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Pharmacotherapy and Placebo Response in Dysthymia

**A thesis presented to the Faculty of Graduate Studies and Research of Carleton University
in Partial fulfillment for the degree of Master of Arts with psychology specialization**

**Jason Kotsopoulos
Department of Psychology
Carleton University**

November, 1999

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Abstract

The prediction of placebo response may provide useful pointers in determining the factors associated with response to antidepressant agents. Despite high positive placebo response rates in depression, few predictors of placebo response have been identified in either major depressive or dysthymic patients. In this study, data from 72 placebo-treated dysthymic patients from three placebo controlled clinical trials were pooled and analysed retrospectively. Demographic variables, symptomatology, and psychosocial factors were analysed for their discriminative utility in predicting placebo response rates. The main findings of the study were: (1) Placebo response rates were 34.8%; (2) Patients with more severe dysthymia, as indicated by overall HAM-D scores, were more likely to be placebo nonresponders; (3) Subjects who scored high on a specific factor of the HAM-D showed reduced response to placebo; (4) Subject's use of avoidance/denial as a coping strategy at baseline was positively related to placebo response while problem focused and emotional focused coping strategies were not significant (5) Demographic characteristics and psychosocial measures such as quality of life, and stressor perception were also non significant.

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Pharmacotherapy and Placebo Response in Dysthymia

It is widely recognized that in many patients, depressive disorders follow a chronic course. These disorders may occur as a residuum of major depression or as mild chronic depressive forms with a fluctuating course (Akiskal, 1990). The diagnostic category of dysthymic disorder was first introduced in DSM-III to include the latter diagnoses and to encompass all chronic low grade depressions of two or more years (Murphy, 1991).

Dysthymic disorder, a term meaning “ill-humoured”, is defined in DSM-IV as “a chronic disturbance of mood involving either depressed mood or loss of interest or pleasure in all or almost all usual activities and pastimes.” (DSM-IV). In DSM-IV the diagnostic characteristics of dysthymia are (A) Chronicity that is a persistent or intermittent depressive manifestations of at least 2 years duration and (B) The presence of two or more of the following: (1) poor appetite or overeating (2) insomnia or hypersomnia (3) low energy or fatigue (4) low self-esteem (5) poor concentration or difficulty making decisions (6) feelings of hopelessness (C) During the 2 year period of the disturbance the person has never been without the symptoms in Criteria A and B for more than 2 months at a time (D) No major depressive episode has been present during the first 2 years of the disturbance (E) There has never been a manic episode, a mixed episode or a hypomanic episode and criteria has never been met for cyclothymic disorder (F) The occurrence does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder (G) The symptoms are not due to the direct physiological effects of a substance or a general medical condition (H) The symptoms

cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

Depressive Personality and its Relationship to Dysthymia

Chronic mood disorders were previously classified with personality disorders, and were often referred to as depressive neuroses. One of the most common clinical constructs used in the description of chronic depressive disorders is the depressive personality (Chodoff, 1972; Kernberg, 1988; Storr, 1980) which was part of the axis II personality disorders in the first and second editions of the Diagnostic and Statistical Manual of Mental Disorder (DSM). Several criteria characterize depressive personality including the presence of low self-esteem, pessimism, self-blame and submissiveness (Chodoff, 1972; Kahn, 1975; Storr, 1980). In DSM-III, the concept of dysthymia replaced the older concepts of depressive personality and neurotic depression. Additionally, dysthymic disorder included patients once characterized by terms such as depressive temperament, reactive depression and chronic minor depression (Ravindran et al., 1993). As a result of DSM-III, dysthymia was considered an affective disorder rather than a personality disorder.

Critics have argued that newer versions of the DSM have been lacking a category for patients who have a depressive character structure but less severe and persistent symptoms than dysthymic illness (Goldstein & Anthony, 1988; Kernberg, 1984). In response to these criticisms, the concept of self defeating personality was added to the DSM-III-R. This disorder is derived from the clinical concept of the masochistic character which is characterized by behaviour that provokes rejecting response by others. Despite,

the introduction of this construct, the classical construct of the depressive personality may still not be represented in current nomenclature (Akiskal, 1989; Goldstein & Anthony, 1988).

The concept of dysthymia was further modified in the DSM-III-R to create a more homogenous subgroup, and DSM-IV further refined the diagnosis (Akiskal, 1990). The modifications were made to take into account the contribution of other physical and psychiatric illnesses, response to medication, and age of onset (Murphy, 1991). One of these revisions involved distinguishing dysthymia proper from major depression with partial remission. While dysthymia proper is a disorder of insidious onset, low grade severity and a chronic course, major depression with partial remission is a low grade depressive state following a major depressive episode.

Primary vs. Secondary Dysthymia

Dysthymia was also categorized as either a primary or secondary disorder. Primary dysthymia is a low-grade depression lasting more than 2 years with a persistent or intermittent course and concurrent character pathology that is not related to pre-existing chronic non mood axis I and axis II disorders. Primary dysthymia differs from secondary dysthymia which develops as a consequence of a chronic disorder of a psychological or physical nature. Secondary dysthymia is secondary to a preexisting chronic non-mood axis I or axis II disorder (Ravindran & Lapierre, 1997a).

Primary dysthymics show many symptoms of depression including anhedonia, sleep disturbance, poor self-esteem, guilty ruminations, hopelessness, suicidal ideation, as well as fatigue and other psychomotor symptoms. The symptoms usually remain less

severe than in major depression but with a more persistent or an intermittent course (Ravindran & Lapierre, 1997a).

Early vs. Late Onset

Dysthymia can be further subdivided according to age of onset. Early onset is used as a specifier if the dysthymic symptoms occurred before age 21 years. Later onset should be used if the onset of the dysthymic symptoms occurred at age 21 or older. The validity of the subclassification of dysthymia into early and late onset has been supported where early onset dysthymia appears to differ significantly from non-bipolar, non-chronic depression. Primary dysthymia usually has an insidious onset beginning in childhood or adolescence. Occasionally, its onset is in early adult life (late onset) (Murphy, 1991).

Character Spectrum Disorders and Subaffective Dysthymia

Akiskal (1983) suggested that primary dysthymia be further subdivided into two distinct subgroups: subaffective dysthymia (SD) and character spectrum disorder (CSD). The SD subtype is seen as a mild chronic primary mood disorder. It has presenting symptoms characteristic of major depression, such as melancholic symptoms, depressive personality traits and short rapid eye movement latency (Akiskal, 1991; Bialik et al., 1994). It also appears frequently with a family history of depression and usually responds well to antidepressant therapy (Akiskal, 1991). In general, subaffective dysthymia is thought to have a predisposing biological depressive substrate. The CSD includes patients with depressive symptoms, as well as significant personality pathology, normal REM latency, polydrug and alcohol abuse and familial alcoholism (Akiskal, 1991). They often have experienced parental loss and broken homes as well (Bialik, 1994). This subgroup

tends to show a poorer response to pharmacotherapy.

Epidemiology

Although there may be disagreement on the classification of dysthymia, there is a consensus that the illness has significant morbidity. The point prevalence for this disorder is estimated at between 3% and 5% of the adult population (Weissman et al., 1988; Hellerstein et al., 1993; Kocsis et al., 1997) with a lifetime prevalence of 4.8% for men and 8% for women as indicated by the national comorbidity study (Kocsis et al., 1997), even though this disorder is traditionally under recognized and pharmacologically under treated (Hellerstein et al., 1993). According to Weissman et al. (1988), dysthymia is particularly predominant among women under 65 years of age, unmarried persons and young persons with low income. Dysthymics also have a high utilization of psychiatric and general health care services, impairments in social and occupational functioning and health related quality of life (Kocsis et al., 1997; Weissman et al., 1988; Kocsis et al., 1988;). In fact, patients with chronic depression often have greater overall impairment in their function than patients with major depression (Howland, 1993).

Dysthymia is associated with increased vulnerability to major depression (Markowitz et al., 1992). When a major depressive episodes is superimposed on a chronic minor depression, the condition is known as “double depression” (Keller, 1983). Dysthymic individuals also have a higher risk for comorbidity with other psychiatric disorders; in fact, it has been estimated that as many as 75% of dysthymics may have coexisting disorders such as substance abuse and anxiety disorders.

Etiology

Recent studies have examined the biological etiology of dysthymia. Several endocrine and immunological characteristics of dysthymia have been identified. Many of the findings have come from neuroendocrine studies related to the dexamethasone suppression test (DST), the thyrotrophin releasing hormone (TRH) and the growth hormone (GH) response to physiological challenges. In general, rates of abnormal DST appear to be significantly different between major depressives and dysthymics. Furthermore, Ravindran et al. (1994a) have also reported a low incidence of DST non-suppression in dysthymic patients. Dysthymia has also been associated with altered adrenal responsiveness to environmental challenge, neurophysiological processes that differ from major depression and an impairment to cope with day-to-day stressors due to impaired resource allocation. It has also been suggested that dysthymia may be associated with an immune activation like that of an acute phase reaction.

There is relatively little information available concerning the genetic factors associated with dysthymia. Early twin studies of neurotic depression indicated that genetic factors may play a smaller role for this type of disorder (Slater and Cowie, 1971). However, there is evidence to suggest that dysthymics have a higher rate of family history of depressive disorder compared to nonchronic depression. Specifically, Klein et al. (1995) assessed first degree relatives of patients with either early-onset dysthymia, episodic major depression and normal controls to determine the frequency of mood, anxiety and personality disorders in these groups. They found a familial association between dysthymia and major depressive disorder, with higher rates of major depression in the

relatives of dysthymics relative to the controls. Also, relatives of dysthymic individuals had higher rates of chronic depression compared to relatives of episodic depressives.

A number of family studies have also suggested a comorbidity between dysthymia and Axis II personality disorders. Specifically, Klein et al. (1995) found that both dysthymia and major depression have a familial association with the personality disorders, although the association was stronger in dysthymia. Riso et al. (1996) also conducted a family study of control and dysthymic subjects with and without cluster B personality disorders (antisocial, narcissistic, borderline and histrionic). Overall, when relatives of all three proband groups were combined, relatives who were dysthymic were significantly more likely to have a co-occurring cluster B personality disorder. This comorbidity is consistent with theories suggesting shared etiological factors between dysthymia and personality disorders.

Some of the most significant data supporting a biological substrate for dysthymia have been derived from the clinical pharmacology of the disorder. The evidence from these clinical trials are consistent with the suggestion that antidepressants are effective for a proportion of dysthymic patients. Many of these antidepressants affect serotonin and norepinephrine and there have also been numerous reports suggesting a role for dopamine in depressive illness (Ravindran et al., 1998a).

Treatment of Dysthymia

Pharmacotherapy

Many published studies of the pharmacological treatment of dysthymia are confounded by a high occurrence of other disorders including major depression

(Hellerstein et al., 1993). A study by Kocsis et al. (1988) demonstrated this confounding relationship where 96% of chronically depressed patients in their study met criteria for “double depression” at some point in their history. Furthermore, other methodological difficulties such as variations in selection criteria among studies, inadequate duration or dosing therapy, small sample sizes the unclear relationship between chronicity and treatment, resistance and difficulties differentiating character pathology from symptoms, have lead to problems (Frances et al., 1989; Kocsis, 1990; Akiskal, 1985). This has limited the overall knowledge of the efficacy of pharmacotherapy in dysthymia, and few integrated reviews on the topic were available prior to 1991. Since then, there have been reviews which have focussed on the older drugs such as the Tricyclic antidepressants (TCA) while the most recent empirical studies have focused on the newer generation of antidepressants affecting the serotonergic system.

Studies with TCAs and MAOIs (older antidepressants)

Howland’s (1993) review of the efficacy of antidepressant treatment, summarized the literature into naturalistic and controlled studies. Several studies demonstrated that Tricyclic antidepressants were effective in treating dysthymics although the treatment response was generally less than that seen in major depression. Both Tricyclic antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) were superior to placebo in most trials, with the latter appearing to have slightly greater efficacy. This may be due to MAOI’s effects on serotonin which may play an important role in dysthymia. A review by Stewart et al. (1992) was quite comprehensive, and focused on dysthymic patients without superimposed major depression. The combined results from these studies

revealed a response rate of 59% for nontricyclics and 60% for Tricyclics. It was suggested that TCAs, MAOIs and several novel antidepressants all appear at least modestly more effective than placebo. Finally, a review by Conte and Karasu (1992) concluded that most TCAs and MAOIs did not differ from one another in terms of their efficacy in treating dysthymia and that antidepressant treatment was superior to placebo in most of the studies under review.

Serotonergic Agents

The newer generation of antidepressants, which include serotonergic agents including SSRI's (e.g. Fluoxetine) and the reversible Monoamine Oxidase Inhibitor Moclobemide, are thought to be as efficacious and definitely much better tolerated than older drugs. In fact, traditional Tricyclic antidepressants may enhance sedating symptoms associated with chronic depression like fatigue, hypersomnia and hyperphagia as opposed to the SSRI's (Howland, 1993). Furthermore, since these patients have mild depressive symptoms, they may be less willing to tolerate side effects to the same extent as major depressives. This may explain the higher drop out rate that has been reported in mild depression (e.g. Last et al., 1985). Therefore, antidepressants such as Fluoxetine and Sertraline with favourable side effect profiles are better tolerated during long term treatment (Howland, 1993). The expectation of these serotonergic agents is that compliance should increase and drop out rates should be reduced. As such, many of these medications have been the preferred antidepressant for clinicians prescribing a therapeutic trial to dysthymic patients.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine

The efficacy and prominence of SSRIs in major depression has also been reflected in dysthymia studies, providing further evidence for Akiskal's (1983) theory that dysthymia may be a more attenuated form of mood disorder. Using better defined DSM-III revised criteria, Rosenthal et al. (1992) examined the efficacy of Fluoxetine (an SSRI) in an open label trial for a period of three months. Their results indicated that 71% of dysthymic (8/11) subjects responded to treatment with 4 of these patients remaining well at a five month follow-up. Similarly, Hellerstein (1992) examined the role of serotonergic agents such as Fluoxetine in the treatment of double depression. After three months of medication, 6 of the 12 Fluoxetine completers responded to treatment. At five months, 7 of the 12 Fluoxetine completers were in remission. Hellerstein et al. (1993) also compared Fluoxetine alone to placebo in the treatment of dysthymia. After an 8-week trial they found that 10 of 16 (62.5%) subjects given Fluoxetine responded to treatment as opposed to 3 of 16 (18.8%) of placebo patients. In another study, Ravindran et al. (1994b) looked at the therapeutic efficacy of Fluoxetine in dysthymia and concluded that primary dysthymics showed a good response (73%). The response rate was significantly higher in subaffective (77%) than character spectrum patients (25%). Nobler et al. (1996) also examined the efficacy of Fluoxetine in dysthymia with a focus on elderly patients. The findings suggested that Fluoxetine was an effective treatment for elderly patients where 60% of the completers were considered responders and the mean Hamilton Depression Rating Scale for Depression (HAM-D) total for the 23 patients decreased from 14.6 to 7.9.

These studies indicated that Fluoxetine may have short term effectiveness in treating dysthymic symptoms but future research may require follow-up studies to determine the persistence of alleviation of dysthymic symptoms.

Sertraline

Thase et al. (1996) looked at the efficacy and safety in using Sertraline Hydrochloride in treating dysthymia. They found response rates for Sertraline were 59% as opposed to 64% for Imipramine and 44% for placebo. Despite the high response rate for Imipramine, there was much more tolerability for Sertraline where a significant portion of Imipramine patients discontinued treatment due to adverse events. Kocsis (1997) also looked at Sertraline and Imipramine and found that both were successful in terms of improving psychosocial functioning and depressive symptoms but fewer patients discontinued Sertraline (6.0%) than Imipramine (18.4%). Ravindran et al. (1997b) looked at the combined efficacy of cognitive therapy and pharmacotherapy with Sertraline in primary dysthymia. They found that treatment with Sertraline reduced HAM-D, HAM-A and MADRS scores with or without cognitive therapy. Fava et al. (1997) also looked at the efficacy of Sertraline in dysthymia and atypical depression in relation to anger attacks. They found that anger attacks ceased in 53 percent of patients receiving Sertraline, 57 of those receiving Imipramine and 37 percent of those in the placebo group. These findings supported previous findings that anger attacks are more prevalent among depressed outpatients than normal subjects.

In terms of the efficacy of SSRIs in treating the various subtypes of dysthymia, Ravindran conducted two studies that examined this issue. In an open six week trial of

SSRIs in 60 patients, Ravindran & Lapierre (1997a) found an overall response rate of 65% in patients with primary dysthymia. When these primary dysthymic patients were subdivided into subaffective and character spectrum subgroups, there was a response rate of 70% in the subaffective condition and 17% in the character spectrum subgroups. Also, most of the noncompleters were character spectrum patients.

Other Serotonergic Agents

5-HT₂ Antagonists

There have been some notable studies that have evaluated the 5-HT₂ antagonist, Ritanserin in the treatment of dysthymia. A double-blind study by Bersani et al. (1991) showed that Ritanserin was superior to placebo with a dose of 10mg daily. Specifically, the therapeutic effect was rated marked or moderate in 75% of the Ritanserin patients as opposed to 18% of the placebo control condition. Bakish et al. (1993) also examined the efficacy of Ritanserin, Imipramine and placebo in the treatment of pure dysthymia. Although Imipramine was slightly greater in efficacy than Ritanserin they found that Ritanserin did produce significant improvements by week 7 of treatment. Furthermore, Ritanserin produced significantly less side effects than did Imipramine.

Busiprone

Busiprone is a relatively selective 5-HT_{1A} receptor agonist with antianxiety and possibly, antidepressant properties (Goa & Ward, 1986). It was investigated in neurotic depression and anxiety states in the elderly in a primary care setting (Bohm et al., 1990). In this study, Busiprone was found to be superior to placebo in both neurotic depressives and anxious patients and was very well tolerated.

Trazodone

The efficacy of Trazodone was examined in two studies previously mentioned where Trazodone was compared to Fluoxetine in the treatment of dysthymia. Hellerstein et al. (1993) examined the long term treatment of double depression and found more positive results for the Fluoxetine trials as opposed to the Trazodone condition. Ten patients began Trazodone trials and only 2 completed three months of medication resulting in a dropout rate of 80% for the Trazodone treatment group. Of the 2 subjects remaining in this condition, 1 of the subjects was considered a responder. Rosenthal et al. (1992) achieved better results with Trazodone where they found that both Fluoxetine and Trazodone were well tolerated by dysthymic patients and a significant proportion showed an alleviation of depressive symptoms. Specifically, 4 of 6 Trazodone completers were responders (66.7%) with dropout rates of 21.4% for Fluoxetine and 33.3% for Trazodone.

Serotonin Norepinephrine Reuptake Inhibitors

There have been very few studies looking at the efficacy of various Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) in the treatment of dysthymia. Venlafaxine belongs to this group of antidepressants and has been demonstrated to be efficacious and safe in major depression (Khan et al., 1991; Shweiger et al., 1991). Venlafaxine, like Tricyclic antidepressants, has a significant effect on the reuptake of both serotonin and norepinephrine, however, it does not inhibit monoamine oxidase. Since the effect of this drug are specific to norepinephrine and serotonin, Venlafaxine may not cause adverse events due to the effects on other neurotransmitters and may be more effective for depressed patients who are refractory to treatment with SSRIs. To date there have been

two studies looking at the efficacy of Venlafaxine in the treatment of dysthymia. In a study by Ravindran et al. (1998b), 11 of 15 subjects (73.3%) showed a significant clinical improvement in terms of their HAM-D scores. There was also a significant reduction in Hamilton anxiety scores, suggesting that Venlafaxine may also be useful in treating people with concomitant anxiety. Furthermore, the antidepressant properties of Venlafaxine were relatively rapid, as clinical changes were observed as early as 4 weeks into treatment. Dunner et al. (1997) also supported the treatment of dysthymic patients with Venlafaxine. In their study, there appeared to be two different groups of responders. One group consisted of 7 of the 14 subjects who seemed to respond quickly to a lower dose of Venlafaxine (75mg) and continued at that dose to eventually meet the criteria for recovery. The other group consisted of the 7 remaining subjects who required a higher dose (225mg) of Venlafaxine to respond. Three of these subjects met recovery criteria and the other four improved only modestly over their baseline condition.

Reversible Inhibitors of Monoamine Oxidase-A (RIMAs)

Moclobemide is the most widely studied of the RIMA's and has been evaluated in most types of depression (Stabl et al., 1989). Moclobemide is a reversible inhibitor of MAO which is relatively selective for MAO-A, and in animal studies has been found to increase the content of serotonin, noradrenaline and dopamine in brain tissue and to preferentially increase the extracellular concentration of serotonin (Haefely et al., 1992). In clinical trials, Moclobemide is an effective antidepressant with minimal adverse events (Stabl et al., 1989). There at least three notable studies on the use of this compound in dysthymic disorder. Botte et al. (1989) conducted a four week trial (300-500mg/daily) in

patients with DSM-III dysthymic disorder and found that 41% of patients responded to Moclobemide while only 17% of placebo patients improved. They also found that the drop out rate was significantly higher in the placebo groups (46% compared to 9% for the drug group). Cassachia and Rosi (1989) carried out a trial of similar duration (mean daily dose of 215mg) comparing it with Imipramine (mean daily dose of 112.5mg) in patients who satisfied DSM-III criteria for dysthymic disorder or major depression. The overall response rates were 75% for Moclobemide and 65% for Imipramine. The response rates for the two depressive subgroups were not reported. Finally, a South American study by Versani et al. (1992) compared Moclobemide, Imipramine and placebo on 315 subjects meeting the criteria for dysthymia (DSM-III-R). Response rates were approximately 60% for patients treated with Moclobemide, 50% for patients treated with Imipramine and 22% for patients receiving placebo.

Psychotherapy of Dysthymia

Until recently, chronic depression was considered a temperamental or character disorder with the treatment of choice being psychotherapy (Kocsis, 1997). The goal of psychotherapy was to let patients target their specific maladaptive behaviours and then transform these habits into more adaptive ones (McCullough, 1991). However, the prognosis was considered to be poor with the failure being attributed to ingrained hopelessness, masochism and self sabotage that was associated with these patients. In addition, the few studies dealing with the psychotherapy of dysthymia suffered from methodological weakness, small numbers or both.

Despite these drawbacks, there are still some promising results for psychotherapeutic treatments. Specifically, Markowitz (1994) surveyed 43 established clinicians about their experiences treating chronic depression with psychotherapy. Most of these clinicians responded (32/43) and reported a mean of 71% rate of symptom improvement among patient treated with either psychotherapy or combined psychotherapy and pharmacotherapy. Psychodynamic therapy also continues to be frequently prescribed for dysthymic patients but there is no evidence that this treatment benefits such patients.

Cognitive Therapy

Cognitive approaches to the treatment of dysthymia have been more frequently studied and have yielded some positive results. Seven different reports have described cognitive behaviour treatment of dysthymic disorder (Harpin et al. 1982; McCullough, 1991; Mercier et al., 1992; Stavynski, 1991; Fennel & Teasdale, 1982; Gonzalez et al., 1985; Dejong et al., 1986) with a cumulative response rate of 41%. This approaches the response rate reported in control trials of antidepressants medication however, the paucity of evidence renders these results as preliminary.

Interpersonal Therapy

In addition to psychotherapy and cognitive therapy, interpersonal therapy has also been examined. Interpersonal therapy is a time limited, manual based psychotherapy where therapy helps the patient recognize links between mood and current interpersonal experiences such as grief, role dispute, role transition or interpersonal deficits. In the few studies that have incorporated interpersonal therapy in the treatment of dysthymic individuals, the outcomes seem to be encouraging but limited.

Combined Treatment

There have been relatively few combined pharmacotherapy and psychotherapy studies in the treatment of dysthymia. However, two notable studies by Becker et al. (1987) and Waring et al. (1988) determined the efficacy of such a combined drug and psychotherapy treatment regimen. Both found that combined therapy significantly improved symptoms of dysthymia. Despite these promising results, discriminating the antidepressant effect of pharmacotherapy from that of psychotherapy has produced difficulties due to the fact that both treatments are known to be effective and sample sizes have been relatively small.

Psychosocial Factors

It needs to be considered that symptom reduction may not be the most suitable criterion in determining optimal treatment efficacy. In fact, improvement in psychosocial deficits may have a greater impact on determining the long-term effects of treatment. Psychosocial impairments are thought to be related to the chronic nature of the illness, as opposed to simply being a product of the disorder. Recent experiments have examined the relationship between depressive symptoms and psychosocial factors including perception of day-to-day stressors (hassles), daily uplifts and coping styles employed (Ravindran et al., 1995a, 1996). Overall, major depression and dysthymia were reported to be associated with increased hassle perception and reduced perception of uplifts relative to controls. Also, the coping styles of patients differed from controls. Specifically, patients showed a disproportionate reliance on emotion focussed coping strategies which involves the use of emotions or thoughts to deal with stressors at the expense of problem focused coping

methods (Ravindran et al., 1995a, 1996).

The impact of cognitive therapy on psychosocial functioning was examined in a study by Ravindran et al. (1995b). Specifically, the effects of either pharmacotherapy or cognitive therapy alone as well as placebo and combined treatments were examined in 98 primary dysthymic patients. Results indicated that the alleviation of depression was associated with reduced stress perception but neither treatment significantly increased perceptions of positive life events. Also, the drug plus cognitive therapy condition effectively reduced reliance on several emotional focussed coping strategies in dysthymic patients while cognitive therapy alone was less effective in this respect. It may be possible that pharmacotherapy is an effective treatment for the symptoms of depression but cognitive therapy may be required to alter perception and appraisal of positive day to day events.

Overall, psychotherapy has proven effective in reducing symptom severity and psychosocial impairment, however, the majority of empirical research remains focussed on pharmacotherapy alone or in combination with various forms of cognitive therapy. Clinicians have accepted pharmacotherapy as an important aspect of depressive treatment and efforts have now been geared towards predicting which patients will respond favourably to this sort of treatment as opposed to those who may not respond.

Predictors of Antidepressant Response

The need for prediction of treatment response in chronic depression is essential for rational treatment planning. Early identification of dysthymic patients response to specific drug therapy is beneficial for both the patient and the health care system. Specifically,

15% to 35% of those treated for major depression do not respond to antidepressant treatment, making early identification of responders to specific treatment a necessity (Nelson et al., 1994). In making the proper decision as to which drug to prescribe, the physician must do this in the manner most likely to benefit the patient, since many depressed patients do in fact receive inappropriate drugs and dosages (Joyce & Paykel, 1989). Identification of the characteristics of patients who will respond to a particular treatment may also be helpful for developing hypotheses about the mechanisms of drug response and failure.

Besides the benefits prediction of pharmacotherapy response may have in treatment planning, it may also be useful in subtyping various depressive disorders. In terms of major depression, differences in pharmacological response have been cited as evidence for the validity of the distinctiveness between psychotic and atypical depression (Nelson et al., 1994). In dysthymia, Akiskal's (1980) original proposal of subgrouping patients into affective, subaffective and character spectrum disorders has been supported in pharmaceutical studies by Ravindran et al. (1994b) as mentioned earlier.

Predictors of Antidepressant Response in Major Depression

The literature concerning predictors of antidepressant response in major depression is inconclusive but can still be used as a guide to research in dysthymia. Despite the success in subgrouping many forms of major depression, there have been few other confirmed predictors that determine who will respond to antidepressant treatment. This is especially true when using demographic and illness characteristics as predictors, since there is conflicting evidence on their validity.

Symptoms as Predictors of Antidepressant Response in Major Depression

Research in the treatment of major depression has suggested the presence of endogenous depression as a potential predictor of response to antidepressant treatment. (Paykel, 1972; Raskin & Crook, 1976). The original concept of endogenous depression was that depression arose from within, in contrast to reactive depression, which was caused by an outside source.

Endogenous depression has consistently been found to have a set of characteristic symptoms, including terminal sleep disturbance, psychomotor retardation, nonreactivity of mood, weight loss and pervasive anhedonia. (Kiloh et al., 1972; Rosenthal & Klerman, 1966). Of these individual symptoms, the presence of psychomotor retardation has been one of the best predictors of a good therapeutic response to antidepressants (Paykel, 1972; Raskin & Crook, 1976).

Although the majority of data supports the theory that endogenous depression responds better to tricyclics than nonendogenous depression, there are some conflicting findings. Simpson (1976) did not find any differences between endogenous and neurotic depressives responses to two dosage levels of Imipramine. Some of the conflicting results may be explained by a finding of a curvilinear relationship between Newcastle endogeneity scores and response to antidepressant medication. The groups with middle range scores had a more favourable response than patients who had very low or very high endogeneity scores. This may reflect the heterogeneity of depressive illness (Abou-Saleh, 1983).

Biological Predictors

Endogenous depression is associated with "biological depression" as a result of endocrine dysfunction. In fact, a large percentage of major depressives show hyperactivity or disinhibition in pituitary adrenocortical function (Brown, 1988). The Dexamethasone suppression test has been utilized as a tool in determining overactivity in the HPA axis. Subjects who show inadequate suppression of cortisol following administration of the DST have been deemed as nonsuppressors or "positive" DST's whereas individuals who suppress cortisol are referred to as "negative" DST's (Peselow et al., 1986). The DST has been used as a predictor for drug response in major depression, indicating that nonsuppressors had a better treatment response to antidepressant than suppressors (Albala, 1981; Nelson et al., 1982; Baldessarini et al., 1985). However, Georgotas (1986) did not find statistically significant difference in response rates between nonsuppressors and suppressors of cortisol following the administration of the DST.

Demographics as Predictors

There have been attempts to predict response to Tricyclic antidepressants according to the age of the subject. This has proven to be a difficult task since age may be confounded by other factors such as severity, type of depression and presence of delusions (Brown, 1983). A study by Nelson (1994) suggested that age among other predictors, was significantly associated with poor response to Desipramine treatment on each of four response measures. Specifically, subjects less than 35 years of age predicted non response to Desipramine treatment. Raskin (1970) found age to be positively related to Imipramine treatment response where patients over 40 years old were more likely to have more severe

depression and to respond to drug treatment. However, evidence from Brown (1983) suggests that older age predicts a poorer response to tricyclic antidepressants in non-psychotic endogenous patients. Specifically, non-delusional endogenous depressive patients over the age of 50 had responded less favourably to Tricyclic antidepressants as compared to a younger sample matched for depressive subtype and severity.

Given the limited information regarding predictors for treatment response in major depression, there is little to go on in terms of applying known predictors of antidepressant response to the treatment of dysthymia. Besides the predictive value of the various subgroupings of dysthymia and the usefulness of the classification scheme provided by Akiskal, other predictors of antidepressant response in dysthymia have not been validated. However, interest in this field is growing and there are many promising results that may help guide future research.

Predictors of Antidepressant Response in Dysthymia

Symptoms as Predictors of Antidepressant Response in Dysthymia

Many dysthymic patients exhibit atypical symptoms such as high anxiety, hypersomnia, hyperphagia, reversed diurnal variation, and weight gain. It has been documented that an atypical presentation is predictive of response to MAOIs in major depression (Leibowitz et al., 1988; Kocsis, 1990). Therefore, such symptoms may also indicate good response to MAOIs in dysthymic patients. However, Ravindran & Lapierre (1997a) found that high self-rated psychic anxiety was associated with a poor response to Fluoxetine. It remains to be determined whether the prognostic significance of different types of anxiety (psychic/somatic) is dependent on the treatment compound and/or the

disorder studied.

Demographics as Predictors

Overall, findings related to gender differences appear contradictory. Ravindran et al. (1994b) found that the treatment response is somewhat higher in females (79%) than in males (65%) which is consistent with the results of Kocsis et al. (1989) who found that 62% of females and 40% of males responded to treatment with Imipramine. However, Akiskal et al. (1980) reported that more male than females dysthymics responded to pharmacotherapy. Whether these differences are related to the different types of pharmacotherapeutic compounds used in these studies remain unclear.

The significance of age of onset in influencing the outcome for dysthymic patients treated with medication remains somewhat controversial. Klein et al. (1988), looked at primary dysthymics treated with pharmacotherapy and reported a response rate of 25% (6 of 24) in early onset compared to 44% (4 of 9) for late onset patients. However, a study by Ravindran & Lapierre (1997a) looking at age of onset in subaffective patients treated with Fluoxetine, produced different results. Antidepressant response rates for late onset (3 of 8; 38%) dysthymics was much lower than that found for early onset (35 of 46; 76%) patients. These conflicting results may be attributable to the use of differing criteria for distinguishing early and late onset patients. Ravindran & Lapierre used Akiskal's criteria for early onset (<25 years) and Klein used the DSM-III-R criteria (<21 years). However, the most probable explanation for the low response rate in Klein's study is that character spectrum disorder (CSD) patients, for whom the age of onset is usually quite early and the response rate is very low, were included. It seems then, that in order to identify a

differential response rate for early and late onset patients, the CSD and subaffective patients should be looked at separately.

Biological Predictors

Although the role of the DST as an indicator of treatment response in dysthymia is unclear, Rihmer et al. (1990) investigated the DST in response to Tricyclic antidepressants in patients with DSM-III dysthymic disorder. They found a positive DST response in 65% of subaffective dysthymics while none of the character spectrum patients responded. The subaffective group also showed an overall positive drug response in the study as compared to the character spectrum group. Schatzberg et al. (1983) reported lower rates of abnormal DST's in patients with DSM-III dysthymic disorder, but there were no details relating these findings to treatment response.

Ravindran et al. (1994a) evaluated cortisol levels following dexamethasone administration as well as platelet monoamine oxidase (MAO) activity for their predictive potential in dysthymia. Few patients in the study had positive DST's but responders had higher mean post-dexamethasone cortisol levels than nonresponders prior to treatment. Dysthymic patients had lower platelet MAO levels than controls and the levels remained low following treatment. Among these patients, responders had lower pretreatment platelet MAO activity than nonresponders.

Ravindran et al (1994c) also looked at urinary metabolites of monoamines and melatonin in dysthymic patients as a function of response to treatment. They found that treatment responders had lower urinary 5-HIAA prior to treatment, and these levels increased with treatment. Nonresponders on the other hand, showed decreased urinary 5-

HIAA levels in response to treatment. These data suggest that urinary 5-HIAA may be a potential predictor of treatment response to Fluoxetine.

In terms of other biological markers in depression, Akiskal et al. (1980) found that treatment responders (mainly the subaffective dysthymic group) had shortened REM latency compared to nonresponders. Several others studies have replicated these findings (Hauri and Sateia, 1984; Berger et al., 1983) however, other studies have failed to observe changes in REM late in DSM-III (Guptaka & Moldofsky, 1986) and DSM-III-R (Arriaga & Paiva, 1990) diagnosed dysthymic patients.

Psychosocial Factors as Predictors

There has been little research assessing the predictive values of psychosocial factors in the effectiveness of pharmacotherapy in the treatment of dysthymia. Ravindran et al. (1995b) assessed whether stress and uplift perception or coping styles used prior to antidepressant treatment might be predictive of treatment success. They found that drug treatment coupled with cognitive therapy was most effective in subjects that initially exhibited the highest degree of uplifts and the greatest use of coping styles that included emotional expression, avoidance/denial, general activity, social support seeking and problem solving. Those subjects who's uplifts where particularly low and had impaired social support and problem solving coping strategies, achieved the least success with drug treatment.

In summary, there is a paucity of information relating to predictors of antidepressant response in depression. As a result, it is difficult to determine which dysthymic patients should be selected for drug treatment. However, the use of placebos in

psychiatric research may provide another approach in determining appropriate selection for pharmacological treatment. Studies designed to compare antidepressants with placebos have shown that approximately 30 to 40% of major depressive patients displayed a therapeutic response to placebo over a 4 to 8 week period (Stewart et al., 1983; Khan et al., 1991; Klerman, 1986). However, placebo response may be problematic in dysthymia research, since high placebo response rates may result in inaccurate data and erroneous conclusions concerning treatment efficacy. Consequently, identification of potential placebo responders and of factors that may reduce the rate of placebo response are necessary.

The Placebo Effect

The placebo effect has been defined as "any medical procedure that produces an effect in a patient because of its therapeutic intent and not its specific nature (chemical or physical)" (Lieberman, 1962). Placebo tablets usually contain starch or other inert substance that are causally ineffective for the diagnosed condition of the patient but are used in a way to allow a patient to believe that it is specific for their condition (Kluge, 1990).

Placebo's have become an integral part of medical science where they are most often used in research using double blind studies. However, they have also been used for (a) Alleviating patients concerns (b) Eliminating possible causes of a particular condition, and (c) for therapeutic purposes, such as addiction, where the patient must not know about it's use (Kluge 1990).

The placebo effects is one of many factors that may influence the course of a depressive illness such as dysthymia. They appear to be as effective as antidepressants treatment for some patients and have even been known to mimic the various adverse effects associated with antidepressants, including drowsiness, blurred vision, and gait disturbances (Doongaji, 1978). Even though placebos may be effective under certain conditions, antidepressants appear to be significantly more effective than placebo's in the treatment of major depression (Fairchild et al., 1985).

Placebo Washout Period

Improvement among placebo treated patients may occur gradually or abruptly. The abrupt improvement may be the result of the optimism felt when going to therapy and it usually occurs early. Gradual improvement takes longer and may result from spontaneous remission during placebo treatment (Quitkin et al., 1991). It has become increasingly common in clinical trials to include 2 placebo phases. The first consists of an initial 7 to 10 day placebo “washout” period after baseline assessment of the study inclusion criteria have been met (Rabkin et al., 1986). During this 10 day period some patients improve and are considered “hidden placebo responders”. Consequently they are eliminated at the outset of the study in order to enhance the real difference between placebo and active treatment groups (Reimherr et al., 1988). It may be possible that the 10 day placebo responder is the most mildly depressed of the original cohort. However, Rivaldi and Rush (1994) reviewed 100 randomized control trials and concluded that there was no difference between trials that included a washout period and those that did not. Reimherr et al. (1988) found that the elimination of 10 day placebo responders actually diminished the

differences observed at the end of the study between placebo and drug treatment groups. However, when Bialik et al. (1994) extended a clinical trial of placebo treatment to 12 weeks, one-third of placebo responders relapsed which may put the actual response rate at 20% to 30%. This indicates that placebo is still an important component of a clinical trial that is not under experimental control. In order to gain a better understanding of the placebo effect the mechanisms underlying this phenomenon must be examined.

Mechanisms of the Placebo Effect

The processes underlying the placebo effect are not fully understood, but possible contributory factors have been offered. Shapiro and Morris (1978) listed 15 possible contributory factors, including expectancy affects and operant conditions where contacts with treatments staff serve as reinforcers. It has also been proposed that analgesia associated with placebo is mediated by endorphin release (Levine et al., 1978). Rabkin et al. (1990) also looked at the effect that pill taking may have on the placebo effect. They discontinued placebo medications for a group of 10-day placebo responders while other responders continued taking placebo for an additional 6 weeks. Half of the patients in each condition relapsed in 6 weeks suggesting that pill taking itself does not maintain improved mood.

Alternative explanations have been proposed to explain the placebo effect and one such phenomenon is spontaneous remission. It is widely recognized in scientific research and may be particularly relevant to depressive disorder. Rabkin (1990) suggested the patients may improve while receiving placebo due to the natural course of the depressive illness or spontaneous remission. However, spontaneous remission in dysthymia has been

found to be relatively low. In fact, two studies by McCullough et al. (1988, 1994) revealed the fact that dysthymia is associated with low remission rates, stable symptom levels and stability of psychosocial functioning levels over an extended time period. Overall, the rate of spontaneous remission in their first and second prospective studies were 18% and 13%, respectively.

Other researchers suggest that statistical regression may also provide the explanation for the placebo effect. This refers to the tendency for extreme measures to move closer to the mean when they are repeated. In fact, Macdonald (1983) found that the numerical size of improvement observed in placebo treated patients was equivalent to the estimate that would occur in biochemical variables due to statistical regression.

Regardless of the underlying mechanisms for the placebo effect, it would be advantageous and cost effective to be able to predict which patients are likely to respond to placebo or other non pharmacological intervention, and which are likely to respond to antidepressant therapy. This would benefit both the patient who would receive the appropriate treatment for their illness, as well as the clinician seeking to judge the efficacy of an antidepressant medication (Bialik et al., 1994).

Predictors of Placebo Response in Depressive Disorders

Literature on placebo response comes mainly from studies of patients with major depression with very little information on placebo response in dysthymia. As in prediction of antidepressant response, there are many conflicting reports as to the predictive validity of various demographics and illness characteristics for placebo response. Nevertheless, the following variables have been identified as potential predictors in research studies.

Symptoms as Predictors of Placebo Response in Major Depression

The issue of endogeneity has received a lot of attention in the literature dealing with predictors of placebo response. It has been proposed that endogenous depression patients respond to antidepressants due to the biological nature of their disorder and are slow to respond to placebo. In early major depression studies, patients with endogenous depression were shown to be associated with a lower placebo response rate than neurotic depression (Kiloh et al., 1962; Raskin & Crook, 1976). More recently, Fairchild et al. (1986) found that endogenously depressed patients did not respond to placebo as frequently as nonendogenous patients; however, endogeneity was not fully indicative of placebo nonresponse since 50% of patients who did not respond to placebo were nonendogenous. Brown et al. (1988) did not find that placebo responders and nonresponders differed on any demographic characteristics with respect to endogeneity.

Comorbid anxiety and anxiety disorders may also be potential predictors of placebo response. In a study by Fairchild et al. (1985), generalized anxiety, panic disorder and obsessive-compulsiveness were grouped together under the variable “anxiety” and was a significant indicator of placebo response for outpatients with unipolar major depression. Rabkin et al. (1986), however, did not replicate these findings with atypical depressives where they concluded that patients with panic attacks were more likely to be placebo nonresponders.

It has been suggested that more severe depressions (characterized by scores of greater than 20 on the HAM-D) have lower placebo response rates (30-35%) than less severe depressions which have response rates approaching 70% (Raskin & Crook, 1976;

Rogers & Clay, 1975). Recent studies by Fairchild & Rush (1991) and Wilcox et al. (1992) have duplicated these results, where placebo response rates were found to be higher for mildly depressed patients. However, other reports comparing placebo responder to nonresponders have not found any significant differences in demographic and clinical variables, such as severity of illness (Brown, 1988; Brown et al., 1988).

Duration of Illness as a Predictor

Another potential predictors of placebo response in major depression includes the duration of the illness. Fairchild & Rush (1991) found that the duration of illness discriminated placebo responders from nonresponders were patients with a more acute depression were more likely to respond to placebo treatment than those suffering from a more chronic depression. Wilcox et al. (1992) however, found that patient with a duration of illness greater than 12 months were more likely to be placebo responders.

Biological Markers as Predictors

In terms of the DST and placebo response, Peselow et al. (1986) found that nonsuppressors predicted a statistically significant poorer response to placebo as opposed to a negative DST. These results were also reflected in a study by Brown (1989) where 16 of 27 (59%) suppressors responded to placebo as opposed to 1 of 12 (8%) nonsuppressors. Ribiero et al. (1993) also found similar results and suggested that a nonsuppressive DST may mark an underlying pathophysiology that must be treated with antidepressants to be reversed.

Demographics as Predictors

Wilcox et al. (1992) concluded that older patients and married patients were more likely to respond to placebo. Bialik et al. (1994) found that females with a single episode of depression had a higher placebo response rate (66.7%) than females with recurrent depressive episodes (13.3%). Other studies in nonclinical settings have failed to show that demographic factors such as age are correlates of placebo response (Ross & Buckalew, 1985; Shapiro & Morris, 1978).

The general lack of clear evidence for pretreatment clinical differences in placebo responders and nonresponders may be attributable to a number of different factors. It is possible that the sensitivity of methods for assessing clinical states are inadequate, the placebo responders are a heterogeneous population, or that the definition of placebo responders varies from one study to another (Brown et al., 1988). In addition, the mechanisms that contribute to placebo response must be clarified to facilitate prediction.

Predictors of Placebo Response in Dysthymia

The search for predictors of placebo response in dysthymia has been fairly limited. Rabkin (1990) designed a study to evaluate the effect of pill taking itself as a predictor of placebo response in dysthymia. In this study, 10 day placebo responders who continued to receiving placebo tablets were compared to patients who had their medication discontinued. Half of the patients in each condition relapsed within 6 weeks proving that pill taking itself may not influence maintenance of placebo response in dysthymia. They did however find that placebo response was more likely to be maintained in patients who were currently married. Bialik et al. (1994) looked at predictors of placebo response in a

groups of depressed patients that included double depressives. They found that females with double depression had a placebo response rate 3 times higher than those with a recurrent disorder. However, placebo responders and nonresponders did not differ on HAM-D total or factor scores at baseline.

Summary

Dysthymia refers to individuals with the disposition to low grade dysphoria and has become a recognized disorder distinguishable from other chronic illnesses. Since it's first inception as depressive personality, dysthymic disorder has undergone numerous changes to accommodate the heterogeneity of the disorder. This includes the subclassification of the disorder into primary and secondary dysthymia, early and late onset and subaffective and character spectrum disorders. Dysthymia is known to affect many people and has high comorbidity with other disorders. The etiology of dysthymia has been examined in terms of biological and genetic aspects. Evidence for the biological etiology of dysthymia has been supported by studies related to the dexamethasone suppression test while evidence for genetic predispositions comes mainly from family studies. The contribution of clinical pharmacology has also been extensively researched, providing more evidence for a biological substrate underlying the disorder. In turn, the treatment of dysthymia has shifted from psychotherapy to a more pharmacological approach focusing on specific serotonergic reuptake inhibitors such as Fluoxetine and Sertraline. With the growing cost of treatment, prediction of treatment response in dysthymia has become an important issue. Prediction of antidepressant response has helped subdivide the disorder into different categories (subaffective and character

spectrum) and may help in determining which patients should receive drug treatment. Biological predictors such as the DST, illness characteristics such as endogeneity, anxiety, and severity of illness, as well as demographic characteristics such as gender and age have been assessed in clinical trials in both dysthymia and major depression. Related to prediction of antidepressant response is the use of placebos in psychiatric research. The placebo condition in a double-blind clinical trial has proven to be an efficacious method of analysing differences between drug and control conditions and has allowed researchers to target the appropriate patients for drug treatment by detecting placebo responders. Although many of the results seem promising, there is still controversy as to the potential predictors of placebo response in major depression, and this has made it more difficult to test potential predictors of placebo response in dysthymia as well.

Aim of the Study

In the first part of the study, the rate of placebo response in dysthymic patients will be assessed. It is expected that placebo response rates should be lower than that usually seen in major depression.

The study will then assess whether various demographic characteristics such as gender, marital status, age, and age onset of dysthymia, predicts placebo response. As mentioned earlier, several studies have examined numerous predictors but yielded inconclusive results. In terms of gender, we predict that we will replicate the findings by Bialik et al. (1995) where females had a placebo response rate three times higher than those of males. With respect to onset age, we predict that late onset primary dysthymics treated with placebo will respond more favourably to treatment than early onset primary

dysthymics. These results have been reported by Klein (1998) in a study looking at prediction of antidepressant response in major depressive patients. We will also determine whether other demographic variables that have received little attention in predicting placebo response in dysthymia may, in fact, be useful predictors. Specifically, older subjects and married subject may respond more favourably to placebo treatment because older subjects may have developed more adequate coping skills as a result of life experience and married subjects may have a stronger sense of social support than their single counterparts.

We will also assess whether various symptoms of dysthymia predict response to placebo treatment. This includes severity of illness, as well as anxiety, somatization, weight, cognitive disturbance, diurnal variation, retardation and sleep disturbance. We predict that atypical symptoms associated with dysthymia, such as high anxiety, hypersomnia, hyperphagia, and weight gain will be predictive of a poorer response to placebo treatment. We also predict that subjects with more severe depression will respond less favourably to placebo treatment.

Finally, we will assess whether various psychosocial factors such as stress perceptions, coping styles and quality of life, predict response to placebo treatment. In a study by Ravindran et al. (1995b), patients with a diminished perception of uplifts tended to be poor antidepressant responders and impairments in problem focussed coping was predictive of poorer response to medication. We predict that we will replicate these findings with placebo treated patients. We also predict that subjects with lower quality of life scores will respond less favourably to placebo treatment.

Hypotheses

The present study is designed to examine predictors of placebo response in dysthymia, and to this end several hypothesis will be explored. First, illness characteristics, such as duration of illness, as well as the presence of specific symptoms (e.g. anxiety) may be predictive of placebo response. Second, demographic factors such as gender, early/late illness onset, prior treatment response, and marital status, may be positive predictors. And finally, it is hypothesized that psychological measures which relate to stress perception and coping styles may be useful as subtle predictors of response to placebo.

Method

Procedure

Inclusion Criteria

Subjects had outpatient status and were between the ages of 18 and 61 with valid informed consent obtained for all participants. Subjects also met DSM-IV criteria for dysthymic disorder for > 5 years with no period of > 2 months free of dysthymic symptoms. If subjects were females of child-bearing potential then they must have had negative pregnancy test results, an acceptable method of contraception and were not planning to become pregnant within 4 months of study entry. Subjects could not have a general medical condition that accounted for the symptoms of dysthymia. Finally, if the patient was taking a medication for a medical condition, the medications were not psychotropic agents, including anxiolytics or a drug likely to interact with Sertraline or Nefazadone.

Exclusion Criteria

Patients were not included in the study if they had another concurrent Axis I psychiatric illness (including evidence of a major depressive episode or evidence of alcohol or drug dependency). Patients having significant physical illnesses, evidence of organic brain disorders, presence of significant abnormalities in laboratory tests made at screening, eating disorders, severe allergies, multiple adverse drug reactions, and who were pregnant or lactating women were excluded.

Patients who received Fluoxetine within 6 weeks, MAOIs within 2 weeks, or other antidepressants within one week before starting double-blind therapy were also excluded as well as patients receiving concomitant medication which could interact with Sertraline such as MAOIs or Tryptophan's.

Subjects

The subjects were 72 patients (ages 22 to 61) who were part of the placebo condition in three different clinical trials assessing the efficacy of antidepressant treatment for dysthymia (1994-1998). These antidepressants included Sertraline, and Nefazadone. The protocol for each trial had received approval by the research and ethics committee and informed consent from patients was obtained after procedures had been fully explained. The diagnostic criteria for this study were those indicated in (DSM-III-R) for dysthymia as well as Akiskal's criteria for primary dysthymia of the subaffective (early and late onset) classification. This was done in order to obtain a more homogenous sample of dysthymic patients. Further information regarding the subjects included, patient characteristics (age, sex, marital status), duration of current episode, presenting and post-

treatment symptoms (standardized clinician and self-rated depression), anxiety ratings and an uncorroborated screening report of family history of Axis I psychiatric illness.

Study Design

In each trial, patients were randomly assigned to either active drug treatment or placebo in a double-blind fashion. During a 4 to 14 day washout period, patient's received placebo with only the patient blind to the treatment. Data were only available for patients meeting inclusion criteria following the washout period. Assessments were completed at admission, baseline and again at 2, 4, 6, 8 and 12 weeks of treatment. The baseline and week 12 data were analysed to determine response to treatment. The criterion for a positive treatment response was a reduction of 50% on the 17-item HAM-D for week 12 and a final score of ten or less. Data from patients completing a minimum of 8 weeks of double blind treatment were included in the analyses. Therefore, if week 12 data were missing they were estimated using week 8 data. A total of 65 patients completed at least 8 weeks of double blind placebo treatment. For six patients, both week 12 and week 8 data were missing (1 placebo responder and 5 placebo nonresponders).

Assessments

Upon admission all patients underwent psychiatric screening, which included the following standardized assessment instruments: the 29 item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967), the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959) and the Clinical Global Impression Scale (CGI) for both severity and improvement. The HAM-D scale served as the efficacy measure in this study.

All subjects were asked to complete a series of questionnaires rating stressful life experiences and coping styles used. These included the Daily Hassles and Uplifts Scales to determine minor life stressors and positive experiences (Kanner et al., 1981), and the Coping Strategies Scales (Beckham and Adams, 1984) to determine the coping styles that subjects employed. Subjects also completed the Health-Related Quality of Life Battery (HRQOL) in order to evaluate quality of life parameters.

Results

Statistical Analysis

Placebo response was measured by two different statistical procedures using categorical and continuous variables. The categorical method of determining placebo response involved classifying subjects as placebo responders if they displayed a 50% reduction in their HAM-D 17-item scores and had a total score of 10 or less at week 12 of treatment. The subjects were then numerically coded and entered into an Analysis of Variance (ANOVA) in order to determine whether they differed significantly from nonresponders on baseline predictors.

Two different measures were used as continuous variables in determining placebo response: The absolute value of the patient's week 12 HAM-D 17-item total scores and the difference scores from baseline to week 12. Predictor variables were correlated with the two dependent variables using a stepwise procedure, as a lack of proven predictors of placebo response in the literature made a priori analyses inappropriate. Using this approach, the contribution of a given predictor is determined with the effects of the other predictors partialled out, or held constant.

A separate analysis using a stepwise procedure was conducted to determine the effects of various baseline predictors on clusters of depressive symptoms, as measured by HAM-D factor scores.

Demographic and Psychiatric History Variables

Table 1 shows that the mean age of the patients was 39.7 ($\pm$ 9.4). From these patients, 64% were females, and 42% were married. The average age of onset of illness was 21 years, the average duration of illness was 18.81 years, and the proportion of patients who received past treatment was 32%.

Baseline measures of demographic characteristics including the duration of illness, age, onset age, past treatment and marital status were not predictive of placebo response at Week 12 of treatment.

Clinical Response

A total of 72 subjects were enrolled in the study. Of these subjects, 6 were unable to remain in the study until the 8th week. The overall rate of placebo response for the 66 remaining patients was 34.8%. Placebo responders of course, had significantly lower scores by week 12 of treatment than did placebo nonresponders and response was also extended to anxiety ratings where HAM-A ($F(1,60) = 49.17, p < .000$) scores were significantly lower in placebo responders (see Figure 1).

Furthermore, a stepwise analysis revealed that only baseline HAM-D total scores were correlated with final HAM-D difference scores ($R^2_{\text{adjusted}} = .109, F(1,44) = 6.486, p < .05$)(see Table 2). In effect, patients with the least severe symptoms at baseline were more likely to respond to placebo by week 12.

Mean age (+/- S.E.):	39.68 ($\pm$ 9.4)	
Gender:	26 males, 46 females	
Past Treatment:	No:	47/70
	Yes:	23/70
Age of Onset:	21	
Marital Status:	Married (& Common Law): 30/72	
	Single: 42/72	
Education:	Partial High School:	8/72
	Complete High School:	12/72
	Partial University/College:	14/72
	Complete University/College:	27/72
	Graduate School:	11/72

Figure 1. Mean (+S.E.M) HAM-D and HAM-A scores at the baseline visit and after 12 weeks of treatment, among dysthymic patients treated with placebo including (a) mean totals for both groups combined (b) means for placebo responders (c) means for placebo nonresponders

* $P < .05$ relative to baseline

** $P < .05$ relative to responders at week 12

Table 2. Final Regression Equation of a Stepwise Analysis Using Week 12 Absolute HAM-D 17-item Values as the Dependent Variable

Variables Entered	Mean Score	B	Beta	Zero Order Correlation	Unique Variance Explained
Cognitive Disturbance	0.593	6.949	2.071	0.286	.044*
Avoidance Coping	43.49	-0.184	-2.092	0.486	.042*

*p<.05

Quality of Life

Baseline quality of life dimensions were not predictive of final Hamilton depression scores regardless of how placebo response was measured. Interestingly, a general measure of life satisfaction was significantly improved at week 12 among all placebo treated patients ($t(41) = -2.534, p < .05$) as shown in Figure 2. However, the effect was largely due to the dramatic increase in life satisfaction among placebo responders, which significantly differed from nonresponders at week 12 ($F(1,39) = 5.843, p < .05$). Also, cognitive functioning ($F(1,39) = 4.87, p < .05$) differed significantly for placebo responders and nonresponders at the end of treatment even though baseline levels did not predict placebo response (see Figure 2).

Hassles and Uplifts

The perceived hassles and uplifts of patients before and after treatment are shown in Figure 3. All placebo treated patients showed a significant decrease in both the reported frequency of hassles ($t(36) = 2.516, p < .05$), as well as the severity of hassles ($t(37) = 3.080, p < .01$), although responders and nonresponders did not differ at week 12. Baseline hassles frequency and severity were not predictive of placebo response at week 12.

As in the case of hassles perception, analysis of perceived uplifts at baseline indicated that neither frequency nor intensity were predictive of placebo response at the end of treatment. Also, uplift frequency and uplift intensity did not significantly increase for placebo responders ($t(11) = -.890, n/s$ and $t(11) = -1.01, n/s$, respectively) and placebo nonresponders ($t(25) = 1.62, n/s$, and $t(25) = 1.437, n/s$, respectively) by the end of treatment.

Figure 2. Mean (+S.E.M) Quality of Life dimensions (cognitive functioning and life satisfaction) at the baseline visit or after 12 weeks of treatment, among dysthymic patients treated with placebo including (a) mean totals for both groups (b) means for placebo responders (c) means for placebo nonresponders

Cognitive Functioning

Life Satisfaction

* $P < .05$ relative to baseline

** $P < .05$ relative to responders at week 12

Figure 3. Mean ($\pm$ S.E.M) perceived hassle and uplift scores at the baseline visit and after 12 weeks of treatment, among dysthymic patients treated with placebo including (a) mean totals for both groups (b) means for placebo responders (c) means for placebo nonresponders

* $P < .05$ relative to baseline

** $P < .05$ relative to responders at week 12

Coping Styles & Clinical Symptoms

Analysis of the coping styles of dysthymic patients over the 12 weeks of treatment confirmed that alleviation of depressive symptoms was accompanied by alterations in some of the subject's coping styles (Figure 4). In particular, passivity decreased for placebo responders ($t(11) = 3.09, p < .010$) and blame decreased for placebo nonresponders ($t(25) = 2.65, p < .05$) by week 12 of treatment.

Figure 4 shows that relative to placebo nonresponders, the responders tended to favour avoidance/denial at baseline of treatment when using a categorical approach in measuring placebo response. Table 3 shows the results of a stepwise analysis using absolute final HAM-D scores which also revealed that avoidance coping strategies were significant on the first step of the equation ($\beta = -.286, p < .05$). On the second step, cognitive disturbance as determined by the HAM-D ratings at baseline, was predictive of placebo response where cognitive disturbance (which included symptoms of guilt, suicide, agitation, derealization, paranoia and obsessive symptoms) were significantly lower in patients with lower final HAM-D scores ($\beta = .289, p < .05$). The full equation for the stepwise analysis using absolute score revealed that when cognitive disturbance was high and avoidance denial was low than placebo response was highest among the placebo treated patients ($r^2_{\text{adjusted}} = .126, F(2,43) = 4.254, p < .05$).

The use of an avoidance/denial coping strategy was also predictive of various HAM-D factor scores at week 12. The full equations for the stepwise analyses showed that increased avoidance was associated with lower scores in terms of cognitive

Figure 4. Mean (+S.E.M) coping scores (blame, avoidance denial, passivity) at the baseline visit and after 12 weeks of treatment, among dysthymic patients treated with placebo including (a) mean totals for both groups (b) means for placebo responders (c) means for placebo nonresponders

* $P < .05$ relative to baseline

** $P < .05$ relative to responders at week 12

+ baseline levels predicted week 12 results ($P < .05$)

Table 3. Final regression equation of a stepwise selection analysis using HAM-D 17-item difference scores between baseline and week 12 as the dependent variable

Variables Entered	Mean Score	B	Beta	Zero Order Correlation	Unique Variance Explained
HAM-D 17-item baseline	18.18	0.603	0.358	0.358	.014*
*p<.05					

disturbance ($r^2_{\text{adjusted}} = .291$, $F(1,42) = 9.820$, $p < .000$) and retardation ($r^2_{\text{adjusted}} = .168$, $F(1,42) = 5.1348$, $p < .01$). Retardation was represented by symptoms such as depressed mood and a decrease in work and activities.

Discussion

The present study investigated placebo response in dysthymia and whether certain patient characteristics, symptomatology and psychosocial variable may be predictive of this response.

Placebo responders are a heterogenous population whose positive response to placebo treatment may be attributed to several factors. This makes the validity of attributing the response to the placebo itself questionable. Subjects may have shown a positive response to placebo due to the natural history of the disorder or to regression towards the mean. They may have also shown positive response due to the influence of the clinical setting, the staff and experimenter attitudes and other environmental factors (Doongaji et al., 1978).

Regardless of what mechanisms underlie the placebo effect, a number of predictors of placebo response have been proposed in both major depression and dysthymia (Fairchild & Rush, 1991; Brown, 1988; Brown et al., 1988; Ross & Buckalew, 1985; Shapiro & Morris, 1978; Wilcox et al. 1992; Bialik et al., 1995; Lasagna et al., 1955; Tibbets & Hawkins, 1956; Joyce, 1959). These predictors include severity of illness, age, gender, marital status, duration of illness and symptomatology. In the present study, these variables were examined, as were several others which in past studies were found to predict response to antidepressant treatment. These variables included the age of onset of the illness and psychosocial measures such as coping styles, stressor perception and quality of life.

The main findings of the study were: (1) Placebo response rates were higher (34.8%) than what has been found in earlier studies looking at dysthymia but consistent with rates found in this laboratory and other recent studies looking strictly at the subaffective subgroup (2) Patients with more severe dysthymia, as indicated by overall HAM-D scores, were more likely to be placebo nonresponders (3) Subjects who scored high on a factor of the HAM-D scale designated as “cognitive disturbance” were less likely to respond to placebo (4) Subject’s use of avoidance/denial as a coping strategy at baseline was positively related to placebo response while problem focused and emotional focused coping strategies were not significant (5) Past demographic characteristics that were predictive of placebo response in major depression including age, gender and age onset were not predictive of placebo response in the current study (6) Other functional predictors examined in the present study such as quality of life, and stressor perception were also non significant.

The results of the study will be interpreted and discussed under the following headings:(1) Placebo response rates (2) Predictors of placebo response including: (a) Demographic Variables (b) Symptoms (c) Coping Strategies (d) Uplifts and Hassles and (e) Quality of Life, (3) Limitations and (4) Implications of the findings of the study.

Placebo Response Rates

Past studies have indicated that placebo response rates among dysthymic patients are lower than among patients with moderate to severe major depression (Kocsis et al., 1988). Whereas placebo response rates in major depression are about 30%, early studies on dysthymia showed a rate of about 20%. The present results, however, indicated a placebo

response rate (34.8%) in dysthymia, comparable to that reported for major depression. While this level of placebo response rate is higher than in earlier studies, it is not unlike that of other reports from this laboratory. In particular, a rate of 33.3% placebo response was reported by Ravindran et al. (1997b, 1999) in two placebo controlled studies assessing cognitive therapy and pharmacotherapy in the treatment of dysthymia. In fact, placebo response rates were equivalent to response rates of a combined placebo and cognitive therapy condition in the latter study. Bialik et al. (1995) also found a high placebo response rate in dysthymia; they suggested that their higher than expected placebo response may have been related to the ambiguities present in the DSM-III criteria for dysthymia, which they used instead of the better defined DSM-III-R or DSM-IV criteria. Further, Thase (1996) found an even higher response rate of 44% in a placebo controlled study examining the effects of Sertraline and Imipramine in the treatment of dysthymia. High levels of placebo response in the present study may have been influenced by the screening process, doctor patient relationships and the amount of supportive therapy given by the research team involved in the study. Moreover, subjects in the present study represented subaffective dysthymia, as opposed to those with character spectrum disorder. It is possible that placebo response rates differ in these two sub-populations of dysthymic patients.

Predictors of Placebo Response

Demographic Variables

The results of the present study confirmed some pretreatment clinical differences between placebo responders and placebo nonresponders among dysthymic patients but

failed to confirm others. For instance, demographic factors such as age, sex, age of onset and marital status did not distinguish between responders and nonresponders. These findings were similar to those reported on placebo response in major depression (Brown, 1988; Brown et al., 1988; Ross & Buckalew, 1985; Shapiro & Morris, 1978). However, duration of illness, which was reported to predict placebo response in major depression studies (Fairchild & Rush, 1991), was not related to placebo response in the present investigation.

Early onset dysthymia has been associated with a reliance on emotion focused coping strategies, more lifetime substance abuse and personality disorders (Klein et al., 1999). It was expected that early onset may be indicative of a more severe form of dysthymia that would not respond to placebo treatment. In fact, a past study by Klein et al. (1988) found that early onset patients were less likely to respond to antidepressant treatment. However, in the present investigation, age onset was not predictive of placebo response. These results may have been influenced by the nature of the subjects selected for the study as they were chosen exclusively from a pool of subaffective dysthymics. This is in contrast to past studies that often included character spectrum patients, who tended to have an earlier onset and lower response rates which may have confounded the results of these studies.

Symptoms

The severity of various clinical symptoms at baseline were found to differ between placebo responders and nonresponders. Responders had a less severe illness (based on the HAM-D) compared to nonresponders. This finding is in concordance with studies by

Fairchild and Rush (1991) and Wilcox et al. (1992) who found placebo responders to have a less severe major depression. Furthermore, in the present investigation, severity of symptoms at baseline of treatment were also related to sleep disturbance scores at week 12. The more severe the symptoms of dysthymia the more sleep disturbances were exhibited.

A factor composition of HAM-D items based on a factor analysis by Cleary & Guy (1975) were examined as potential predictors of placebo response in the present investigation. The six factors were designated as “anxiety”, “weight”, “cognitive disturbance”, “diurnal variation”, “retardation”, and “sleep disturbance”. The third factor, “cognitive disturbance”, was found to be less pronounced in placebo responders than for nonresponders. This cluster, includes symptoms such as derealization, paranoia, guilt, obsessive compulsion, and suicidal tendencies. It may be possible that the presence of these symptoms may reflect a more severe illnesses that may be less responsive to placebo therapy.

Coping Strategies

Coping strategies were one of the psychosocial variables examined in the present investigation to determine if they would differentiate placebo responders from nonresponders. As mentioned earlier, the two most frequently studied forms of coping are problem focused coping, which involves direct action on the environment to alter threatening circumstance, and emotional focused coping which involves the use of emotion or thoughts to deal with stressors (Carver & Scheir, 1994). It has been shown that many depressed subjects can be distinguished from control subjects by the style of coping they use. Ravindran et al. (1995b) found that impairment of problem focused coping was

predictive of poor response to antidepressant treatment. Additionally, recovery from depression has also been associated with changes in coping styles where patients were found to rely less on inappropriate emotion focussed coping strategies by the end of treatment (Ravindran et al. 1995a). In the present study, there was no differentiation between problem focused coping and emotion focussed coping strategies. It is possible that these findings may reflect a general difference between drug and placebo treatment in terms of psychosocial outcomes. It may be that coping is unrelated to response in placebo studies; however it was interesting to see that patients who displayed an avoidance/denial style of coping at baseline were most likely to exhibit a placebo response in the present investigation. Subjects who displayed higher levels of denial may have experienced the most significant reduction in their symptoms as a result of taking action and seeking treatment for their illness.

High levels of avoidance/denial at baseline also predicted decreases in the cluster of symptoms categorized as “cognitive disturbance” and “retardation” at week 12. These results may be related to the reduction of avoidance coping strategies which have adversely affected the patient’s daily functioning and activities.

Uplifts & Hassles

It has been reported that with alleviation of dysthymia, there is a concurrent diminution of perceived hassles, and that this effect exceeds that of placebo treated subjects. In the present study, a reduction of hassles was apparent irrespective of whether subjects displayed a placebo response or not. At first blush, this would appear contradictory; however, all placebo treated subjects in this study showed a marked

reduction of HAM-D scores which may have positively affected their perception of stressful events as well.

Along with an increase in hassles perception, it has been reported in past studies that depressed patients do not display the optimism that is characteristic of non depressed individuals (Alloy & Abramson, 1988). Similarly, a decrease in uplift perception is often associated with depressed individuals; however, uplift perception was not predictive of placebo response in this study. Interestingly, placebo responders did not show any general increase in uplifts perception by week 12 of treatment as has been previously presented by Ravindran et al. (1997b). It has been suggested that the absence of an increase in uplifts perception may be related to the anhedonia associated with dysthymia. Anhedonia may be so deeply ingrained that patients recognize when hassles are diminished, but may be less attuned to variations in uplifting events. There are also cognitive theories which may help explain this phenomenon. Beck's model of depression explains the cognitive process of depressed individuals which may influence their perception of daily events. He describes a negative cognitive pattern associated with depressed subjects where they may misinterpret positive things in negative ways and may negatively construe situations where there may be alternate explanations available. Furthermore, stable cognitive patterns known as schemas, are dysfunctional for depressed individuals. Schemas are a set of expectations about what things will look like and how events will proceed. They help an individual screen out, differentiate and code stimuli that confront them. Depressed people tend to have overactive dysfunctional schemas which may interfere with the matching of an appropriate schema to a particular situation. It may

be that uplifting events are negatively distorted to fit these dysfunctional schemas of depressed individuals. Overall, it is possible that treatment may be needed to increase uplift perception, alternatively reduced frequency and intensity of uplifts may be a trait characteristic of individuals vulnerable to dysthymia.

Quality of Life

Besides stress and coping measures, quality of life was another measure of functioning examined as a potential predictor of placebo response. Overall, this measure proved not to be predictive; however, by week 12 of treatment, responders showed significantly higher levels of cognitive restructuring, a subcategory of the quality of life scale. Also, the life satisfaction component of the scale significantly improved for both responders and nonresponders during the course of treatment.

The Health Related Quality of Life Battery used in the present investigation was previously shown to distinguish between depressed and nondepressed patients, before and after recovery from illness. However, the Health Related Quality of Life Battery is a subjective scale and should be considered cautiously as both objective and subjective factors should be taken into consideration when measuring quality of life. Subjective factors reflect the patient's point of view and include perceptions of life satisfaction, happiness, social relations and feeling of well being. Subjective scales do not always accurately reflect the patient's quality of life. For example, a patient who does not expect full recovery from a disability may be quite satisfied with a partial recovery. On the other hand, a patient with unrealistic expectations will be dissatisfied even when the full possible benefits of a health intervention has been reached. In general, the attribution style of the

patient may distort the evaluation of the health intervention (Jenkins, 1992).

Objective factors, on the other hand, include variables such as the patient's physical and clinical symptoms (Sainfort et al., 1996). These scales may also prove to be inaccurate measures of quality of life facets. Objective measures are viewed favourably by clinicians because they reflect accepted norms and address directly behaviour that can be manipulated and measured. However, assessment areas that are most important to clinicians in judging the patient's quality of life might be very different from those judged important by patients. Even among patients, there may be differences as to which domains they feel are most important in quantifying their life satisfaction (Saintfort et al., 1996). There are also discrepancies between clinicians and patients in their view of the overall outcome of the treatment (Hunt & McKenna, 1992). Clinicians may be satisfied that the patients quality of life has improved, while the patients may feel worse than before. Furthermore, in cases where others are involved in the care of the patients (nurses, family members, volunteers), there may be different views of the patient's clinical status and life quality which should be taken into consideration. Objective indicators may also be biased by the observer's own values and opinions. In fact, physicians tend to assign lower scores to the patient's quality of life than patients do themselves (Heitanen, 1996). Overall, both the patient's view on life satisfaction and the clinician's objective measurements should be considered when assessing the patient's quality of life.

Limitations

Besides the small sample size, one of the major limitations in studies of this nature is the classification of response. A change of 50% in terms of the Hamilton Depression

Scale (used often as the criteria for response) may mean something different for a patient with a large number of severe symptoms relative to that of a patient with comparatively minor symptoms. In this study, we dealt with this problem by using a variety of approaches in measuring placebo response including both regression and ANOVA analyses. Unfortunately, these approaches may produce varying results making it harder to clarify valid predictors.

Another limitation of the present study involved the variability in the severity of depressive symptoms within the disorder itself. Dysthymic disorder is known for intermittent symptoms that often fluctuate in intensity. There appears to be a need for a specific instrument for dysthymia that is sensitive to mild fluctuating symptoms of the illness in order to accurately measure this construct. The Beck depression inventory was derived from empirical data from patients treated with psychotherapy while the HAM-D is designed to better measure episodic states of depression and is heavily weighted toward neurovegetative symptoms of depression. These symptoms are not as frequent or dominant in dysthymia as in major depression. The Cornell scale (CDRS) may be a more appropriate scale for measurement of dysthymic individuals. In fact, the CDRS was designed specifically to be more sensitive to the characteristic symptomatology of dysthymia and is proven to be accurate in measuring change during treatment (Mason et al., 1993).

Other factors that could influence placebo response and should be taken into consideration in future studies include personality variables. Personality variables tend to be beyond the control of either the patient or the researcher and future studies ought to identify their effect in order to eliminate their extraneous influence. Research into

personality variables was very common in some of the earlier studies examining placebo reactors but often produced varying results. A notable study by Lasagna et al. (1955) found that placebo responders tend to be immature, eccentric, anxious and less rigid subjects. Some investigators claimed that placebo responders were less likely to have a history of neurotic traits or hysterical personality but were more likely to exhibit high levels of anxiety (Tibbets & Hawkings, 1956). Other investigators, such as Joyce (1959), found that placebo responders among medical students were sociable and extroverted but lacking in self confidence.

One specific personality variable that has received extensive research in past studies of placebo response was suggestibility. Highly suggestible subjects are believed to be more affected by the clinical setting and more likely to respond strongly to placebo. Linton & Langs (1962) describe the personality of highly suggestible people as less introspective and self-examining. Placebo nonresponders on the other hand, are believed to have a greater sensitivity to internal cues such as the ability to self-examine and the ability to be self critical. These traits allow the subject to evaluate their own reaction and be able to determine that what they are experiencing is not out of the ordinary. Highly suggestible people may be lacking these abilities and may be more likely to accept the suggestion that they have been treated and respond accordingly.

Recent studies have also looked at the hypnotizability of individuals which may also prove to be a relevant factor in predicting placebo response. Hypnotizability, refers to the degree of response to cues or subtle suggestions from the environment as to how to behave. Farthing et al. (1997) conducted a study looking at the effectiveness of an internal

distraction task coupled with an external distraction task in reducing the pain induced by immersing a hand in ice water. Analgesia suggestion and guided imagery were used as internal distractors while work memory and pursuit rotor tasks were external distractors. Subjects who were labelled as highly hypnotizable achieved greater pain reduction than low hypnotizable subjects. Highly suggestible individuals may be more capable of vivid mental imagery and deeper imaginative involvement and may be more effective at diverting attention to controlling pain, regardless of whether internal or external distractors are used. There is a possibility that this trait may be also associated with placebo response in depression and it may be wise to measure hypnotizability in future studies looking at variables that may influence placebo response.

Future studies should include longer follow-up periods following the acute treatment phase in order to assess whether or not placebo response endures as long as antidepressant response. One previous study by Shea et al. (1992) included an 18 month follow-up of patients with major depression who had responded to treatment with cognitive behaviour therapy, interpersonal therapy, Imipramine, or placebo. They found that for all patients who recovered after 16 weeks of treatment, rates of relapse during the follow-up period did not differ significantly among the four treatments. Specifically, 36% for those treated with cognitive behaviour therapy relapsed, 33% for those treated with interpersonal therapy, 50% for those treated with Imipramine and 33% for those treated with placebo. Since the patients involved in this study were strictly major depressives, it is not yet clear whether these results would be replicated in dysthymia. Furthermore, proven predictors of placebo response in dysthymia may be only predictive of acute recovery and

a follow-up study may be necessary to show if these predictors would remain significant with time.

Implications

The present investigation brings up some interesting topics. With a general response to antidepressant treatment for dysthymia approaching 60% and a placebo response rate around 30%, almost half of responders may actually be placebo responders. With such a high rate of placebo response it may be necessary to include placebo treatment as a options in treatment. In fact, Brown (1994) has proposed that most depressed patients should be offered an initial treatment of four to six week of placebo treatment. If they do not show substantial improvement within two weeks or recovery within six weeks they should then be offered antidepressant medication. As mentioned earlier, finding proven predictors of placebo response would help in selecting which patients are most likely to respond to placebo treatment and should therefore be offered this form of therapy. This treatment would not only be the most appropriate for these types of patients but it would also be a cost efficient solution which may help limit the costs of health care.

The results of the present study may also have practical application in the treatment of dysthymia. As mentioned earlier, it was mostly psychosocial and cognitive measures that distinguished responders from nonresponders to placebo treatment. In this respect, the results of the present study indicate that cognitive behavioural therapy may be useful in treating dysthymia. Cognitive behavioural therapy may help in the development of adaptive behaviour and in the improvement of negative self -perception. Additionally, this form of therapy may teach specific coping skills that have been suggested to increase

quality of life. These are important areas to be addressed in future studies since there is a high rate of recurrence of major depression and dysthymia.

References

- Abou-Saleh, M.T. & Coppen, A. (1983). Classification of depression and response to antidepressive therapies. British Journal of Psychiatry, 143, 601-603.
- Akiskal, H.S. (1983). Dysthymic disorder: Psychopathology of proposed chronic depressive subtypes. American Journal of Psychiatry, 140, 11-20.
- Akiskal, H.S. (1985). A proposed clinical approach to chronic and "resistant" depressions: Evaluation and treatments. Journal of Clinical Psychiatry, 46, 32-36.
- Akiskal, H.S. (1991). Chronic depression. Bulletin of the Menninger Clinic, 55, 156-171.
- Akiskal, H.S. (1990). Towards a definition of dysthymia: boundaries with personality and mood disorders. In S.W. Burton & H.S. Akiskal (Eds.), Dysthymic disorder, Royal College of Psychiatrists.
- Akiskal, H.S., Rosenthal, T.L., Haykal, R.F., Lemmi, H., Rosenthal, R.H., Scott-Strauss, A. (1980). Characterological depressions. Archives of General Psychiatry, 37, 777-783.
- Akiskal, H.S. & Weise, R.E. (1992). The clinical spectrum of so-called "minor" depressions. American Journal of Psychotherapy, 46, 90-22.
- Albala, A.A. (1981). Changes in serial dexamethasone suppression tests among unipolar depressives receiving electroconvulsive treatment. Biological Psychiatry, 16, 551-560.
- Alloy, L.B. & Abramson, L.Y. (1988). Depressive realism: Four theoretical perspectives. In Cognitive Processes in Depression, L.B. Alloy (Eds.), Cognitive Processes in

Depression, (pp. 223-265), New York: Guilford Press.

Arriaga, F. & Paiva, T. (1990). Clinical and EEG sleep changes in primary dysthymia and generalized anxiety: a comparison with normal controls. Neuropsychobiology, 24, 109-114.

Bakish, D., Lapierre, Y.D., Weinstein, R., Klein, J., Weins, A., Jones, B., Horn, E., Browne, M., Bourget, O., Blanchard, A. (1993). Ritanserin, Imipramine and placebo in the treatment of dysthymic disorder. Journal of Clinical Psychopharmacology, 13, 409-414.

Baldessarini, R.J. & Aran, G. (1985). Does the dexamethasone suppression test have clinical utility in psychiatry? Journal of Clinical Psychiatry, 46, 25-29.

Becker, R.E., Heimberg, R.G., Bellack, A.S. (1987). Social skills training treatment for depression, New York: Pergamon.

Bersani, G., Pozzi, F., Marini, S., Grispi, A., Pasini, A., Ciani, N. (1991). 5-Ht₂ receptor antagonism in dysthymic disorder: A double-blind placebo-controlled study with ritanserin. Acta Psychiatrica Scandinavica, 83, 244-248.

Bialik, R.J., Ravindran, A.V., Bakish, D., Lapierre, Y.D. (1995). A comparison of placebo responders and nonresponders in subgroups of depressive disorder. Journal of Psychiatry & Neuroscience, 20, 265-270.

Bohm, C., Robinson, D.S., Gammans, R.E. (1990). Bupropion therapy for elderly patients with anxiety or depressive neurosis [letter]. Journal of Clinical Psychiatry, 51, 309.

Botte, L. (1989). Moclobemide versus placebo in the treatment of depression. A multicentre study in Belgium. Symposium presentation cited in Stabl et al. (1989).

- Brown, W.A., Dornseif, B.E., Wernicke, J.F. (1988). Placebo response in depression: a search for predictors. Psychiatry Research, 26, 259-264.
- Brown, R.P., Sweeney, J., Frances, A., Kocsis, J.H., Loutsch, E. (1983). Age as a predictor of treatment response in endogenous depression. Journal of Clinical Psychopharmacology, 3, 176-178.
- Brown, W.A., Johnson, M.F., Chen, M.G. (1992). Clinical features of depressed patients who do and do not improve with placebo. Psychiatry Research, 41, 203-214.
- Brown, W.A. (1994). Placebo as a treatment for depression. Neuropsychopharmacology, 4, 265-269.
- Carver, C., Scheier, M. (1994). Situational coping and coping dispositions in a stressful transaction. Journal of Personality and Social Psychology, 66, 185-195.
- Casacchia, M. & Rossi, A. (1989). A comparison of Moclobemide and Imipramine in the treatment of depression. Symposium presentation cited in Stabl et al., (1989).
- Cassano, G.B., Perugi, G., Marenmani, I., Akiskal, H.S. (1990). Social adjustment in dysthymia. In Burton S.W. and Akiskal H.S. (Eds.), Dysthymic Disorders, (pp. 78-85),. London: Gaskell
- Chodoff, P. (1972). The depressive personality. Archives of General Psychiatry, 27, 666-673.
- Conte, H.R. & Karasu, B.T. (1992). A review of treatment studies of minor depression: 1980-1991. American Journal of Psychotherapy, 46, 58-74.
- De Jong, R., Treiber, T., Henrich, G. (1986). Effectiveness of two psychological treatments for inpatients with severe and chronic depressions. Cognitive Therapy

Research, 10, 645-663.

De Lisio, G., Maremmani, I., Perugi, G., Cassano, G.B., Deltito, J., Akiskal, H.S. (1986).

Impairment of work and leisure in depressed outpatients. Journal of Affective Disorder, 10, 79-80.

Doongaji, V.N., Vahia, V.N., Bharucha, M.P.E. (1978). On placebos, placebo responses

and placebo responders: a review of psychological, psychopharmacological and psychophysiological factors. Journal of Postgraduate Medicine, 24, 147-157.

Downing, R.W. & Rickels, K. (1973). Predictors of response to amitriptyline and placebo

in three outpatient treatment settings. The Journal of Nervous and Mental Disease, 156, 109-127.

Dunner, D.L., Hendrickson, H.E., Bea, C., Budech, C.B. (1997). Venlafaxine in dysthymic

disorder. Journal of Clinical Psychiatry, 58, 528-531.

Eysenck, H.J. (1994). The outcome problem in psychotherapy: What have we learned.

Behaviour Research Therapy, 32, 477-495.

Fairchild, C.J., Rush, A.J., Vasavada, N., Giles, D.E., Khatami, M. (1985). Which

depressions respond to placebo? Psychiatry Research, 18, 217-226.

Farthing, G.W., Venturino, M., Brown, S.W., Lazar, J.D. (1997). Internal and external

distraction in the control of cold-pressor pain as a function of hypnotizability The International Journal of Clinical and Experimental Hypnosis, 4, 433-446.

Fava, M., Nierenberg, A.A., Quitkin, F.M., Zisook, S., Pearlstein, T., Stone, A.,

Rosenbaum, J.F. (1997). A preliminary study on the efficacy of Sertraline and

Imipramine on anger attacks in atypical depression and dysthymia.

Psychopharmacology Bulletin, 33, 101-103.

Fennel, M.J.V., & Teasdale, J.D. (1982). Cognitive therapy with chronic, drug-refractory depressed outpatients: a note of caution. Cognitive Therapy Research, 6, 455-460.

Frame, C.L., Johnstone, B., Giblin, M.S. (1988). Dysthymia. In M. Hersen & C. G. Last (Eds.), Child Behaviour Therapy Casebook, New York: Plenum Press.

Frances, A., Kocsis, J., Marin, D., Manning, D., Markowitz, J., Mason, B., Widiger, T. (1989). Diagnostic criteria for dysthymic disorder. Psychopharmacology Bulletin, 25, 325-329.

Freeman, E.W., Rickels, K., Sondheimer, S.J., Denis, A., Pfeifer, S., Weil, S. (1994). Nefazadone in the treatment of premenstrual syndrome: a preliminary study. Journal of Clinical Psychopharmacology, 14, 180-186.

Friedman, R.A., Parides, M., Baff, R., Moran, M., Kocsis, J.H. (1995). Predictors of response to desipramine in dysthymia. Journal of Clinical Psychopharmacology, 15, 280-283.

Georgotas, A., Stokes, P., McCue, R.E., Dubow, A., Welkowitz, J., Friedman, E., Fanelli, C., Chang, I., Cooper, T.B. (1986). The usefulness of DST in predicting response to antidepressants: a placebo-controlled study. Journal of Affective Disorders, 11, 21-28.

Goa, K.L. & Ward, A. (1986). Buspirone: A preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs, 32, 114-129.

Goldstein, W.N. & Anthony, R.N. (1988). The diagnosis of depression and the DSM's. American Journal of Psychotherapy, 42, 180-196.

- Gonzalez, L.R., Lewinsohn, R.M., Clarker, G.N. (1985). Longitudinal follow-up of unipolar depressives: an investigation of predictors of relapse. Journal of Consulting in Clinical Psychology, 53, 461-469.
- Gowdey, C.W. (1983). A guide to the pharmacology of placebos. Canadian Medical Association, 128, 921-925.
- Haefely, W., Burkard, W.P., Cesura, A.M., Kettler, R., Lorez, H.P., Martin, J.R., Richards, J.G., Scherschlicht, R., Da Prada, M. (1992). Biochemistry and pharmacology of Moclobemide, a prototype RIMA. Psychopharmacology, 106 Suppl, S6-14.
- Hamilton, M. (1967). Development of a rating scale for primary depressive illness. British Journal of Social and Clinical Psychology, 6, 278-296.
- Hamilton, M. (1959). The assessment of anxiety states by rating. British Journal of Medical Psychology, 32, 50-55.
- Harpin, R.E., Liberman, R.P., Marks, I., Stern, R., Bohannon, W.E. (1982). Cognitive-behavior therapy for chronically depressed patients: A controlled pilot study. Journal of Nervous and Mental Disease, 170, 295-301.
- Hauri, P. & Sateia, M.J. (1984). REM sleep in dysthymic disorders. Sleep Research, 13, 119.
- Hellerstein, D.J., Yanowitch, P., Rosenthal, J., Samstag, L.W., Maurer, M., Kasch, K., Burrows, L., Poster, M., Cantillon, M., Winston, A. (1993). A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. American Journal of Psychiatry, 150, 1169-1175.
- Hellerstein, D.J., Yanowitch, P., Rosenthal, J., Hemlock, C., Kasch, K., Samstag, L.W.,

- Winston, A. (1994). Long-term treatment of double depression: A preliminary study with serotonergic antidepressants. Progress in Neuro-psychopharmacological & Biological Psychiatry, 18, 139-147.
- Hietanen, P. (1996). Measurement and practical aspects of quality of life in breast cancer. Acta Oncologica, 35, 39 - 42.
- Hirschfeld, R.M.A. (1986). Psycho-social predictors of chronicity in depressed patients. British Journal of Psychiatry, 148, 648-654.
- Howland, R.H. (1993). Chronic depression. Hospital and Community Psychiatry, 44, 633-639.
- Hunt, S., McKenna, S. (1992). The QLDS. A scale for the measurement of quality of life in depression. Health Policy, 22, 307 - 319.
- Insel, T.R., Goodwin, F.K. (1983). The dexamethasone suppression test: Promises and problems of diagnostic laboratory tests in psychiatry. Hospital and Community Psychiatry, 34, 1131-1138.
- Jenkins, D. Assessment of outcomes of health intervention (1992). Social Science Medicine, 35, 367- 375.
- Joyce, P.R. & Paykel, E.S. (1989). Predictors of drug response in depression. Archives of General Psychiatry, 46, 89-97.
- Joyce, C.R. (1959). Consistent differences in individual reaction to drugs and dummies. British Journal of Pharmacology, 14, 512-521.
- Kahn, E. (1975). The depressive disorder. Folia Psychiatrica et Neurological Japonica, 29, 291-303.

- Kanner, A.D., Coyne, J.C., Schaefer, C., Lazarus, R.S. (1980). Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. Journal of Behavioral Medicine, 4, 1-37.
- Keller, M.B., Klerman, G.L., Lavori, P.W., Coryell, W., Endicott, J., Taylor, J. (1984). Long-term outcome of episodes of major depression. JAMA, 252, 788-792.
- Keller, M.B., Lavori, P.W., Endicott, J., Coryell, W., Klerman, G.L. (1983). "Double depression": Two-year follow-up. American Journal of Psychiatry, 140, 689-694.
- Keller, M.B., Shapiro, R.W., Lavori, P.W., Wolfe, N. (1982). Recovery in major depressive disorder. Archives of General Psychiatry, 39, 905-908.
- Kernberg, O.F. (1988). Clinical dimensions of masochism. Journal of the American Psychoanalytic Association, 36, 1005-1029.
- Kernberg, O.F. (1984). Severe personality disorders: Psychotherapeutic strategies. New Haven, CT: Yale University Press.
- Khan, A., Dager, S.R., Cohen, S., Avery, D.H., Scherzo, B., Dunner, D.L. (1991). Chronicity of depressive episode in relation to antidepressants-placebo response. Neuropsychopharmacology, 4, 125-130.
- Kiloh, L.G., Andrews, G., Neilson, M., Bianchi, G. (1972). The relationship of the syndromes called endogenous and neurotic depression. British Journal of Psychiatry, 121, 183-196.
- Klein, D.N., Taylor, E.B., Dickstein, S., Harding, K. (1988). Primary early-onset dysthymia: comparison with primary non-bipolar non-chronic major depression on demographic, clinical, familial, personality, and socioenvironmental

- characteristics and short-term outcome. Journal of Abnormal Psychology, 97, 387-398.
- Klein, D.N., Riso, L.P., Donaldson, S.K., Schwartz, J.E., Anderson, R.L., Ouimette, P.L., Lizardi, H., Aronson, T.A. (1995). Family study of early-onset dysthymia. Mood and personality disorders in relatives of outpatients with dysthymia and episodic major depression and normal controls. Archives of General Psychiatry, 52, 487-496.
- Klein, D.N. (1990). Depressive personality: reliability, validity, and relation to dysthymia. Journal of Abnormal Psychology, 99, 412-421.
- Klerman, G.L. & Weissman, M.M. (1992). The course, morbidity, and costs of depression. Archives of General Psychiatry, 49, 831-834.
- Kluge, E.H. (1990). Placebos: some ethical considerations. Canadian Medical Association, 142, 293-295.
- Kocsis, J.H., Mason, B.J., Frances, A.J., Sweeney, J., Mann, J.J., Marin, D. (1989). Prediction of response of chronic depression to imipramine. Journal of Affective Disorders, 17, 255-260.
- Kocsis, J.H., Frances, A.J., Voss, C., Mann, J.J., Mason, B.J., Sweeney, J. (1988). Imipramine treatment for chronic depression. Archives of General Psychiatry, 45, 253-257.
- Kocsis, J.H., Zisook, S., Davidson, J., Shelton, R., Yonkers, S., Hellerstein, D.J., Rosenbaum, J., Halbreich, U. (1997). Double-blind comparison of Sertraline, Imipramine, and placebo in the treatment of dysthymia: Psychosocial outcomes.

- American Journal of Psychiatry, 154, 390-395.
- Kocsis, J.H., Friedman, R.A., Markowitz, J.C., Leon, A.C., Miller, N.L., Gniwesch, L., Parides, M. (1996). Maintenance therapy for chronic depression. Archives of General Psychiatry, 53, 769-774.
- Lapierre, Y.D. (1994). Pharmacological therapy of dysthymia. Acta Psychiatrica Scandinavica, 89, 42-48.
- Lasagna, L., Von Felsinger, J.M., Beecher, H.K. (1955). Drug-induced mood changes in man. Observations on healthy students, chronically ill patients, and "postaddicts". JAMA, 157, 1106-1020.
- Levine, J.D., Gordon, N.C., Fields, H.L. (1978). The mechanism of placebo analgesic. Lancet, I, 654.
- Lieberman, R. (1962). An analysis of the placebo phenomenon. Journal of Chronic Disease, 15, 761.
- Linton, H.B. & Langa, R.J. (1962). Placebo reactions in a study of lysergic acid diethylamide (LSD-25). Archives of General Psychiatry, 6, 369-383.
- MacDonald, C.J., Mazzuca, S.A., McCabe, G.P. (1983). How much of the placebo "effect" is really statistical regression? Statistics in Medicine, 2, 417-427.
- Marin, D.B., Kocsis, J.H., Frances, A.J., Parides, M. (1994). Desipramine for the treatment of "pure" dysthymia versus "double" depression. American Journal of Psychiatry, 151, 1079-1080.
- Markowitz, J.C. (1994). Psychotherapy of dysthymia. American Journal of Psychiatry, 151, 1114-1121.

- McCullough, J.P., McCune, K.J., Kaye, A.L., Braith, J.A., Friend, R., Roberts, C., Belyea-Caldwell, S., Norris, S.L., Hampton, C. (1994). One-year prospective replication study of an untreated sample of community dysthymia subjects. The Journal of Nervous and Mental Disease, 182, 396-401.
- McCullough, J.P., Kasnetz, M.D., Braith, J.A. (1988). A longitudinal study of an untreated sample of predominantly late onset characterological dysthymia. Journal of Nervous Mental Disease, 176, 658-667.
- McCullough, J.P. (1991). Psychotherapy for dysthymia: a naturalistic study of ten patients. Journal of Nervous and Mental Disease, 179, 734-740.
- Mercier, M.A., Stewart, J.W., Quitkin, F.M. (1992). A pilot sequential study of cognitive therapy and pharmacotherapy of atypical depression. Journal of Clinical Psychiatry, 53, 166-170.
- Murphy, D.G.M. (1991). The classification of treatment of dysthymia. British Journal of Psychiatry, 158, 106-109.
- Nelson, J.C., Mazure, C.M., Jatlow, P.I. (1994). Characteristics of desipramine-refractory depression. Journal of Clinical Psychiatry, 55, 12-19.
- Nelson, W.H., Orr, W.W., Stevenson, J.M., Shane, S.R. (1982). Hypothalamic-pituitary-adrenal axis activity and tricyclic response in major depression. Archives of General Psychiatry, 39, 1033-1036.
- Nobler, M.S., Devanand, D.P., Kim, M.K., Fitzsimons, L.M., Singer, T.M., Turret, N., Sackeim, H.A., Roose, S.P. (1996). Fluoxetine treatment of dysthymia in the elderly. Journal of Clinical Psychiatry, 57, 254-256.

- Paradiso, S., Lamberty, G.J., Garvey, M.J., Robinson, R.G. Cognitive impairment in the euthymic phase of chronic unipolar depression. (1997). The Journal of Nervous and Mental Disease, 185, 748-754.
- Paykel, E.S. (1972). Depressive typologies and response to amitriptyline. British Journal of Psychiatry, 120, 147-156.
- Paykel, E.S., Freeling, P., Hollyman, J.A. (1988). Are tricyclic antidepressants useful for mild depression? A placebo controlled trial. Pharmacopsychiatry, 21, 15-18.
- Peselow, E.D., Lautin, A., Wolkin, A., Rohrs, C., Novatt, A., Siekierski, J., Rotrosen, J. (1986). The dexamethasone suppression test and response to placebo. Journal of Clinical Psychopharmacology, 6, 286-291.
- Preskorn, S.H., Weller, E.B., Hughes, C.W., Weller, R.A., Bolte, K. (1987). Depression in prepubertal children: dexamethasone nonsuppression predicts differential response to imipramine vs. placebo. Psychopharmacology Bulletin, 23, 128-133.
- Quitkin, F.M., McGrath, P.J., Rabkin, J.G., Stewart, J.W., Harrison, W., Ross, D.C., Tricamo, E., Fleiss, J., Markowitz, J., Klein, D.F. (1991). Different types of placebo response in patients receiving antidepressants. American Journal of Psychiatry, 148, 197-202.
- Quitkin, F.M., Rabkin, J.G., Stewart, J.W., McGrath, P.J., Harrison, W., Ross, D.C., Tricamo, E., Fleiss, J., Markowitz, J., Klein, D.F. (1991). Heterogeneity of clinical response during placebo treatment. American Journal of Psychiatry, 148, 193-196.
- Rabkin, J.G., McGrath, P.J., Quitkin, F.M., Tricamo, E., Stewart, J.W., Klein, D.F. (1990). Effects of pill-giving on maintenance of placebo response in patients with chronic

- mild depression. American Journal of Psychiatry, 147, 1622-1626.
- Rabkin, J.G., Stewart, J.W., McGrath, P.J., Markowitz, J.S., Harrison, W., Quitkin, F.M. (1987). Baseline characteristics of 10-day placebo washout responders in antidepressant trials. Psychiatry Research, 21, 9-22. .
- Rabkin, J.G., McGrath, P., Stewart, J.W., Harrison, W., Markowitz, J.S., Quitkin, F. (1986). Follow-up of patients who improved during placebo washout. Journal of Clinical Psychopharmacology, 6:5, 274-8.
- Raskin, A., Schulterbrandt, J.G., Reatig, N., Chase, C., McKeon, J.J. (1970). Differential response to chlorpromazine, Imipramine, and placebo. Archives of General Psychiatry, 23, 164-173.
- Raskin, A. & Crook, T.H. (1976). Sensitivity of rating scales completed by psychiatrists, nurses and patients to antidepressant drug effects. Journal of Psychiatric Research, 13, 31-41.
- Ravindran, A.V., Charbonneau, Y., Griffiths, J. (1995b). Measures of stress and coping in dysthymia: Possible predictors of antidepressant response. XV World Congress of Social Psychiatry.
- Ravindran, A.V. & Lapierre, Y.D. (1997a). Primary dysthymia: Predictors of treatment response. In H.S. Akiskal & G.B. Cassano (Eds.), Dysthymia and the Spectrum of Chronic Depressions. Guildford Publications, Inc.
- Ravindran, A.V., Charbonneau, Y., Zaharia, M., Al-Zaid, K., Wiens, A., Anisman, H. (1998b). Efficacy and tolerability of Venlafaxine in the treatment of primary dysthymia. Journal of Psychiatry & Neuroscience, 23, 288-292.

- Ravindran, A.V., Chudzik, J., Bialik, R.J. (1993). Serotonin in primary dysthymia. The 146th Annual Meeting of the American Psychiatric Association.
- Ravindran, A.V., Griffiths, J., Merali, Z., Anisman, H. (1996). Primary dysthymia: A study of several psychosocial, endocrine and immune correlates. Journal of Affective Disorders, 40, 73-84.
- Ravindran, A.V., Bialik, R.J., Lapierre, Y.D. (1994b). Therapeutic efficacy of specific serotonin reuptake inhibitors (SSRIs) in dysthymia. Canadian Journal of Psychiatry, 39, 21-26.
- Ravindran, A.V., Bialik, R.J., Brown, G.M., Lapierre, Y.D. (1994a). Primary early onset dysthymia, biochemical correlates of the therapeutic response to fluoxetine: I. Platelet monoamine oxidase and the dexamethasone suppression test. Journal of Affective Disorders, 31, 111-117.
- Ravindran, A.V., Bialik, R.J., Brown, G.M., Lapierre, Y.D. (1994c). Primary early onset dysthymia, biochemical correlates of the therapeutic response to Fluoxetine: Urinary metabolites of serotonin, norepinephrine, epinephrine and melatonin. Journal of Affective Disorders, 31, 119-123.
- Ravindran, A.V., Charbonneau, Y., Telner, J., Bialik, R.J., Ellis, J., Wiens, A., Griffiths, J., Zaharia, M., Waddell, C., Merali, Z., Lapierre, Y., Anisman, H. (1997b). Treatment of primary dysthymia with cognitive therapy and pharmacotherapy - A comparative study. 47th Annual Meeting of the Canadian Psychiatric Association, September.

- Ravindran, A.V., Merali, Z., Anisman, H. (1998a). Dysthymia: A biological perspective. In: J. Licinio, C.L. Bolis, & P. Gold (eds.), Dysthymia: From Clinical Neuroscience to Treatment. World Health Organization, 21-44.
- Ravindran, A.V., Griffiths, J., Waddell, C., Anisman, H. (1995a). Stressful life events and coping styles in relation to dysthymia and major depressive disorder: Variations associated with alleviation of symptoms following pharmacotherapy. Progress in Neuro-psychopharmacology & Biological Psychiatry, 19, 637-653.
- Reimherr, F.W., Ward, M.F., Byerley, W.F. (1989). The introductory placebo washout: a retrospective evaluation. Psychiatry Research, 30, 191-199.
- Revicki, D.A., Turner, R., Brown, R., Martindale, J.J. (1992). Reliability and validity of a health-related quality of life battery for evaluating outpatient antidepressant treatment. Quality of Life Research, 1, 257-266.
- Ribeiro, S.C.M., Tandon, R., Grunhaus, L., Greden, J. (1993). The DST as a predictor of outcome in depression a meta-analysis. American Journal of Psychiatry, 150, 1618-1629.
- Riso, L.P., Klein, D.N., Ferro, T., Kasch, K.L., Pepper, C.M., Schwartz, J.E., Aronson, T.A. (1996). Understanding the comorbidity between early-onset dysthymia and cluster B personality disorders: A family study. American Journal of Psychiatry, 153, 900-906.
- Rogers, S.C., Clay, P.M. (1975). A statistical review of controlled trials of Imipramine and placebo in the treatment of depressive illness. British Journal of Psychiatry, 127, 599-603.

- Rosenthal, J., Hemlock, C., Hellerstein, D.J., Yanowitch, P., Kasch, K., Schupak, C., Samstag, L., Winston, A. (1992). A preliminary study of serotonergic antidepressants in treatment of dysthymia, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 16, 933-941.
- Rosenthal, S.H., Klerman, G.L. (1966). Content and consistency in the endogenous depressive pattern. British Journal of Psychiatry, 112, 471-484.
- Sainfort, F., Becker, M., Diamond, R. (1996). Judgements of quality of life of individuals with severe mental disorders: patient self-report versus provider perspectives. American Journal of Psychiatry, 153, 497 - 502.
- Schatzberg, A.F., Rothschild, A.J., Stahl, J.B., Bond, T.C., Rosenbaum, A.H., Lofgren, S.B., MacLaughlin, R.A., Sullivan, M.A., Cole, J.O. (1983). The dexamethasone suppression test: Identification of subtypes of depression. American Journal of Psychiatry, 140, 88-91.
- Schweiger, E., Weise, C., Clary, C. (1991). Placebo-controlled trial of Venlafaxine for the treatment of major depression. Journal of Clinical Psychopharmacology, 11, 233-236.
- Scott, J. (1988). Chronic depression. British Journal of Psychiatry, 153, 287-297.
- Shapiro, A.K. & Morris, L. (1978). The placebo effect in medical and psychological therapies. In Garfield, S. and Bergen, A., (Eds.), Handbook of Psychotherapy and Behavior Change, (p.369) 2nd ed. New York: Wiley.
- Shea, M.T., Elkin, I., Imber, S.D., Sotsky, S.M., Watkins, J.T., Collins, J.F., Pilkonis, P.A., Beckham, E., Glass, D.R., Dolan, R.T., Parloff, M.B. (1992). Course of

- depressive symptoms over follow up: Findings from the national institute of mental health treatment of depression collaborative research program. Archives General Psychiatry, 49, 782-787.
- Shelton, R.C., Davidson, J., Yonkers, K.A., Koran, L., Thase, M.E., Pearlstein, T., Halbreich, U. (1997). The undertreatment of dysthymia. Journal of Clinical Psychiatry, 58, 59-65.
- Simpson, G.M., Lee, H.J., Cuculic, Z., Kellner, R. (1976). Two dosages of Imipramine in hospitalized endogenous and neurotic depressives. Archives of General Psychiatry, 33, 1093-1102.
- Slater. E. & Cowie, V. (1971). The genetics of mental disorder. London: Oxford University Press.
- Spiker, D.G. & Kupfer, D.J. (1988). Placebo response rates in psychotic and nonpsychotic depression. Journal of Affective Disorders, 14, 21-23.
- Stabl, M., Biziere, K., Schmid-Burgk, W., Amrein, R. (1989). Review of comparative clinical trials. Moclobemide vs. tricyclic antidepressants and vs. placebo in depressive states. Journal of Neural Transmission - Supplementum, 28, 77-89.
- Stewart, J.W., Quitkin, F.M., Klein, D.F. (1992). The pharmacotherapy of minor depression. American Journal of Psychotherapy, XLVI, 23-36.
- Stewart, J.W., Quitkin, F.M., Liebowitz, M.R. (1983). Efficacy of desipramine in depressed outpatients: Response according to research diagnostic criteria diagnoses and severity of illness. Archives of General Psychiatry, 40, 202-207.

- Storr, A. (1980). The art of psychotherapy, New York: Methuen.
- Stravynski, A., Shahar, A., Verreault, R.: A pilot study of the cognitive treatment of dysthymic disorder. Behavioural Psychotherapy, 4, 369-372.
- Tibbets, R.W. & Hawkins, J.R. (1956). The placebo response. Journal of Mental Science, 102, 60-66.
- Thase, M.E., Fava, M., Halbreich, U., Kocsis, J.H., Koran, L., Davidson, J., Rosenbaum, J., Harrison, W. (1996). A placebo-controlled, randomized clinical trial comparing sertraline and Imipramine for the treatment of dysthymia. Archives of General Psychiatry, 53, 777-784.
- Waring, E.M., Chamberlaine, C.H., McCrank, E.W., Stalker, C.A., Carver, C., Fry, R., Barnes, S. (1988). Dysthymia: a randomized study of cognitive marital therapy and antidepressants. Canadian Journal of Psychiatry, 33, 96-99.
- Weissman, M.M. & Akiskal, H.S. (1984). The role of psychotherapy in chronic depressions: a proposal. Comprehensive Psychiatry, 25, 23-30.
- Weissman, M.M., Leaf, P.J., Bruce, M.L., Florio, L. (1988). The epidemiology of dysthymia in five communities: rates, risks, comorbidity and treatment. American Journal of Psychiatry, 145, 815-819.
- Wilcox, C.S., Cohn, J.B., Linden, R.D., Heiser, J.F., Lucas, P.B., Morgan, D.L., DeFrancisco, D. (1992). Predictors of placebo response: a retrospective analysis. Psychopharmacology Bulletin, 28, 157-162.