of the mirtazapine only group was 28-50 (mean=38.3; SD=8.12).

Gender

There were an equal number of men and women randomly assigned to both treatment groups.

Table C5-7 shows the educational background of participant's in each group

Schooling	Combined group	Mirtazapine group
Left school no exams	9	5
Year 11	0	1
Sixth form	1	2
2 year college	0	0
4 year college	0	2
Graduate/ professional school	0	0

Most of the combined IPT and mirtazapine group (n=9) and half of the mirtazapine only group had left school without any exams. Only one participant in the IPT and mirtazapine group had been educated to A' level. A greater proportion of the mirtazapine only group were educated to either A level (n=2) or degree level (n=2).

Table C5-8 shows the occupation of participant's in each group

	Combined group	Mirtazapine only
Unemployed	6	4
Unskilled work	1	1
Semi-skilled work	0	1
Skilled work	0	2
Professional work	0	1
Off sick	2	1
Retired early	1	0

Nine of the participants in the combined IPT and mirtazapine group were not working, the only participant who did work was undertaking unskilled work, whereas five of the participants in the mirtazapine only group were in employment (3/5 were undertaking skilled or professional employment, one was carrying out skilled work and only one of the participants were carrying out unskilled work). Four participants in the mirtazapine only group were unemployed and one was on sick leave from work.

Table C5-9 shows the social contacts of participant's in each group

	Combined group	Mirtazapine only
No social contacts	1	1
Minimal social contacts with relatives	7	5
Small number of friends	2	4

There was a relatively even spread of the reported use and availability of social contacts in both treatment groups.

Table C5-10 shows the marital status of participant's in each group

	Combined group	Mirtazapine only
Married	5	6
Widowed	0	0
Divorced or annulled	4	1
Never married	1	3

There were similar numbers of married participants in the two treatment groups and a higher number of divorcees in the combined IPT and mirtazapine group

Table C5-11 shows the alcohol and drug use of participant's in each group

	Combined group	Mirtazapine only
No alcohol	3	5
No drugs	10	9
Occasional < 5 units per week	0	3
Regular >10 units/week	4	1
>20 units/week	2	1
>30 units/week	1	0
Occasional cannabis use	0	1

The combined IPT and mirtazapine group demonstrated a higher general alcohol intake per week.

Interventions

Sample selection

Participants were recruited from psychiatrists and General Practitioners in Sunderland from October 2000 to June 2001. All participants were white Caucasian. The severity of depression was measured at baseline using the Hamilton Depression Rating Scale (Hamilton, 1960), and a minimum score of 18 was necessary to enter the study. In order to obtain a homogeneous sample and minimise confounding variables exclusions to the study included drug and alcohol abuse, Parkinson's disease, or previous head injuries.

Interpersonal Psychotherapy

The Interpersonal Psychotherapy was delivered as per manual (Klerman et al 1984) by two trained IPT therapists. During the acute phase of treatment participants were offered 16 weekly sessions of IPT. The frequency of the IPT sessions was reduced to monthly between week 16 and week 52. Weekly meetings for supervision took place between the therapists to minimise drift. Permission to tape each psychotherapy session was requested from each participant; the psychotherapy sessions were then rated using the National Institute Mental Health (NIMH) Adherence Rating Scale at the end of the trial.

IPT therapists

There were 2 Interpersonal Psychotherapists for this study, one male (PC) and one female (ER). Both therapists were experienced psychiatric nurses and IPT

therapists and had received training in IPT to research level. The author of the study (ER) had received her initial IPT training from Professor JC Markowitz, Director of Psychotherapy Research, Cornell University, New York. He himself had been trained, and supervised by Gerald Klerman, the originator of Interpersonal Psychotherapy. Professor Markowitz also conducted research using IPT with Gerald Klerman.

As the author was a research therapist for a previous IPT depression study (Martin et al 2001) she had already obtained the necessary training, supervision and experience for research validation for an Interpersonal Psychotherapy trial. Supervision received by the author, prior to this first trial, had been provided by Kathleen Clougherty M.S.W., a psychiatric social worker from New York. Ms Clougherty is a highly experienced IPT therapist, trained by Klerman, and has published research and provided IPT as an IPT research therapist involving depressed HIV positive patients (Markowitz et al, 1995). Research validation requires that the therapist achieves three cases of successfully delivered IPT according to the model. During this validation every IPT session was audiotaped and sent to New York where the supervising therapist would listen to the tapes and provide telephone supervision between each therapy session. A small number of sessions were also supervised face to face. The author achieved the necessary level for the provision of IPT in a research environment and was found to adhere to the model.

Following an introductory course from Professor Markowitz the male therapist (PC) had each session of three cases supervised by (ER) before he started providing Interpersonal Psychotherapy for this study. Both therapists at the start of the trial had achieved adherence to the model of Interpersonal Psychotherapy (Klerman 1984).

IPT therapy raters

Two trained IPT therapists were used in this study to rate the psychotherapy sessions. The author, (ER) rated all of the sessions which were delivered by IPT therapist (PC). A second rater, a Consultant Psychiatrist (SDM) was also a trained IPT therapist who received his initial training from Prof JC Markowitz, and had seen a number of IPT cases. In order to establish rater agreement both of the raters listened to

an IPT case together (not any of the participants used for this trial) and rated the IPT session using the NIMH adherence monitoring rating scale.

Mirtazapine

Mirtazapine was prescribed at a starting dose of 30mg each day, and if necessary could be increased to a maximum of 45mg daily. Medication was prescribed by one of two research psychiatrists who were working on this trial; a research registrar (ST) or a Consultant Psychiatrist (SDM). Antidepressant trial medication was prescribed at the start of treatment, week 3 and week 6. At each medication review the prescribing psychiatrist was instructed to review depressive symptoms, assess for any adverse events and issue a prescription and to avoid any psychotherapeutic interventions. This review would take no longer than 20 minutes. After 16 weeks the participants were provided a prescription for their antidepressant which could be obtained from an external pharmacy. After 16 weeks it was the responsibility of the participant to obtain further medication from their GP or treating psychiatrist.

A research pharmacist (JH) was responsible for the dispensing and return of the trial medication, she would make a note of any medication returns in order to monitor compliance. Adverse events were noted at each visit.

Clinical ratings

Measurements of depression, anxiety and social functioning of each participant were taken at baseline and repeated after six weeks of active treatment; this would provide an indication of early responders to treatment, additionally it would provide the data to assess any clinical correlates with the dopamine D2 receptor brain imaging scans which were performed at week 0 and again at week 6. Clinical measurements were repeated at week 16, the end of the acute phase of IPT and then at 6 months and 12 month follow up in order to establish longer term efficacy of the two treatment conditions. The rating scales used for this project were the clinician rated Hamilton Depression Scale (1960) and

Hamilton Anxiety Scale (1969) which were administered by a blinded rater. Following the clinical ratings the rater supplied the Beck Depression Inventory (Beck, 1961) and the Social Adaptation Scale (Weissman and Bothwell, 1976) which are participant rating forms for depression and social functioning. The ratings occurred five times over the period of the study: weeks 0, 6, 16, 26 and 52.

As the author randomised the treatment groups and was an IPT therapist, blinded ratings were carried out by two experienced psychiatric nurses who had been qualified for a minimum of 18 years. Both nurses were unaware of the treatment each participant received and did not work in the same department where the research was undertaken. Participants were advised not to tell the raters what treatment they were receiving. This ensured they remained blind to treatment for the duration of the trial.

Each nurse received training on the respective rating scales and carried out role play under supervision of the author. They then watched the video tape of a patient and scored it using relevant clinical rating scales to establish inter-rater reliability. At the appropriate time point the nurse rater completed the Hamilton Depression Scale and Hamilton Anxiety Scale, and at the same time she asked subjects to complete the self rating depression scale (Beck Depression Inventory) and Social Adaption Scale (SAS).

Safety issues

In the case of major relapse or possible increases in suicidality all participants were given the contact details of the author or her deputy in the case of deterioration, for the duration of the trial. This was in addition to usual access to psychiatric support services and the participants GP.

Results

The results from the study are presented below including changes in clinical scores relating to the participants depression, anxiety and social functioning.

This is followed by dose data for each arm. For the Interpersonal Psychotherapy intervention dose and adherence monitoring are reported and then the dose, compliance and adverse events related to the use of mirtazapine.

Clinical ratings

The results for the clinical measurements of depression, anxiety and social functioning for the participants individually and as a group are reported at the five time points (Week 0, week 6, week 16, week 26, and week 52). Of the total clinical data presented only two ratings at week 16 were not carried out, this was because the participants did not attend for the assessment interview. There was one participant in each treatment group (M16 and F17). For the purposes of statistical analysis the last observation (week 6) was carried forward in both of these cases.

Table C5-12 below shows the individual participants Hamilton Depression scores at baseline and over the year at week 6, week 16, week 26 and week 52. The "X" signifies ratings which could not be obtained. The shaded area represents the combined IPT and mirtazapine treatment, and the clear area shows the mirtazapine only group. None of the IPT and mirtazapine group deteriorated as measured by the Hamilton Depression Scale on every point in time. Eight of the ten participants in the mirtazapine only group deteriorated as demonstrated by an increase in their Hamilton scores in 13/40 measurements.

A 40% reduction in Hamilton depression scores is an accepted minimum level of a Hamilton depression score which demonstrates a response to treatment; there were 27/40 occasions when there was at least a 40% reduction in the Hamilton depression scores in the combined IPT and mirtazapine group compared to 10/40 occasions in the mirtazapine only group; this is indicated on the table below by an asterisk.

Table C5-12 shows the total scores of the participants Hamilton depression scores at baseline and after week 6, week 16, week 26 and week 52

Participants	Week 0	Week 6	Week 16	Week 26	Week 52
F01	28	27	17*	14*	14*
F05	27	15*	18	12*	23
F11	34	19*	21	14*	11*
F12	30	18*	21	17*	13*
F21	27	18	12*	15*	13*
MO4	34	18*	8*	10*	24
M06	28	21	23	16*	8*
M15	32	12*	23	14*	8*
M16	39	31	X	14*	8*
M23	18	17	9*	8*	7*
F03	31	21	31	33	19
F10	34	24	43	35	26
F17	28	27	X	15*	18
F19	28	24	8*	14*	31
F20	32	33	22	18*	37
M08	29	34	31	33	27
M07	28	28	32	10	24
M18	34	12*	3*	17*	27
M22	30	35	30	32	28
M24	20	12*	11*	10*	22

** demonstrates at least a 40% reduction in the Hamilton depression scores from the baseline measurement.*

Table C5-13 shows the mean Hamilton Depression scores for both treatment groups and the total groups at baseline and for the time periods over the year. A score of 26 signifies severe depression on the Hamilton Depression scale. The mean scores of the each treatment group and the total group demonstrates severe depression. The combined IPT

group showed a gradual reduction in the mean Hamilton scores from week 6 (moderate depression) to week 52 (mild depression). The mirtazapine only group in contrast remained the upper end of moderately depressed throughout the rating periods.

Table C5-13 shows the mean scores (SD) for the Hamilton depression scale at Week 0, week 6, week 16, week 26 and week 52

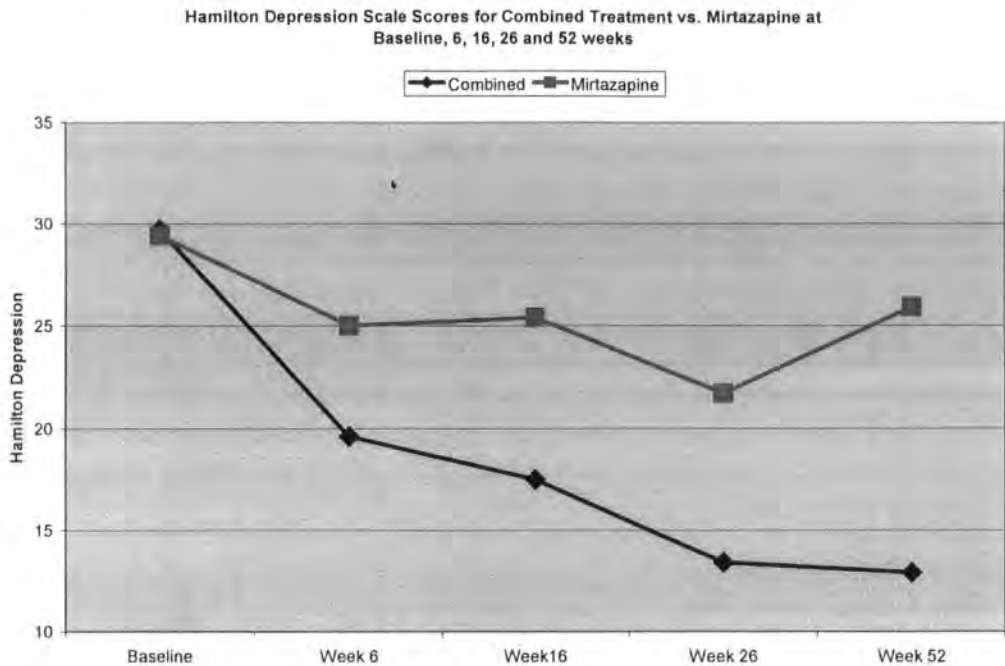
	Week 0	Week 6	Week 16	Week 26	Week 52
Total group	29.5 (4.77)	22.3 (7.40)	21.4(11.21)	17.5 (8.47)	19.4 (8.79)
IPT and mirtazapine	29.7 (5.69)	19.6 (5.58)	17.5 (5.85)	13.4 (2.71)	12.9 (6.19)
mirtazapine	29.4 (4.03)	25 (8.26)	25.4 (14.02)	21.7 (10.28)	25.9 (5.62)

**Note that on the above table there were data sets missing at week 16 for two subjects therefore the last observation was carried forward to calculate the mean scores.*

The data was analysed from the Hamilton depression scores using a two way repeated measures analysis of variance (ANOVA). These analyses permitted the evaluation of effects of time, treatment and the interaction between treatment by time on the Hamilton depression scores.

Mauchly's test indicated that the assumption of sphericity had been violated for the effects of time (Chi squared (9) = 18.12, P=0.035. Therefore the degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity (epsilon = 0.776). There was a significant effect of time F (3.1, 55.8) = 10.5, p= 0.001 and treatment F (1, 18) = 9.36, p= 0.007. Critically, there was a significant interaction effect between treatment and time F (3.1, 55.8) = 2.9, p = 0.041. To explore the interaction, pairwise comparisons were conducted at each time point and showed significant improvements on depression scores from baseline to weeks 6, p =0.003; week 16, p =0.009; week 26, p = 0.001; week 52, p =0.001).

Table C5-14 shows a graph of the Hamilton depression scores at baseline and weeks 6, 16, 26 and 52



The between group differences demonstrated significant differences in the two treatment groups $F(1, 18) = 9.36, p = 0.007$. Subsequent t tests revealed statistically significant differences between the groups which emerged by week 26 $t = -2.47, df 10.25, p = 0.033$ and week 52, $t = -4.95, df 17.87, p = 0.001$ (Bonferroni corrected).

Table C5-15 below shows the individual participants Beck Depression Inventory scores at baseline and over the year at week 6, week 16, week 26 and week 52. The “X” signifies ratings which could not be obtained. The shaded area represents the combined IPT and mirtazapine treatment, and the clear area shows the mirtazapine only group. Five of the ten participants in the IPT and mirtazapine group deteriorated at some point (7 out of a total of 40 measurements) in their treatment and six of the mirtazapine only group deteriorated 10 out of a total of 40 measurements.

There were 19/40 occasions when there was at least a 40% reduction in the Beck Depression scores in the combined IPT and mirtazapine group

compared to 4/40 occasions in the mirtazapine only group; this is indicated on the table below by an asterisk.

Table C5- 15 shows the total scores of the participants Beck Depression Inventory depression scores at baseline and after week 6, week 16, week 26 and week 52.

Participants	Week 0	Week 6	Week 16	Week 26	Week 52
F01	31	34	21	26	16*
F05	46	35	27*	26*	28*
F11	54	27*	32*	38	30*
F12	31	18*	36	18*	23
F21	41	33	18*	23*	21*
MO4	40	30	22*	4*	50
M06	37	44	42	43	34
M15	51	30*	37	35	24*
M16	36	39	X	17*	23*
M23	29	20	18	17*	16
F03	34	40	39	37	33
F10	30	41	49	27	22
F17	35	34	X	30	28
F19	34	24	15*	30	33
F20	35	44	30	25	38
M08	32	31	32	29	43
M07	30	29	35	30	25
M18	29	22	6*	17	14*
M22	40	47	25*	33	33
M24	33	25	22	22	31

** demonstrates at least a 40% reduction in the BDI scores from the baseline measurement.*

Table C5-16 shows the mean Beck Depression scores for both treatment groups and the total group at baseline and for weeks 6, 16, 26, and 52. A score of 40 signifies extreme depression on the Beck depression Inventory and 31+ signifies severe depression. The mean scores of the each treatment group and the total group demonstrates severe depression. The combined IPT group showed a gradual reduction in the mean Beck Depression Inventory scores from week 6 (bordering moderate depression) to week 26 (moderate

depression), there was a slight increase in the scores at week 52 (middle of moderately depressed category). The mirtazapine only group in contrast remained at the low end of the severely depressed category for 2 out of 4 of the ratings (weeks 6 and 16) and remained the upper end of moderately depressed for the last two clinical rating periods (Week 26 and 52)

Table C5-16 shows the mean scores (SD) for the Beck Depression Inventory at Week 0, week 6, week 16, week 26 and week 52

	Week 0	Week 6	Week 16	Week 26	Week 52
Total group	36.4 (7.10)	32.3 (8.33)	29.6 (11.33)	26.3 (9.05)	28.2 (9.10)
IPT and mirtazapine	39.6 (8.57)	31.0 (7.96)	29.0(8.91)	24.7 (11.62)	26.5 (10.02)
mirtazapine	33.2 (3.22)	33.7 (8.89)	30.2 (13.83)	28 (5.64)	30 (8.23)

**Note that on the above table there were data sets missing at week 16 for two participants therefore the last observation was carried forward to calculate the mean scores.*

The data was analysed from the Beck Depression Inventory scores using a two way repeated measures analysis of variance. These analyses permitted the evaluation of effects of time, treatment and the interaction between treatment by time on the Beck Depression Inventory scores.

Using a repeated measures ANOVA there was only a significant effect detected for time $F(4, 15) = 11.46, p = 0.001$. However, there were no significant differences noted between treatment groups ($F(1, 18) = 0.039, p = 0.845$) or in the time X group interaction ($F(4, 72) = 1.55, p = 0.196$).

Table C5- 17 shows a graph of the Beck Depression Inventory scores at baseline and weeks 6, 16, 26 and 52

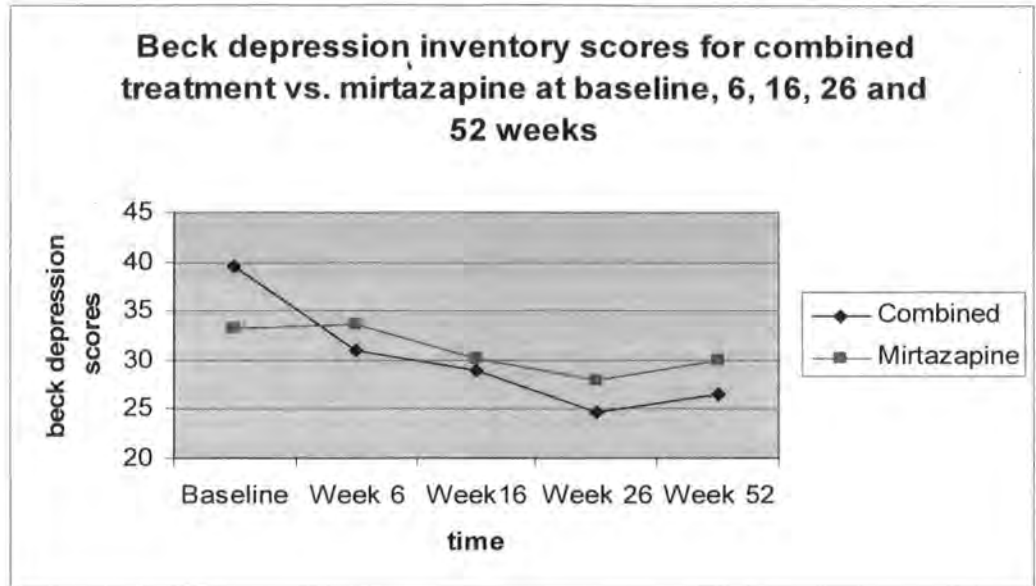


Table C5-18 below shows the individual participants Hamilton Anxiety scores at baseline and over the year at week 6, week 16, week 26 and week 52. The “x” signifies ratings which could not be obtained. Two of the ten participants in the IPT and mirtazapine group demonstrated increased anxiety at some point in their treatment (3 out of a total of 40 measurements) and 4 of the mirtazapine only group deteriorated (9 out of a total of 40 measurements).

There were 25/40 occasions when there was at least a 40% reduction in the Hamilton Anxiety scores in the combined IPT and mirtazapine group compared to 12/40 occasions in the mirtazapine only group; this is indicated on the table below by an asterisk.

Table C5-18 shows the total scores of the participants Hamilton Anxiety scores (HAS) at baseline and after week 6, week 16, week 26 and week 52

Participants	Week 0	Week 6	Week 16	Week 26	Week 52
F01	17	17	26	19	7*
F05	32	18*	19*	13*	27
F11	29	19	18	9*	7*
F12	25	17	18	13*	11*
F21	20	25	20	13	12*
MO4	38	18*	9*	4*	17*
M06	36	20*	19*	10*	13*
M15	31	4*	14*	6*	4*
M16	29	25	X	14*	9*
M23	13	8	8	5*	5*
F03	24	16	34	25	14*
F10	23	15	39	28	24
F17	29	27	X	18	14*
F19	29	17*	13*	16*	28
F20	35	33	26	23	32
M08	29	24	24	27	20
M07	24	21	25	13*	17
M18	23	11*	4*	17	11*
M22	24	31	27	26	19
M24	19	10*	8*	8*	16

* demonstrates at least a 40% reduction in the HAS scores from the baseline measurement.

Table C5-19 below shows the mean Hamilton Anxiety scores for both treatment groups and the total group at baseline and for weeks 6, 16, 26, and 52. There are no published cut scores for the interpretation of the Hamilton Anxiety scores. The author therefore examined the percentage

reduction in the mean scores relative to the baseline measurement. The combined IPT and mirtazapine group reduced by 37% and 39% at weeks 6 and 16 respectively, and demonstrated greater reductions signifying improvements in anxiety symptoms at the longer term follow ups of 26 and 52 weeks (61% and 59% respectively). The mirtazapine only group showed a 21% reduction in scores after 6 weeks, however this improvement was not sustained as the mean scores showed just 8% reduction at week 16. The greatest reduction in the Hamilton Anxiety scores in the mirtazapine only group were at week 26 (33%) and this score was reduced slightly at week 52 (25%).

Table C5- 19 shows the mean scores (SD) for the Hamilton anxiety scale at baseline and after week 6, week 16, week 26 and week 52. Plus percent changes in reductions in HAS scores from baseline measurements (brackets)

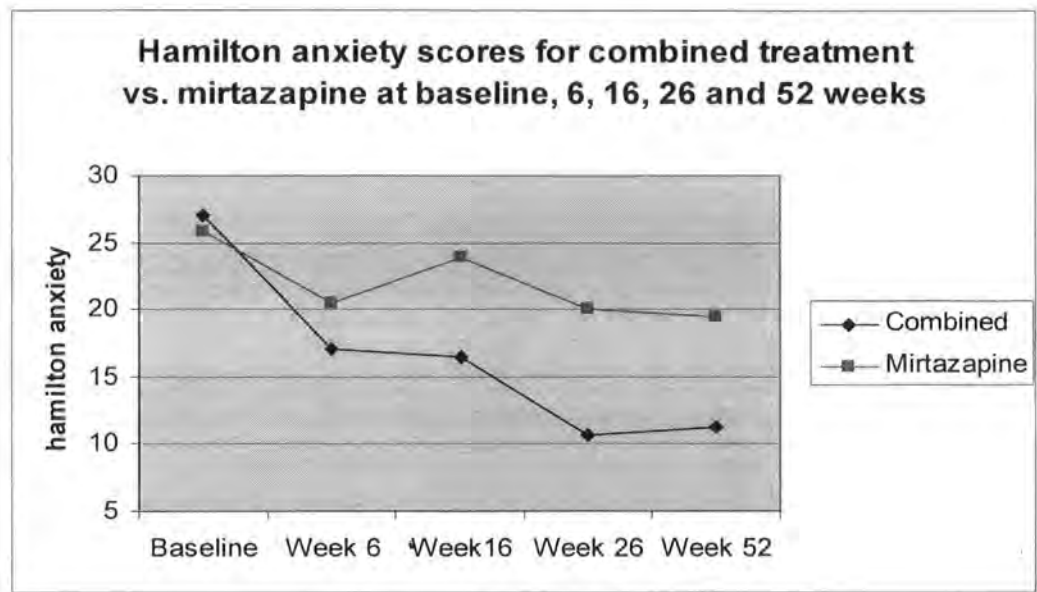
	Week 0	Week 6	Week 16	Week 26	Week 52
Total group	26.4 (6.46)	18.8 (7.38)	20.2 (9.93)	15.3 (7.45)	15.3 (7.82)
IPT and mirtazapine	27 (8.16)	17.1 (6.60) (37%)	16.5 (5.38) (39%)	10.6 (4.69) (61%)	11.2 (6.81) (59%)
mirtazapine	25.9 (4.55)	20.5 (8.06) (21%)	23.9 (12.02) (8%)	20.1 (6.71) (33%)	19.5 (6.70) (25%)

**Note that on the above table there were data sets missing at week 16 for two participants therefore the last observation was carried forward to calculate the mean scores.*

The data was analysed from the Hamilton anxiety scores using a two way repeated measures analysis of variance. These analyses permitted the evaluation of effects of time, treatment and the interaction between treatment by time on the Hamilton depression scores.

There was a significant effect of time, $F(4, 72) = 12.16, p = 0.001$ and treatment $F(1, 18) = 5.34, p = 0.033$. Critically, there was a significant interaction effect between treatment and time $F(4, 72) = 2.56, p = 0.044$. To explore the interaction, pairwise comparisons were conducted at each time point and showed significant improvements on anxiety scores from baseline to weeks 6, $p = 0.004$; week 26, $p = 0.001$; week 52, $p = 0.001$).

Table C5-20 shows a graph of the Hamilton anxiety scores at baseline and weeks 6, 16, 26 and 52



In order to explore the differences between the treatment groups, t tests were conducted and revealed statistically significant differences between the groups which emerged by week 26 $t = -3.67$, $df\ 18$, $p = 0.002$ and week 52, $t = -2.75$, $df\ 18$, $p = 0.013$ (Bonferroni corrected).

Table C5-21 below reports the total scores for the individual participants for Social Adaption Scores for each treatment group. The normal range for this scale is 35-52. There was one participant in each group which fell within the normal range for social adaptation at the start of treatment. For most of the time the participants in both groups fell below the normal range, this occurred slightly more often in the IPT and mirtazapine group (38/40 vs. 34/40). The double asterisk has marked those participants who were within the normal range according to this scale.

Table C5-21 shows the total scores of the participants Social Adaption scores at baseline and after week 6, week 16, week 26 and week 52

Participants	Week 0	Week 6	Week 16	Week 26	Week 52
F01	36**	31	31	34	48**
F05	13	21	34	15	15
F11	16	26	31	26	27
F12	27	32	24	28	17
F21	16	20	20	13	15
MO4	30	24	30	47**	28
M06	19	21	12	5	25
M15	18	14	24	23	24
M16	30	28	xx	25	26
M23	20	31	25	25	29
F03	20	14	19	23	19
F10	35	34	17	30	28
F17	17	22	xx	12	10
F19	19	17	32	18	18
F20	30	19	24	24	16
M08	17	24	24	11	24
M07	35**	35**	33	35**	31
M18	32	44**	52**	36**	38**
M22	13	9	9	9	8
M24	24	25	24	28	27

**** denotes the normal range for the social adaptation scores**

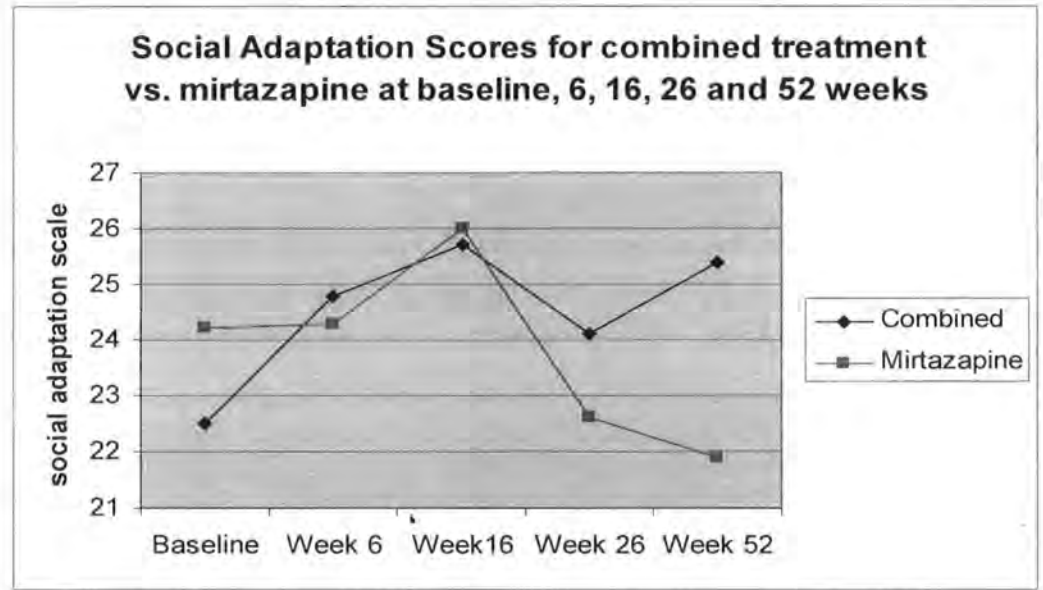
Table C5-22 below shows the mean Social Adaptation Scores for both treatment groups and the total group at baseline and for weeks 6, 16, 26, and 52. Both treatment groups have similar mean scores at baseline which continue throughout treatment. All of the mean scores at each time point fall below the normal range (35).

Table C5-22 shows the mean scores (SD) for the Social Adaption Scores at baseline and after week 6, week 16, week 26 and week 52

	Week 0	Week 6	Week 16	Week 26	Week 52
Total group	23.3 (7.76)	24.5 (8.38)	25.8 (9.59)	23.3 (10.51)	23.6 (9.42)
IPT and mirtazapine	22.5 (7.66)	24.8 (5.86)	25.7 (6.8)	24.1 (11.62)	25.4 (9.56)
mirtazapine	24.2 (8.17)	24.3 (10.67)	26 (12.21)	22.6 (9.84)	21.9 (9.45)

The data was analysed from the Social Adaptation scores using a two way repeated measures analysis of variance. These analyses permitted the evaluation of effects of time, treatment and the interaction between treatment by time on the Social Adaptation Scores. There were no significant effects for time ($F(4, 72) = 1.2, p = 0.30$), treatment ($F(1, 18) = 0.013, p = 0.91$), or the interaction between time and treatment ($F(4, 72) = 0.16, p = 0.96$).

Table C5-23 shows a graph of the Social Adaptation scores at baseline and weeks 6, 16, 26 and 52



Interpersonal Psychotherapy

The Interpersonal Psychotherapy provided in this study was carried out by two research trained IPT therapists. The author (ER) provided IPT for 7 participants, and the IPT therapist (PC) provided IPT for three of the participants. The author recorded the number of IPT sessions received by each participant, including the period of time the psychotherapy was delivered (encompassing acute and maintenance phases of treatment). This information provides an indication of the dose of IPT each participant received during the acute and maintenance phases of treatment. The problem area which was the focus during acute and maintenance therapy was also noted in each participant.

At the start of treatment participants were asked if the acute Interpersonal Psychotherapy sessions could be audiotaped for the purpose of monitoring adherence to the model of IPT. Four of the participants agreed to have their

sessions taped; two participants from each therapist. Out of a possible 43 acute phase IPT sessions, 22 (49%) were actually taped; this was due to technical difficulties. Due to the limited number of tapes available to monitor for the purposes of adherence, every tape was rated.

Dose of Interpersonal Psychotherapy treatment

The author planned to use the established doses of acute IPT (up to 16 weekly sessions) followed by monthly IPT maintenance sessions (Elkin et al 1989, Frank et al 1991). Table C5-24 below shows the number of IPT sessions each participant received during acute and maintenance treatment, including which therapist provided the IPT. During the first 6 weeks 50% of participants had received the full dose of 6 weekly sessions, 40% received a moderate/full dose of 4-5 sessions. One participant (10%) had attended for just 2 sessions of IPT in the first 6 weeks of treatment.

During the maintenance IPT therapy 30% of the participants received an optimum dose, 30% received a moderate and a further 30% received a low dose of psychotherapy treatment. One participant (021) received 12 IPT sessions over a period of 10 months; this was due to psychotherapy sessions being tapered from weekly, during the acute phase treatment to fortnightly before receiving monthly maintenance IPT sessions.

Table C5-24 shows the number of IPT sessions the participant received during the first six weeks, and acute and maintenance phases

	Early Acute phase IPT	16 week 'Acute phase IPT	Maintenance phase IPT	IPT delivered over total year
<i>Participant ID number</i>	<i>Total number of sessions from weeks 0-6</i>	<i>Number of sessions/ number of weeks</i>	<i>Number of sessions/ number of months</i>	<i>Total number of IPT sessions/months</i>
001	6	16/16	7/6	23/12
005	6	17/22	7/6	24/12
*011	6	12/12	7/7	19/9.5
*012	4	13/16	3 /4	16/8.5
021	5	10/10	12/10	22/12
004	6	12/15	5/6	17/12
006	6	8/8	5/5	13/9
*015	4	10/15	4/3	14/7
016	2	7/6	3/6	10/9
023	4	8/14	5/9	13/11

**The shaded area above represented the sessions provided by the therapist PC, the clear areas are those provided by the author (ER).*

Table C5-25 reports the mean number of completed IPT sessions during early acute, acute and maintenance phases of treatment. Each phase of treatment fell slightly below the optimum mean dose of IPT treatment; however the therapy provided could be still considered a reasonable therapeutic dose.

Table C5-25 shows the mean number of IPT completed by week 6, during acute and maintenance treatment phases and after one year (Optimum dose in brackets)

	Weeks 0-6	Acute IPT	Maintenance IPT	Total IPT over 12 months
Mean	4.9 (6)	11.3 (16)	5.8 (8)	17.1 (24)
Range	2-6	7-17	3-12	10-24

There was clearly a broad range in the dose of IPT administered during all phases of treatment. Only half of the group received the optimum dose of 6 IPT sessions after the initial six weeks; a further 4 participants received a moderate dose (4-5 sessions) of IPT and only one participant received an extremely low dose (2 sessions) of IPT for this period.

The mean number of IPT sessions (11.3) received by the total group during the acute phase would represent a moderate dose. Only two of these participants received the optimum dose as specified in the manual (Klerman et al 1984); a further five participants received moderate doses (10-13 sessions) and three participants received low dose IPT (7 or 8 sessions). The maintenance phase of treatment reflected the broadest range (3-12) of IPT sessions which were delivered over 3-10 months. Taking into account the time period for which the IPT maintenance sessions were delivered, the majority of participants (n=9) received an optimum dose of treatment. The remaining 2 participants received IPT at half of the current established maintenance dose (participants M16; M23).

Table C5-26 shows the mean number of IPT sessions delivered (total IPT group) and the total time (months) of therapy

Therapist	PC, N=3	ER, N=7
Mean number of acute IPT sessions	11.7	11.1
Mean number of maintenance IPT sessions	4.6	6.3
Mean number of total IPT sessions (acute and maintenance)	16.3	17.4
Mean time in months IPT provided	8.3	11
Range of time in months the IPT was provided	7-9.5	9-12

There were few differences between therapists in the number of acute Interpersonal Psychotherapy sessions provided to each participant. On average, therapist (ER) provided slightly more of the total (1) and maintenance (2) IPT sessions than the therapist (PC); however, these sessions were delivered over a longer period of time (11 vs. 8.3) months.

Interpersonal Psychotherapy problem areas

The problem areas agreed with the therapist and participant were recorded for both phases of treatment.

Table C5-27 demonstrates the problem area which was the focus of treatment

Participant	IPT Acute focal area	IPT-M focal area
001	Dispute, transition	Dispute transition
005	Transition	Transition
011	Dispute, transition	Transition
012	Dispute	Transition
021	Transition, dispute	Transition, dispute
004	Transition	Transition
006	Dispute, transition	Dispute, transition
015	Transition	Transition
016	Transition	Transition
023	Transition	Transition

There were no participants whose depression was classified as having apparently been caused or maintained by two of the four problem areas; namely, complicated bereavement or interpersonal deficit.

IPT therapist adherence monitoring

Only the acute phase sessions of the IPT were rated encompassing the initial and middle phases of both treatments. Both raters (ER, and SDM) independently listened to the complete IPT session which was to be rated. The author (ER) rated the sessions delivered by the therapist (PC) and rater SDM separately rated the sessions provided by ER. The rating scale allowed the rater to assess if particular treatment strategies for IPT were employed. Furthermore, the level of competence achieved by each therapist was assessed as well as the level of difficulty for each participant during the session.

Initial phase of IPT - adherence monitoring

The tasks of the initial sessions of IPT are listed in the table below. These form the NIMH adherence monitoring assessment of the initial phase of treatment as used in the Elkin study (1989). This part of the assessment allows the rater to establish whether the task has been performed. There are no ratings for the

quality of the intervention at this stage of the treatment. A score of "1" indicates the tasks have been achieved and a score of "2" indicates that during the session rated the task had not been performed.

Table C5-28 shows the tasks of the initial sessions on the NIMH adherence rating form

	Tasks – Initial session(s)
A	Inquire re: chief complaint and depressive symptoms
B	History of current depressive episode and treatment if any
C	Brief social history
D	Inquiry re: patients expectation of psychotherapy
E	Explanation of IPT and it's basic assumptions
F	Translation of chief complaint (depressive symptoms) into interpersonal context
G	Reassurance of patient re: positive prognosis
H	Explanation of IPT techniques
I	Contract setting Re: administrative details, ie length of sessions, frequency, duration of treatment, appointment times, etc
J	Interpersonal Inventory (detailed review of patient's important relationships)
K	Feedback to patient Re: therapist general understanding of the patients interpersonal difficulties (IPT problem areas)
L	Contract setting Re: treatment goals
M	Explanation of therapist and patient tasks in working toward treatment goals

Table C5-29 shows the results of the therapist adherence monitoring for the initial sessions

Participants	Session	Therapist / Rater	A	B	C	D	E	F	G	H	I	J	K	L	M
F011	1	PC/ER	1	1	1	2	2	2	1	2	2	1	2	2	2
F011	2	PC/ER	1	1	1	2	1	2	1	2	2	1	1	2	2
F012	1	PC/ER	1	1	1	2	1	2	1	1	2	1	2	2	2
F012	2	PC/ER	2	2	2	2	1	1	1	1	2	1	2	2	2
M023	1	ER/SDM	1	1	1	1	1	1	1	1	2	1	2	1	1
F021	1	ER/SDM*	1	1	1	1	1	1	1	1	2	1	1	2	2
F021	2	ER/SDM	1	1	1	1	1	1	1	1	2	1	1	1	1

Four participants, treated by both therapists were rated for adherence to the initial phase of IPT. Although the IPT manual highlights that the initial phase may spread to 3 sessions, only the first 2 were rated. From a possible 91 responses, nearly two thirds (n=57) of the strategies were achieved (13 tasks involving 7 psychotherapy sessions) during the sessions rated. Of the remaining third (n=34) of the strategies not observed during the rated period, the most common was "item I" – ("Contract setting Re: administrative details, i.e. length of sessions, frequency, duration of treatment, appointment times, etc"). Neither therapist fulfilled this criterion for any of the participants. However, this activity would have been likely to have taken place before the subject

started their IPT treatment, and explained by the author as part of the research study. Similarly, item “D” – *“inquiry re patients’ expectation of psychotherapy”* may have been addressed before sessions 1 and 2. The remaining items (F, K, L, and M) were more likely to be addressed at the end of the initial phase of treatment and may have been observed if session 3 was recorded.

Middle phase of IPT - adherence monitoring

The goal directed activities identified in the IPT treatment manual (Klerman et al 1984) which enable the therapist to maintain a therapeutic strategy for the entire problem areas (role dispute, role transition, interpersonal deficit and complicated bereavement) are listed in tables below. As previously used in the initial phase, the raters use the codes “1” = *yes*, “2” = *no* to establish if the goal directed activity is present or not. However, unlike the initial phase, if the goal directed activity is present, the raters have an opportunity to grade the quality of that intervention, using a likert scale with a score ranging from “1” *excellent* to “7” *poor*.

Role disputes - therapist adherence monitoring

The areas identified in the IPT treatment manual (Klerman et al 1984) which enable the therapist to maintain a therapeutic strategy for a role dispute are listed in the table below. Each rater listened to the complete IPT session on the audiotapes and completed the ratings below.

Table C5-30 shows the goal directed activity for role disputes on the NIMH adherence rating form

	Goal directed activity for role disputes
A	Review depressive symptoms
B	Relate depressive symptom to overt or covert dispute with significant other with whom the patient is currently involved
C	Determine the stage of the dispute
D	Explanation of how non-reciprocal role expectations relate to the dispute
E	Exploration and discussion of differences in expectations and values
F	Exploration of parallels in other relationships
G	Exploration and discussion of options available to the patients
H	Discussion of communication patterns (structural, emotional, expectational and wish aspects)

Quality of intervention

Excellent							Poor	
1	2	3	4	5	6	7		

Table C5-31 shows the results of the therapist adherence monitoring for role disputes

(a score of 1="yes" which is followed by a rating for quality; 2 = "no", item not evident)

Participants	Session	Therapist / Rater	A	B	C	D	E	F	G	H
F012	12	PC/ER	1/1	1/3	1/3	2	1/3	2	1/2	1/3
F012	13	PC/ER	1/3	1/3	1/2	1/3	1/3	2	1/2	1/3
F011	5	PC/ER	1/2	1/3	2	2	1/4	2	1/3	1/3
F011	6	PC/ER	1/2	1/2	1/2	1/3	1/3	1/3	1/3	2
F011	7	PC/ER	1/2	1/1	1/2	1/3	1/3	2	1/2	2
F011	9	PC/ER	1/1	1/2	1/3	1/3	1/2	2	2	1/3
F011	11	PC/ER	1/2	1/3	1/2	1/3	1/3	2	1/3	1/4
F021	6	ER/SDM	1/2	1/2	1/2	1/2	1/2	2	1/2	1/2
mean	scores	quality	1.9	2.4	2.5	2.4	2.9	3	2.4	3

Mean scores of quality are calculated for strategy rated as present.

The sessions rated ranged from 6-13, which represented a fair spread of sessions during the middle of phase of IPT. Three of the four participants who agreed to have their IPT sessions audiotaped had a role dispute as a focal area. One participant had role dispute as a single focus (012), and another had two focal areas identified, the role dispute in this case was the primary focus (011). A third participant also had two focal areas, however the role dispute was secondary to the role transition (021) As two of the three of the participants above were treated by therapist PC most of the ratings concerning role disputes evaluated his psychotherapy sessions. Most of the goal directed activity was achieved and carried out to a high standard (mean score of the quality of the rating ranged from 1.9-3). The most common goal directed activity which least achieved was *Item F "Exploration of parallels in other relationships"*. This however, had been addressed by the therapist (PC) with one subject (F011) during one session in the middle phase and would not necessarily be the focus of every session.

Role transitions - therapist adherence monitoring

The table below are the areas identify the areas which enable the therapist to maintain the therapeutic strategies for role transitions as directed in the Interpersonal Psychotherapy treatment manual (Klerman et al 1984).

Table C5-32 shows the goal directed activity for role transitions on the NIMH adherence rating form

(a score of 1="yes" which is followed by a rating for quality; 2 = "no", item not evident)

	Goal directed activity for role transitions
A	Review depressive symptoms
B	Relate depressive symptom to coping with some recent life change
C	Review positive and negative aspects of old role and possible new ones
D	Explore feelings about what is lost
E	Explore feelings about change itself
F	Explore opportunities in the new role
G	Realistic evaluation about what is lost
H	Encourage appropriate release of affect
I	Encourage development of social support system and new skills called for in new role

The sessions were rated from 3-14. All of the participants had a role transition as a focal area, one of whom had role transition as a single focus throughout the acute and maintenance treatment (023), a second had role transition as a primary focal area or two focal areas (role dispute and role transition), and the last participant had moved from a focal area of role dispute to role transition. Nearly all of goal directed activity was achieved and carried out to a high standard (mean score of quality of the rating ranged from 1.7-2.9). The 2 items which were not achieved were item F "Explore opportunities in the new role" and item I "Encourage development of social support system and new skills called for in new role" (Participant 021; session 3). As this was very early into the middle phase of treatment, this goal directed activity would not usually be addressed at this early stage; later sessions with the same participant demonstrate that this goal directed activity was achieved.

Table C5-33 shows the results of the therapist adherence monitoring for role transitions

(a score of 1="yes" which is followed by a rating for quality; 2 = "no", item not evident)

Participants	Session	Therapist /Rater	A	B	C	D	E	F	G	H	I
F012	14	PC/ER	1/2	1/3	1/2	2	1/2	1/3	2	1/3	1/2
F011	9	PC/ER	1/1	1/2	1/3	1/3	1/2	1/3	2	1/3	1/3
F011	10	PC/ER	1/2	1/3	1/3	1/3	1/3	1/3	1/3	1/2	1/2
F021	3	ER/SDM	1/1	1/2	1/2	1/2	1/2	2	1/2	1/2	2
F021	4	ER/SDM	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2
F021	5	ER/SDM	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2
M023	3	ER	1/2	1/1	1/2	1/2	1/2	1/2	1/2	1/2	1/2
Mean	score s	quality	1.7	2.1	2.9	2.3	2.1	2.1	1.6	2.3	1.9

Mean scores of quality are calculated for strategy rated as present.

Complicated bereavement and interpersonal deficit were not the focus of IPT for any of the participants used in this study; therefore the strategies to be employed by the therapists for these problem areas could not be evaluated.

Therapist strategy in IPT

The rating scale developed for the NIMH study included a section evaluating the overall strategy of the approach used in psychotherapy. Specifically, items G and H are approaches used in CBT and psychodynamic psychotherapy. This is included to ensure the therapist adheres to the model of IPT and does not drift into alternate psychotherapeutic approaches. As was the case with the monitoring of the interpersonal problem areas (role transition, role dispute, complicated bereavement and interpersonal deficit) the adherence raters continue to use the codes "1" = yes, "2" = no. When the goal directed activity is present, the quality of the therapists' interventions is also rated, from "1" excellent to "7" poor.

Table C5-34 shows the therapist strategy for goal directed activity (interpersonal focus) the on the NIMH adherence rating form

(a score of 1="yes" which is followed by a rating for quality; 2 = "no", item not evident)

	Therapist strategy rating form Goal directed activity
A	Exploration of recent and remote losses and reactions to these losses
B	Facilitation of mourning
C	Exploration of ways patient can develop and/or resume relationships and activities
D	Information gathering and exploration re: nature of disputes and/or role transition
E	Exploration and discussion of possible changes that could be made
F	Review of past and current relationships in detail
G	Review of self concept, with emphasis on self destructive, unrealistic attitudes/expectations
H	Careful attention to the positive and negative elements of the patient/therapist relationship

Table C5-35 shows the results for the therapist adherence monitoring for therapist strategy

(a score of 1="yes" which is followed by a rating for quality; 2 = "no", item not evident)

Participants	Session	Therapist / Rater	Focus	A	B	C	D	E	F	G	H
F012	12	PC/ER	RD	2	2	1/3	1/3	1/3	2	2	2
F012	13	PC/ER	RD	2	2	1/3	1/3	1/3	2	2	2
F012	14	PC/ER	RT	2	2	1/3	1/3	1/3	2	2	2
F011	3	PC/ER	RD	2	2	1/3	1/4	2	2	2	2
F011	5	PC/ER	RD	1/3	1/3	1/2	1/3	1/2	1/3	1/3	2
F011	6	PC/ER	RD	2	2	1/3	1/3	1/3	1/3	2	2
F011	7	PC/ER	RD	1/2	1/2	1/2	1/2	1/2	2	1/3	2
F011	9	PC/ER	RD/RT	1/3	1/3	1/2	1/2	1/3	1/4	2	2
F011	10	PC/ER	RT	1/2	2	1/3	1/3	2	2	2	2
F011	11	PC/ER	RD	1/3	1/3	1/2	1/3	2	2	2	2
F021	3	ER/SDM	RT	1/2	1/2	2	1/2	2	2	2	2
F021	4	ER/SDM	RT	1/2	1/2	1/2	1/2	1/2	2	2	2
F021	5	ER/SDM	RT	1/2	1/2	1/2	1/2	1/2	2	2	2
F021	6	ER/SDM	RD	2	2	1/2	1/2	1/2	1/3	2	2
M023	3	ER/SDM	RT	1/2	1/2	1/2	1/2	1/2	1/3	2	2
	Mean	scores	quality	2.3	2.4	2.4	2.6	2.4	3.2	3	-

Mean scores of quality are calculated for strategy rated as present.

Excluding Items G and H which are not IPT approaches, the analysis of the results demonstrate that two thirds of the goal directed strategies were met by the therapists, and that the quality of the intervention was good (mean score for the quality of the goal directed activity 2.3-3.2). However, further analysis needs to address the fact that each session was rated individually for goal directed activity. There are occasions when the strategies are inappropriate for the problem area; for example, strategies A and B (A- *exploration of recent and remote losses and reactions to these losses*; B - *facilitation of mourning*) focus primarily on role transitions. Furthermore, the timing of the session needs to be considered; for instance, Item F (*Review of past and current relationships in detail*) may typically be addressed at the early stage of treatment. Moreover, it is not reasonable or practical to expect every single goal directed activity to be achieved at every single IPT session.

For each participant and for Items A, B, C, D and E the entire goal directed activities were addressed during the some stage of the middle phase of IPT treatment. Regarding *Item F* ("Review of past and current relationships in detail"), this goal directed activity was achieved for three out of four of the participants used in these ratings during some stage of their middle phase of

treatment. The taped sessions of the fourth participant were late middle phase treatment; hence it would be unlikely that a review of past and current relationships would be performed at such a late stage into IPT treatment. Item G (*Review of self concept, with emphasis on self destructive, unrealistic attitudes/expectations*) was noted to have occurred twice with the same participant (F011) and therapist (PC). The IPT focal area of dispute had led the therapist to explore the participants own expectations of the relationship in question, and assess its' impact on her depressive symptoms. This strategy when conceptualised in this way fits into the model of IPT.

Therapist overall competence

An item towards the end of the NIMH rating scale allows a general rating of the overall competence of the therapist during the IPT sessions. Additionally, an assessment by the adherence rater is made of how receptive the subject is during the sessions. Finally, the rater is asked if the IPT used in this study would be of sufficient quality to justify using the same therapist in an IPT outcome study in the future.

How would you rate the clinician OVERALL in this session as an interpersonal psychotherapist?

<i>poor</i>	<i>barely adequate</i>	<i>mediocre</i>	<i>satisfactory</i>	<i>good</i>	<i>very good</i>	<i>excellent</i>
0	1	2	3	4	5	6

How difficult did you feel the patient was to work with?

<i>Not difficult very receptive</i>			<i>moderately difficult</i>			<i>extremely difficult</i>
0	1	2	3	4	5	6

If you were conducting an OUTCOME study in interpersonal psychotherapy, do you think you would select this therapist to participate at this time (assuming the session is typical?)

<i>Definitely not</i>	<i>Probably not</i>	<i>Uncertain/borderline</i>	<i>Probably yes</i>	<i>Definitely yes</i>
0	1	2	3	4

Table C5-36 shows the scores for the therapist overall competence ratings

Participants	Session	Therapist / Rater	Overall IPT	Outcome study	Patient difficulty
F011	1	PC/ER	5	4	1
F011	3	PC/ER	5	4	1
F012	1	PC/ER	5	3	2
F012	2	PC/ER	4	3	3
F012	12	PC/ER	4	3	2
F012	13	PC/ER	4	3	2
F012	14	PC/ER	4	3	2
F011	5	PC/ER	4	3	1
F011	6	PC/ER	4	3	0
F011	7	PC/ER	5	4	0
F011	9	PC/ER	4	3	0
F011	10	PC/ER	5	4	0
F011	11	PC/ER	4	3	0
F021	3	ER/SDM	5	4	2
F021	4	ER/SDM	5	4	2
F021	5	ER/SDM	5	4	2
F021	6	ER/SDM	5	4	2
M023	3	ER/SDM	5	4	2
M023	1	ER/SDM	5	4	2
F021	1	ER/SDM	6	4	2
F021	2	ER/SDM	6	4	2
	mean	scores	4.71	3.57	1.42

Both of the IPT therapists during this study adhered to the model of IPT and provided the treatment consistently. The ratings relating to the overall competence of the therapist ranged from 4 ("good") to 6 ("excellent"). The mean score was high 4.71 demonstrating the overall competence of the therapist to be somewhere between "good" and "very good". Furthermore, the adherence raters found that the therapists were providing IPT well enough to be considered for another outcome study. The participants were not considered to be difficult to work with psychologically, only one participant was considered moderately difficult and the remaining participants fell just below this category.

Mirtazapine

The table C5-37 lists the dose of mirtazapine prescribed for each participant and includes the compliance to the antidepressant medication

Participant ID	Week 0	Week 3	Week 6	Week 16	Compliant
F01	30mg	30mg	45mg	Stopped mirtazapine (week 7)	Compliant
F05	30mg	30mg	30mg	45mg	Compliant
F11	30mg	30mg	30mg	30mg	Compliant
F12	30mg	30mg	30mg	30mg	Compliant
F21	30mg	30mg	30mg	30mg stopped mirtazapine week 30	Compliant
MO6	30mg	30mg	30mg	30mg	Compliant
M04	30mg	45mg	45mg	45mg	Compliant
M15	30mg	45mg	45mg	45mg	Compliant
M16	30mg	30mg	30mg	45mg	Took only half of the tablets
M23	30mg	30mg	45mg	45mg	Compliant
F03	30mg	30mg	30mg	30mg	Compliant
F10	30mg	30mg	45mg	Stopped mirtazapine (week 10)	Missed 2 doses week 0-3, missed 7 doses week 3-6
F17	30mg	45mg	45mg	45mg	Compliant
F19	30mg	45mg	45mg	45mg	3 doses missed week 3-6
F20	30mg	30mg	45mg	45mg	Compliant
M07	30mg for 2 days then 45mg	45mg	45mg	45mg	Compliant
M08	30mg	30mg	45mg	45mg	Compliant
M18	30mg	30mg	30mg	30mg	Missed 2 doses week 0-6
M22	30mg	45mg	45mg	45mg	Compliant
M24	30mg	45mg	45mg	45mg	Compliant

Only four of the participants appeared to have compliance difficulties with the medication prescribed; three participants in the mirtazapine only group missed occasional doses of medication (M18, F19, and F10). Only one participant in the combined mirtazapine and IPT group demonstrated compliance problems and missed more sustained periods of medication (M16). The author assessed

the impact on the therapeutic dose of mirtazapine taken for each participant taking into account the medication returned. This is shown in the table below. Two of the participants in the combined group (F21 and F01) and one (F10) participant in the mirtazapine only group stopped taking their mirtazapine in favour of an alternative antidepressant medication.

Table C5-38 shows the mean dose of mirtazapine in milligrams taken for each participant

Participant	Week 0-3	Week 4-6	Week 7-16
F01	30	30	Xx
F05	30	30	30
F11	30	30	30
F12	30	30	30
F21	30	30	30
MO6	30	30	30
M04	30	37.5	42.2
M15	30	37.5	42.2
M16	15	15	45
M23	30	30	39.4
F03	30	30	30
F10	27.1	20	Xx
F17	30	37.5	45
F19	30	38.6	45
F20	30	30	39.4
M07	40.7	44.3	44.7
M08	30	30	39.4
M18	30	28.6	30
M22	30	37.5	42.2
M24	30	37.5	42.2

It appears from the compliance monitoring that 16 out of 20 participants complied with their prescribed medication, two of the four participants still received mirtazapine at a therapeutic recommended dose (F19, M18). Participant F10 received a recommended clinical dose between weeks 0-3 (27.1mg) and received a low dose at weeks 3-6, however, this would still have some therapeutic effects. It is unlikely that these doses would be prescribed for

patients with treatment resistant depression; furthermore, the participant would have been likely to take the medication on an adhoc basis and this is not recommended as a therapeutic strategy. There were slightly higher doses of mirtazapine taken for the medication only group for the first 16 weeks of the study. This has been presented in a table below. Two participants withdrew from mirtazapine treatment between week 6 and week 16.

Table C5-39 shows the mean dose of mirtazapine (allowing for non compliance) for the total group and each treatment group at each time period

	Total group	IPT and mirtazapine	Mirtazapine only
Weeks 0-3	29.6	28.5	30.8
Weeks 4-6	31.7	30	33.4
Weeks 7-16	37.6	35.4	39.8

**Note that the above data excludes the 2 subjects who discontinued the mirtazapine treatment at week 7 (F01) and week 10 (F10).*

Although there are slight differences in the mean dose of the mirtazapine only group versus the combined group, it is unlikely to have a significant clinical effect as there is no evidence for 5mg variations yielding a differential clinical effect; clinical experience also bears this out.

Adverse events

Table C5-40 shows the adverse events reported for each participant

Participant	Week of study	Adverse event	Trial medication stopped
F01	2	swollen knees	yes
	7	weight gain	
	51	erratic mood	
F11	7	Cold	Yes
F21	14	Itchy face	
F21	30	weight gain	
M04	6	increased anxiety symptoms	
MO6	4	Cold	
M15	4	Damaged ligament to left knee	
M16	33	Chest infection	
M23	5	Flu	
F03	12	Agitated and took 10 clonazepam	
F10	6	Rage/irritability attacks	Yes
	10	Rage/irritability attacks and anxiety	
M07	1	Low potassium level	

Three participants stopped treatment with mirtazapine due to adverse events; two were due to weight gain and one due to increased anxiety symptoms.

Concomitant medication

Table C5-41 shows the use of concomitant medication used for each participant

Subject ID	Week number	Trial drug stopped	medication
F01	7	yes	Citalopram 60mg Epilim chrono
F21	30	yes	Venlafaxine 75mg
F21	34		GP stopped Venlafaxine
M04	6		Lorazepam 1mg nocte Lorazepam 0.5mg BD
M06	6		Lemsip PRN
M23	5		Lemsip PRN
F03	10		Clonazepam 500mcg PRN
	10		Zimovane 7.5mg
F10	6		Amisulpride 100mg BD
	7		Carbamazepine 100mg BD
	10	yes	Stop carbamezepine
			Venlafaxine 75mg then
	11		Venlafaxine 150mg
	12		Stop venlafaxine
			Start Seroxat 50mg
	18		Seroxat 60mg
	18		Diazepam 5mg BD, 2mg BD
	18		Zimovane 7.5mg
M07	3		Zimovane 7.5mg 4 weeks Lorazepam 1mg

Chapter Six - Sequential dopamine D2 receptor mapping in treatment resistant depression

Introduction

I123- Iodobenzamide (IBZM) is a radioligand which has a strong affinity for the neurotransmitter dopamine, specifically the subtype dopamine D2 receptor (Kung et al, 1989; Seibyl et al, 1992). The I123 IBZM ligand is administered intravenously to an individual and binds to the dopamine D2 receptor sites and emits radiation apparently as one gamma ray photon per adhered molecule per receptor, as well as from free ligand. Single Photon Emission Computed Tomography (SPECT) imaging then maps the binding of this radioligand to the dopamine D2 receptor sites in the brain and computes their precise location. These functional brain scans can give us some insight into the dopaminergic activity in depressed patients compared to controls; they can also identify functional changes in the dopaminergic system in response to antidepressant treatment. As dopamine has been implicated in depressive disorder, SPECT functional brain imaging allows us to carry out in vivo assessments of depressed individuals to gain a greater awareness of the functioning of the brain in depression.

There is a paucity of literature available examining dopamine D2 receptors using SPECT scans in depressed patients. Of the studies reviewed, findings demonstrate that depressed subjects who respond to treatment with total sleep deprivation (Ebert et al 1994), or SSRI treatment (Klimke et al, 1999) show decreased IBZM binding ratios on the right basal ganglia (Ebert et al 1994) compared to non responders. Only one study has examined depressed patients who had not responded to a trial of tricyclic antidepressant medication (Klimke et al, 1999). No study has evaluated the effect of treatment resistant depression using IBZM SPECT imaging.

Design

This was a parallel group study of a comparison of IBZM SPECT before and after 6 weeks of treatment with mirtazapine alone or mirtazapine plus Interpersonal Psychotherapy in treatment resistant depressed participants.

Method

Twenty three participants who had been unresponsive to at least 6 weeks of an adequate dose of an antidepressant agreed to enter the trial. Three subjects (largely due to "personal reasons") withdrew their consent before the study commenced. This clinical trial received ethical approval from Sunderland Ethics Committee in advance of the start of study. In addition, Professor David Williams, Chief Medical Physicist obtained the necessary consent from Administration of Radioactive Substances Committee (ARSAC) for the use of the IBZM SPECT scans at the same time.

Before treatment started, a baseline assessment of clinical symptoms was conducted by the author using the Structured Clinical Interview for the DSM IV (SCID). Demographic information for each participant was collected at the same time.

All participants took a single oral dose of 120mg potassium iodide the day before each IBZM SPECT scan, a standard procedure used to protect the thyroid gland during scanning. Following a three day antidepressant washout phase, IBZM SPECT scans took place at week 0, before either treatment had started. A psychiatric nurse who was blind to the subjects treatment condition rated depression and anxiety (using the Hamilton depression scale and the Hamilton anxiety scale) on the same day as the first IBZM SPECT scan. The subjects were given the Beck Depression Inventory and the Social Adaptation Scale at the same time by the blinded rater who would collect the ratings. After 6 weeks of randomly assigned treatment with mirtazapine or mirtazapine plus

Interpersonal Psychotherapy the same process of ratings was carried out. This took place on the same day or one day either side of the IBZM SPECT scan.

SPECT procedure

Quality control and performance tests

The Medical Physics Department in Sunderland Royal Hospital arranged a quality control programme to monitor the camera performance. This took place before any participants entered the trial. The quality control measures helped to establish the sensitivity and uniformity of the scans and the range of expected results. Performance tests used the ligand I-123 before imaging any participants with I-123 IBZM; the camera uniformity of response to I-123 was routinely measured before scanning using I-123 IBZM.

In order to establish the best settings for imaging with IBZM two performance tests were carried out. One test measured the performance perimeters, and the second used a phantom (or model) which simulates the basal ganglia (the area most concentrated with dopamine receptors). The images were acquired (obtained) using 2 ligands, technetium and I123; this helped the medical physicists establish which collimators were needed to achieve the best quality of the image. The tests showed that a long time (1 hour) was needed to obtain a good quality SPECT image. A method was devised for scanning in four consecutive sections so that should the participant become restless or move, the data from the whole scan would not be lost.

Scanning method

The author accompanied each subject during their first IBZM SPECT scan, which took place at Sunderland Royal Hospital. The whole procedure would take about three and a half hours. The participants were asked to lie quietly on a bed for a few minutes, and then a technician administered an intravenous injection of the IBZM radioligand into the back of the participant's hand. Participants were requested to close their eyes during this procedure and for a couple of minutes

afterwards to allow an equal distribution and uptake of the IBZM radioligand. After a short period the participants was then taken to a comfortable waiting area for a small snack and drinks, and wait for two hours. During this time the participant was asked not to walk around, or to read any complex (such as crossword puzzles) upsetting or distressing material to restrict the effect this may have on the functioning of the brain.

The participants were scanned two hours post injection and the scan took one hour, ending at three hours post injection. The MEAP collimators were used and the data was acquired on 128 x 128 matrix with a pixel size of 4.5mm. The camera made 32 steps per 180 degree rotation acquiring two sets of projection data at each. The camera first rotated clockwise then anticlockwise, and then repeated the movement. Four rotations were given 256 projections altogether which were combined to give a projection data for one rotation of 64 projection. The acquisition times were 28 seconds per step giving a total scanning time of one hour.

Reconstructions

All the scans were reconstructed using filtered back projection. In order to choose a filter, a study of the basal ganglia phantom was reconstructed using different filters and different orders, and different cut off values for each filter. A Stretch Gaussian filter was chosen with optimum filtration and cut off. Attenuation is the process by which radiation is reduced in intensity when passing through matter due to either absorption or scatter. During reconstruction, attenuation correction was applied and the effects of small changes in the value of the attenuation co-efficient was investigated and found to be negligible.

Analysis of Regions of Interest (ROI) using BRASS to obtain IBZM uptake values

The Brain Registration and Analysis Software Suite (BRASS) is a quantitative analysis program for the automatic fitting of brain perfusion

(blood flow) scans which provides quantification and localisation of abnormal perfusion regions. It was originally developed to analyse cerebral blood flow SPECT images (Radau et al, 2001, Slomka et al, 2001) and later developed to analyse other images including iodine-123-IBZM dopamine receptor images (Radau et al, 2000). The program fits and compares participant images to three-dimensional references templates created from images of normal controls (Slomka et al, 1995). Each participant is aligned to each other and the template. Defects are quantified against a database of ten normal control participant on the voxel level; therefore the marked voxels can be assessed statistically, using the standard deviation criterion. Defects can also be determined by analysis within a 3 dimensional map of regions of interest.

BRASS used in this study uses *anisotropic-linear scaling* (linear transformation of areas) tending to a different shape to compensate for the anatomic variations between the brains of various individuals.

Results

Overview

A number of nuclear masses which have concentrations of dopamine producing cells are located in the midbrain and hypothalamus (van den Pol et al, 1996). Components of these masses are collectively known as the basal ganglia, groupings of which are known as the right or left striatum. IBZM is a radioligand with a strong affinity for dopamine D2 receptors. The use of SPECT allows in vivo studies of the dopamine D2 activity of depressed participants. Correlations of clinical variables associated with depression can also be assessed. Radiopharmaceuticals including IBZM, also demonstrate non specific binding which potentially could confound interpretation of the results. In order to address this issue, functional imaging studies compare the binding of the area under investigation, with another unrelated region of interest. By comparing the mean counts in these two areas a control for the non specific binding characteristics of the radiopharmaceutical is introduced. As the cerebellum does not contain

dopaminergic pathways and had not been implicated in depression, it was chosen as a reference region.

In addition to a straight forward comparison of the two treatment groups, the author wished to assess if there were any changes in dopamine function brought about in relation to a number of important variables. These included: responders versus non-responders, the level of treatment resistant depression, agitated participants versus non-agitated participants and gender.

Treatment groups

The mean uptake ratio, standard deviation and standard error for each participant in each treatment group are reported in table C6-1.

Table C6-1 demonstrating mean uptake ratios for treatment group in the striatum using the cerebellum as a reference region

		Week 0	Week 6
Treatment group	IPT and mirtazapine N=9	Right-90.98, sd 54.55, se18.19	Right-87.30, sd, 61.15, se 20.38
		Left-88.06, sd64.60, se 21.53	Left-91.73, sd 64.51, se 21.50
	Mirtazapine only N=10	Right-112.45, sd 50.50, se 16.83	Right-118.26, sd 45, se 15
		Left-108.29, sd 41.42, se 13.80	Left-114.62, sd 39.78, se 13.26

A Treatment Group repeated measures analysis of variance (ANOVA) did not detect any significant effects of Time ($F=0.000$, $p= 0.99$) or Hemisphere ($F= 0.056$, $p= 0.815$) and there were very small effect sizes and low power for both variables as demonstrated by a partial eta squared 0.000, 0.004 and power of 0.05 and 0.056 respectively. The two way interactions of Time X Group ($F0.162$, $p= 0.85$), Hemisphere X Group ($F=0.24$, $p= 0.79$) and Time X Hemisphere ($F=0.20$, $p= 0.66$) also did not detect any significant interaction and demonstrated similarly low effect sizes and insufficient power (partial eta squared 0.02, 0.029, 0.012; power 0.071, 0.081, 0.070 respectively). The three way interaction, Time X Group X Hemisphere yielded similar results ($F=0.203$, $p= 0.819$, partial eta squared 0.025, power 0.076). The failure to detect any significant changes using the repeated measures ANOVA model in addition to the small effect sizes leaves little doubt there are no differences in IBZM uptake binding between the two treatment groups.

Responders / nonresponders

The mean uptake ratio, standard deviation and standard error for responders and non-responders are reported in table C6-2.

Table C6-2 demonstrating mean uptake ratios in the striatum for responders and non-responders using the cerebellum as a reference region

		Week 0	Week 6
Responders vs. non- responders	Responders N=7	Right-66.36, sd 42.64, se 16.12 Left-57.40, sd 38.14, se 14.41	Right-55.69, sd 35.98, se 13.60 Left-61.79, sd 34.44, se 13.10
	Non-responders N=12	Right-116.41, sd 51.42, se 14.84 Left-116.14, sd 51.86, se 14.97	Right-123.61, sd 50.70, se 14.64 Left-120.73, sd 53.72, se 15.51

The reduction in the clinical scores on the clinician rated Hamilton Depression Scale provided an indication of the range and level of response to treatment in between IBZM SPECT scans. This is presented in the table below.

Table C6-3 shows the percent change scores in the Hamilton depression scale

Responders ≥40%	Partial responders 25-39%	Poor responders 0-24%	Deterioration Minus scores
F05 (45%)	F21 (33%)	F01 (3.6%)	
F11 (45%)	M06 (25%)	M16 (21%)	
F12 (40%)		M23 (6%)	
M04 (48%)			
M15 (63%)			
M18 (63%)	F03 (33%)	F17 (4%)	F20 (-3%)
M24 (40%)	F10 (30%)	F19 (15%)	M07 (-17%)
		M08 (0%)	M22 (-16%)
N=7	N=4	N=6	N=3

Due to small numbers the SPECT analysis compared responders (at least 40% reduction in Hamilton depression scores) to non-responders (less than a 40% reduction in scores). SPECT analyses of the level of response during the six weeks of treatment using BRASS followed by SPSS analysis are detailed below.

There were 7 participants who demonstrated a minimum of 40% reductions in the Hamilton depression scores after 6 weeks of treatment and 12 who had not. A Response X Time X Hemisphere repeated measures ANOVA detected a significant main effect of Response $F(1,17) = 7.67, p=0.013$, indicating that there was a smaller mean uptake ratio in the striatum using the cerebellum as a reference region among responders when compared to non-responding participants (60.32 (SE 16.92) vs. 119.23 (SE 12.92). The effect size was large as demonstrated by a partial eta squared 0.311, (power = 0.74). Neither of the main other effects of Time (week 0 vs. week 6), or Hemisphere (right vs. left striatum), were significant ($F = 0.048, df = 1, p=0.83$; $F = 0.20, df = 1, p=0.66$ respectively). Further, none of the two way interactions (Time X Response, $F = 0.52, df = 1, p=0.48$; Hemisphere X Response $F = 0.00, df = 1, p=0.98$; Time X Hemisphere $F = 1.64, df = 1, p=0.22$) were significant; additionally small effect sizes were evident for each of the two way interactions (0.029; 0.00; 0.088 respectively). The three way interaction (Hemisphere X Response X Time) approached significance ($F = 3.31, df = 1, p=0.087$), there were moderate effect sizes (partial eta squared 0.163) and although there was low power (0.403) in this study for this effect (accounting for over half the variance found for the significant response effect) we cannot exclude the possibility of a three way interactional effect superimposed on the response main effect given the large interaction effect size, low power, and a result approaching significance. Thus although responders demonstrated a significantly lower mean IBZM uptake than non responders this effect may be somewhat influenced by the combined effects of time and hemisphere.

Level of treatment resistant depression

The author established the different levels for treatment resistant depression based on the number of failed antidepressant trials, the total number of months depressed during the participants' lifetime and the duration of the current depressive episode. All of this data considered in combination would indicate where each participant would be classified in the spectrum of treatment resistance.

The author did not use the Thase / Rush guidance on levels of treatment resistant depression. This was for a number of reasons: Using this guidance, participants must have been prescribed at least one course of tricyclic antidepressant treatments in order to reach the minimum level of treatment resistance. There were participants who had numerous failed antidepressant medications, none of which were a tricyclic antidepressants and therefore were not considered resistant to treatment according to Thase/Rush guidance. Furthermore, these guidelines were published in 1995, when the clinical use of the tricyclic antidepressants was more common. Since the introduction of the newer generation of the antidepressants such as the SSRI's or the SNRI's, prescription habits have changed. More choice and concerns about safety and tolerability led to a reduction in the prescriptions for tricyclic antidepressants.

Another consideration to note is the limited evidence to date regarding switching classes of antidepressant medication in order to increase the potency of the antidepressant treatment. There are suggestions which support the changes within the same antidepressant class, outlining that there are significant pharmacokinetic and pharmacodynamic differences to justify this approach (Fava, 2001; Bondolfi et al, 1996). Bearing this in mind, the author felt it was inappropriate to exclude changes within classes from the assessment of the levels of TRD.

The author considered the number of previous failed antidepressant treatment trials to be a baseline for establishing the level of treatment resistance. This was split into categories of mild (only one previous failed antidepressant trial), moderate (two failed antidepressant trials), or severe (three or more failed antidepressant trials). Furthermore, the number of previous months depressed during the participant's lifetime was examined within each basic category, this may allow for the overlap between the number of failed antidepressant treatments and the duration of life time depressive episodes. Three categories were included: 12 months or less of lifetime depression, 13-29 months of lifetime depression and at least 30 months of lifetime depression. The three levels are demonstrated in the table below.

Table C6-4 demonstrates the definition of the levels of treatment resistant depression for this study

MILD – 1 x failed antidepressant treatment

- a). 1 x failed antidepressant treatment plus ≤ 12 months life time depression
- b). 1 x failed antidepressant treatment plus 13 -29 months life time depression
- c). 1 x failed antidepressant treatment plus ≥ 30 months life time depression

MODERATE – 2 x failed antidepressant treatment

- a). 2 x failed antidepressant treatment plus ≤ 12 months life time depression
- b). 2 x failed antidepressant treatment plus 13 -29 months life time depression
- c). 2 x failed antidepressant treatment plus ≥ 30 months life time depression

SEVERE - 3 x failed antidepressant treatment

- a). 3 x failed antidepressant treatment plus ≤ 12 months life time depression
- b). 3 x failed antidepressant treatment plus 13 -29 months life time depression
- c). 3 x failed antidepressant treatment plus ≥ 30 months life time depression

Table C6-5 below shows increasing treatment resistance based on the number of failed antidepressant trials added to the increasing time suffering with depressive symptoms during the participant's lifetime. There were 7 participants who were categorised as in the middle / upper range of mild treatment resistance, 5 in the combination group and 2 in the mirtazapine only group. A further 7 participants were categorised as moderately treatment resistant, only one was at the lower end of the category and the remaining 6 bordered the severe category. Most of these participants were in the medication only group (5 vs. 2 in the combined treatment group). Finally, eight (40%) of the study group were categorised as severely resistant to treatment; there were more participants allocated to the combined group in this category.

Table C6-5 demonstrates the levels of treatment resistant depression for all the participants in the study

ID	Mild			Moderate			Severe		
	a	b	c	a	b	c	a	b	c
1									X
5									X
11						X			
12		X							
21						X			
4								X	
6			X						
15		X							
16									X
23								X	
3						X			
10			X						
17						X			
19									X
20									X
7		X							X
8		X							
18				X					
22						X			
24						X			

Impact of the levels of treatment resistant depression (TRD)

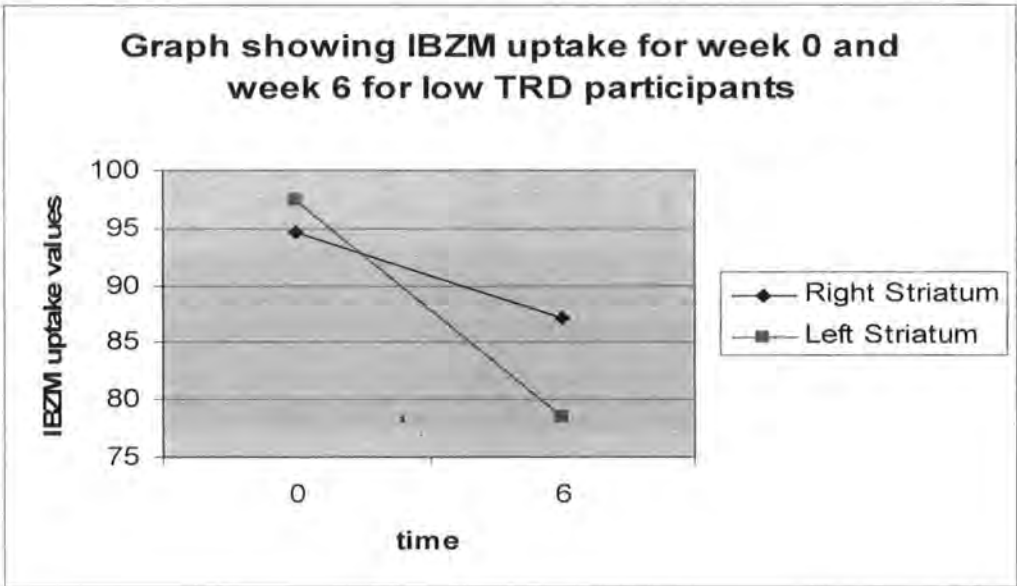
The mean uptake ratio, standard deviation and standard error for each level of treatment resistant depression are reported in table C6-6.

Table C6-6 demonstrating mean uptake ratios for TRD level in the striatum using the cerebellum as a reference region

		Week 0	Week 6
Levels of TRD	High TRD N=7	Right-87.60, sd 57.13, se 21.59 Left-77.52, sd 48.97, se 18.51	Right-80.54, sd 32.94, se 12.45 Left-90.91, sd 24.85, se 9.39
	Moderate TRD N=6	Right-113.43, sd 58.19, se 23.75 Left-111.38, sd 68.85, se 28.11	Right-131.06, sd 74.68, se 30.49 Left-129.04, sd 80.95, se 33.05
	Low TRD N=6	Right-94.62, sd 49.60, se 20.25 Left-97.45, sd 48.36, se 19.74	Right-87.16, sd 50.30, se 20.54 Left-78.44, sd 43.26, se 17.66

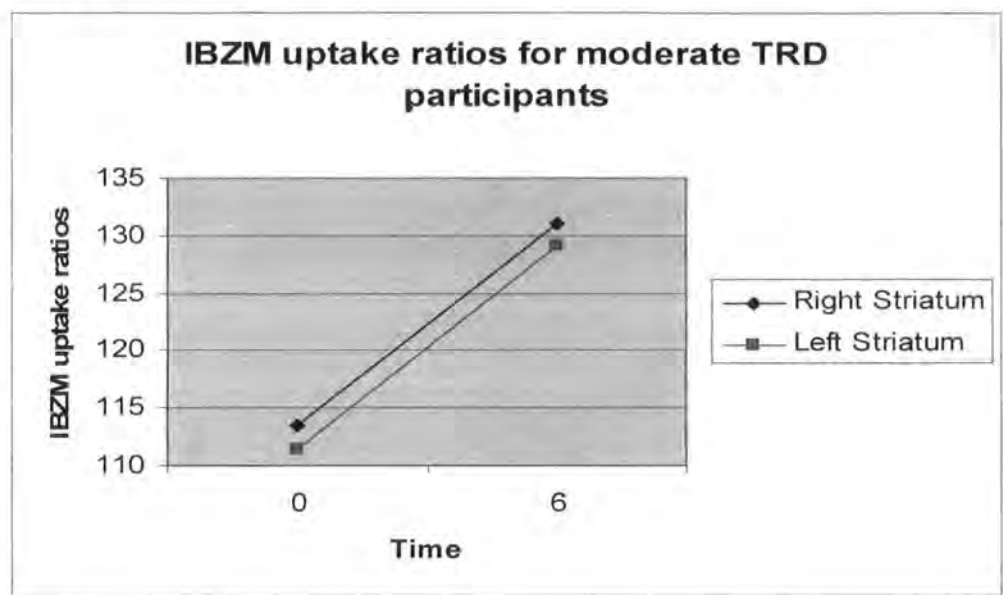
Participants were separated into three levels of resistant depression, low (n=6), moderate (n=6) and high (n=7). A TRD Level X Time X Hemisphere repeated measures of variance analysis detected a significant 3 way interaction $F(2, 16) = 5.46, p = 0.016$. The TRD effect was large accounting for over 40% of the variance (partial eta squared 0.406, power of 0.771). To explore the interaction, separate repeated measures ANOVA's were conducted for each level of TRD. No effects were found for the low and moderate TRD levels (although the Time X Hemisphere interaction for the moderate TRD group was approaching significance $F(1, 5) = 5.194, df, 5, p=0.072$ with a large effect size of 0.51 but inadequate power 0.451). The graphs below (C6-5 and C6-6) demonstrate the non-significant pattern of change in the right and left striatum in participants with low and moderate levels of treatment resistant depression.

Graph C6-7 showing IBZM uptake for week 0 and week 6 for low TRD participants



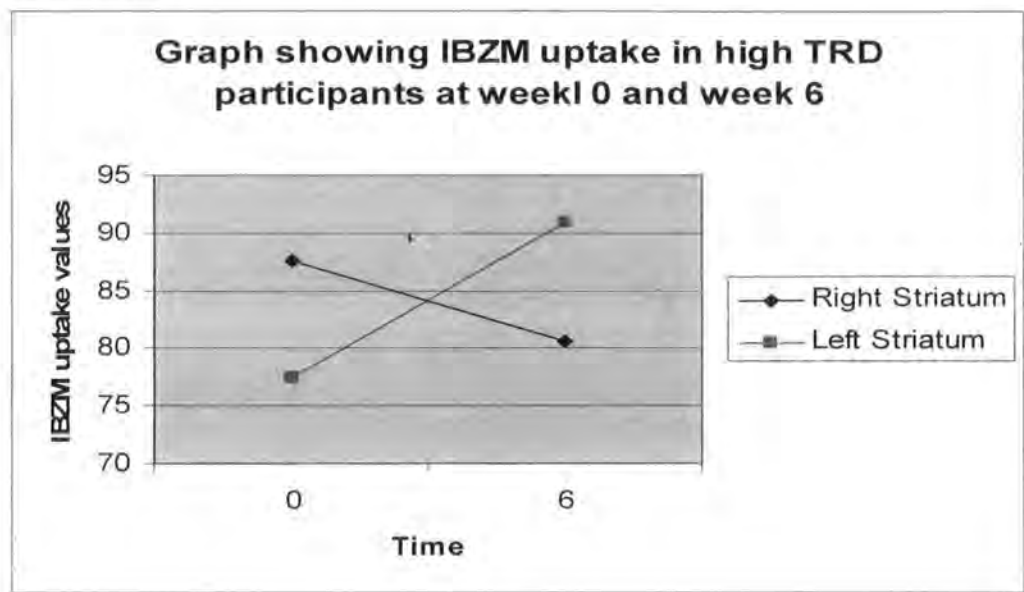
Although there are decreased binding patterns in the low TRD group and increased IBZM binding in the moderate TRD group, the degree of change was not statistically significant, but may have been contributing to the significant three-way interaction effect.

Graph C6-8 showing IBZM uptake for week 0 and week 6 for moderate TRD participants



A significant interaction between time and hemisphere was detected among the high TRD participants $F(1, 16) = 31.593, p = 0.001$. There was both a large effect size of 0.84 and high power (0.99). No differences between the mean uptake ratios were detected for either the right or left striatum using the cerebellum as a reference region at week 0 ($t = 1.61, p = 0.158$) and week 6 ($t = -1.86, p = 0.113$) however significant differences ($t = 5.62, p = 0.001$) were observed in the change scores in both the right (7.06, SE 11.19) and left (-13.39 SE 11.41) striatum (7.06 vs. -13.39). Thus there was an asymmetrical IBZM binding in high TRD participants with a decreased binding on the right and an increased binding on the left which can be clearly seen on graph C6-7 below.

Graph C6-8 showing IBZM uptake for week 0 and week 6 for high TRD participants



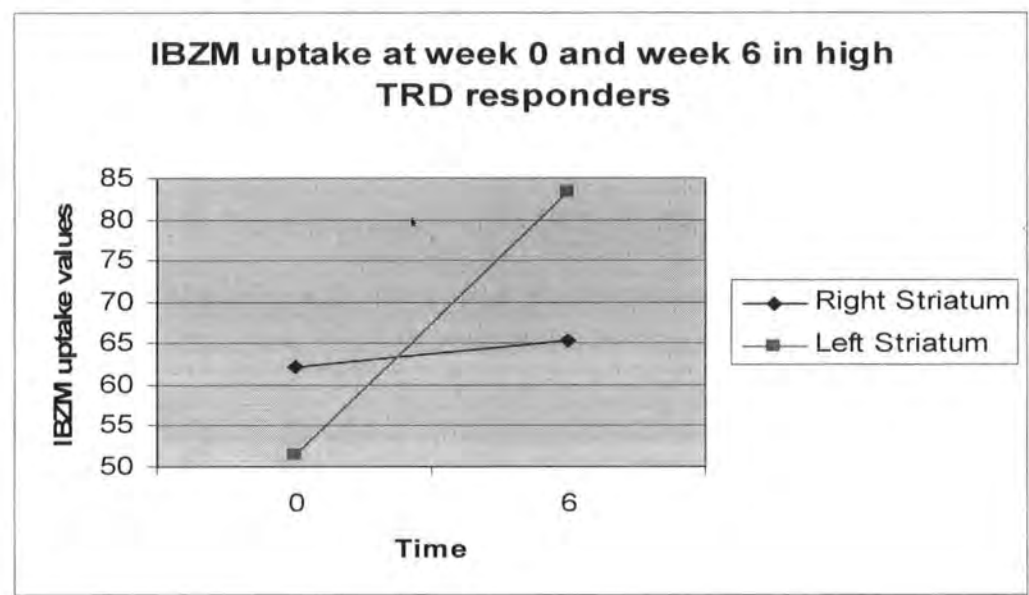
Although the 7 high TRD participants were analysed as a group as described above, inspection of individual response data showed that three of these participants had in fact responded to 6 weeks of antidepressant treatment with IPT and mirtazapine (n=2) or mirtazapine alone (n=1).

There were no plans at the start of the trial to investigate this further as one consequence of multiple testing is to increase the risk of a type I error. However, the author considered that the retrospective data collection approach may have incorrectly identified participants to be high TRD, and having responded to just 6 weeks of antidepressant therapy these participants may not be as severely resistant to treatment.

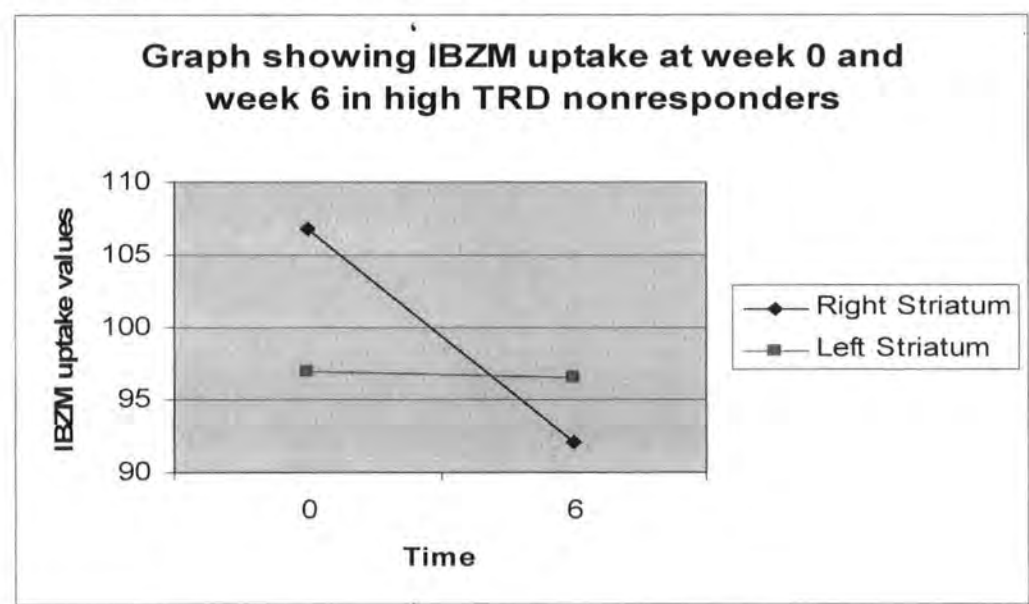
A subsequent analysis splitting this small group of seven on response in order to address any response interaction effects was conducted. There was a significant effect of Time X Hemisphere ($F(1,5)=79.53$, $p=0.0001$) which accounted for 94% of the variance (partial eta 0.941) with a high power (1.0). There was a significant three way interaction for Time X Hemisphere X Response ($F(1,5)=8.97$, $p=0.03$) with a partial eta of 0.642 and power of 0.671. There was no significant interaction for Time ($F(1,5)=0.205$, $p=0.671$) or Time X Response ($F(1,5)=1.29$, $p=0.307$) detected. The table below shows the mean IBZM uptake ratio in the right and left striatum using the cerebellum as a

reference region in the high TRD responders (n=3) and the high TRD non-responders (n=4).

Graph C6-10 showing IBZM uptake for week 0 and week 6 for high TRD responding participants



Graph C6-11 showing IBZM uptake for week 0 and week 6 for high TRD non-responding participants



Agitation

The author wished to examine the impact of agitation on the IBZM uptake in the participants studied. This could be examined using Item 9 on the Hamilton depression scale (agitation) to assess high levels of agitation (a minimum score of 2). There were 13 subjects however who remained significantly agitated on item 9 of the Hamilton depression scale at both weeks 0 and 6. This data is listed on the table below.

Table C6-12 demonstrates significant symptoms of agitation at weeks 0 and 6 in each treatment group

Week 0 and 6 IPT group	F01, F11, F12, M04,
Week 0 and 6 mirtazapine group	F03, F10, F17, F19, F20, M08, M18, M22, M24

The mean uptake ratio, standard deviation and standard error for are reported for agitation in table C6-13.

Table C6-13 demonstrating mean uptake ratios for agitated participants in the striatum using the cerebellum as a reference region

		Week 0	Week 6
Agitation	Agitated N=13	Right-116.10, sd 53.39, se 14.80	Right-114.72, sd 58.14, se 16.13
		Left-112.10, sd 56.06, se 15.55	Left-111.47, sd 59.06, se 16.39
	Non-agitated N=6	Right-58.72, sd 25.87, se 10.56	Right-63.62, sd 32.10, se 13.10
		Left-56.38, sd 24.93, se 10.18	Left-72.04, sd 34.65, se 14.15

There were 13 participants in this study who obtained high scores (above 2) on the Hamilton depression scale and 6 non-agitated participants. An Agitation X Time X Hemisphere repeated measures ANOVA detected a significant main effect of agitation $F(1, 17) = 4.67, p = 0.045$, indicating there was a larger mean uptake ratio in the striatum using the cerebellum as a reference region among agitated participants (113.60 (SE 13.24) vs. 62.69 (SE 19.49). This difference corresponded to a large effect size as demonstrated by a partial eta squared 0.215; however, power was barely adequate (0.531). Neither of the other main effects of time (week 0 vs. week 6) or hemisphere (right vs. left striatum) were significant ($F = 0.51, df = 1, p = 0.48$; $F = 0.97, df = 1, p = 0.93$ respectively). Further, none of the two way interactions (Time X Agitation, $F = 0.76, df = 1, p = 0.40$; Hemisphere X Agitation, $F = 0.97, df = 1, p = 0.34$; Time X Hemisphere, $F = 1.14, df = 1, p = 0.30$) nor the three way interaction were significant ($F = 0.87, p =$

0.36). Small to medium effect sizes were evident which at this point probably cannot be attributed to anything other than natural variance in a trial given that the agitation main effect is more than 4 times greater (partial eta squared results for Time = 0.029, Hemisphere = 0.000, Time X Agitation = 0.043, Hemisphere X Agitation = 0.054, Time X Hemisphere = 0.063). Given these effect sizes and sample sizes, there was low power to detect any of the interactions under analysis (0.104, 0.13, and 0.14 respectively).

The agitation effect was large, accounting for approximately 21% of the variance (partial eta squared 0.215 power of 0.531) whereas none of the other effects accounted for more than 6%. This indicates that the agitation effect accounted for between three and four times more the variance than any other effects. Consequently, given both the low absolute effect sizes of these other effects and the fact that agitation accounts for a great deal more variance, it is unlikely that the other non significant effects would be of interest. Thus it is concluded that more agitated participants showed greater IBZM uptake than less agitated participants.

Gender

The mean uptake ratio, standard deviation and standard error for are reported for gender in table C6-14.

Table C6-14 demonstrating sex differences in the mean uptake ratios in the striatum using the cerebellum as a reference region

		Week 0	Week 6
Gender	Male N=9	Right-67.06, sd 43.48, se 14.49 Left-66.50, sd 41.59, se 13.86	Right-67.96, sd 46.54, se 15.51 Left-67.27, sd 34.90, se 11.63
	Female N=10	Right-125.80, sd 46.66, se 14.76 Left-119.71, sd 54.07, se 17.10	Right-126.14, sd 50.64, se 16.01 Left-127.59, sd 55.03, se 17.40

A Gender X Time X Hemisphere repeated measures ANOVA detected a significant effect of gender $F(1,17) = 7.4, p = 0.015$, indicating that there was a larger mean uptake ratio in the striatum among females when compared to males (124.24 (SE 14.47) vs. 67.37 (SE 15.46)). Neither of the other main effects of Time (week 0 versus week 6), or Hemisphere (right versus left striatum) were significant ($F = 0.16, df = 1, p = 0.69$; $F = 0.65, df = 1, p = 0.65$ respectively). Further, none of the two way

interactions (Time X Gender $F = 0.071$, $df = 1$, $p = 0.79$; Hemisphere X Gender $F = 0.069$, $df = 1$, $p = 0.79$; Time X Hemisphere $F = 0.59$, $df = 1$, $p = 0.47$) nor the three way interaction were significant ($F = 0.58$, $df = 1$, $p = 0.54$). The gender main effect was large, accounting for approximately 30% of the variance (partial eta squared 0.302, power 0.705) whereas none of the other effects accounted for more than 3% (partial eta squared, Time = 0.01, Hemisphere = 0.03). This indicates that the gender effect accounted for ten times more variance than hemisphere and 20 times more than any of the other interaction effects (Time X Gender = 0.002, Hemisphere X Gender = 0.023, Time X Hemisphere = 0.033, Time X Hemisphere X Group = 0.033). Consequently, given both the low absolute effect sizes and the fact that gender accounts for a great deal more variance, it is unlikely that other non significant effects would be of interest. It is thus concluded that there was a significantly greater IBZM uptake in the striatum among women compared to men.

Chapter seven - Patterns of change

Reliable Change Index

In order to evaluate depressive symptoms during this psychotherapy trial the author used the clinician rated Hamilton depression scale and the self report Beck Depression Inventory as measures of depression. Typically, psychiatric research identifies percentage reductions in the depression rating scales, with 50% reduction demonstrating a significant improvement. However, there are limitations to this approach; for example a 50% reduction in the Hamilton depression scores from 36 (severe) to 18 (moderate), or from 18 (moderate) to 9 (mild) yield very different clinical presentations. Although the scores have fallen by more points in the first case, this patient is still moderately depressed, in fact, sufficiently depressed to enter a clinical trial for depression. Hence it is reasonable to assume despite the 50% improvements in depression scores, there remains a significant debilitating effect of the depression. In contrast the second example has demonstrated a 50% reduction in scores but would be only considered mildly depressed, with limited, if any impact on their social and interpersonal functioning. In addition to this approach the author used a reliable change index (RCI) (Jacobson and Truax, 1991) which is alternative strategy than that used by general psychiatric researchers; it is conceptually superior to percentage change or Clinical Global Impression ratings in that it takes into account the reliability of the rating scale. A RCI is computed by dividing the difference between the pre-treatment and post-treatment scores by the standard error of the difference between the two scores. A RCI of a greater score than 1.96 is a change of a large magnitude which cannot be attributed to chance ($p < 0.05$) and so is attributed to the treatment. Indeed all measures are to varying degrees unreliable. A RCI score of less than 1.96 is not considered reliable and may reflect fluctuations of an imprecise measuring instrument.

Based on data from the literature and this study a drop of 4 points on the Hamilton Depression scale and 11 on the Beck Depression Inventory would signify a reliable change in depression scores. The model is then extended further to identify a specific point at which the reliable change becomes a clinically significant improvement (Jacobson and Truax, 1991). This can be difficult to conceptualise or measure in statistical terms, and often “rules of thumb” or published cut scores are used. Jacobson and Truax (1984) approached this statistically by using the concept that at the beginning of therapy clients enter treatment as part of a dysfunctional population; and leave following successful treatment as part of a normal or functional population (Jacobson and Truax, 1984). This is demonstrated by post treatment levels of functioning falling outside of the dysfunctional population, within the range of the non-clinical population and closer to the mean of the functional population than the dysfunctional population.

In order to identify participants who have demonstrated clinically significant and reliable change, data needed to be obtained for the normal population and the dysfunctional population (i.e. TRD population). This was obtained from data published in previous studies and is presented in the tables below (C7-1, C7-2, C7-3, and C7-4). The individual study means and standard deviations were weighted by the sample size. Larger numbers of treatment resistant depression studies of the Hamilton Depression Scale were published than for the Beck Depression Inventory. Similarly, there were more data available for non-clinical participants on the Hamilton Depression Scale than the Beck Depression Inventory.

Jacobson and Truax (1991) suggest that when these data are available the point which lies at the intersection between the two distributions is the recommended cut off point (cut score C) for clinically significant change. This would be a Hamilton depression score of 12 and a Beck Depression Inventory score of 16.

Table C7-1demonstrating Hamilton Depression scores taken from clinical population in previous TRD studies

Study	n	m	sd
Avery et al 05	35	23.50	3.90
Avery et al 05	33	23.50	2.90
Carpenter 02	13	21.90	3.80
Carpenter 02	13	22.50	5.80
Dannon and Grunhaus 01	17	22.50	8.00
deMontigny 99	159	25.60	
Dinan and Moybayed 92	13	25.00	7.20
Fava 94	41	18.10	2.30
Fava 02	101	20.70	2.90
Gitlin 1987	16	23.10	4.00
Grunhaus 03	20	25.50	5.90
Grunhaus 03	20	24.40	3.90
Huang 05	11	26.90	6.00
Joffe 93	17	20.20	5.40
Joffe 93	17	18.80	3.50
Joffe 93	16	18.70	4.50
Karp 05	46	22.30	3.70
Katona 95	17	18.30	3.80
Katona 95	16	18.70	3.30
Katona 95	12	17.30	3.10
Katona 95	17	19.90	4.30
Kauffmann 04	12	21.86	2.31
Kennedy 2003	21	23.10	3.90
Kennedy 2003	23	24.20	5.20
Little 98	19	22.20	4.20
MCKewan 88	114	26.70	
Nelsen and Dunner 95	26	22.70	5.20
Neirenberg 94	41	26.60	
Neirenberg 94	43	30.00	
Papakostas 2003	92	21.30	3.90
Perez 99	80	20.50	4.10
Perry 2004	21	29.00	7.00
Perry 2004	17	30.00	7.00
Petersen 01	92	21.30	3.90
Rush 05	210	28.80	5.70
Sackheim 01	60	36.80	5.80
Thase 02	117	24.60	6.40
Thase 02	50	25.00	6.00
Thase 1997	106	21.00	3.50
Whyte 04	25	21.20	3.50
Whyte 04	28	17.50	3.50
TOTAL	1847	23.21	4.58

Table C7-2 demonstrating results of Hamilton Depression scores taken from non-clinical population studies

The data in the table below was obtained from a review conducted by Zimmerman et al (2004).

Study	n	m	sd
Atmaca 02	16	5.10	2.10
Blackburn 86	31	2.20	2.30
Bungener 96	14	1.90	1.60
Bungener 96	34	5.50	4.20
Ceulemens 84	20	4.10	4.40
Fassino 02	80	2.90	1.60
Fasseno 02	80	3.20	1.70
Fava 82	40	6.10	5.00
Georgotas 86	25	1.90	
Gorand 95	10	3.00	0.70
Grundy 96	44	2.70	2.40
Gur 02	20	3.60	3.50
Hu 00	47	8.40	5.50
Kish 94	24	1.30	2.20
Lanquillon 00	15	0.60	1.10
Martin 94	31	4.10	4.00
Naranjo 84	16	0.80	1.30
Noder 90	13	1.50	1.80
Rehm and O'Hara 85	17	3.40	3.20
Rothrock 02	40	3.30	5.60
Rubin 02	20	0.20	0.40
Salctu 96	29	2.90	2.40
Scanlan 98	92	2.00	2.30
Szelenberger 01	14	0.50	1.20
Wahby 90	43	1.50	0.60
White 00	15	2.90	0.40
Williams 91	84	3.30	
Zorzon 01	110	3.10	3.60
TOTAL	1014	3.2	3.2

Table C7-3 demonstrating Beck Depression Inventory scores taken from clinical population in previous TRD studies

Study	n	m	sd
Avery 2005	35	28.10	8.70
Avery 2005	33	28.40	8.00
Gittlin 1987	16	29.10	6.70
Kaplan and Klinetob 2000	20	25.00	
Kennedy 2003	21	30.00	10.10
Kennedy 2003	23	28.50	9.30
Triggs 1999	10	32.00	8.00
TOTAL	158	28.7	6.7

Table C7-4 demonstrating results of Beck Depression Inventory scores taken from non-clinical population studies

Study	n	m	sd
Dent and Salkovskis, 1986	243	6.26	5.33
Lightfoot and Oliver, 1985	204	6.71	6.48
TOTAL	447	6.47	5.9

Using the approach suggested by Jacobson and Truax (1991) data for the normal population and a treatment resistant depressed population was gathered by the author (Hamilton depression scores; non clinical –mean 3.20, range 0.2-8.4, SD 3.20; treatment resistant depression data, mean 23.21, range 17.3-36.8, SD 4.58. Beck Depression Inventory scores; non clinical – mean 6.47, range 6.26-6.71, SD 5.9; treatment resistant depression data, mean 28.7, range 25-32, SD 6.47). There were more data available for the Hamilton Depression Scores for both the clinical and non-clinical scores compared to the Beck Depression Inventory. A total of 28 studies recruited 1847 TRD patients who were evaluated with the Hamilton Depression Scale, whereas only 5 studies of 158 TRD patients were rated using the Beck Depression Inventory. Although there were more subjects per study (n=447) reported in two studies for the non-clinical data using the Beck Depression Inventory; a review by Zimmerman and colleagues (2004) using the Hamilton Depression Scale reported data on 1014 subjects from 26 studies. The statistical formula used for computation of cut score C providing the point lies between the two groups is presented below.

$$C = \frac{(S2 \times M1) + (S1 \times M2)}{S1 + S2}$$

Where

- M1 = mean of the clinical / dysfunctional population
- M2 = mean of the non-clinical / normal population
- S1 = standard deviation of the clinical / dysfunctional population
- S2 = standard deviation of non-clinical / dysfunctional population

Using the above formula the cut scores for the Hamilton Depression (12) and Beck Depression Inventory (16) were identified which could be used to demonstrate clinically significant change.

Results section for the reliable change index (RCI) scores

Ten participants from each treatment group were measured over four time points (week 6, 16, 26 and 52). The differences from baseline to each of the four time points was calculated and compared to the RCI's for the Hamilton Depression scores and Beck Depression Inventory scores respectively. There were twice as many reliable improvements noted in the IPT group (n=36/40) compared to mirtazapine only group (n=18/40) on the Hamilton Depression Scale. Virtually identical results were observed in the Beck Depression Inventory. The column labelled 52-16 highlighted participants who had reliably deteriorated from week 16 by the end of the trial (IPT group, n=2; mirtazapine only group, n=4). A similar pattern was evident on the Beck Depression Inventory measurements although on this measure fewer participants deteriorated from between week 16 – week 52 in the IPT group versus mirtazapine (1 vs. 6 respectively). Participants who demonstrated reliable change in Hamilton Depression and Beck Depression Inventory scores are listed in the table below (table C7-5)

Table C7-5 demonstrating reliable change in Hamd and BDI scores

	HamD					BDI				
	6	16	26	52	52-16	6	16	26	52	52-16
F01			X	X		X		X	X	
F05	X	X	X		X	X	X	X	X	
F11	X	X	X	X		X	X	X	X	
F12	X	X	X	X		X		X	X	
F21	X	X	X	X		X	X	X	X	
M04	X	X	X	X	X	X	X	X		X
M06	X	X	X	X						
M15	X	X	X	X		X	X	X	X	
M16	X	X	X	X				X	X	
M23		X	X	X		X	X	X	X	
F03	X			X						
F10	X			X					X	
F17			X	X				X	X	
F19		X	X		X	X	X	X		X
F20		X	X		X		X	X		X
M07			X						X	
M08										X
M18	X	X	X	X	X	X	X	X	X	X
M22							X	X	X	X
M24	X	X	X		X	X	X	X		X

Participants who demonstrated reliable change on the Hamilton Depression Scale and the Beck Depression Inventory (table C7-5) who in addition showed clinically significant change, i.e. their score fell below the respective cut scores, are highlighted in table C7-6 and C7-7. These tables identify two aspects of treatment; initial response, and the effects of this initial response over time. In terms of the initial response, participants who demonstrated changes by 6 weeks were considered “early responders”, 16 weeks “acute responders”, 26 weeks “delayed responders” and 52 weeks were “eventual responders”. This last category helped to differentiate between those participants who did not demonstrate changes in their depression scores, that is the “non responders” of the group. Response to treatment was recorded in the left side of the table (tables C7-6, C7-6).

The response over time was recorded in the shaded grey area in the right hand side of the table and included those participants who demonstrated a *sustained improvement*, (sustained reduction in depression scores or maintenance of improvement in scores); a “*deterioration after a response*” (initial response followed by a deterioration), or participants who followed a “*fluctuating course*” (participants who initially responded and then relapsed over the course of a year).

Table C7-6 demonstrating clinically significant and reliable change response and treatment effects over time – Hamilton depression score of 12 or below

Treatment response						Treatment effects over time		
	Early 6/52	Acute 16/52	Delayed responder	Eventual responder	Non- Responder	Sustained improvement	Deterioration after response	Fluctuating course
F01					X			
F05					X			
F11				X				
F12					X			
F21					X			
M04		X	X				X	
M06				X				
M15				X				
M16			X					X
M23		X	X	X		X		
F03					X			
F10					X			
F17					X			
F19		X					X	
F20					X			
M07			X				X	
M08					X			
M18		X					X	
M22					X			
M24		X	X				X	

Five participants had a Hamilton depression score of below 12 by the end of 16 weeks of acute treatment; two in the combined treatment group and three in the mirtazapine only group. By 26 weeks a further 2 participants demonstrated clinically significant improvements in depression scores, one from each treatment group. When considering the effects of treatment over time 3 participants demonstrated reduction in scores below the cut score by the end of treatment and all were from the combined treatment group; additionally, one participant from the combined treatment group sustained their clinical improvement from 16 weeks onward. Only one of the participants in the combined group deteriorated after a response, in contrast 4 of the mirtazapine only group deteriorated after a response; 2 participants shortly after the 16 week acute treatment and another 2 after six months.

Table C7-7 demonstrating clinically significant response and reliable change and treatment effects over time – Beck Depression Inventory scores of 16 or below

	Treatment response					Treatment effects over time		
	Early 6/52	Acute 16/52	Delayed responder	Eventual responder	Non- Responder	Sustained improvement	Deterioration after response	Fluctuating course
F01					X			
F05					X			
F11					X			
F12					X			
F21					X			
M04					X			
M06					X			
M15					X			
M16					X			
M23					X			
F03					X			
F10					X			
F17					X			
F19		X					X	
F20					X			
M07					X			
M08					X			
M18		X		X				X
M22					X			
M24					X			

Only two participants demonstrated a clinically significant treatment response using the reliable change index cut scores of 16 on the Beck Depression Inventory, both were receiving mirtazapine alone and the response was evident by the end of the 16 weeks of acute treatment.

One of these participants deteriorated after this initial response and the other followed a fluctuating course. Eighteen participants (90%) of the participants studied did not reach clinically significant improvements in Beck Depression Scores at any time point.

The reliable change index and cut scores were calculated using the data gathered by the author for clinical (TRD) and non-clinical populations. Much more data was available on the Hamilton Depression Scale than the Beck Depression Inventory; this suggested that the cut score used in this study for the Hamilton Depression Scale is likely to be more robust. Further, one important consideration of the reliable change index model is the data assumes a symmetrical distribution. This is unlikely for both depression scores on the non-clinical data as many subjects often score "0", leading to a positively skewed distribution.

Participants in this study were severely depressed as measured by the Hamilton Depression Scale and Beck Depression Inventory at baseline; additionally, most (n=15) had moderate/high levels of treatment resistant depression. The cut scores used in this trial for this treatment population were very stringent and are based on a recovery model. Taking into account the severity of depression, high levels of resistance and limited potency of antidepressant therapy, such rigorous cut score may not have been the best approach. An improvement model may have been more appropriate, i.e. where a cut score may be used to demonstrate when the participant has demonstrated significant improvements although may not be near to a full recovery. For example, the appropriate group reference could be those who have shown recovery from a first episode of depression providing scores are not used to define the groups.

Alternative methods of assessing outcome could be used in difficult to treat groups such as treatment resistant depression, for instance recognising improved social, interpersonal or work functioning, or if the participant continues to fulfil the diagnostic criteria for the index

diagnosis(es). The Structured Clinical Interview (SCID) conducted at the start of the trial may have provided this information and given some indication of functioning of the participant in a broader and more clinically meaningful way.

Chapter eight - Discussion

This research is original in a number of different ways: It is the first study to date to have assessed the feasibility, applicability and efficacy of IPT augmented to antidepressant medication in a treatment resistant depressed population. Furthermore, the sequential mapping of the dopamine D2 receptors using IBZM SPECT has never been undertaken in treatment resistant depression, or when addressing the potential effects of any psychotherapeutic approach. The statistical analysis of the clinical data has also been extended to include reliable change i.e. that which is both considered to have statistical significance taking into account consistency of the rating instrument and clinical meaning in terms of improved depression scores.

Thesis study 1: Interpersonal Psychotherapy for treatment resistant depression, a parallel trial

Twenty treatment resistant depressed participants received either mirtazapine alone (30-45mg) or mirtazapine at the same dose augmented to IPT. Up to 16 weekly IPT sessions were provided during the acute phase of treatment and followed by monthly maintenance sessions. On the clinician rated Hamilton Depression Scale and the Hamilton Anxiety Scale both treatment groups showed an improvement over time. Significant differences emerged between the two groups favouring the IPT group at week 26 and were maintained at week 52. There were no significant treatment effects noted on the Beck Depression Inventory.

Differences between the Hamilton Depression Scale and Beck Depression Inventory were unexpected. One possibility is that the raters used in this study were not blind to the treatment. However, neither of the clinical raters were working on the research unit and were geographically located in another department away from the research unit building; hence they were excluded from exposure to participants attending appointments. In addition, the author ensured appointments for

IPT were not made at a time when either of the two raters would attend the unit. The blind raters were aware that all of the participants, regardless of their treatment group would need to attend the research unit for appointments; further, they were unaware of the timing of interviews for the research protocol. Finally, participants were informed by the author not to tell the rater of their treatment allocation at the start of the trial, and were reminded of this request at the beginning of each rating session by the blinded rater. Both of the raters were informed at the start of the study to inform the author if they became aware of the treatment allocation; neither of the two raters informed the author that this had occurred. Hence, although blindness cannot be guaranteed it is unlikely that the raters influenced the discrepant results.

There have been differences between in self rated (Beck Depression Inventory) and clinician rated scales (Hamilton Depression Scale) which have been reported in other trials, including one trial of IPT (Sayer et al, 1993; Aben et al, 2002; Enns et al, 2000; Domkin et al, 1994; Mufson et al, 1996). Higher neuroticism (Enns et al, 2000; Domken et al, 1994) and lower agreeableness (Enns et al, 2000) and lower self-esteem (Domken et al, 1994) have significantly correlated with discrepant scores. An alternative possibility is that the varying personality profiles or levels of self esteem for each participant may have contributed to the discrepant results. This cannot be confirmed as there were no measures of personality functioning conducted during this trial. Although both rating scales assess depressive symptoms, there are distinct differences in specific symptoms covered in each scale. The Beck Depression Inventory is more heavily focused on cognitive and affective aspects of depression and the Hamilton Depression Scale includes symptoms such as somatic and general anxiety, agitation, diurnal variation in mood, paranoia and obsessive compulsive symptoms. This may have accounted for the discrepant results.

Characteristics of depression of the participants

A quasi-systematic literature search and use of meta-analytic approaches conducted by the author of previous studies of a TRD

samples allowed an estimate of baseline moderate depression scores on both of these scales (HamD 24.17, BDI 28.43). This contrasted with the participants used in this study who were severely depressed at the start of the trial (HamD 29.5; BDI, 36.4) and who demonstrated strong within subject effect sizes for treatment (HamD ES 1.25, CI 1.13-1.36; BDI, ES 1.00, CI 0.87-1.13). This is an important factor as the severity of depression at the start of treatment has been shown to slow recovery rates and is also linked to a poor outcome (Keller et al, 1992; Hirshfield et al, 1998; O'Leary et al, 2000; Ezquiaga et al, 1998; Bromberger et al, 1994). Although the effect sizes were large, the mean scores post-treatment remain within the mild (IPT plus mirtazapine group) and moderate (mirtazapine group) on the Hamilton depression and moderate (both treatment groups) Beck Depression Inventory respectively. Thus large changes for severely depressed patients still result in significant mean residual levels of depression.

In order to establish the level of treatment resistance the author needed to consider a number of factors which included the number of failed antidepressant treatments, the duration of the current depressive episode and the duration of lifetime depression. There were no statistically significant differences between the two groups relating to these characteristics of depression although power to detect them have been low.

In terms of the number of previous depressive episodes there were 6 of the 20 participants who had entered the study with their first episode of depression (2 in the IPT group and 4 in the mirtazapine only group). Of the 6 subjects with no previous major depressive episode their current depressive episode ranged from >18-48 months. Only one participant in this group had received just one trial of an antidepressant, four had received 2 trials and one participant had received 3 trials of antidepressants. The mean number of major depressive episodes was 2 for the IPT group and 1.5 for the mirtazapine only group; the difference represents small to moderate effect size of 0.35 (CI 0.14-0.84). The

number of failed antidepressant trials between the two treatment groups (IPT and medication mean = 2.6 ± 1.57 ; mirtazapine only 2.3 ± 1.15) were similar, with small effect sizes demonstrated by 0.21 (CI 0.20-0.22). The mirtazapine only group demonstrated a longer duration (months) of current depressive episode (21.05 ± 12.05 vs. 12.93 ± 10.06), yielded by medium to large effect sizes of 0.73 (CI 0.24-1.22). Similarly, the IPT group had a longer lifetime of depression than the mirtazapine only group (mean 67.8, sd 88.13 vs. 41.4, sd 21.62 respectively) with moderate effect sizes of 0.44 (CI 0.08-0.9). Not surprisingly, this was reflected in the diagnosis of the participants; 80% of the IPT group were diagnosed with "double depression" (major depression and dysthymic disorder), whereas only 40% of the mirtazapine only group were diagnosed double depressives. This may have impacted on the outcome of the study, evidence suggests that chronic forms of depression such as double depression, or the index episode lasting more than 2 years have been associated with poorer outcome in some studies (O'Leary et al, 2000; Corryell et al, 1990; Mynors-Wallis and Gath, 1997; Keller et al, 1983; Keller et al, 1992; Mueller et al, 1996; 1999); although this has not been confirmed in others (Stewart et al, 1989; Fava, 1997).

On balance, the differences in characteristics of depression between the two groups were evenly spread and would not be likely to favour one particular treatment group. Larger effect sizes in favour of the mirtazapine group with regard to length of current episode and was offset by the greater number of "double depressives" in the combined group and the greater lifetime duration.

Participants with a comorbid diagnosis of anxiety including generalised anxiety disorder and agoraphobia with or without panic symptoms were included in this trial as this type of comorbidity is considered to represent a common clinical presentation. Anxiety disorders have been associated with a poorer response to antidepressant treatment (Fava, 1997; Kupfer and Spiker, 1981) however; there was an equal spread across both treatment groups of co-morbid anxiety disorders.

Defining TRD for this study

In order to define the level of TRD the author used the number of failed antidepressant trials as a baseline, the greater the number of failed antidepressant trials indicates an increasing level of treatment resistance; a failed trial of antidepressant medication was a minimum of 6 weeks at a therapeutic dose. Additionally, the length of time the participants have been depressed in months was then added which would provide further information regarding the level of treatment resistance, these two factors together would provide data on the spectrum of resistance to treatment in the participants used in this study (as shown in Chapter 6; Table C6–4 on page 217). Eight (40%) of the total group studied were categorised as severe TRD, a further 6 (30%) were in the upper bound of the moderate category; two (10%) bordered moderate TRD and a further three participants were assigned the mid range of the mild category.

It should be noted however that there were problems associated with retrospective data collection for this study; this included poor documentation in the medical notes, particularly with regard to recording depressive symptoms and treatment response, lack of information and poor memory of medication dose and response which underestimates the number of failed treatments reported in this trial.

Clearly, the lack of a universally agreed and accepted definition of TRD presented a challenge for the author. Previous definitions suggested in the literature are useful for theoretical considerations; however, they may not provide an operational tool that can be applied in clinical practice and research. One definition of many which had been suggested and is currently being used in a large multisite research trial in the US was the Thase/Rush definition. Although there are clear similarities which include the increasing number of failed antidepressant treatments used, there were distinct differences between this definition and the one used by the author for this study.

The Thase/Rush definition meant that all participants would have received at least one trial of a tricyclic antidepressant by stage III. This does not always happen in clinical practice, many of the participants had not received a trial of tricyclic antidepressants and yet have received a number of antidepressant medications from a different class, the author believed this would exclude a significant number of participants which should still be considered resistant to treatment. Furthermore, the Thase/Rush definition assumes a hierarchy of antidepressant efficacy, the monoamine oxidase inhibitors (MAOI's) being considered superior to tricyclic antidepressants (TCA's) and serotonin specific reuptake inhibitors (SSRI's) and the TCA's superior to SSRI's (Thase et al,1992). However, this hierarchy has not been supported by meta-analyses on antidepressant trials (Mace, 2000). The Thase/Rush definition also assumes the response of two antidepressants from different classes is more effective than two agents from the same class.

Whilst switching within the TCA's have not been supported by available data (Charney et al, 1986; Reimherr et al, 1984), there is evidence that patients who are unresponsive to an SSRI may respond to a second trial with a different SSRI (Brown and Harrison, 1992; Peselow et al, 1989; Joffe et al, 1996; Thase et al, 1997a; Thase et al, 2001). Switching from one agent that affects one neurotransmitter system such as an SSRI to a different antidepressant such as a SNRI has been suggested to be more effective and forms the basis of clinical practice (Fava, 2003) but has not been studied in clinical trials (Charney et al, 1998). Additionally, the Thase /Rush levels of TRD were first published over a decade ago, and therefore were being developed before this time. Since then prescribing habits of psychiatrists have changed considerably, newer generations of antidepressants from a number of different classes have now become available. Moreover, literature regarding the efficacy of particular classes of antidepressants used in TRD remains in its infancy, indeed, switches to antidepressants in the same class has been suggested when varying effects of pharmacokinetics and pharmacodynamics of different

antidepressants within the same class are considered (Bondolfi et al, 1996).

Demographics

An equal number of men and women were recruited to this study. The geographical area of recruitment was homogeneously an area of low socio-economic status, with poor health and high unemployment; this was reflected in the participants who were recruited. Decreased subjective social support has been found to predict poor depression outcome (Bosworth et al, 2001; Hirschfield et al, 1998; O'Leary et al, 2000; Ezquiaga et al, 1998) and poor social adjustment and interpersonal relationships have been associated with resistance in depression (Freidman et al, 1995). There were differences in the employment profile of the two treatment groups. There was higher unemployment in the combined group (70% vs. 40%) at baseline. Additionally, those participants who were employed were predominantly assigned to the mirtazapine only group (50% vs. 10%) and they consisted of professional, skilled or semi-skilled workers. This was in sharp contrast to the single participant (10%) in the IPT group who was an unskilled worker. Unemployment has been causally related to depression (Zimmerman and Katon, 2005) with twice the rates of depression reported (Dolley et al, 1994); in addition, unemployment can prolong depressive symptoms (Frese and Mohr, 1987).

There were also differences in the educational attainment of the participants between the two groups. Only one (10%) of the participants in IPT had studied to A' level compared to 4 (40%) in the mirtazapine only group.

Regular alcohol use was greater in the IPT group (70% vs. 20%). This could contribute to the response to treatment for the treatment groups. Moderate (Worthington et al, 1996) or even mild (Thase, 2003) alcohol consumption has been associated with poorer response to antidepressant treatment (Fava, 2003).

The resulting differences between the groups regarding employment, education, and the use of alcohol is a limitation of this small study; however, attempts to further control for this during randomisation were considered inappropriate given the small numbers involved.

About half of the total group was married and nearly half of the IPT group had been divorced. Divorce or being separated has been associated as a risk factor for the onset or maintenance of depression (Weissman, 1987; Rounsaville et al, 1979; Bruce and Kim, 1992).

This study recruited a small sample of participants who were randomly assigned to two treatment groups. The randomisation proved to be effective in obtaining a general balanced range of depressive symptoms and characteristics of depression and concurrent anxiety disorders. However, differences in the employment profiles, educational status and the use of alcohol emerged between groups which could bias treatment outcome in favour of the mirtazapine only group (Zimmerman and Katon, 2005; Worthington et al, 1996; Thase et al, 2003; Fava et al, 2003).

As the author needed to control for gender as a confounding variable when using the IBZM SPECT scans, further controls regarding demographic or clinical characteristics were considered too restrictive, particularly in such a small sample size. As there is clearly such a difference in IBZM binding between the sexes, this was considered by the author a priority. There are many variables which are known to contribute to treatment outcome and prognosis in depression; randomisation in larger studies may eliminate group differences which emerged in this small study. Alternatively, stratification or matching on other characteristics such as diagnosis, severity of depression and levels of treatment resistant depression could be built in as design features.

IPT therapists

There were two research trained IPT therapists who provided IPT during this trial, one male and one female; both of whom received research

training prior to commencement of the study. This is strength of the study; previous clinical trials have been criticised for not validating therapists before the study (Martin et al, 2001) or for using novice therapists (De Mello et al, 2002). The research training for each therapist met the criteria set by Gerald Klerman, the key originator of IPT. Furthermore, the research training was provided and validated by experienced IPT therapists / researchers who were both trained by Klerman and conducted research under his guidance. This demonstrates high quality research trained therapists and meets the standards previously established in clinical trials of IPT (Elkin et al, 1989; Klerman et al, 1974; Markowitz et al, 1994).

Although a small study, the provision of IPT by two therapists increases generalisability and allows attribution of the results to the therapy rather than the therapist. The author provided IPT to more participants (n=7) than the male IPT therapist (PC, n=3), this was due to workload within the research department. An equal balance of IPT sessions by both therapists would enhance generalisability of the findings when comparing therapists, help increase our understanding of the specific mechanism of antidepressant action of IPT.

Weekly peer supervision took place between the two therapists to minimise drift; this contributes to the rigour of the study, a third therapist providing weekly supervision would have enhanced the quality further still. Although it was planned to tape all sessions, only three participants agreed to audio-taping of their IPT sessions; these were rated at the end of the trial for the purpose of formal adherence monitoring and quality assessments and will be discussed later. Concurrent monitoring by independent raters would increase the rigour of the study by ensuring quality was achieved throughout and detecting early signs of drift. IPT appeared to be well tolerated by participants with treatment resistant depression and none of the participants who were randomised to treatment refused treatment with either therapist.

Format and delivery of IPT

The timing of the acute phase of the IPT was the same as recommended in the original treatment manual (Klerman et al, 1984), 16 IPT sessions were delivered weekly. Psychoeducation regarding depression is provided routinely in IPT for major depressive disorder. The therapist uses the sick role by framing the depression as a medical illness, and where problems exist with specific symptoms of depression such as poor drive, motivation or anhedonia, patients are encouraged to blame symptoms of depression and not themselves. IPT for treatment resistant depression emphasizes this approach as depressed patients often feel guilty and blame themselves for a lack of response; in treatment resistant depression this may be more evident especially if there have been lengthy periods of depression. In addition to strategies used in IPT for major depression, the IPT therapist included specific education about treatment resistant depression as well as major depression.

Sixteen sessions of acute IPT were offered to all of the participants assigned to the psychotherapy. The mean number of acute sessions received by the participants was 11.3 which are below the recommended dose of psychotherapy. The mean number of maintenance IPT sessions was 5.8 which were lower than the optimum dose which would have been 8-10 sessions. The IPT from one therapist was delivered in 8.3 months vs. 11 months, although there were a similar number of mean sessions delivered by both therapists; this has the effect of a lower dose of IPT for the therapist who delivered the treatment over a longer period of time. The difference in time is minimal and the small numbers involved make investigation difficult.

The maintenance psychotherapy sessions were offered to participants in the study on a monthly basis, and IPT sessions were agreed at the end of each therapy session at a mutually convenient time. The amount of sessions received by the participants for both the acute and maintenance phases of treatment fell below the recommended optimum dose. This may have been due to a number of different reasons. The poor socio-

economic status of the participants recruited to this trial may have led to increased difficulties on their part to commit the time for therapy; family commitments, financial constraints, problems with travel arrangements to the hospital for therapy may also have attributed to a lower attendance. The participant may also have felt that depressive symptoms had improved to a level which had improved functioning and as a result did not place importance on the frequency of psychotherapy treatment; indeed, this may have also had the same effect on the therapist.

Dose of IPT

When designing the research protocol the author did not establish a system which would enforce attendance at weekly intervals for 16 weeks during the acute phase and then monthly sessions for the maintenance phase; instead the treatment with IPT was outlined to the participants as a model at the start of treatment and it was agreed that the psychotherapy sessions would be arranged at a mutually convenient time. This inadvertently may have led to reduced adherence to the specified doses. Higher doses of IPT have been provided previously in other trials of dysthymic or partially responding patients (Scocco and Frank, 2002; deMello et al, 2001; Markowitz et al, 1992); and have ranged from 16-22 IPT sessions delivered over a shorter period of time. Positive outcomes have been present in most studies (Scocco and Frank, 2002; Markowitz et al, 1992); however, beneficial effects from one study took time to emerge (deMello et al, 2001). Lower doses of IPT, for example, ten sessions over 6 months, have also been provided in dysthymia studies (Mason et al, 1993; Browne et al, 2002). Extremely low doses of IPT (mean 8.6; median 10) were provided over a six month treatment phase, during the large Canadian trial of IPT in dysthymic patients. This perhaps led to the superior response rates of therapeutic doses of sertraline (50-200mg) compared to low dose IPT (59% vs. 46% respectively) at six months.

Fixed dose was an a priori decision based on the recommendations from the original treatment manual; the dose of the antidepressant

mirtazapine used in this trial was set at 30-45mg. There were no opportunities to increase the dose of mirtazapine further or switch to alternate antidepressant(s). Systematic variable dose of psychotherapy, pharmacotherapy or their combination would require a much bigger study. Similarly, maximum tolerated dose could still have been used but would be answering a different question, and in a smaller group of participants introduce even greater variability. Future studies should evaluate the efficacy of a staged approach to increasing the potency of both the IPT and the antidepressant medication in a resistant depressed population.

The low numbers of participants recruited to this study limit its findings which should be viewed as preliminary; a larger sample size may have detected significant differences which have not appeared in this small group. Although there were significant improvements from baseline at every time point and significant differences on the Hamilton depression scale between the two groups in favour of the IPT group by week 26, earlier changes may have been detected had the optimum dose of IPT been received by the participants in this study. Slower recovery rates have been reported in patients who have had a longer duration of depressive symptoms and increased severity of depressive symptoms at the index episode (Keller et al, 1992; Mueller et al, 1999; Leon et al, 2003); both of these characteristics applied to the IPT group. Further studies which increase the potency of IPT with the use of more frequent sessions would give us more insight into the efficacy of treatment in this difficult to treat group.

Quality of IPT

The quality of IPT and adherence monitoring was conducted at the end of the trial with the use of audiotapes of IPT sessions. Only four (40%) of the IPT group agreed to have their psychotherapy sessions tape recorded; of these only half of these sessions were recorded; 13/25 (52%) of the sessions provided by PC and 8/18 (44%) of the sessions provided by the author ER. Most of the sessions taped were during the

acute phase (95.3%) of IPT and one session was taped during an early session of the maintenance phase (4.7%) treatment. Both therapists adhered to the model of IPT and received a high quality rating score for the problem areas focused on during psychotherapy treatment two thirds of the strategies were met during the initial phase of IPT, however, the third session of IPT was not recorded and these strategies may have been met during these sessions or else when the author has interviewed the participants before starting psychotherapy sessions.

There were only two focal areas of a possible four identified during therapy with all of the participants in the IPT group. This may be due to a number of reasons. Firstly, role transition and role dispute are typically the most common of focal areas used in IPT (Markowitz et al, 2000), interpersonal deficit is usually recommended as a focal area only if there are no other focal areas to concentrate on during therapy sessions, and complicated bereavement is usually less common a focal area compared to both role dispute and role transitions. A second consideration is the relatively young age group of the participants used in this study. The oldest participant was 52 and it is unlikely that participants with a mean age of 39.5 would have experienced much bereavement; this is a more common focal area in a study of elderly depressed subjects (Wolfson et al, 1997). Thirdly, the small numbers of participants receiving IPT limit the likelihood of less common focal areas being present.

There was good agreement on the focal area identified with each therapist, both during weekly peer supervision and during the formal adherence monitoring with the use of the NIMH rating scale. Although there is little data on therapists agreement on focal areas in IPT one inter rater reliability study has demonstrated close agreement between IPT therapists in identifying problem areas and potential treatment foci (Markowitz et al, 2000).

Most of the taped sessions evaluating role dispute were from the therapist PC. 83% of the goal directed strategies were met and were of a

high quality (role dispute = 1.9-3 out of a possible score of 7; where “1” represents excellent and “7” is poor). The strategies which were not met (17%) included strategies which were not appropriate for the timing of the IPT sessions. There were nearly equal numbers of sessions from each therapist rated for role transition and most of the strategies were achieved (93.7%) with a high quality rating (1.7-2.9 out of a possible score of 7). The overall strategy rating demonstrated that both therapist adhered to the model of IPT and did not use alternative psychotherapeutic approaches such as CBT.

There were potentially serious limitations of the results of the adherence monitoring which reduce generalisability of the findings; under half of the participants agreed to the sessions being taped and only half of these sessions were recorded. Nearly all of these sessions were during the acute phase of therapy, and only two of possible four problem areas were evident in therapy.

Although the taped sessions demonstrated that both IPT therapists were adherent to the model and maintained a high quality of interventions, we cannot confirm this was the case in the sessions which were not taped. Previous psychotherapy trials have recorded all psychotherapy sessions, randomly selected tapes and rated a segment of the study (Elkin et al, 1989; Frank et al, 1991). Due to the limited number of tapes available, every tape was rated, this excludes the random selection of sessions for rating. However, the whole of the 50 minute session was rated for adherence monitoring, which is strength of this smaller study. Future trials should record all of the IPT sessions and systematically sample from each phase of treatment and include acute, intermediate and end phase of IPT as well as IPT as the maintenance treatment. This may help provide the data to address questions regarding the specific mechanism of action of IPT.

The most common focal areas of role transition and role dispute were the only problem areas identified for all of the participants in the study,

reflecting what is seen in clinical practice. The brain imaging component of this trial led to recruitment restrictions, specifically, there were smaller numbers of participants recruited and there was a tight age range (28-55). A larger number of participants recruited to the trial may have extended the focal areas and increase our understanding of the applicability and efficacy of IPT in treatment resistant depression.

Research unit

The participants for this study were all treated in the single research site at Cherry Knowle Hospital, Sunderland. This was a two storey building which included a pleasantly decorated waiting room and conservatory with pleasant views of the countryside. The staff aimed to provide a peaceful and aesthetic environment. There were comfortable easy chairs, relaxing music, and tea, coffee, soft drinks, biscuits and sweets were provided. Staff were all friendly and approachable and all participants were seen at the appointment time given. The IBZM SPECT brain imaging scans were conducted at Sunderland Royal Infirmary. This medical physics department was a purpose built department and building works had just been completed at the start of the study. The staff aimed to be as approachable as in the research department and offered participants tea, coffee, sandwiches and biscuits. None of the participants were kept waiting for their appointment. The author met each participant at medical physics department to introduce the medical physics staff and deal with any additional questions they may have. Participants made their own way to the follow up scan 6 weeks later.

The attention received by each participant at the start of the trial may have had an impact on the depression scores at the start of treatment. In fact Markowitz (personal communication) reports sharp reductions in Hamilton depression scores at the start of research trial after psychologists use a Structured Clinical Interview for Diagnostic and Statistical Manual (SCID DSM IV, APA 2000). If a long and relatively tedious interview such as the SCID can contribute to a reduction in Hamilton depression scores, it is reasonable to assume that the impact

of a brain scan in addition to clinical assessments with SCID and depression rating scales may also contribute to reduction in depression scores. However, the research protocol at the start of the trial included more than the brain scans. There was a comprehensive assessment of physical, psychological and social factors, including: the SCID, routine blood tests, clinical ratings of depression, anxiety and social functioning, and finally the first of two brain scans. Feedback from some participants at the time included comments such as “they felt their depression was taken seriously”. The brain scanning as part of the research is likely to have reinforced a biological component of depression which reinforced the approach used in IPT for depression when providing the sick role. All of these interventions in combination help to provide hope that things will improve.

Furthermore, the facilities on offer both at the research unit and medical physics department and the prompt, friendly and professional service may also have had an impact on depressive symptoms. This treatment is in sharp contrast to the usual care offered in an NHS outpatient department and may have contributed to the very low attrition rates of the study. Participants from both treatment groups received care at the same settings.

The attrition rates in both treatment groups of this study were low and were much lower than rates reported in other studies (Browne et al, 2002; deMello et al, 2001; Frank et al, 2000). This may be due in part to the quality of the service and the attention participants received from both departments throughout the course of treatment. Indeed, recruitment and retention of subjects to the research unit for other clinical trials during the same time was excellent, which would suggest the environment of the Unit has contributed to the retention rates. The environment of the research unit would be in sharp contrast to the usual care on the NHS, particularly when taking into account the catchment area for the study. Although this would limit the generalisability of the findings, the physical and psychological environment provided from this

research site is an interesting area which warrants further study, particularly if there is potentially a positive treatment outcome as a result of increased engagement and compliance with therapy.

Conclusion

There is a paucity of literature reviewing psychotherapy generally in treatment resistant depression, and there are suggestions that psychotherapy should be reviewed in this area (NICE, 2004; Fava et al, 2003; Rush et al, 2004; Wisniewski et al, 2004). This is the first and only study of IPT in this population. IPT appears to be well tolerated and has demonstrated promising initial results. This is especially important when considering the participants were recruited from an area of high social deprivation.

After random allocation to a treatment group there were no differences between the groups regarding depression scores, anxiety scores and social functioning; although the study is not powered for detect any small to moderate differences.. At baseline, the IPT group demonstrated differences to the mirtazapine only group in education, employment profile and alcohol use. Furthermore, nearly all (80%) of the IPT group had a concurrent diagnosis of dysthymic disorder compared to 40% of the mirtazapine only group. All of these variables have been shown to have a negative effect on treatment outcome.

Significant differences emerged between the groups after 6 months which was sustained at 12 months. These delayed antidepressant effects of IPT have been reported in previous trials (Klerman et al, 1979; Mufson et al, 1996). What is particularly relevant is that IPT was potentially disadvantaged at the start of the study, demonstrating more baseline factors that are negative prognostic indicators. In addition, the mean dose of IPT received by each participant was moderate as was the dose of mirtazapine. This provides promising initial data on the efficacy of IPT in TRD, even at a moderate dose; although it appears the beneficial effects take time to emerge.

The participants in this study had their levels of treatment resistant depression assessed retrospectively. There are various problems associated with retrospective data collection which include incorrect assessment of the degree of response due to the patients recall biases, misclassification of non response of patients who have relapsed after an initial response and inaccurate documentation (Fava et al 2003). However, when reviewing the data in medical notes the author maintained a high threshold for including previous treatment trials and episodes of depression, which would reduce the likelihood of assigning a diagnosis of treatment resistant depression inappropriately, if anything an underestimation of failed previous trials was likely.

The sequenced treatment alternatives to relieve depression study (STAR*D) is currently reviewing CBT as part of a sequential strategy and when the current protocol is complete the authors plan to review alternative antidepressant psychotherapies (Fava et al, 2003). This will be helpful as the STAR*D study only evaluates CBT as a psychotherapeutic intervention, alongside a specific sequential strategy for antidepressant therapy (either alone or in combination). This study, like others will only answer some of the questions raised in relation to treatment resistant depression; the prospective data collection will allow us an insight into the incidence of TRD, in the U.S. at least. The treatment will be provided over a number of sites, albeit all in the U.S. which increases the generalisability of the findings. Moreover, we will gain at least some insight into the efficacy of a staged approach in managing treatment resistant depression.

Evaluation of the effects of the dose of IPT and also antidepressant medication should be assessed in future trials; this should include increasing dose of either therapy alongside combination and augmentation strategies. In addition, studies comparing alternative antidepressant psychotherapies such as cognitive behaviour therapy or cognitive behavioural analysis system of psychotherapy (McCullough et al, 2000) should be included in future studies.

Evaluation of treatments should include health and social care costs and include a longer period of follow up. This is particularly important given the evidence that health and social care cost increase with greater levels of TRD (Greenberg et al, 2004), and studies of major depression have found that increased treatment effectiveness is positively correlated with significant reductions in treatment costs (Simon et al, 2000; Mitchell et al, 1997; Thompson et al, 1997). Similarly, poor psychosocial functioning has been found in patients with TRD (Petersen et al, 2004) and impairments in work and social functioning, both feature of TRD (Hays et al, 1995; Greden et al, 2001) have been found to worsen outcome in treatment resistant depression (Corey-Lisle et al, 2004; Petersen et al, 2004; Mintz et al, 1992; Fawcett, 1994).

Future studies should use the reliable change index and clinically significant change as outcome measurements as this would enhance the quality of the data and help with interpretation of results. For example a clinically significant change explicitly tells us the participant has improved to an extent that their new level of functioning falls within the healthy population, whereas percent reductions in depression scores does not provide this critical information.

Perhaps the most important issue raised by this study, is the lack of universally agreed and accepted definition of treatment resistant depression. This is urgently needed for further studies for work in both research and clinical practice. The lack of a universally acceptable definition in the TRD literature makes interpretation of literature difficult. The author selected the most basic and common definition in terms of failure of an antidepressant trial. There are still shortcomings in the literature regarding a practical and workable definition. Little attention has been given to combination or augmentation strategies, and interestingly no definition acknowledges any psychotherapy with proven antidepressant efficacy as a failed trial. An agreed definition as part of the Diagnostic and Statistical Manual for Mental Disorders and the

International Classification of Disorders for use in a clinical and research setting is needed and would improve interpretation of research findings.

Thesis study 2: Sequential dopamine D2 receptor scanning with the use of IBZM SPECT

The clinical characteristics of the participants used in this study have been described earlier in this chapter. All 20 of the participants received both IBZM SPECT scans pre and post six weeks of treatment. This is the first IBZM SPECT study to have made a direct comparison of two treatment conditions; previous studies have compared depressed patients to controls (D'Haenen and Bossuyt, 1994; Ebert et al, 1994; Ebert et al, 1996; Klimke et al, 1999; Shah et al, 1997; Parsey et al, 2001). Although one German study (Larisch et al, 1997; Klimke et al, 1999) evaluated depressed patients who had been non responsive to a tricyclic antidepressant, this is the only IBZM SPECT study to have examined the specific effect of treatment resistant depression and dopamine D2 receptor activity.

Cerebellum as a reference region

Previous IBZM SPECT depression studies have chosen the frontal cortex or the cerebellum as a reference region in order to obtain uptake values allowing for non specific binding of the radioligand. The frontal cortex was not used as a reference region for this study for a number of reasons: There is a substantial body of literature which demonstrates altered blood flow (Mayberg et al, 1994; Sackheim et al, 1990) and metabolism (Martinot et al, 1990; Little et al, 1996; Buschbaum et al, 1997) in major depression. Reduced cerebral blood flow has been shown to have an effect on the IBZM uptake (Larisch et al, 1997). Additionally, the frontal cortex contains dopamine d2 receptors (Doucet et al, 1986); the counts in this region would be an indication of both the non-specific and specific binding which would confound the mean ratio of counts in the striatum. Finally, we cannot exclude the possibility that low dopamine D2 densities are increased in major depression. In contrast the cerebellum is not reported to have any post synaptic dopamine D2

receptors and the cerebellum has not been shown to be altered in mood disorders (Larisch et al, 1997).

Treatment groups

1123 IBZM is a benzamide derivative with a high affinity for D2/3 receptor selectivity (Verhoeff et al, 1992); IBZM counts reflect the binding of the ligand to dopamine D2 and D3 receptors with at least partial displacement of endogenous dopamine by the ligand and any dopamine antagonists (Laruelle et al, 1995). Repeated measures ANOVA revealed no differences in the IBZM binding ratios between the two treatment groups using the cerebellum as a reference region. These results were not surprising given the two treatment groups contained both treatment responders and treatment non responders; five (50%) of the participants in the IPT group and one (10%) of the participants in the mirtazapine only group were responders (minimum of a 40% reduction in Hamilton depression scores between scans).

There have been reports of differences in uptake ratios of responders versus non responders (Ebert et al, 1994; Ebert et al, 1996 Klimke et al, 1999) which could confound the situation and may have led to the negative results.

Another consideration is that there was only one pharmacological treatment which was provided to both treatment groups during this trial, the antidepressant mirtazapine. The direct action of mirtazapine is to enhance noradrenergic and serotonergic function neurotransmission, additionally; mirtazapine may also have an indirect action on the mesolimbic dopaminergic system (Rogoz et al, 2002). An alternative pharmacological agent with direct specific dopaminergic effects used as a comparison may give us more insight into the distinct pharmacological actions of antidepressant medication and the role of dopamine function.

Although functional imaging studies in major depression have shown that response to either IPT or antidepressant medication led to regional

activation of blood flow with HMPAO SPECT (Martin et al, 2001) and glucose metabolism with a PET study (Brody et al, 2001) no other studies have demonstrated or suggested changes in neurotransmitter function, particularly in such a complex condition as treatment resistant depression. The limited time in between the first and second scan may also account for negative findings, particularly as IPT has been shown to take longer to have an antidepressant effect than antidepressant medication (Klerman et al, 1974; Frank et al, 1991).

Responders versus nonresponders

30% of the total sample responded to treatment after six weeks demonstrated by at least a 40% reduction in the Hamilton depression scores. Of this group 83.3% had been treated with IPT and mirtazapine, and only one participant (16.6%) was treated in the mirtazapine only group.

There was a smaller mean uptake ratio in responders versus non-responders using the cerebellum as a reference region. Furthermore, responding participants demonstrated decreased IBZM striatal binding after six weeks of antidepressant treatment. Numerous in vivo studies with benzamides have shown that reduced receptor occupancy is an acute result of increased dopamine release (Hall et al, 1990; Dewey et al, 1993; Laruelle et al, 1995; Smith et al, 1995; Laruelle et al, 2000; Ebert et al, 1996). The decreased binding of IBZM in responders may reflect increases in post synaptic dopamine release which is competing with the IBZM ligand for receptor occupancy (Logan et al, 1991; Rognan et al, 1990).

These results are in good agreement with three previous German studies which have reported similar changes in IBZM uptake ratios in responders versus nonresponders. In the first IBZM SPECT study of depression Ebert and colleagues (1994) found that total sleep deprivation (TSD) responders demonstrated significantly reduced IBZM binding compared to non responders and controls. The same group (Ebert et al, 1996)

conducted a second trial comparing 10 depressed patients after three weeks of tricyclic antidepressant medication. After antidepressant therapy the relative D2 dopamine receptor occupancy significantly decreased in 5 responders and remained unchanged or increased in 5 non responders. Finally, Klimke and colleagues (1999) compared 15 hospitalised depressed patients to 17 controls. Nine responders demonstrated lower baseline IBZM uptake ratios compared to 6 nonresponders and 17 controls ($p < 0.05$). In contrast to the Ebert's study (1996), responders to six weeks of SSRI treatment demonstrated increased IBZM binding; however, the baseline IBZM uptake ratios were low in the responders in the Klimke but not the Ebert group. One of the German studies recruited a homogeneous sample of DSM IV major depressed patients, who were similar to the group reported in this thesis in that they had not responded to a trial of a tricyclic antidepressant. Furthermore the level of depression was also in the severe range (HamD 27.3), another similarity with participants reported in this thesis. However, different patterns of change have been reported in response to antidepressant therapy. Klimke et al (1999) demonstrated increased binding in responders and Ebert and colleagues during both studies (1994, 1996) reported decreased binding in responders and increased binding or no change in non responders. Chronic administration of antidepressants, has been shown to enhance dopamine function, and may account for the patterns of change in two studies (Ebert et al, 1994; 1996) but not a third (Klimke et al, 1999). There is an emerging hypothesis which suggests that the pathogenesis of depression is likely to involve the plasticity of neuronal pathways (Vaidya and Duman, 2001). Stress and antidepressants have been shown to have reciprocal interactions on neuronal growth, vulnerability and synaptic plasticity (Reid and Stewart, 2001). Hence the increased binding in responders (Klimke et al, 1999) and decreased binding (Ebert et al, 1994; 1996) reported in these studies may reflect the ability of responders to change, a concept that neuroplasticity might be characteristic of responders. Furthermore, differences in scanning methods and patient groups may also have contributed to the discrepant results.

Negative findings to a pharmacological challenge have been recently published from a group in New York (Parsey et al, 2001) when they compared the dopamine D2 receptor availability and amphetamine induced dopamine release in nine untreated depressed patients and 10 controls. No differences were detected between patients and controls in the dopamine D2 receptor availability either before or after the amphetamine challenge. A number of factors, different to previous studies may have led to these negative results. IBZM was administered by continuous infusion, which consisted of one single scan, lasting 360 minutes which was used to measure two clinical states (pre and post amphetamine challenge). Additionally, patients were less depressed (mean HamD 21 ± 5), and the authors were measuring transient improvements in specific symptoms of depression rather than substantial and sustained improvements in depressive symptoms as evaluated in previous studies.

The patients studied in Parsey's group were completely drug naïve whereas previous studies involved patients who had a history of antidepressant use; this is an important difference as there is a substantial body of literature which demonstrates that chronic treatment with antidepressants, notably tricyclic antidepressants, increases responsiveness of dopamine D2/D3 receptors in the mesolimbic system (Demonstis et al, 1990; Asakura et al, 1992).

One negative study reported no differences in the dopamine D2 activity after an amphetamine challenge (Parsey et al, 2001). A number of factors may have led to the discrepant results. A general criticism of these studies will be found later, however, one factor which has not been discussed in previous studies is the time passed in between scans. This has varied greatly from one study to the next. Klimke et al (1999) took 40.1 (sd 8.8) days, 3 weeks was reported for Ebert et al (1996), 2 days for Ebert's sleep deprivation study (1994) and just 5 hours for the amphetamine challenge where data was analysed for the first 240 minutes and compared to the last 120 minutes. IBZM SPECT has a high

affinity for dopamine D2/D3 receptors thus reflecting the number of receptor sites. There is evidence that although antidepressant therapy may immediately increase monoamine neurotransmitters such as serotonin, subsequent down-regulation of post synaptic receptors takes 2-3 weeks (Preskorn, 1993). Immediate receptor action does not correspond with clinical change but receptor downregulation over a small number of weeks does (Bauman and Roehat, 1995; Laifenfeld et al, 2005) as reuptake inhibition is immediate but clinical response takes 2-3 weeks. Limited time in between scans may not account for this and will not demonstrate changes which may be in process. Furthermore, regional cerebral blood flow changes have been demonstrated in depression (Bench et al, 1992; Austin et al, 1992; Mayberg et al, 1994; Sackheim et al, 1990), which activate with treatment (Martin et al, 2001; Mayberg et al, 2004); Larisch et al (1997) have found that IBZM images correlate highly with regional cerebral blood flow as measured with HMPAO SPECT, hence may have contributed to the lack of response given the limited time.

The studies published to date including data in this thesis have all been limited by small sample sizes. Although samples selected may be homogenous in relation to diagnosis (Klimke et al, 1999; Parsey et al, 2001; Ebert et al, 1996) other studies have included depression with melancholic features, bipolar disorder and psychotic depression (Ebert et al, 1994; Shah et al, 1997). Dopamine dysfunction demonstrated by lower HVA levels (Roy et al, 1985; Asberg et al, 1984), and PET studies (Baxter et al, 1985; Buschbaum et al, 1986) and have been reported in melancholic depression in all of these clinical areas. Additionally, there have been studies which evaluate patients with severe depression (Ebert et al, 1994; Ebert et al, 1996; Klimke et al, 1999) and those who have studied less severe depression (Parsey et al, 2001; D'haenen and Bossuyt, 1994).

Gender

Women in this study demonstrated a higher IBZM uptake in the striatum compared to men. This supports the findings of Shah et al (1997) who

compared 9 male and 6 female depressed patients to the same number and sex distribution of controls. There have not been other IBZM depression studies reporting gender differences in binding. There are limited studies which have reviewed dopamine activity using IBZM SPECT in depression, moreover, of these studies some groups have recruited all male (Ebert et al, 1994; 1996), predominantly male (Parsey et al, 2001) or predominantly female patients (D'Haenen et al, 1994). Although Klimke's group did not report differences they made no references to the earlier work of Shah's (1997) group which may mean that this was not evaluated by Klimke and colleagues (1999) during this study. In a SPECT study Pilowsky and colleagues (1994) have reported increased right striatal IBZM uptake in women versus men in healthy volunteers.

Despite the limited data on gender differences in dopamine function measured by IBZM SPECT, there have been reports of differences in dopaminergic transmission between sexes using alternative measurements of dopamine function. One post mortem study reported lower dopamine levels in women in the putamen compared to men (Konradi et al, 1992). A number of studies report higher plasma HVA levels (Sumiyoshi et al, 1997) in women including schizophrenic patients (Koreen et al, 1994), and women who were post-menopausal or who had undergone hysterectomies or oophorectomies (Di Paolo et al, 1989). Animal studies (Kazandjian et al, 1987; Hafner et al, 1993) support the role of hormones and dopamine function and have suggested modulation of dopamine function by oestrogen.

In addition, gender differences have been reported in the pharmacokinetics and pharmacodynamic properties of psychotropic medications (Frackiewicz et al, 2000; Yonkers et al, 1992). Women have demonstrated higher plasma concentrations of tricyclic antidepressants (Hildebrandt et al, 2003) or, may have an enhanced response to non-tricyclic antidepressants (Yonkers et al, 1992). This may have accounted

for the differences in IBZM binding between men and women in this study.

Agitation

Agitated participants demonstrated a higher mean IBZM uptake in the striatum compared to non-agitated participants. Although this is the first IBZM SPECT study in depression to identify altered dopamine function in depressed patients with agitation, there is evidence in the literature that agitation, which can be present in depression as well as other psychiatric conditions, may be mediated by dysregulation of dopaminergic, serotonergic, noradrenergic and GABAergic systems (Lindenmayer, 2000). Slightly elevated cerebral spinal fluid HVA levels (Lykouras et al, 1995) have been demonstrated in agitated patients compared to non agitated patients. Furthermore, a study of psychotic patients have found that CSF HVA levels were elevated in those with delusions and agitation, but normal in those with just delusions (Lykouras et al, 1994). In addition, agents which reduce dopaminergic tone alleviate symptoms of agitation (Lindenmayer, 2000; Sachs, 2006). Although limited, there is evidence that dopamine abnormalities exist in agitation. The finding of increased IBZM uptake in the participants in this study extends these limited data. Further studies are warranted to replicate and substantiate the findings of this study; and may help with the management of agitation in the future. For example, the use of dopaminergic antidepressants in agitated depression may provide superior results to an SSRI; these are important questions which need to be addressed with the use of randomised controlled trials.

Levels of TRD

Having separated participants into levels of treatment resistant depression (low, n=6; moderate, n=6; high, n=7) statistically significant effects of IBZM binding was only evident in the high TRD group. IBZM binding showed non significant decreases in the low TRD participants and non significant increases in the moderate TRD participants; both the left and the right striatum demonstrated the same pattern of response

after six weeks of treatment. This was in sharp contrast to the high TRD group where significant differences in the change scores of the right and left striatum which was demonstrated by marked asymmetrical binding patterns; increased binding in the left striatum and decreased binding in the right striatum.

Although the 7 high TRD participants were analysed using the repeated measures ANOVA model as described above, three of these participants had in fact responded to 6 weeks of antidepressant treatment with IPT and mirtazapine (n=2) or mirtazapine alone (n=1). This response may be predictable as both treatments are potent antidepressant therapies; additionally, the attention received during the clinical trial may also contribute to positive effects (Benetti et al, 2005). However, one alternative possibility is that the retrospective data collection may have inadvertently identified some patients as a high level of TRD when in fact they may have been less resistant to treatment. Further analysis of this small group yielded the same pattern of asymmetrical binding in the responders and single non responding participant. The responding participants demonstrated statistically significant increases in binding in the left striatum after six weeks of treatment. Although there were extremely strong effect sizes (partial eta squared 0.98 & 0.84; and good power 0.99 & 0.78 respectively) the small sample size used in this analysis would restrict these findings which should therefore be viewed with caution.

One possibility which could explain the changes is that the receptors in the responding participants may have changed from a low to a high affinity state (Ebert et al, 1994) or alternatively participants have increases in the density of dopamine D2 receptors (Klimke et al, 1999) and/or an increased affinity for the ligand (D'Haenen and Bossuyt, 1994; Klimke et al, 1999).

The examination of dopamine D2 function in treatment resistant depression with the use of IBZM SPECT has never previously been

assessed. There were statistically significant changes in dopamine function which were evident only in the high level of TRD group. Statistically significant changes in IBZM binding after antidepressant therapy apparently occurred in both the left and the right striatum; a finding which has been reported in a previous study (Larisch et al, 1997). The asymmetrical changes in IBZM uptake demonstrated by decreased binding in the right and increased binding in the left striatum in the 7 high TRD participants was unexpected and has never been reported in previous IBZM SPECT depression studies. IBZM binding has previously appeared to follow the same direction in the right and left striatum (Klimke et al, 1999; Ebert et al, 1994; Ebert et al, 1996).

There are known factors which have been shown to alter dopamine function which would have impacted on a TRD group. Chronic treatment with antidepressant medication increases the sensitivity of the dopamine D2/D3 receptors; the participants in the high level TRD group had also suffered from depressive symptoms for longer and would have had a greater exposure to antidepressants over time. Studies in animals have shown that chronic stress leads to changes in dopamine D2 receptor function (Papp et al, 1994; Dziedzicka et al, 1997). Moreover, the hypothesis of transmitter/receptor neuroplasticity in depression should be considered. Antidepressant medication does not involve only the critical site of action, studies in humans and animals demonstrate that interaction between the dopaminergic, serotonergic and noradrenergic neurotransmitters occur (Smith et al, 1995; Dewey et al, 1995; Baldessarini and Marsh, 1990; Awouters et al, 1990; Ainsworth et al, 1998; Carbonari et al, 1998). IBZM binding may not be due to primary changes in dopamine function but may also reflect the possibility of improved participants' ability to respond to pharmacological stimuli such as antidepressants. Alternatively, the increasing levels of severity and chronicity of the level of TRD may lead to an inability to respond in a healthy way. Asymmetrical changes in dopamine d2 uptake as measured by IBZM SPECT have been reported in studies of schizophrenia (Pilowsky et al, 1994).

There are limitations in the studies reported. Different scanning methods involving slightly different preparations of the IBZM radiotracers, different delivery of the radioligand (single injection versus continuous infusion), different region of interest to compare as a reference region and finally the use of a single headed, double headed and triple headed gamma camera may have contributed to resolution differences in all of the above studies.

Conclusion

This study is innovative in a number of ways: It is the first IBZM SPECT study to explore dopamine D2 receptor function in a treatment resistant depressed population; no previous IBZM SPECT study has compared more than one antidepressant treatment at the same time or examined the potential effect of antidepressant psychotherapy on dopamine function. Although one of the largest IBZM SPECT depression studies, like other studies the limited size restricts findings which should be viewed as preliminary. However, sizable effect sizes and power, especially in the high TRD group, were evident. The analytical strategy used enabled a better balance of type I and type II errors. The repeated measures approach across both hemispheres and time allowed a greater power (and hence reduced type II error) to examine the between group differences which comprised of responders, agitation, gender and levels of TRD. The approach that followed up only significant interaction minimised the number of tests and so provided a degree of control over a type I error. Although there were no significant differences between the treatment groups at baseline, most of the responders (83%) significantly, were from the combined IPT and medication group. Significant differences were noted in responders vs. nonresponders; agitated vs. non-agitated participants; men and women, and participants with a high level of TRD.

To further investigate the role of dopamine, additional studies consisting of homogenous groups are necessary. The evaluation of dopaminergic function with different classes of antidepressants should include medication which specifically targets the dopaminergic system such as amisulpride or bupropion. Alternative assessments of dopamine function such as measures of the dopamine metabolite HVA in the plasma or urine could be taken in isolation or

concurrently with a functional brain imaging scan. This may also help us build a clearer picture of the evidence for dopamine abnormalities in depression. Neuroimaging studies in depression have largely focused on response to pharmacotherapy; although there are a small number reviewing non-pharmacological approaches such as total sleep deprivation and IPT.

Neuroimaging techniques such as SPECT, PET and functional MRI with antidepressant psychotherapy would help us to understand the relationship between psychological approaches and physiological response; furthermore, this would allow researchers to study drug free participants allowing a greater understanding of functioning of the brain in depression without any potential confounding variables.

A number of studies examining brain function across a range of clinical presentations of depression is needed which should cover the spectrum of response, partial response and non-response to antidepressant treatment. This should range from first episode drug free major depression to those patients who are highly resistant to numerous antidepressant treatments. Although this particular study assessed brain dopamine function after 6 weeks, longer term evaluation in the management of chronic and disabling conditions such as treatment resistant depression would be helpful to appreciate comprehensively the variation over time of dopamine in depression. Given the current radiation ethical restrictions of a maximum of two scans per year, these data has to be obtained through a separate study. This reinforces the need for standardised imaging techniques including the use of camera, radiopharmaceuticals and analysis.

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