Treatment of Severe Depression

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Although all forms of depression are potentially disabling, severe depressive episodes are associated with the greatest hazards of morbidity and mortality. Hence, severe depression constitutes one of the greatest challenges faced by clinical psychiatrists. However, the vast majority of severe depressive states are treatable, resulting in benefits to patients, their families, and society that are commensurate with the hazards. This article first addresses various definitions of severe depression, its incidence, and associated comorbidity. Next, the pathophysiology of severe depressive states is reviewed. Finally, the strengths and limitations of various treatment approaches are discussed, including psychotherapy, antidepressant pharmacotherapy, and electroconvulsive therapy (ECT).

DEFINITIONS

The severity of depressive episodes traditionally has been described from 3 perspectives: symptom intensity, diagnostic subtypes, and degree of functional impairment. Two additional descriptors are also relevant—suicidality and inpatient status. These 5 elements are incorporated, either implicitly or explicitly, in all formulations of severe depression.

Symptom Intensity

Major depressive disorder and its more common “boundary” conditions, dysthymic disorder and adjustment disorder with depressed mood, are largely defined by the number, duration, and intensity of the symptoms associated with depressive states. Depressive states are, in turn, symptomatically heterogeneous and include some symptom clusters that are positively correlated (e.g., weight loss and agitation or hypsomnolence and weight gain) and some that are essentially incompatible (e.g., weight loss and increased appetite or hypsomnolence and early morning awakening).2,3 These correlations are never larger than modest, however, and most researchers have found that the largest component of symptom “structure” is based on a single dimension of overall severity.4,5

For the past 40 years, overall severity has been assessed by standard rating scales such as those developed by Hamilton6 and Beck and colleagues.7 Each scale scores for the presence of particular symptoms and, if present, the intensity of those symptoms using simple ordinal ratings. The psychometric characteristics of these scales have been studied extensively and have been found to be adequate, although not ideal.4,5 Currently, the Hamilton Rating Scale for Depression (HAM-D)6 is always administered by a clinical evaluator, while the Beck Depression Inventory (BDI)7 is used almost as a self-reporting instrument. Thus, the scales provide highly correlated but complementary information, with the former measure more heavily weighted by the so-called neurovegetative symptoms (i.e., sleep, appetite, and psychomotor disturbances) and the latter more strongly influenced by cognitive symptoms (i.e., pessimism and negative self-appraisals).

Figure 1 illustrates the distribution of severity scores among a large group of depressed outpatients seeking treatment (M.E.T., unpublished data, 1999). Both the HAM-D (N = 164) and the BDI (N = 162) display relatively normal distributions of scores in this study group, although it should be noted that the low end of the scoring distribution is truncated and perhaps distorted by the nature of the study group (i.e., patients seeking treatment who were already determined to meet diagnostic criteria for major depressive disorder). The upper “tail” of the distribution is also truncated by exclusion of patients with psychotic features and those who require emergent hospitalization.
From a simple descriptive perspective, these distributions could be divided into halves (e.g., a median split), thirds (i.e., tertiles), or fourths (i.e., quartiles). The approach that perhaps best approximates our scientific vocabulary is the tertile split, which yields subgroups with mild, moderate, and severe clinical syndromes. Defined this way, the upper tertile of severe depression would be identified by a score of about 25 or higher on the original 17-item HAM-D. Applying the same logic to the BDI would yield threshold scores of about 28 and 34, respectively, for moderate and severe depression. The arbitrariness of this approach should be obvious, and the average score of one study group may be several points higher or lower than another.

The major strengths of this dimensional approach are its objectivity and simplicity. Such an approach is not foolproof; however, there are a number of versions of the HAM-D, providing up to 11 additional items. In practice, many investigators have adopted the convention of basing severity on the original 17 items. When this is done, a score of 20 or above has evolved as the threshold for a moderate-to-severe grouping.8,9 There are numerous other limitations, including the need to ensure the reliability of the HAM-D. More important, a rating of severe on the HAM-D or BDI may reflect different constellations of symptoms for different patients. For example, concomitant anxiety often inflates HAM-D scores,10 and a premorbid (prior to the onset of the depressive episode) tendency to view self, world, and future negatively amplifies BDI scores.11 More subtle age- and gender-based differences in symptom expression introduce another source of variability.12,13 Last, neither the original 17 items of the HAM-D nor the most commonly used version of the BDI weigh the so-called reverse neurovegetative symptoms (i.e., overeating, weight gain, and hypersomnolence), even though one or more of these symptoms are experienced by up to 50% of depressed outpatients.14

A number of other depression rating scales have been introduced over the past decades, including a self-report analogue of the HAM-D,15 an alternate clinician-administered scale (Montgomery-Asberg Depression Rating Scale, or MADRS),16 and an assessment of reverse neurovegetative symptoms intended to supplement the HAM-D.17 Most recently, Rush and colleagues have introduced the Inventory for Depressive Symptoms,18,19 which includes matched self-report and clinician-administered versions. Although these scales each offer selected advantages when compared to the venerable ancestors, the HAM-D and BDI, they have not yet replaced the older scales as standard measures of severity.

**Diagnostic Subtypes**

The clinical heterogeneity of depressive states has fueled an interest in a classification of subtypes that actually long predates the introduction of objective rating scales. The best-validated subtypes associated with severe symptom ratings are the melancholic (previously called endogenous or endogenomorphic depression), recurrent (unipolar),22 and psychotic (delusional)23 forms of what is now known as major depressive disorder. Although many episodes of bipolar depression are symptomatically mild, those associated with an admixture of hypomanic or manic symptoms are among the most severe and challenging conditions faced by clinicians.24 Similarly, although dysthymic disorder is in part defined by subsyndromal symptom intensity, the presentation of so-called double depres-
sion (a current major depressive episode superimposed on antecedent dysthymia) is also overrepresented within a grouping of severely symptomatic patients.25

The triad of recurrent, melancholic, and psychotic subtypes represents the core of the construct commonly referred to as biological depression.26 As will be discussed subsequently, these interrelated subtypes share certain pathophysiologic characteristics, and they have the most ominous prognoses without definitive treatment.

The subtypes of depression most commonly associated with lower symptom severity scores include the single episode (or simple), seasonal, and atypical forms. In the first case, it should be noted that at least 50% of patients who are treated for a single episode will develop a recurrent depressive episode.27 In the latter 2 cases, an association with reverse neurovegetative symptoms (which are not scored on the HAM-D or MADRS) artificially suppresses assessments of syndromal severity.28

**Functional Impairment**

Measures of functional impairment have modest correlations with assessments of symptom severity, generally on the order of Pearson r values of 0.4–0.5. This association between functional impairment and symptom severity is muted somewhat by individual differences in premorbid functioning.

The most commonly used measure of functioning is the Global Assessment of Functioning (GAF) scale,29 a 0–100 point scale. Most GAF scores of depressed patients range between 40 and 80. Severe functional impairment is typically represented by scores of 49 and below.

Alternate self-reported measures of functional capacity include the Endicott Work Productivity Scale30 and several versions of the Medical Outcomes Study scale.31 Research using the latter scale has demonstrated that the day-to-day impairments associated with depression surpass those associated with most other common chronic medical illnesses, approximating the functional impairment associated with congestive heart failure.32,33

**Epidemiology**

As illustrated in Figure 1, about one third of depressed outpatient meet the requirements for being severely depressed. By contrast, almost all depressed inpatients in the United States currently meet at least 1 criterion for severity. Inpatients typically have average scores of about 1 standard deviation higher on measures such as the HAM-D or BDI.34 Factors such as incapacity and suicidality further distinguish between patients who are treated as inpatients or outpatients.

Patients with severe depressive episodes tend to have a longer duration of illness and a lower probability of spontaneous remission.35 Incomplete remission, in turn, is associated with a greater risk of early relapse, especially without preventative treatment.36–38 There is some evidence that people who have suffered a severe episode of depression are also at greater risk of subsequent recurrent episodes.39

Although a majority of depressive disorders are comorbid with at least one other psychiatric or general medical condition, severe episodes are even more likely to be complicated by comorbidities.1 As noted earlier, comorbid anxiety disorders are associated with higher HAM-D severity scores.10 Personality disorders may have a parallel effect by heightening perceived dysphoria.1 People with well-documented personality disorders also tend to have less social support (a natural buffer against depression) and experience more adverse life events (a common precipitant of dysphoria), which may both amplify and prolong depressive episodes.11

Other types of comorbidity may intensify depressive syndromes by altering central nervous system (CNS) responses. For example, the effects of alcoholism, other substance abuse disorders, and eating disorders may deplete or impair monoaminergic neurotransmission.40 Central nervous system stress response systems may be chronically dysregulated in posttraumatic stress disorder (PTSD) and other conditions that are linked to intense or chronic repetitive traumatic exposure.41,42 General medical comorbidities may have parallel effects on CNS functioning. A number of conditions, such as endocrinopathies, left and anterior cerebrovascular infarcts, and certain malignancies, directly induce depressive symptoms.43 A general medical disorder also may have indirect effects on depressive symptoms that are mediated by symptomatic treatments (e.g., corticosteroids or antihypertensive medications) or drug–drug interactions.

**Pathophysiology**

The pathophysiology of severe depression may reflect the impact of 3 interdependent processes on CNS functioning: aging, recurrent affective illness, and heredity.26 The best-documented biological changes associated with severe depression are hypercortisolism, abnormal sleep neurophysiology, and increased sympathoadrenal activity.26,44 Together, these disturbances reflect a state of hyperarousal within the limbic–brain stem circuits that normally regulate affect and vegetative functions such as sleep and appetite.26,45 For example, an increase in the phasic activity of rapid eye movement (REM) sleep could simultaneously reflect a homeostatic mechanism triggered by waking dysphoria, the loss of inhibitory serotonergic tone from neurons in the dorsal raphe nuclei, or disinhibited cholinergic input from pontine neurons.46 Nevertheless, these changes are not specific to depression; marked stress can induce similar changes in some nondepressed people, and “biological false positive” results are commonly associated with normal aging.26 Sleep and cortisol abnormalities, however, are more prevalent and pro-
nounced among patients with recurrent depression even after taking into account the effects of age. Although not all severely depressed patients manifest objective signs of dysfunction within these systems, most do, and it is possible that imprecision in diagnosis and the indirect measurement of these neurobiological processes have placed an external limit on research in this area.

Longitudinal studies indicate that effective treatment usually normalizes sleep and hypothalamic-pituitary-adrenocortical (HPA) abnormalities. There is also evidence to suggest that persistent sleep or HPA disturbances, despite effective treatment, are associated with greater risk of relapse.

More recently, research utilizing positron emission tomography (PET) scans to measure cerebral blood flow and regional glucose metabolism has yielded complementary findings. The most commonly reported abnormalities revealed by PET scans include reduced glucose utilization in regions of the prefrontal cortex and increased glucose utilization in paralimbic structures. Several groups have correlated changes in cerebral blood flow with severity ratings, and the few studies that have been done in remitted patients suggest that these abnormalities are state dependent. Unfortunately, these expensive and labor-intensive studies have not been completed in large series of patients, and radiation exposure limits the number of sequential scans that can be completed for each patient during longitudinal follow-up.

Other neurobiological features associated with depression appear to be more state independent or trait-like. These more static indicators, including a premature loss of slow-wave sleep and a blunted nocturnal release of growth hormone, are of interest because they could reflect functional consequences of inherited vulnerabilities. Several lines of evidence suggest that diminished serotonergic tone may represen one such systemic risk factor. Although people with this kind of decreased serotonergic tone may be at greater risk for many forms of psychopathology that involve poor impulse control (e.g., alcoholism, arson, violence, etc.), the co-occurrence of severe depression and decreased central serotonin neurotransmission may convey a particularly high risk of completed suicide.

**TREATMENT**

**General Principles**

Episodes of severe depression are, on average, less likely to remit spontaneously during a 6- to 8-week interval and tend to be less responsive to attention placebo interventions. For these reasons, studies of novel antidepressants are increasingly limited to more severely symptomatic groups of patients. Such studies, however, must be designed with caution, because a single high symptom score does not define a specific subtype of depression. Some patients who experience an intense but transient exacerbation may rapidly improve when they receive psychotherapeutic support. Thus, efforts to enroll only those with severe depression into studies inadvertently run the risk of artificially distorting sample composition. It is the combination of symptom severity, functional impairment, and persistence despite adequate therapeutic support that may identify the subset of depressed patients who have the best responses to pharmacotherapy relative to other interventions.

Another important aspect of care for severely depressed patients is suicide prevention. Up to 80% of severely depressed people have or will have suicidal ideations. The risk of completed suicide is higher when there is a history of serious attempts, a family history of suicide, the construction of a well-developed plan, the presence of psychotic symptoms, or evidence of substance abuse. Older men represent the group at the highest risk for suicide. Suicidality, a consequence of intense subjective suffering, demoralization, and neurobiological risk, must be addressed vigorously. Addressing suicidality includes direct inquiry and risk assessment, ensuring adequate safety and psychosocial support, and identifying explicit short-term goals and reasons for living. Not infrequently, hospitalization is necessary to ensure safety until the crisis has passed. Although no single treatment is particularly indicated or contraindicated for suicidal individuals, a course of ECT should be considered, and the potential lethality of the tricyclic antidepressants (TCAs) should not be overlooked.

Last, it is likely that patients with severe depression will warrant more frequent follow-up visits and may require longer courses of treatment to achieve optimal outcomes. For the patient with an initial BDI score of 40, a 50% reduction in symptom severity is indeed a welcomed accomplishment. However, that patient still has a level of symptomatology that is 4 times greater than normal, and the level of residual symptoms is still consistent with a mild major depressive episode. It may be necessary to wait up to 12 or even 16 weeks during acute phase therapy for a full remission to develop. Moreover, the clinician should be prepared to make additional adjustments in the treatment plan to ensure that a partial response is converted to a complete remission.

**Psychotherapy**

Modern, depression-focused interventions such as Beck’s model of cognitive-behavioral therapy (CBT) and the interpersonal psychotherapy (IPT) of Klerman, Weissman, and colleagues have been tested in numerous clinical trials and generally found to be as effective as TCAs for treatment of outpatients with major depressive disorder. Although there is some evidence that patients with higher scores on the HAM-D are less responsive to CBT, not all centers have found this to be the case. In our studies at the University of Pittsburgh, women with higher HAM-D scores were less likely to respond than those with lower scores. Further, findings from the multi-
center study of Elkin and colleagues, which showed some evidence of differences across sites in CBT response among severely depressed patients, suggest that the implementation of therapy may have influenced the outcome.71

There is no evidence from outpatient studies that HAM-D severity adversely affects IPT response.3,72,73 However, in one study, higher levels of interpersonal difficulties74 or poorer global functioning75 were associated with poorer outcomes. Reynolds and colleagues76 recently found poor response to IPT, but not nortriptyline, in a study of depressed elderly subjects with complicated bereavement. Thus, the severity of the interpersonal dysfunction, rather than symptom severity, may mitigate against response to IPT alone.

Research in our group has also linked poor response to both CBT and IPT to a pattern of disturbances in all-night electroencephalographic recordings.73,76,77 Specifically, patients with abnormal sleep profiles characterized by poor sleep efficiency, reduced REM latency, and increased REM density were less responsive to CBT or IPT than patients with more normal sleep profiles. In one study, IPT nonresponders with abnormal sleep profiles were treated with antidepressants, and 75% responded, indicating that the abnormal sleep profile did not reflect a poorer prognosis per se.73 Although Buysse and colleagues78 recently failed to replicate the value of the 3 variations in sleep profile in a study of 111 women with recurrent depression treated with IPT, nonresponse was significantly greater in patients with poorer subjective sleep and increased REM indices. Studies by our group79 and others80–82 have found a similar association between psychotherapy nonresponse and various measures of hypercortisolism. It seems likely that patients with sleep and cortisol abnormalities manifest the aforementioned dysregulation of cortical-limbic–brain stem neural circuits, which in turn may adversely affect the ability to use psychotherapy effectively.83

In summary, there is evidence that some aspects of severity, broadly defined, negatively impact the response to psychotherapies such as IPT and CBT. It seems prudent to be selective in assigning severely depressed patients to treatment with psychotherapy alone. Issues such as case complexity, past treatment history, gender (CBT), interpersonal difficulties (IPT), and patient preference should be taken into account. In any event, psychotherapists who treat severely depressed patients should monitor symptomatic progress and, if there is no clear-cut benefit within 4 to 6 weeks, promptly consider the addition of pharmacotherapy to maximize the chances of recovery.

### Pharmacotherapy

The selective serotonin reuptake inhibitors (SSRIs) have now become the leading class of antidepressants throughout most of the world and, as such, are considered first in this review. The SSRIs have been studied extensively, and, despite their overall efficacy, there is an unresolved controversy about their usefulness in severe depression. For example, in the meta-analysis conducted by Anderson and Tomenson,84 the SSRIs and TCAs were found to be comparably effective except in 3 types of comparisons: studies of inpatients, studies of subjects with higher intake severity scores, and studies using clomipramine (the most serotoninergic TCA) as the comparator. However, other reviewers, such as Pande and Sayler85 and Hirschfeld,86 have concluded that there was no evidence of differential efficacy in severe depression.

Three inpatient reports stand out in this regard.87–89 The 2 randomized controlled trials conducted by the Danish University Antidepressant Group (DUAG)87,88 contrasted clomipramine with an SSRI, citalopram, and paroxetine, respectively. As summarized in Figure 2, both studies observed large effects favoring the TCA in these severely depressed and predominantly melancholic hospitalized study groups. In the third report, Roose and colleagues89 contrasted the outcome of fluoxetine treatment in a series of hospitalized depressed elderly patients with cardiovascular disease with that in an earlier but comparable cohort of patients treated with nortriptyline (Figure 3). When compared with clomipramine, nortriptyline is much more selective for noradrenaline reuptake inhibition. Results again strongly favored the TCA, and the advantage was largely apparent among the subset of 34 patients with melancholia. Subsequently, Nelson and colleagues90 conducted a multicenter trial of ambulatory depressed patients with significant cardiovascular disease and found that nortriptyline and paroxetine were equally effective. It is not clear if the differences between these studies are attributable to the high prevalence of melancholia in the inpatient studies or to an interaction between sample composition and type of antidepressant. What is clear, however, is that the SSRIs have a large safety advantage over the TCAs and that the findings of these 3 inpatient studies have limited relevance to ambulatory practice.

There is also some evidence that venlafaxine at higher doses may have a stronger antidepressant effect than
SSRIs. Like clomipramine, venlafaxine has significant effects on both serotonin and norepinephrine reuptake, particularly at higher dosages. Prior to the introduction of the extended-release formulation, dosing complexity and tolerability were somewhat problematic for venlafaxine as compared with the SSRIs, and there continues to be a 9% risk of blood pressure elevation at doses of 300 mg/day or higher. Nevertheless, venlafaxine must be considered one of the best-studied newer antidepressants for treatment of severe depression.

Among the other newer antidepressants available in the United States, bupropion, nefazodone, and mirtazapine have not been extensively studied in severe depression. Each of these agents is distinguished by a low incidence of sexual side effects, although bupropion is better known for activating or nonsedating effects and nefazodone and mirtazapine are known for beneficial effects on sleep and anxiety.

Several early studies of bupropion established its usefulness in severe depression, although bupropion is better known for activating or nonsedating effects and nefazodone and mirtazapine are known for beneficial effects on sleep and anxiety. Several early studies of bupropion established its usefulness in severe depression, although these trials employed high doses (> 400 mg/day) that are now explicitly discouraged by the manufacturer because of an increased risk of seizures. To my knowledge, the sustained-release formulation of bupropion has not been studied in a severely depressed group of patients.

A series of studies has confirmed that nefazodone has more beneficial effects on electroencephalographic sleep profiles and subjective sleep quality than fluoxetine. However, nefazodone and fluoxetine had similar overall efficacy in these reports. There is one placebo-controlled inpatient study documenting the efficacy of nefazodone in a relatively severely depressed group of inpatients.

Inpatient studies of mirtazapine have been conducted in Europe, and there is 1 published comparative study suggesting an advantage for mirtazapine over fluoxetine. At the least, bupropion, nefazodone, and mirtazapine provide useful alternatives for severely depressed patients who cannot tolerate or do not respond to more widely prescribed agents.

The newest antidepressant worldwide, reboxetine, is a selective norepinephrine reuptake inhibitor (selective NRI) that provides a safer alternative to older noradrenergic medications such as desipramine, maprotiline, and nortriptyline. Reboxetine (at doses of 4–5 mg b.i.d.) appears to be comparable in efficacy to TCAs and fluoxetine. Interestingly, Massana found reboxetine to be more effective than fluoxetine in a pooled analysis of 549 patients with a pretreatment 21-item HAM-D score of 22 or higher (Figure 4). A number of additional comparative studies are underway.

Psychotherapy and Pharmacotherapy Combinations

Although widely endorsed by professional groups and consumers, the combination of psychotherapy and pharmacotherapy has failed to show much advantage when provided routinely to depressed outpatients. More recently, however, Thase and colleagues found that the combination of psychotherapy and pharmacotherapy offered a large advantage over psychotherapy alone for the subset of depressed outpatients with recurrent illness and higher severity (Figure 5). Reynolds and colleagues similarly found that maintenance treatment with the combination of IPT (monthly) and nortriptyline was significantly better than either monotherapy in preventing recurrent depression in an older group of outpatients with unipolar depression. Severe recurrent depression thus represents an important indication for the combination of psychotherapy and pharmacotherapy.

Antipsychotics

Both conventional neuroleptics and newer agents such as risperidone and olanzapine are selectively indicated in...
combination with antidepressants for the treatment of psychotic depressions. If such combined treatment is ineffective, ECT should be considered the next treatment of choice for psychotic depression.

Given the early discussion of the possible limitations of SSRIs for some forms of severe depression, it is paradoxical that one group of Italian investigators has reported good results with SSRI monotherapy for patients with psychotic depression. Although their results are interesting, replication by studies using rigorous double-blind factorial design (including neuroleptic comparators) is essential before this practice can be recommended.

**Electroconvulsive Therapy**

ECT is the best-proven treatment for severe depression (especially the melancholic and psychotic subforms), and various modifications to its administration have greatly lessened the risk of complications. In fact, an increasingly larger percentage of ECT is now provided on an ambulatory basis. ECT is, nevertheless, an imperfect treatment, and contemporary response rates in tertiary care centers typically range between 50% and 70% instead of the more commonly cited rates between 80% and 90%. Although their results are interesting, replication by studies using rigorous double-blind factorial design (including neuroleptic comparators) is essential before this practice can be recommended.

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**CONCLUSION**

Severe depressive states are heterogeneous, and knowledge of phenomenology, pathophysiology, and differential therapeutics is required for treatment. Although the SSRIs continue to be an important class of medication for treatment of severe depressions, emerging lines of evidence suggest the value of antidepressants with either selective noradrenergic or dual effects on central neurotransmission. Psychotherapy may have more limited utility as a monotherapy but offers potentially valuable adjunctive effects. Last, ECT should not be overlooked when pharmacotherapies fail or urgency of response is paramount.

**Drug names:** bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), reboxetine (Vestra), risperidone (Risperdal), venlafaxine (Effexor).


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Treatments of Severe Depression
At its most severe, depression can be life-threatening because it can make you feel suicidal. It feels like I’m stuck under a huge grey-black cloud. It’s dark and isolating, smothering me at every opportunity. The sort of treatment you’re offered for depression will depend on how much your symptoms are affecting you, and it should take into account your personal preference for what sort of treatment you find helps you. See our pages on seeking help for a mental health problem for more information on speaking to your doctor and having your voice heard. Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working. To be diagnosed with depression, the symptoms must be present for at least two weeks. Some forms of depression are slightly different, or they may develop under unique circumstances, such as: Persistent depressive disorder (also called dysthymia) is a depressed mood that lasts for at least two years. A person diagnosed with persistent depressive disorder may have episode In its most severe form, depression causes severe morbidity and may require inpatient treatment. Patients requiring admission, compared with those able to be treated as outpatients, are more likely to be suicidal, have psychomotor retardation, reduced interest in work and activities [2], and have significant neurocognitive dysfunction [3]. Patients who are hospitalised for depression also have a very poor longer-term outcome, with a high rate of completed suicide (7% in 15 years with the. Our study of inpatients in Christchurch suffering from a MDE showed effect size differences from healthy control participants of 0.8-1.0 in most aspects of neurocognitive functioning [3].