Challenges in the Treatment of Depression with Psychotic Features

Anthony J. Rothschild

Major depression with psychotic features (MDpsy), a disorder with considerable morbidity and mortality, is more common than is generally realized and is a most difficult form of depression to treat. Patients with MDpsy exhibit more frequent relapses and recurrences and have increased use of services, greater disability, and a poorer clinical course when compared with nonpsychotically depressed patients. Patients with MDpsy demonstrate distinct biological abnormalities in studies of the hypothalamic–pituitary–adrenal (HPA) axis, dopaminergic activity, enzyme studies, brain imaging, electroencephalogram sleep profiles, and measures of serotonergic function when compared with nonpsychotic depression. The social and occupational impairment in MDpsy has been hypothesized to be secondary to subtle cognitive deficits caused by the higher cortisol levels frequently observed in MDpsy patients. Several studies support a relationship between bipolar disorder and MDpsy, particularly in young-onset MDpsy. The most efficacious treatments for MDpsy include the combination of an antidepressant and an antipsychotic, amoxapine, or electroconvulsive therapy. Atypical antipsychotic medications may have particular relevance for the treatment of MDpsy because of the potential for reduced risk of extrapyramidal side effects and tardive dyskinesia, as well as antipsychotic and possibly antidepressant qualities. Based on the observations that MDpsy patients exhibit marked dysregulation of the HPA axis and elevated cortisol levels, several antiglucocorticoid strategies have been employed to treat MDpsy patients. Many questions regarding the acute and long-term treatment of MDpsy remain for future studies to address. Biol Psychiatry 2003;53:680–690 © *2003 Society of Biological Psychiatry*

Key Words: Major depression with psychotic features, psychotic depression, delusional depression

Introduction

Major depression with psychotic features (MDpsy), a disorder with considerable morbidity and mortality, is more common than is generally realized and is encountered frequently in clinical practice. In a study of consecutively admitted patients hospitalized for major depression, Coryell et al (1984) reported that 25% of the patients met criteria for MDpsy. In the Epidemiologic Catchment Area Study (Johnson et al 1991), 14.7% of patients who met criteria for major depression had a history of psychotic features. Although the prevalence may be as high as 45% in samples of elderly patients with major depression (Meyers and Greenberg 1986), MDpsy is not limited to older people and can occur in younger people as well. Unfortunately, MDpsy is often not diagnosed accurately because the psychosis may be subtle, intermittent, or concealed, leading to a misdiagnosis of nonpsychotic depression.

There has been a long-standing debate as to whether MDpsy is a distinct syndrome or merely represents a more severe depressive subtype (reviewed in Schatzberg and Rothschild 1996); however, in several studies, severity alone did not account for differences between MDpsy and nonpsychotic depression on measures of symptoms (Coryell et al 1984), hypothalamic–pituitary–adrenal (HPA) axis activity (Brown et al 1988), sleep (Thase et al 1986a), and treatment response (Chan et al 1987; Glassman et al 1977). Other studies that have controlled for the presence of endogenous features have also observed that the differences between MDpsy and nonpsychotic depression are not simply due to differences in endogenicity. This includes studies of differentiating symptoms (Parker et al 1991), HPA axis activity (Brown et al 1988; Evans et al 1983; Rihmer et al 1984), and treatment response (Avery and Lubrano 1979; Chan et al 1987).

The systematic study of MDpsy has been limited by several factors: 1) the fact that the disorder does not exist as a distinct diagnostic subtype in the DSM-IV (American Psychiatric Association Committee on Nomenclature and Statistics 1994; Schatzberg and Rothschild 1992); 2) very few psychiatric researchers have made the study of

From the Department of Psychiatry, University of Massachusetts Medical School, Worcester, Massachusetts.

Address reprint requests to Anthony J. Rothschild, M.D., University of Massachusetts Medical School, Department of Psychiatry, 361 Plantation Street, Worcester MA 01605.

Received June 6, 2002; revised September 11, 2002; accepted September 17, 2002.

0006-3223/03/$30.00
doi:10.1016/S0006-3223(03)01747-X

MDpsy a priority; 3) difficulties in enrolling patients with this disorder in research studies; and 4) the fact that the diagnosis is often missed by clinicians.

The degree of morbidity and mortality seen among patients with psychotic depression underscores the importance of intelligent and empirically guided treatment decisions, but the nature of the illness itself makes controlled treatment studies extremely difficult to execute. As a result, there have been very few controlled studies regarding the acute treatment of psychotic depression and no long-term maintenance treatment studies.

The purpose of this article is to review our current understanding of the treatment of major depression with psychotic features. First, the difficulties in accurately diagnosing MDpsy will be discussed. Next, there will be a brief review of the studies of family history, course, and biology of MDpsy. This is followed by a discussion of the possible relationship between MDpsy and bipolar disorder. The remainder of the paper is devoted to the treatment of MDpsy and is divided into sections by treatment modality: tricyclic antidepressants (TCAs), electroconvulsive therapy (ECT), combined antidepressant/antipsychotic treatment, studies with selective serotonin reuptake inhibitors (SSRIs), lithium augmentation, the role of atypical antipsychotics, hypercortisolemia and antiglucocorticoid strategies, and treatment guidelines.

Diagnosis

According to DSM-IV criteria (American Psychiatric Association Committee on Nomenclature and Statistics 1994), one cannot make the diagnosis of MDpsy unless one can detect the presence of delusions or hallucinations in the context of a major depressive episode; however, because the detection of delusions and hallucinations is often difficult in patients with MDpsy (Rothschild and Schatzberg 1993), a number of research groups have explored whether there are other characteristics that may help distinguish between psychotic and nonpsychotic depressed patients. Several groups have reported that patients with MDpsy demonstrate a more frequent and severe psychomotor disturbance (either retardation or agitation) than do nonpsychotic depressed patients (Charney and Nelson 1981; Coryell et al 1984; Frances et al 1981; Glassman and Roose 1981; Lykouras et al 1986; Nelson and Bowers 1978). Patients with MDpsy have also been reported to exhibit more pronounced paranoid symptoms (Frances et al 1981; Lykouras et al 1986), cognitive impairment (Basso and Bornstein 1999; Belanoff et al 2001b; Jeste et al 1996; Nelson et al 1998; Rothschild et al 1989; Schatzberg et al 2000; Simpson et al 1999), hopelessness (Frances et al 1981), hypochondriasis (Coryell et al 1984; Glassman and Roose 1981), anxiety (Charney and Nelson 1981; Glassman and Roose 1981), early insomnia (Frances et al 1981; Lykouras et al 1986), middle insomnia (Lykouras et al 1986), and constipation (Parker et al 1991) when compared with nonpsychotic depressed patients. Patients with MDpsy also do not show a diurnal variation in mood as compared with endogenously depressed, nonpsychotic patients (Parker et al 1991).

In younger adults, or when the psychotic symptoms are prominent, the differential diagnosis of MDpsy from schizoaffective disorder and schizophrenia can be difficult. The diagnosis of MDpsy requires that the psychotic symptoms are present only in the context of the episode of major depression. Several biological differences between MDpsy and schizophrenia have been observed on measures of HPA axis activity and all-night sleep electroencephalographic studies, which may occasionally be useful in the clinical setting (reviewed in Rothschild and Schatzberg 1994).

Family History

In some studies, the first-degree relatives of patients with MDpsy exhibit higher rates of depression (Leckman et al 1984; Nelson et al 1984) and the psychotic subtype (Leckman et al 1984) than do the family members of patients with nonpsychotic depression, although not all studies are in agreement (Bond et al 1986; Coryell et al 1982, 1984; Frangos et al 1983; Maj et al 1991; Price et al 1984). In one study (Bond et al 1986), when the MDpsy group was divided by degree of HPA axis dysregulation, the familial prevalence of depression was significantly higher in the families of MDpsy patients with high post-dexamethasone cortisol levels (>15 μg/dL) when compared with families of probands with low or intermediate post-dexamethasone cortisol levels (0–14.9 μg/dL). In one study, the relatives of patients with MDpsy were six times more likely to have bipolar disorder than were the relatives of patients with nonpsychotic major depression (Weissman et al 1984), although this has not been observed in other studies (Coryell et al 1984; Price et al 1984).

Course

Patients with MDpsy exhibit more frequent relapses or recurrences than patients with nonpsychotic depression (Aronson et al 1987, 1988a, 1988b; Baldwin and Jolley 1986; Coryell et al 1996; Helms and Smith 1983; Lykouras et al 1986; Murphy 1983; Nelson and Bowers 1978; Robinson and Spiker 1985a; Rothschild and Schatzberg 1993; Spiker et al 1985); although not all studies are in agreement (Coryell et al 1987; Lykouras et al 1994).

Patients with MDpsy (when compared with nonpsychotically depressed patients) have increased use of services, greater disability, and poorer clinical course at both short- (Coryell et al 1986; Rothschild et al 1993b) and longer-term follow-up (Coryell et al 1996). In the Epidemiologic Catchment Area Study, patients with MDpsy had a greater number of attempted suicides and lifetime hospitalizations than nonpsychotic depressed patients (Johnson et al 1991). A 25-year retrospective analysis of suicides among patients hospitalized previously for major depression demonstrated that patients who had delusions during their index episode of depression had a five-fold increased likelihood of suicide compared with patients with nonpsychotic depression (Roose et al 1983). Several studies have demonstrated residual social and occupational impairment in MDpsy patients despite improvement in psychotic and depressive symptoms at 1-year (Rothschild et al 1993b), 5-year (Coryell et al 1990), and 10-year follow-up (Coryell et al 1996), whereas a 40-year follow-up with structured interviews found no consistent trends distinguishing MDpsy from nonpsychotic depression on marital, occupational, residential, or symptomatic outcome ratings (Coryell and Tsuang 1982). In the Depression Collaborative Study, Coryell et al (1987) reported that despite substantially greater levels of impairment during the 5 years preceding intake into the study, patients with unipolar MDpsy were as likely to recover as were patients with unipolar nonpsychotic depression during a 2-year follow-up period. Patients with MDpsy were more psychosocially impaired at 6 months, but these differences resolved during the ensuing 18 months (Coryell et al 1987). The social and occupational impairment observed in MDpsy has been hypothesized to be secondary to subtle cognitive deficits caused by the higher cortisol levels frequently observed in MDpsy patients (Rothschild et al 1993b; Schatzberg and Rothschild 1988).

Biology

There exists considerable evidence from studies of the HPA axis, studies of dopaminergic activity, enzyme studies, brain imaging, electroencephalographic sleep profiles, and measures of serotonergic function that points to distinct biological abnormalities in MDpsy as compared with nonpsychotic depression. Details of these biological studies are summarized elsewhere (Schatzberg and Rothschild 1992). For example, several groups have reported specific abnormalities in HPA axis activity of patients with psychotic depression. Patients with MDpsy are among those with the highest rates of nonsuppression on the dexamethasone suppression test (Anton 1987; Anton and Burch 1990; Chan et al 1987; Kantor and Glassman 1977; Leckman et al 1984; Nelson and Davis 1997; Nelson et al 1984; Robinson and Spiker 1985; Rothschild 1985; Schatzberg et al 2000; Spiker et al 1985b), and many of them have markedly elevated post-dexamethasone cortisol levels. A meta-analysis of 12 different studies, with a combined sample size of approximately 1000 depressed patients, indicated that when inpatient status was controlled for, psychosis, but not melancholic symptoms, was associated with increased dexamethasone suppression test nonsuppression rates (Nelson and Davis 1997). Significant elevation in 24-hour measures of urinary free cortisol levels have also been observed in patients with MDpsy (Anton 1987).

Several studies have demonstrated that MDpsy patients have an activation of the dopaminergic system (Devanand et al 1985; Mazure et al 1987; Rothschild et al 1987) and higher levels of cerebrospinal fluid 5-hydroxyindoleacetic acid (Aberg-Wistedt et al 1985) that is not seen in patients with nonpsychotic depression. Other investigators have reported that unipolar MDpsy patients have lower serum dopamine-beta-hydroxlyase (DBH) activity (the enzyme that converts dopamine to norepinephrine) (Meltzer et al 1976; Mod et al 1986), and unipolar nonpsychotic depressed patients have higher serum DBH activity (Matuzas et al 1982; Mod et al 1986) than do healthy control subjects. The low levels of DBH activity in MDpsy have been hypothesized to be a potential marker of relative risk for developing pronounced increases in dopamine levels in the face of chronic elevation of cortisol levels (Schatzberg et al 1985).

Imaging studies have also revealed distinct abnormalities in MDpsy patients. Our group observed that depressed patients with psychotic symptoms had cognitive impairment that was statistically associated with an increased ventricle-to-brain ratio (Rothschild et al 1989). Other investigators, using magnetic resonance imaging (Kim et al 1999), have reported decreased prefrontal cortex volume in MDpsy patients compared with age- and gender-matched patients with nonpsychotic depression. In studies using electroencephalographic sleep profiles that specifically controlled for the effects of age, severity, agitation, and other clinical characteristics, patients with MDpsy were found to have increased wakefulness, a higher percentage of stage one sleep, a decreased percentage of rapid eye movement (REM) sleep, and decreased REM activity compared with nonpsychotic depressed patients (Thase et al 1986b).

Relationship to Bipolar Disorder

Several studies support a relationship between MDpsy and bipolar disorder. Strober and Carlson (1982) observed 60 adolescents hospitalized with unipolar major depression.

They reported a 20% conversion rate to bipolar disorder, predicted in part by a depressive symptom cluster consisting of mood-congruent psychotic features (75% of converters vs. 6% of nonconverters, $p < .001$), psychomotor retardation, and rapid symptom onset. Similarly, Akiskal et al (1983) observed a 20% conversion rate to bipolar disorder in a follow-up of 206 unipolar depressed outpatients. Major depression with psychotic features was significantly more common ($p < .01$) in patients who converted to a bipolar diagnosis (42%) than among nonconverters (15%). Furthermore, patients who switched to bipolar illness were significantly younger at illness onset than those who did not switch ($p = .003$), with 71% of onsets in the bipolar group occurring before age 25 compared with 32% in the nonbipolar group. In another study, Aronson et al (1988b) observed that bipolar patients, at index episode of psychotic depression, presented at an earlier age than recurrent unipolar patients (29.7 years vs. 44.3 years, respectively, $p = .028$). Taken together, these data suggest that bipolar disorder may often present as MDpsy in adolescence or young adults. Whether, as Strober and Carlson (1982) suggest, young age is the critical variable accounting for the predictive relationship between psychoticism and bipolarity warrants further research.

Treatment

Tricyclic Antidepressants

When the TCAs were introduced for the treatment of depression, reports began to appear that they were not as effective for MDpsy as in depression in general (Angst 1961; Friedman et al 1961; Hordern et al 1963). One example of this is the landmark DeCarolis study (Avery and Lubrano 1979), which observed a 40% response rate in MDpsy patients treated with 200–350 mg/day of imipramine for at least 25 days. Those patients who did not respond to the imipramine then received ECT; for these patients the response rate was 83%. In a meta-analysis of 12 studies of 1054 depressed patients, Chan et al (1987) calculated that 127 (35%) of 363 patients with MDpsy responded to TCA therapy, in contrast to 464 (67%) of 691 patients with nonpsychotic major depression ($\chi^2 = 104.2$, $p < 2 \times 10^{-24}$).

Electroconvulsive Therapy

Major depression with psychotic features responds well to ECT, to the combination of an antidepressant and an antipsychotic, and to amoxapine (Schatzberg and Rothschild 1992). In current clinical practice in the United States, the availability, cost, stigma, and side effects associated with ECT have limited its use as a first-line treatment, with many physicians and patients opting for trials of medications as first-line treatment. The demonstration that MDpsy responds better to ECT than pharmacotherapy (Pande et al 1990; Parker et al 1992) might suggest that ECT should be used as the primary treatment. Unfortunately, it is difficult to draw broad conclusions from these studies, because the ECT treatment was compared with several different combinations of medications, at varying doses and for different periods of time (Rothschild 1996).

Data demonstrating that the initiation of ECT within 5 days of admission shortens lengths of stay and reduces treatment costs are consistent with the early use of this treatment (Olfson et al 1998); however, basing a treatment standard for MDpsy on the effectiveness and cost-saving aspects of the rapid use of ECT has important public health implications: 1) ECT does not provide a treatment alternative for the large numbers of patients who prefer pharmacologic treatment. Thus, subjects with MDpsy recruited into a multicenter ECT study had failed an average of four pharmacotherapy trials before admission (Mulsant 1997), although only 4% had received intensive combination treatment; 2) hospital treatment with ECT is associated with longer lengths of stay when treatment is not instituted rapidly (Olfson et al 1998; Strotskopf and Horn 1992; Wilson et al 1991); 3) minority ethnic groups, patients with low incomes, and those residing in rural areas are less likely to receive ECT during a psychiatric hospitalization (Olfson et al 1998); 4) ECT has been associated with high rates of early relapse (Sackeim et al 1990, 2001); and 5) the demonstration that ECT is effective acutely does not address the need for an easily administered pharmacotherapy to treat early relapses and avoid subsequent hospitalizations (Spiker et al 1985b).

Combined Antidepressant/Antipsychotic Treatment

Presently, it is the strong recommendation of the American Psychiatric Association (2000) Practice Guidelines that MDpsy should be treated pharmacologically using a neuroleptic combined with an antidepressant, although the duration of antipsychotic treatment is not discussed. This recommendation is in large part based on the landmark study of Spiker et al (1985b), who demonstrated that a combination of antipsychotic and antidepressant medications leads to improvement in 70%–80% of patients with MDpsy. They compared the combination of amitriptyline and perphenazine with amitriptyline alone and perphenazine alone in the treatment of patients with psychotic depression over a 5-week period. Using a 50% reduction in Hamilton Rating Scale for Depression (HRSD) and

Brief Psychiatric Rating Scale (BPRS) total scores and a final HRSD score of less than 12 as response criteria, 14 of 18 patients (78%) treated with the combination responded, in contrast to 7 of 17 patients (41%) treated with amitriptyline alone and 3 of 16 patients (19%) treated with perphenazine alone. Seven of the 13 patients who failed to respond to perphenazine were not psychotic at the completion of the study but were still depressed; however, recent studies of the treatment of an acute episode of MDpsy in older adults (Mulsant et al 2001) found that the addition of a moderate dose of perphenazine to nortriptyline did not improve efficacy and may indicate that the treatment of MDpsy may be different in older people.

Anton and Burch (1990) subsequently conducted a randomized, double-blind investigation that explored whether the efficacy of combination amitriptyline plus perphenazine could be matched by monotherapy with amoxapine, an antidepressant derivative of the antipsychotic medication loxapine, with dopamine antagonist activity. Previous open-label trials with amoxapine had produced response rates of 60%–80% in the treatment of psychotic depression (Anton and Sexauer 1983). Response rates defined by Clinical Global Impression improvement criteria were 82% for amoxapine and 86% for amitriptyline plus perphenazine. Using a 50% reduction in HRSD score as criteria for response yielded response rates of 71% and 81% for amoxapine and amitriptyline plus perphenazine, respectively. Extrapyramidal symptoms were significantly more frequent in the amitriptyline plus perphenazine group.

Studies with Selective Serotonin Reuptake Inhibitors

The introduction of the SSRI antidepressants has resulted in many physicians using these new medications to treat psychotic depression; however, despite their wide use in clinical practice, patients with psychotic depression were excluded from the double-blind, controlled clinical trials of all new nontricyclic, nonmonoamine oxidase inhibitor antidepressants that have come on the market in the United States since 1988. Our group was the first to report the use of SSRIs in the treatment of psychotic depression (Rothschild et al 1993a). Thirty patients with the diagnosis of psychotic depression were treated in a nonblind study for 5 weeks with the combination of 20–40 mg/day of fluoxetine plus 32 mg/day of perphenazine. Twenty-two of the 30 patients (73%) had a 50% or greater reduction in HRSD and BPRS scores at week 5 compared with baseline scores. The combination of fluoxetine plus perphenazine was associated with fewer anticholinergic side effects than had previously been reported in studies of TCAs and antipsychotics. The successful treatment of patients with psychotic depression with an SSRI plus antipsychotic was replicated (Wolfersdorf et al 1995) in a nonblind, clinical trial of 14 inpatients with psychotic depression treated with paroxetine (20 mg/day) in combination with zotepine (150–200 mg/day) or haloperidol (2.5–10 mg/day). Eight of 14 patients (57%) had a 50% reduction in HRSD scores by day 21 of treatment. The authors also had the overall impression that the combination of SSRIs with antipsychotic offered improved tolerability as compared with that of the TCA combination described in the literature. One group has described the successful treatment of patients with MDpsy with SSRI monotherapy (Gatti et al 1996; Zanardi et al 1996, 2000) or venlafaxine monotherapy (Zanardi et al 2000); however, the treatment of MDpsy with SSRI monotherapy has been questioned because of the use of a rating scale that lacked validity data and the absence of a placebo control in these studies (Rothschild and Phillips 1999).

Lithium Augmentation

Lithium augmentation of antidepressants for nonpsychotic depression is a frequently used strategy, particularly for partial responders (Bauer and Dopfmer 1999). Unfortunately, this strategy has not been adequately studied for the treatment of MDpsy. In uncontrolled studies, lithium augmentation of an antipsychotic and an antidepressant has been efficacious for MDpsy (Price et al 1983). In a retrospective chart review of MDpsy patients who were refractory to treatment with desipramine plus 12–64 mg of perphenazine or 4–20 mg of haloperidol, 8 of 9 patients with bipolar MDpsy, but only 3 of 12 patients with unipolar MDpsy recovered when 600–1200 mg/day of lithium was added (Fisher's Exact Test, $p = .003$) (Nelson and Mazure 1986). Similarly, in a study from our group (Rothschild et al 1993a) of eight patients who did not respond to 5 weeks of treatment with the combination of fluoxetine and perphenazine, three of three patients with bipolar MDpsy responded to lithium augmentation, in contrast to none of five unipolar MDpsy patients ($p < .01$).

Role of Atypical Antipsychotics

Atypical antipsychotic medications may have particular relevance for MDpsy because of the potential for reduced risk of extrapyramidal side effects and tardive dyskinesia, as well as antipsychotic and possibly antidepressant qualities. This is particularly noteworthy in light of recent observations that a significant minority of MDpsy patients still needed antipsychotic treatment even after 4 months of combined antidepressant and antipsychotic treatment

(Rothschild and Duval, in press). The theoretical basis for the efficacy of the atypical antipsychotic agents for the treatment of psychotic depression includes their effects on serotonin type-2 receptors and the improvement in depressive symptoms seen in patients with schizophrenia (Rothschild 1996). Several case reports and retrospective chart reviews have suggested that clozapine (Banov et al 1994; Chacko et al 1993; Dassa et al 1993; Naber et al 1992; Parsa et al 1991; Ranjan and Meltzer 1995; Sajatovic et al 1991; Wood and Rubenstein 1990), risperidone (Hillert et al 1992; Jacobson 1995; Keck et al 1995), olanzapine (Adli et al 1999; DeBattista et al 1997; Malhi and Checkley 1999; Nelson et al 2001; Rothschild et al 1999), and quetiapine (Zarate et al 2000) as monotherapy or in combination with antidepressants, may be effective in patients with psychotic depression.

In one double-blind, multicenter, parallel group trial, the efficacy of risperidone monotherapy was compared with a combination of haloperidol and amitriptyline over 6 weeks in patients with psychotic depression (Muller-Siecheneder et al 1998). Although both treatments were effective in producing clinically relevant score reductions on the Positive and Negative Symptom Scale for Schizophrenia, BPRS, and Bech-Rafaelson Melancholia Scale, the reductions were significantly larger in the amitriptyline plus haloperidol group.

In a recently completed, 8-week, double-blind study, 249 patients with MDpsy were randomized to one of three treatment groups: olanzapine 5–20 mg/day plus fluoxetine 20–80 mg/day; olanzapine 5–20 mg/day plus placebo; or placebo (Dube et al 2002). The olanzapine plus fluoxetine group had statistically significantly greater HRSD-24 total score improvement compared with the placebo treated group within the first week of treatment and at every subsequent visit. The olanzapine monotherapy treated group was not statistically significantly different from the placebo or olanzapine plus fluoxetine groups. The olanzapine plus fluoxetine group also had significantly better HRSD-24 response (55.6%) than the olanzapine monotherapy (35.6%; $p = .027$) or placebo (29.8%; $p = .003$) groups.

Further study of atypical antipsychotic medications for the treatment of MDpsy is important for two reasons: first, it is conceivable that they may be more effective than traditional antipsychotic medications; and second, even if they are equally effective compared with traditional antipsychotic medications, they are less likely to cause short-term side effects, such as dysphoria and akathisia, and long-term side effects, such as tardive dyskinesia. These are important issues for patient compliance, given that a significant minority of patients with psychotic depression may need to stay on maintenance antipsychotic medication for quite some time (Rothschild and Duval, in press).

Hypercortisolemia and Antiglucocorticoid Strategies

Several years ago, our group hypothesized that the development of delusions in depressed patients is secondary to the effects of hypercortisolemia (Schatzberg et al 1985) and that acute improvement in psychotic symptoms in MDpsy may occur after cortisol levels are lowered or the effects of cortisol are blocked with cortisol-receptor antagonists in the brain (Schatzberg and Rothschild 1988). As discussed above, patients with MDpsy exhibit a marked dysregulation of the HPA axis in the acute episode. In longitudinal studies, many MDpsy patients continue to exhibit elevated cortisol levels despite symptomatic improvement (Rothschild 1999; Rothschild et al 1993b). Significant correlations have been observed between elevated cortisol levels and poor social and occupational functioning at 1 year (Rothschild et al 1993b) and 15 months (Rothschild, unpublished data) after the index episode. Similar observations were noted in hypercortisolemic, nonpsychotic depressed patients (Rothschild, unpublished data; Rothschild et al 1993b). The poor social and occupational functioning appears to be secondary to the deleterious effects of elevated cortisol on cognition (Rothschild, unpublished data; Rothschild et al 1993b).

Based on these observations, several antiglucocorticoid strategies have been employed to treat MDpsy patients. One strategy is to use cortisol synthesis inhibitors, such as metyrapone, aminoglutethimide, and ketoconazole. Several studies in hypercortisolemic psychotic and nonpsychotic depressed patients have had mixed results (Amsterdam et al 1994; Anand et al 1995; Ghadirian et al 1995; Murphy and Wolkowitz 1993; Ravaris et al 1988; Thakore and Dinan 1995; Wolkowitz et al 1993). A complicating factor has been that these medications have significant side effects, including the potential for adrenal insufficiency and hepatic injury.

A second approach is to use the steroid mifepristone (presently available only for patients enrolled in research protocols), which has antiprogesterone activity but is also an effective antagonist of glucocorticosteroid action in vitro and in vivo (Gaillard et al 1984; Herrmann et al 1982; Lamberts et al 1991; Proulx-Ferland et al 1982). Relatively high doses of mifepristone (400 mg to 800 mg per day) rapidly reversed psychosis and suicidal thinking in two patients with Cushing's syndrome (caused by metastatic adrenal cancer) (Van der Lely et al 1991). Mifepristone use has also been reported in a patient with Cushing's syndrome who had both depressive and psychotic symptoms that were unresponsive to antidepressants alone, and only partially responsive to an antidepressant/antipsychotic combination. Treatment with high doses of mifepristone (up to 1400 mg every day) resulted in both his physical and psychiatric symptoms resolving

quickly (Nieman et al 1985). In depression, Murphy et al (1993) administered mifepristone at 200 mg/day for 8 weeks to four patients with chronic, nonpsychotic depression with modest improvement in HDRS scores in three of the four patients. In MDpsy, Belanoff et al (2001a) reported on five patients who participated in a 4-day, double-blind, placebo-controlled, crossover study using 600 mg of mifepristone as monotherapy. All five patients showed substantial improvement in their HDRS scores, and four of the five exhibited substantial improvement in BPRS scores, with little improvement with placebo.

In a recently published, larger study (Belanoff et al 2002), 30 patients with MDpsy with HDRS scores of 18 or greater were assigned in an open-label trial to receive 50 mg, 600 mg, or 1200 mg of mifepristone for 7 days. All the subjects completed the protocol, and side effects were mild and sporadic. Thirteen of 19 subjects in the combined 600- and 1200-mg group had a 30% or greater decline in their BPRS scores, compared to 4 of 11 in the 50-mg group. Twelve of 19 subjects in the 600- and 1200-mg group showed a 50% decline in the BPRS positive symptom subscale, compared with 3 of 11 in the 50-mg group. Eight of 19 subjects in the 600- and 1200-mg group had a 50% decline in the HRSD-21, compared with 2 of 11 in the 50-mg group. The differences in improvement between the 50-mg dose and the 600-mg/1200-mg doses were not statistically significantly different; in part, this may have been because of the small sample size of the study. Furthermore, because the patients were required to be on stable doses of antidepressants and/or antipsychotics for only 1 week, it is conceivable that some of the improvement may have been due to the antidepressant and antipsychotic medication that had been started 2–3 weeks before the addition of mifepristone. Nevertheless, the improvement seen with the addition of mifepristone warrants further study using a double-blind, placebo-controlled design.

Treatment Guidelines

In summary, the most effective treatment for an acute episode of MDpsy is either ECT or the combination of an antidepressant with an antipsychotic medication, which is the strong recommendation of the American Psychiatric Association (2000) Practice Guidelines for the treatment of MDpsy. The decision initially faced by the clinician and patient is which treatment to use. Although there has been no prospective study comparing these two very different treatment modalities, there is the suggestion in the literature that ECT may be slightly more effective (Kroessler 1985; Pande et al 1990; Parker et al 1992); however, from a practical standpoint, because MDpsy is frequently a recurrent illness and ECT has been associated with high rates of early relapse (Sackeim et al 1990, 2001), the identification of an effective medication regimen may aid prophylaxis (Charney and Nelson 1981). In addition, a large number of patients and their relatives will prefer pharmacologic treatment, because they find both the idea and experience of ECT, and the possible side effects of confusion and memory disruption, unacceptable (American Psychiatric Association 2000; Flint and Rifat 1998; Parker et al 1992); however, in certain situations, such as life-threatening symptoms, a history of previous good response to ECT, or an older patient (Flint and Rifat 1998), ECT may be preferred over medications.

Although there have been no prospective studies comparing TCAs and SSRIs (combined with an antipsychotic) for the treatment of MDpsy, there are several studies that strongly suggest that SSRIs combined with an antipsychotic are an effective treatment for the acute episode of MDpsy (Dube et al, unpublished data; Rothschild et al 1993a; Wolfersdorf et al 1995). Given the recently completed, double-blind, placebo-controlled study of 249 patients with MDpsy that indicated that an olanzapine/fluoxetine combination was a well-tolerated treatment associated with a significant and quick (within 7 days) reduction in depressive symptoms compared with placebo (Dube et al, unpublished data), the combination of an SSRI and an atypical antipsychotic is an attractive option for the treatment of MDpsy.

Conclusions

In summary, MDpsy is associated with significant morbidity and mortality. Currently, the most effective treatments include the combination of an antidepressant with an antipsychotic, or ECT. Recent studies suggest that atypical antipsychotic medications may be effective (when combined with an antidepressant) for the acute treatment of MDpsy; however, there remain many questions for future research. Those that seem of greatest importance include the following: 1) the efficacy and safety of atypical antipsychotic medication for maintenance treatment; 2) the efficacy and safety of glucocorticoid antagonists such as mifepristone; 3) decision trees to delineate the second and third lines of treatment when the first treatment is ineffective (Parker et al 1991); 4) the length of time patients should be maintained on medications; 5) the efficacy of bilateral versus unilateral ECT; 6) the delineation of the clinical characteristics of responders to medication treatments versus ECT treatments; 7) differences in response to medication treatments and ECT in younger versus older patients; 8) the role of maintenance ECT; and 9) optimal treatment for patients with bipolar disorder with an episode of MDpsy. The answers to these questions would be of significant practical utility to clinicians

treating patients with MDpsy, a most difficult-to-treat form of depression.

Supported in part by the Irving S. and Betty Brudnick Endowed Chair in Psychiatry, University of Massachusetts Medical School.

Aspects of this work were presented at the conference, "Difficult-to-Treat Depression" held April 21–22, 2002 in San Francisco, California. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted grant provided by Eli Lilly and Company.

References

Aberg-Wistedt A, Wistedt B, Bertilsson L (1985): Higher CSF levels of HVA and 5-HIAA in delusional compared to non delusional depression. *Arch Gen Psychiatry* 42:925–926.

Adli M, Rossius W, Bauer M (1999): [Olanzapine in the treatment of depressive disorders with psychotic symptoms]. *Nervenarzt* 70:68–71.

Akiskal HS, Walker P, Puzantian VR, King D, Rosenthal TL, Franon M (1983): Bipolar outcome in the course of depressive illness: Phenomenological, familial, and pharmacologic predictors. *J Affect Disord* 5:115–128.

American Psychiatric Association (2000): Practice guideline for the treatment of major depressive disorder (revision). *Am J Psychiatry* Suppl 157:(suppl 4).

American Psychiatric Association Committee on Nomenclature and Statistics (1994): *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Association.

Amsterdam J, Mosley PD, Rosenzweig M (1994): Assessment of adrenocortical activity in refractory depression: Steroid suppression with ketoconazole. In: Nolan W, Zohar J, Roose S, Amsterdam J, editors. *Refractory Depression.* Chichester, UK: John Wiley & Sons, 199–210.

Anand A, Malison R, McDougle CJ, Price LH (1995): Antiglucocorticoid treatment of refractorydepression with ketoconazole: A case report. *Biol Psychiatry* 37:338–340.

Angst J (1961): A clinical analysis of the effects of Tofranil in depression. *Psychopharmacologia* 2:381–407.

Anton RF Jr (1987): Urinary free cortisol in psychotic depression. *Biol Psychiatry* 22:24–34.

Anton RF Jr, Burch EA Jr (1990): Amoxapine versus amitriptyline combined with (208) perphenazine in the treatment of psychotic depression. *Am J Psychiatry* 147:1203–1208.

Anton RF, Sexauer JD (1983): Efficacy of amoxapine in psychotic depression. *Am J Psychiatry* 140:1344–1347.

Aronson TA, Shukla S, Gujavarty K, Hoff A, DiBuono M, Khan E (1988a): Relapse in delusional depression: A retrospective study of the course of treatment. *Comp Psychiatry* 29:12–21.

Aronson TA, Shukla S, Hoff A (1987): Continuation therapy after ECT for delusional depression: A naturalistic study of prophylactic treatments and relapse. *Convuls Ther* 3:251–259.

Aronson TA, Shukla S, Hoff A, Cook B (1988b): Proposed delusional depression subtypes: Preliminary evidence from a retrospective study of phenomenology and treatment course. *J Affect Disord* 14:69–74.

Avery D, Lubrano A (1979): Depression treated with imipramine and ECT: The DeCarolis study reconsidered. *Am J Psychiatry* 136:559–562.

Baldwin RC, Jolley DJ (1986): The prognosis of depression in old age. *Br J Psychiatry* 574–583.

Banov MD, Zarate CA Jr, Tohen M, Scialabba D, Wines JD Jr, Kolbrener M, et al (1994): Clozapine therapy in refractory affective disorders: Polarity predicts response in long-term follow-up. *J Clin Psychiatry* 55:295–300.

Basso MR, Bornstein RA (1999): Neuropsychological deficits in psychotic versus nonpsychotic unipolar depression. *Neuropsychology* 13:69–75.

Bauer M, Dopfmer S (1999): Lithium augmentation in treatment-resistant depression: Meta-analysis of placebo-controlled trials. *J Clin Psychopharmacol* 19:427–434.

Belanoff J, Flores B, Kalezhan M, Sund B, Schatzberg A (2001a): Rapid reversal of psychotic major depression using mifepristone. *J Clin Psychopharmacol* 21:516–521.

Belanoff JK, Kalehzan M, Sund B, Fleming Ficek SK, Schatzberg AF (2001b): Cortisol activity and cognitive changes in psychotic major depression. *Am J Psychiatry* 158:1612–1616.

Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C, et al (2002): An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* 52:386–392.

Bond TC, Rothschild AJ, Lerbinger J, Schatzberg AF (1986): Delusional depression, family history, and DST response: A pilot study. *Biol Psychiatry* 21:1239–1246.

Brown RP, Stoll PM, Stokes PE, Frances A, Sweeney J, Kocsis JH, Mann JJ (1988): Adrenocortical hyperactivity in depression: Effects of agitation, delusions, melancholia, and other illness variables. *Psychiatry Res* 23:167–168.

Chacko RC, Hurley RA, Jankovic J (1993): Clozapine use in diffuse Lewy body disease. *J Neuropsychiatry Clin Neurosci* 5:206–208.

Chan CH, Janicak PG, Davis JM, Altman E, Andriukaitis S, Hedeker D (1987): Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. *J Clin Psychiatry* 48:197–200.

Charney DS, Nelson J (1981): Delusional and nondelusional unipolar depression: Further evidence for distinct subtypes. *Am J Psychiatry* 138:328–333.

Coryell W, Endicott J, Keller M (1987): The importance of psychotic features to major depression: Course and outcome during a 2-year follow-up. *Acta Psychiatr Scand* 75:78–85.

Coryell W, Keller M, Lavori P, Endicott J (1990): Affective syndromes, psychotic features and prognosis I: Depression. *Arch Gen Psychiatry* 47:651–657.

Coryell W, Leon A, Winokur G, Endicott J, Keller MB, Akiskal H, Solomon D (1996): The importance of psychotic features to long term course in depressive disorders. *Am J Psychiatry* 153:483–489.

Coryell W, Pfohl B, Zimmerman M (1984): The clinical and neuroendocrine features of psychotic depression. *J Nerv Ment Dis* 172:521–528.

Coryell W, Tsuang MT (1982): Primary unipolar depression and the prognostic importance of delusions. *Arch Gen Psychiatry* 39:1181–1184.

Coryell W, Tsuang MT, McDaniel J (1982): Psychotic features in major depression: Is mood congruence important? *J Affect Disord* 4:227–236.

Coryell W, Zimmerman M (1986): Demographic, historical, and symptomatic features of the nonmanic psychoses. *J Nerv Ment Dis* 174:585–592.

Coryell W, Zimmerman M, Pfohl B (1986): Outcome at discharge and six months in major depression. The significance of psychotic features. *J Nerv Ment Dis* 174:92–96.

Dassa D, Kaladjian A, Azorin JM, Giudicelli S (1993): Clozapine in the treatment of psychotic refractory depression. *Br J Psychiatry* 163:822–824.

DeBattista C, Solvason HB, Belanoff J, Schatzberg AF (1997): Treatment of psychotic depression. *Am J Psychiatry* 154:1625–1626.

Devanand DP, Bowers MB, Hoffman FJ Jr, Nelson JC (1985): Elevated homovanillic acid in depressed females with melancholia and psychosis. *Psychiatry Res* 15:1–4.

Evans DL, Burnett G, Nemeroff CB (1983): The dexamethasone suppression test in the clinical setting. *Am J Psychiatry* 140:586–589.

Flint AJ, Rifat SL (1998): The treatment of psychotic depression in later life: A comparison of pharmacotherapy and ECT. *J Geriatr Psychiatry* 13:23–28.

Frances A, Brown RP, Kocsis JH, Mann JJ (1981): Psychotic depression: A separate entity? *Am J Psychiatry* 138:831–833.

Frangos E, Athanassenas G, Tsitourides S, Psilolignos P, Katsanou N (1983): Psychotic depressive disorder: A separate entity? *J Affect Dis* 5:259–265.

Friedman C, Bowbray MS, Hamilton VJ (1961): Imipramine (Tofranil) in depressive states. *J Ment Sci* 107:948–953.

Gaillard RC, Riondel A, Muller AF, Herrmann W, Baulieu EE (1984): RU 486: A steriod with antiglucocorticosteroid activity that only disinhibits the human pituitary-adrenal system at a specific time of day. *Med Sci* 81:3879–3882.

Gatti F, Eelini L, Gasperini M, Perez J, Zanardi R, Smeraldi E (1996): Fluvoxamine alone in the treatment of delusional depression. *Am J Psychiatry* 153:414–416.

Ghadirian AM, Englesmann F, Dhar V, Filipini D, Keller R, Chouinard G, Murphy BEP (1995): The psychotropic effects of inhibitors of steroid biosynthesis in depressed patients refractory to treatment. *Biol Psychiatry* 37:369–375.

Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleiss JL (1977): Clinical implications of imipramine plasma levels for depressive illness. *Arch Gen Psychiatry* 34:197–204.

Glassman AH, Roose SP (1981): Delusional depression: A distinct clinical entity? *Arch Gen Psychiatry* 38:424–427.

Helms PM, Smith RE (1983): Recurrent psychotic depression: Evidence of diagnostic stability. *J Affect Disord* 5:51–54.

Herrmann W, Wyss R, Riondel A, Philibert D, Teutsch G, Sakiz E, Baulieu EE (1982): Effet d'un steroide anti-progesterone chez la femme Interuption du cycle menstrul et de la grossese au debut [The effects of an antiprogesterone steroid in women: interruption of the menstrual cycle and of early pregnancy]. *C R Seances Acad Sci III* 294:933–938.

Hillert A, Maier W, Wetzel H, Benkert O (1992): Risperidone in the treatment of disorders with a combined psychotic and depressive syndrome-a functional approach. *Pharmacopsychiatry* 25:213–217.

Hordern A, Holt NF, Burt CG, Gordon WF (1963): Amitriptyline in depressive states: Phenomenology and prognostic considerations. *Br J Psychiatry* 109:815–825.

Jacobson FM (1995): Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry* 56:423–429.

Jeste DV, Heaton SC, Paulsen JS, Ercoli L, Harris J, Heaton RK (1996): Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. *Am J Psychiatry* 153:490–496.

Johnson J, Horwath E, Weissman MM (1991): The validity of major depression with psychotic features based on a community sample. *Arch Gen Psychiatry* 48:1075–1081.

Kantor SJ, Glassman AH (1977): Delusional depressions: Natural history and response to treatment. *Br J Psychiatry* 131:351–360.

Keck PE Jr, Wilson DR, Strakowski SM, McElroy SL, Kizer DL, Balistreri TM, et al (1995): Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. *J Clin Psychiatry* 56:466–470.

Kim DK, Kim BL, Sohn SE, Lim SW, Na DG, Paik CH, et al (1999): Candidate neuroanatomic substrates of psychosis in old-aged depression. *Prog Neuropsychopharmacol Biol Psychiatry* 23:793–807.

Kroessler D (1985): Relative efficacy rates for therapies of delusional depression. *Convuls Ther* 1:173–182.

Lamberts SW, Koper JW, Jong FH (1991): The endocrine effects of long-term treatment with mifepristone (RU 486). *J Clin Endocrinol Metab* 73:187–191.

Leckman JF, Weisman MM, Prusoff BA, Caruso KA, Merikangas KR, Pauls DL, Kidd KK (1984): Subtypes of depression: Family study perspective. *Arch Gen Psychiatry* 41:833–838.

Lykouras E, Christodoulou GN, Malliaras D, Stefanis C (1994): The prognostic importance of delusions in depression: A 6-year prospective follow-up study. *J Affect Disord* 32:233–238.

Lykouras E, Malliaras D, Christodoulou GN, Papakostas Y, Voulgari A, Tzonou A, Stefanis C (1986): Delusional depression: Phenomenology and response to treatment, a prospective study. *Acta Psychiatric Scand* 73:324–329.

Maj M, Starace F, Pirozzi R (1991): A family study of DSM-III-R schizoaffective disorder, depressive subtype, compared with schizophrenia and psychotic and nonpsychotic major depression. *Am J Psychiatry* 148:612–616.

Malhi GS, Checkley SA (1999): Olanzapine in the treatment of psychotic depression. *Br J Psychiatry* 174:460.

Matuzas W, Meltzer HY, Uhlenhuth EH, Glass RM, Tong C (1982): Plasma dopamine-B-hydroxylase in depressed patients. *Biol Psychiatry* 17:1415–1424.

Mazure CM, Bowers MB, Hoffman F Jr, Miller KB, Nelson JC (1987): Plasma catecholamine metabolites in subtypes of major depression. *Biol Psychiatry* 22:1469–1472.

Meltzer HY, Cho HW, Carroll BJ, Russo P (1976): Serum dopamine-B-hydroxylase activity in the affective psychoses and schizophrenia. *Arch Gen Psychiatry* 33:585–591.

Meyers BS, Greenberg R (1986): Late-life delusional depression. *J Affect Disord* 11:133–137.

Mod L, Rihmer Z, Magyar I, Arato M, Alfoldi A, Bagdy G (1986): Serum DBH activity in psychotic vs. nonpsychotic unipolar and bipolar depression. *Psychiatry Res* 19:331–333.

Muller-Siecheneder F, Muller MJ, Hillert A, Szegedi A, Wetzel H, Benkert O (1998): Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. *J Clin Psychopharmacol* 18:111–120.

Mulsant BH, Haskett RF, Prudic J, Thase ME, Malone KM, Mann JJ, et al (1997): Low use of neuroleptic drugs in the treatment of psychotic major depression. *Am J Psychiatry* 154:559–561.

Mulsant BH, Sweet BA, Rosen J, Pollack BG, Zubenko GS, Flynn T, et al (2001): A randomized double-blind comparison of nortriptyline plus perphenazine vs. nortriptyline plus placebo in the treatment of psychotic depression in late life. *J Clin Psychiatry* 62:597–604.

Murphy BEP, Filipini D, Ghadirian AM (1993): Possible use of glucocorticoid receptor antagonists in the treatment of major depression: Preliminary results using RU 486. *J Psychiatr Neurosci* 18:209–213.

Murphy BEP, Wolkowitz OM (1993): The pathophysiologic significance of hyperadrenocorticism: Antiglucocorticoid strategies. *Psychiatr Ann* 23:682–690.

Murphy E (1983): The prognosis of depression in old age. *Br J Psychiatry* 142:111–119.

Naber D, Holzbach R, Perro C, Hippius H (1992): Clinical management of clozapine patients in relation to efficacy and side effects. *Br J Psychiatry* 160:54–59.

Nelson EB, Rielage E, Welge JA, Keck PE Jr (2001): An open trial of olanzapine in the treatment of patients with psychotic depression. *Ann Clin Psychiatry* 13:147–151.

Nelson EB, Sax KW, Strakowski SM (1998): Attentional performance in patients with with psychotic and nonpsychotic major depression and schizophrenia. *Am J Psychiatry* 155:137–139.

Nelson JC, Bowers MB (1978): Delusional versus unipolar depression: Description and drug response. *Arch Gen Psychiatry* 35:1321–1328.

Nelson JC, Davis JM (1997): DST studies in psychotic depression: A meta-analysis. *Am J Psychiatry* 154:1497–1503.

Nelson JC, Mazure CM (1986): Lithium augmentation in psychotic depression refractory to combined drug treatment. *Am J Psychiatry* 143:363–366.

Nelson WH, Khan A, Orr WW (1984): Delusional depression: Phenomenology, neuroendocrine function, and tricyclic antidepressant response. *J Affect Disord* 6:297–306.

Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, et al (1985): Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab* 61:536–540.

Olfson M, Marcus S, Sackeim HA, Thompson J, Pincus HA (1998): Use of ECT for the inpatient treatment of recurrent major depression. *Am J Psychiatry* 155:2–29.

Pande A, Grunhaus L, Hasket R, Haskett R, Greden JF (1990): Electroconvulsive therapy in delusional and nondelusional depressive disorder. *J Affect Disord* 19:215–219.

Parker G, Hadzi-Pavlovic D, Hickie I, Boyce P, Mitchell P, Wilhelm K, Brodarty H (1991): Distinguishing psychotic and non-psychotic melancholia. *J Affect Disord* 22:135–148.

Parker G, Roy K, Hadzi-Pavlovic D, Pedic F (1992): Psychotic (delusional) depression: A meta-analysis of physical treatments. *J Affect Disord* 24:17–24.

Parsa MA, Ramirez LF, Loula CE, Meltzer HY (1991): Effect of clozapine on psychotic depression and parkinsonism. *J Clin Psychopharmacol* 11:330–331.

Price LH, Conwell Y, Nelson JC (1983): Lithium augmentation of combined neuroleptic-tricyclic treatment in delusional depression. *Am J Psychiatry* 140:318–322.

Price LH, Nelson JC, Charney DS, Quinlan DM (1984): Family history in delusional depression. *J Affect Disord* 6:109–114.

Proulx-Ferland L, Cote L, Philibert D, Deraedt R (1982): Potent antiglucocorticoid activity of RU486 on ACTH secretion in vitro and in vivo in the rat. *J Steroid Biochem* 17:27.

Ranjan R, Meltzer HY (1995): Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. *Biol Psychiatry* 40:253–258.

Ravaris CL, Sateia MJ, Beroza KW, Noordsy DL, Brinck-Johnsen T (1988): Effect of ketoconazole on a hypophysectomized, hypercortisolemic, psychotically depressed woman. *Arch Gen Psychiatry* 45:966–967.

Rihmer Z, Arato M, Szadoczky E, Revai K, Demeter E, Gyorgy S, Udvarhelyi P (1984): The dexamethasone suppression test in psychotic versus nonpsychotic depression. *Br J Psychiatry* 145:508–511.

Robinson DG, Spiker DG (1985): Delusional depression: A one year follow-up. *J Affect Disord* 9:79–83.

Roose SP, Glassman AH, Walsh BT, Woodring S, Vital-Herne J (1983): Depression, delusions, and suicide. *Am J Psychiatry* 140:1159–1162.

Rothschild AJ (1985): Delusional depression: A review of the literature and current perspectives. *McLean Hosp J* 10:68–83.

Rothschild AJ (1996): Management of psychotic, treatment-resistant depression. *Psychiatr Clin North Am* 19:237–252.

Rothschild AJ, Bates KS, Boehringer KL, Syed A (1999): Olanzapine response in psychotic depression. *J Clin Psychiatry* 60:116–118.

Rothschild AJ, Benes F, Hebben N, Woods B, Luciana M, Bakanas E, et al (1989): Relationships between brain CT scan findings and cortisol in psychotic and nonpsychotic depressed patients. *Biol Psychiatry* 26:565–575.

Rothschild AJ, Duval SE (in press): How long should patients with psychotic depression stay on the antipsychotic medication? *J Clin Psychiatry*.

Rothschild AJ, Phillips KA (1999): Selective serotonin reuptake inhibitors and delusional depression. *Am J Psychiatry* 156:977–978.

Rothschild AJ, Samson JA, Bessette MP, Carter-Campell JT (1993a): Efficacy of combination fluoxetine and perphenazine in the treatment of psychotic depression. *J Clin Psychiatry* 54:338–342.

Rothschild AJ, Samson JA, Bond TC, Luciana MM, Schildkraut JJ, Schatzberg AF (1993b): Hypothalamic-pituitary-adrenal axis activity and one-year outcome in depression. *Biol Psychiatry* 34:392–400.

Rothschild AJ, Schatzberg AF (1993): Psychotic depression: A newly recognized subtype. *Clin Neurosci* 1:75–80.

Rothschild AJ, Schatzberg AF (1994): Diagnosis and treatment of psychotic (delusional) depression. In: Grunhaus L, Greden JF, editors. *Severe Depressive Disorders.* Washington, DC: American Psychiatric Press, 195–207.

Rothschild AJ, Schatzberg AF, Langlais PJ, Lerbinger JE, Miller MM, Cole JO (1987): Psychotic and nonpsychotic depressions: I. Comparison of plasma catecholamines and cortisol measures. *Psychiatry Res* 20:143–153.

Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al (2001): Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy. A randomized controlled trial. *JAMA* 285:1299–1307.

Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S (1990): The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol* 10:96–104.

Sajatovic M, Verbanac P, Ramirez LF, Meltzer HY (1991): Clozapine treatment of psychiatric symptoms resistant to neuroleptic treatment in patients with Huntington's chorea. *Neurology* 41:156 [letter].

Schatzberg AF, Posener JA, DeBattista C, Kalehzan M, Rothschild AJ, Shear PK (2000): Neuropsychological deficits in psychotic versus nonpsychotic major depression and no mental illness. *Am J Psychiatry* 157:1095–1100.

Schatzberg AF, Rothschild AJ (1988): The roles of glucocorticoid and dopaminergic systems in delusional (psychotic) depression. *Ann N Y Acad Sci* 537:462–471.

Schatzberg AF, Rothschild AJ (1992): Psychotic (delusional) major depression: Should it be included as a distinct syndrome in DSM-IV? *Am J Psychiatry* 149:733–745.

Schatzberg AF, Rothschild AJ (1996): Psychotic (delusional) major depression: Should it be included as a distinct syndrome in DSM-IV. In: Widiger TA, Frances AJ, Pincus HA, Ross R, First MB, Davis WW, editors. *DSM-IV Source Book,* Vol. 2. Washington, DC: American Psychiatric Press, 127–180.

Simpson S, Baldwin RC, Jackson A, Burns A (1999): The differentiation of DSM-IIIR psychotic depression in later life from nonpsychotic depression: Comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features. *Biol Psychiatry* 45:193–204.

Spiker DG, Stein J, Rich CL (1985a): Delusional depression and electroconvulsive therapy: One year later. *Convuls Ther* 1:167–172.

Spiker DG, Weiss JC, Dealy RS, Griffin SJ, Hanin I, Neil JF, et al (1985b): The pharmacological treatment of delusional depression. *Am J Psychiatry* 142:430–436.

Strober M, Carlson G (1982): Bipolar illness in aldolescents with major depression: Clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. *Arch Gen Psychiatry* 39:549–555.

Strotskopf C, Horn SD (1992): Predicting length of stay for patients with psychosis. *Health Serv Res* 26:743–766.

Thakore JH, Dinan TG (1995): Cortisol synthesis inhibition: A new treatment strategy for the clinical and endocrine manifestations of depression. *Biol Psychiatry* 37:364–368.

Thase ME, Kupfer DJ, Ulrich RF (1986a): Current status of sleep EEG in the assessment and treatment of depression. In: Burrows GO, Werry JS, editors. *Advances in Human Psychopharmacology,* Vol. 4. Greenwich, CT: JTI Press.

Thase ME, Kupfer DJ, Ulrich RF (1986b): Electroencephalographic sleep in psychotic depression: A valid subtype? *Arch Gen Psychiatry* 43:886–893.

Van der Lely A-J, Foeken K, van der Mast RC, Lamberts SWJ (1991): Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med* 114:143–144.

Weissman MM, Prusoff BA, Merikangas KR (1984): Is delusional depression related to bipolar disorder? *Am J Psychiatry* 141:892–893.

Wilson KG, Kraitberg NJ, Brown JH, Bergamn JN (1991): Electroconvulsive therapy in the treatment of depression: The impact on length of stay. *Comp Psychiatry* 32:345–354.

Wolfersdorf M, Barg R, Konig F, Leibfarth M, Grunewald I (1995): Paroxetine as antidepressant in combined antidepressant-neuroleptic therapy in delusional depression: Observation of clinical use. *Pharmacopsychiatry* 28:56–60.

Wolkowitz OM, Reus VI, Manfredi F, Ingbar J, Brizendine L, Weingartner H (1993): Ketoconazole administration in hypercortisolemic depression. *Am J Psychiatry* 150:810–812.

Wood MJ, Rubinstein M (1990): An atypical responder to clozapine. *Am J Psychiatry* 147:369 [letter].

Zanardi R, Franchini L, Gasperini M, Perez J, Smeraldi E (1996): Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. *Am J Psychiatry* 153:1631–1633.

Zanardi R, Franchini L, Serretti A, Perez J, Smeraldi E (2000): Venlafaxine versus fluvoxamine in the treatment of delusional depression: A pilot double-blind controlled study. *J Clin Psychiatry* 61:26–29.

Zarate CA Jr, Rothschild AJ, Fletcher KE, Madrid A, Zapatel J (2000): Clinical predictors of acute response with quetiapine in psychotic mood disorders. *J Clin Psychiatry* 61:185–189.