Review

The burden of severe depression: A review of diagnostic challenges and treatment alternatives

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Abstract

Among the factors making recognition of severe depression problematic for clinicians are the heterogeneous nature of the condition, lack of standardized definitions, and concomitant comorbidities that confound differential diagnosis of symptoms. The spectrum of severity in depressive disorders is extraordinarily broad, and severity assessment is comprised of several metrics including symptom intensity, diagnostic subtypes, suicidality risk, and hospitalization status. The overall diagnosis is achieved through consideration of symptom types and severities together with the degree of functional impairment as assessed by the psychiatric interview. It is likely that no single fundamental neurobiological defect underlies severe depression. The chronicity and heterogeneity of this disorder lead to frequent clinic visits and a longer course of treatment; therefore, successful approaches may require an arsenal of treatments with numerous mechanisms of action. The categories of drugs used to treat severe depression are detailed herein, as are several non-pharmacologic options including a number of experimental treatments. Pharmacotherapies include tricyclic antidepressants, selective serotonin reuptake inhibitors, atypical antidepressants such as serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors, and combination and augmentation therapies. Drugs within each class are not equivalent, and efficacy may vary with symptom severity. Patient adherence makes tolerability another critical consideration in antidepressant choice. The role of non-pharmacological treatments such as electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation remain active avenues of investigation. Improved knowledge and treatment approaches for severe depression are necessary to facilitate remission, the ideal treatment goal.
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1. Introduction

Major depressive disorder (MDD), a highly debilitating and widely distributed illness in the general population, is ranked by the World Health Organization as among the most burdensome diseases to society, with lifetime prevalence rates in the US as high as 17% and 12-month prevalence rates estimated at 1.7% to 8.6% (Kessler et al., 2003). Thus, nearly 30 million of the US adult population may be affected by MDD, with approximately one-third being classified as severely depressed (Thase, 2000).

Severe depression has profound social and economic consequences, with individuals often experiencing high rates of complicating comorbidities and mortality (e.g., increased risk and poor outcome of cardiovascular disease and suicidality), reduced quality of life, and significant personal and societal costs due to decreased work productivity, increased absenteeism, and utilization of health care services (Katon, 2003; Keitner et al., 1994; Simon, 2003; Valuck, 2004; Whooley and Browner, 1998). The serious impairment inflicted by severe depression is due, in part, not only to an illness of longer duration, with a lower likelihood of spontaneous remission and increased risk of recurrent episodes, but also to the underdiagnosis and lack of effective treatment for those afflicted (Thase, 2000).

Longer duration of illness and greater symptom severity have obvious negative implications for patient well-being and outcomes. Five-year follow-up data (Keller et al., 1992) from the National Institute of Mental Health Collaborative Depression study indicated an inverse association between length of illness and rate of recovery. Ten-year data (Judd et al., 2000) from the same study demonstrated a correlation between symptom severity and psychosocial impairment. These findings confirm that failing to provide adequate treatment to patients with severe depression yields greater illness duration and disability.

Despite the significant need for effective treatments for severely depressed patients, relatively few prospective treatment trials have been reported, and most evidence for effectiveness is derived from retrospective and pooled analyses of trials conducted in the moderately-to-severely ill. Relevant material for this review was identified via MEDLINE pairing "severe depression" individually with "clinical trial" and drug class as well as individual drug names as search terms. A similar search strategy was employed to identify articles pertaining to non-pharmacologic treatments such as ECT. Additionally, publications reporting pooled and meta-analyses of antidepressant treatments were reviewed. Treatment options appearing in this review are summarized in Table 1.

Table 1
Treatment strategies for severe depression

Selective serotonin reuptake inhibitors
- Fluvoxamine
- Paroxetine
- Escitalopram
- Fluoxetine
- Citalopram
- Sertraline

Tricyclic antidepressants
- Clomipramine
- Nortriptyline
- Amitriptyline

Newer generation antidepressants
- Venlafaxine
- Milnacipran
- Duloxetine

Other novel pharmacotherapies
- Mirtazapine
- Bupropion
- Nefazodone
- Trazodone
- Moclobemide

Non-pharmacologic treatments
- Electroconvulsive therapy
- Transcranial magnetic stimulation
- Vagus nerve stimulation
- Deep brain stimulation

Combination therapies
- Fluoxetine + heterocyclic antidepressant
- Desipramine + fluoxetine

Augmentation agents
- Lithium
- Triiodothyronine
- Buspirone
- Atypical antipsychotics
  – Risperidone
  – Olanzapine
  – Ziprasidone
  – Aripiprazole
- Dopamine agonists
  – Pramipexole

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2. Severe depression diagnosis and definitions

The heterogeneous nature of severe depression is problematic for the treating physician in part due to the lack of standardized definitions, as well as to concomitant comorbidities that confound the true presentation of the disease. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)(2000a) categorizes major depression as mild, moderate, or severe, based on the intensity of depressive symptoms. The clinical assessment of severe depression, therefore, is multidimensional, comprising several metrics such as symptom intensity, diagnostic subtype, resistance to treatment, suicide risk, and hospitalization status (Kienke and Rosenbaum, 2000; Schatzberg, 1999; Thase, 2000). However, these are not diagnostically pathognomonic. For example, although many patients with severe depression may require hospitalization, this cannot be considered as a sole criterion for defining severity because hospitalization in the United States varies according to the patient's access to resources and local treatment practices (Montgomery and Lecrubier, 1999). The presence of melancholia has been used as an indicator of severe depression by some clinicians, but it is not in itself a satisfactory definition because melancholia also has a range of severities. A severity ranking, therefore, would need to accompany a diagnosis of melancholia. Thus, it is a combination of overall symptom severity and the degree of functional impairment that guides the clinician in reaching a diagnosis.

Although no universal definition of severe depression exists for use in the clinic or in treatment trials, in the latter the severity of depression is typically determined by a high score on a standard symptom severity rating instrument such as the Hamilton Rating Scale for Depression

(HAMD) or the Montgomery–Asberg Depression Rating Scale (MADRS). Although somewhat arbitrary, threshold scores greater than 25–28 on the first 17 items of the HAMD and 28–30 on the MADRS scales commonly are employed as cut-off values to define severe depression (Hamilton, 1960; Montgomery and Asberg, 1979; Montgomery and Lecrubier, 1999). In an empirical study to validate the MADRS cut-off scores to define severe depression, best separation between moderate and severe depression occurred with a MADRS score of ⩾31 (Muller et al., 2003). Differentiation of the varying severities of depression has considerable clinical ramifications because there is evidence to suggest that antidepressants exhibit differential efficacy based on depressive symptom severity (Angst et al., 1995; Hirschfeld, 1999; Kasper et al., 1997). Subtypes of MDD commonly associated with severe symptom levels include melancholic, recurrent, and psychotic depression (Thase, 2000).

To a certain extent the challenge of achieving remission has clouded the distinctions between severe, treatment-resistant, and chronic depression. Failure to respond to two or more adequate antidepressant trials is a defining feature of treatment-resistant depression (Ananth, 1998), but the level of symptoms may be mild or moderate just as well as severe. As such, severe depression may prove to be resistant to treatment, but treatment-resistant depression is not necessarily severe depression. Similarly, depression that lasts for at least two years generally is considered chronic depression (Rush et al., 1998), but there is no symptom severity criterion associated with chronic depression. Severe depression may prove to be chronic, but chronic depression need not be severe. Nevertheless there is value in considering therapies that have shown promise against refractory and chronic depression in the context of severe depression treatment.

There are several limitations that require consideration when deciphering the severe depression literature. The critical distinction between the two most widely used scales, HAMD and MADRS, is the inclusion of somatic criteria in the HAMD (i.e., a depressed patient with significant somatic symptoms likely will be considered a severe depressive, but may not be according to MADRS criteria), as well as the presence of comorbid anxiety, both of which increase HAMD scores. One of the major limitations of the standard HAMD is its lack of consideration for reverse neurovegetative symptoms, such as overeating, weight gain, and hypersomnia as manifested in atypical depression (Dunlop and Ninan, 2003; Thase, 2000), although there are expanded versions of the HAMD (e.g., HAMD-28) that do include these atypical symptoms.

2.1. Defining treatment efficacy

In clinical trials, the homogeneous patient populations and differing methodologies, such as study duration, dosing regimen, and response and remission criteria, render comparisons between studies particularly challenging. In a typical 8-week study, a responder has been traditionally defined as a patient demonstrating a 50% or greater reduction from baseline HAMD or MADRS score. However, a severe depressive will have a higher baseline score and, as such, may meet the study criteria for response, yet still exhibit significant depressive symptoms and functional impairment (Schatzberg, 1999; Zajecka, 2003). Conversely, a failure to meet the response criteria at study endpoint may be more a function of the acute study timeframe than the efficacy of the drug. Additionally, patients who are severely depressed may require more aggressive dose titration and monitoring to achieve a robust response. However, many clinical studies are not designed to allow for such flexibility in treatment protocols (Nierenberg, 1994; Schatzberg, 1999). For example, early comparator studies of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have demonstrated a relatively low rate of efficacy with SSRIs in severely depressed and melancholic patients. However, these studies may have favored TCAs because of the short trial duration and non-specific symptom severity reduction, such as sleep or anxiety, due to the antihistaminic side effects of TCAs (Amsterdam, 1998).

Ultimately, the recommended treatment goal for depression is remission (Zajecka, 2003), which typically is defined operationally in treatment studies as a score of ⩽7 on the HAMD. An analysis (Hawley et al., 1997) designed to assess an objectively defined remission cut-off point on the MADRS yielded a valid remission definition as a score ⩽10, and this has recently been confirmed in a second study (Zimmerman et al., 2004), which states that a cutoff MADRS ⩽10 maximizes the level of agreement with the HAMD ⩽ 7 definition of remission. In the clinical setting, remission is more functionally defined as the sustained absence of symptoms and reestablishment of social and occupational functioning.

3. Treatment of severe depression

Because severe depression is a chronic and heterogeneous disease, and afflicted individuals are less likely to remit spontaneously, an arsenal of treatments with different mechanisms of action may be required to ensure successful treatment. The pharmacologic treatment strategies currently available include TCAs, SSRIs, serotonin-noradrenergic reuptake inhibitors (SNRIs), and other atypical antidepressant drugs such as monoamine oxidase inhibitors (MAOIs), and combination antidepressant/antipsychotic drug therapy, as well as antidepressants combined with a variety of augmentation agents such as thyroid hormone, lithium, and others. Non-pharmacologic options also exist such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). Various psychotherapies (generally in combination with pharmacologic therapies) are also employed in the treatment of severe depression; however, the focus of this review is limited to

somatic approaches. The choice of treatment for MDD and its subtypes involves weighing the relative efficacy, side effect profile, and safety of a treatment against the severity of illness as well as patient acceptance.

For nearly three decades since their introduction in the 1950s, the TCAs and MAOIs were the dominant pharmacological treatments for depression. Several older placebo-controlled and open-label trials of TCAs have demonstrated efficacy for treating severe depression. However, due to the lack of validated instruments for defining severe depression and measuring symptom improvement, these studies have limited utility for comparison to current studies. The TCAs, although somewhat homogeneous in structure, differ in potency, with the tertiary amines generally considered dual serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors, and the secondary amines considered more selective in blocking NE uptake. The TCAs also have potent anticholinergic and antihistaminergic effects (Roose, 2003), and these attributes are associated with an unfavorable side effect profile and increased rates of non-compliance as well as serious safety issues (Roose, 2003; Schatzberg, 1999). Although TCAs are no longer considered first-line treatments for mild or moderate depression, they remain a treatment choice for severe melancholic or refractory depression (Bhatia and Bhatia, 1997; Broquet, 1999; Fava, 2000; Krishnan, 2001; Quitkin, 2002; Thase et al., 1992). Therefore, for these severe depression subtypes, TCAs have remained the standard by which other agents are judged and are often used as comparators in clinical trials.

The first generation, irreversible MAOIs also exhibit significant tolerability and safety issues (i.e., potential for drug–drug interactions and the requirement for dietary restrictions) that narrow their role in depression treatment (Lecrubier, 1994). Currently, MAOIs are utilized in the clinical setting for treatment-resistant cases and in atypical depression, although reversible MAO-A inhibitors (RIMAs), not available in the US, appear to have improved tolerability and safety profiles compared with older MAOIs.

3.1. Selective serotonin reuptake inhibitors

SSRIs are now generally acknowledged to be the first-line treatment for depression, due to their superior tolerability, decreased potential for cardiovascular side effects, and greater safety in overdose compared to TCAs (Boyce and Judd, 1999; Henry et al., 1995). Substantial clinical evidence indicates that SSRIs are efficacious in the treatment of severe depression with or without melancholia (Amsterdam, 1998). In a four-week randomized, double-blind, placebo-controlled study of patients with DSM III-defined MDD treated with fluvoxamine ($n = 104$), subjects were stratified into three severity groups corresponding to mild (HAMD = 15–20), moderate (HAMD = 21–25), and severe (HAMD = 26–38) (Ottevanger, 1994). In the severely depressed patient group, fluvoxamine (mean daily dose 149–214 mg/day) was shown to be superior compared to placebo ($n = 100$, $p = 0.002$) based on HAMD scores. In another study, patients with severe depression (mean baseline $HAMD_{24} = 30$) were randomly assigned to eight weeks of double-blind treatment with escitalopram ($n = 147$) or placebo ($n = 153$). At endpoint, approximately half of escitalopram-treated patients (overall mean daily dose = 18 mg) were responders, which was statistically significantly superior to placebo response rates (Ninan et al., 2003). A safety and efficacy study examining paroxetine treatment of severely depressed patients with melancholia with mean baseline HAMD scores >25 supports the efficacy of SSRIs in this subtype of depression (Dunbar et al., 1991; Nemeroff, 1994). In this double-blind, randomized, parallel-group study, therapeutic response was defined as a 6-week endpoint HAMD <10, a 50% improvement in baseline HAMD score, or a CGI-I score = 1 or 2. Patients treated with paroxetine ($n = 240$, 20–50 mg/day) showed significant improvement in HAMD scores relative to placebo ($n = 240$) at treatment week 2 to study endpoint, with response rates of 30–50% versus a 13–23% response rate in the placebo group (Nemeroff, 1994).

In re-analyzed pooled data (Pande and Sayler, 1993), 3183 outpatients and inpatients treated with fluoxetine for MDD were stratified into three severity groups based on HAMD score (mild $\leqslant 17$, moderate $\leqslant 18–24$, and severe $\geqslant 25$), fluoxetine-treated patients exhibited a significantly greater response rate compared to the placebo group in all severity subgroups. Importantly, the authors did not report any differences in response and remission rates between the inpatient and outpatient populations.

3.2. Comparisons of SSRIs with TCAs

Results from several earlier studies comparing SSRIs with TCAs in the treatment of severely depressed and melancholic patients suggested that TCAs were more effective than SSRIs (Citalopram, 1986, Paroxetine, 1990; Roose et al., 1994). Two randomized, controlled studies by the Danish University Antidepressant Group (DUAG) compared clomipramine (150 mg/day) with citalopram (40 mg/day) or paroxetine (30 mg/day) in depressed inpatients and found the TCA to be superior to the SSRI, with remission rates (HAMD $\leqslant 7$) of 57–60% in the clomipramine group compared to 22% with paroxetine or 28% with citalopram (Citalopram, 1986, Paroxetine, 1990). Although these studies typically have been discussed in terms of greater efficacy of TCAs compared to SSRIs, they did not specifically conduct a severity subtype analyses (Amsterdam, 1998; Hirschfeld, 1999). The advantage of clomipramine compared to citalopram may have been due to the short duration of the study (in that the sedating effects of the TCA could have resulted in a more rapid improvement in the three HAMD items that measure sleep disturbance), the increased compliance and adherence to dosing schedules of inpatients, or the mean baseline

HAMD scores which were not of sufficient severity to reflect severe depression.

Similarly, another study of hospitalized depressed patients with concomitant heart disease (mean baseline HAMD = 26) found nortriptyline ($n = 42$) to be superior to fluoxetine ($n = 22$) (Roose et al., 1994). The proportion of responders in the intent-to-treat (ITT) population (i.e., all patients with any treatment response data) was significantly greater in the nortriptyline (150 mg/day) group than in the fluoxetine (20 mg/day) group (67% versus 23%) and in those melancholic patients who completed the trial (83% versus 10%). However, the patients in this study were not randomly assigned to treatment groups and response to drug was assessed retrospectively.

In a meta-analysis by Anderson of 25 randomized, controlled, double-blind studies comprising 1377 patients in which SSRIs were compared to TCAs, the author concluded that TCAs were significantly more effective than SSRIs in depressed inpatients (Anderson, 1998). However, when individual TCA studies were analyzed, only one TCA, amitriptyline, demonstrated an advantage compared to the SSRIs. When dropout rates due to adverse effects alone were considered, significantly more patients on TCAs discontinued. The value of this analysis is limited, however, in that many of the studies had small numbers of patients and did not specify the severity of depression. Despite the various limitations of these studies, they do provide some evidence that TCAs may have advantages over SSRIs in subtypes of depressed patients, such as those who are melancholic or require hospitalization (Hirschfeld, 1999).

In contrast, several clinical trials and other pooled meta-analyses have suggested comparable efficacy of SSRIs and TCAs in treating severely depressed patients. An 8-week, double-blind study compared the efficacy and safety of sertraline ($n = 82$) and clomipramine ($n = 84$) in 166 outpatients with severe depression. In this study, the mean baseline MADRS and HAMD values were 34.5 and 29.8, respectively (Lepine et al., 2000). HAMD scores decreased by nearly 60% in the sertraline (50–200 mg/day) group and 57% in the clomipramine (50–150 mg/day) group, with similar percentages of patients in each treatment group completing the study. Sertraline was as effective as clomipramine, with 74% of patients in the sertraline group and 71% of clomipramine patients being classified as responders at the endpoint as classified by a CGI-I score of 1 or 2. There were more withdrawals due to adverse events in the clomipramine groups than in the sertraline groups (17% versus 12%). Anticholinergic events such as dry mouth, tremor, and constipation were more prevalent in the TCA group.

Similar results were seen in a multicenter, double-blind study comparing the efficacy of fluvoxamine (100–250 mg/day) and clomipramine (100–250 mg/day) in 86 severely depressed inpatients (Zohar et al., 2003) and in a randomized trial of paroxetine (20 mg/day) versus clomipramine (75 mg/day) in 121 severely depressed adolescents (aged 12–20 years) (Braconnier et al., 2003). No age-related

effects were detected in the latter trial, which is in contrast to earlier TCA and SSRI comparator studies (Citalopram, 1986, Paroxetine, 1990). As expected, anticholinergic side effects occurred most often in the TCA groups.

An analysis of 18 randomized, double-blind clinical trials of inpatients and outpatients with severe depression (mean baseline HAMD scores 24–34) determined that overall response rates ($\geqslant 50\%$ improvement in HAMD scores) ranged from 53–64% for SSRIs and 43–70% for TCAs (Hirschfeld, 1999). The report analyzed study results with regard to hospitalization status, depression subtype, and patient population (e.g., elderly or adult) and the overall conclusions were that SSRIs and TCAs displayed comparable efficacy in inpatients, outpatients, and patients with melancholia. However, as noted in other SSRI and TCA studies, anticholinergic and cardiovascular effects were much more prevalent with TCAs than SSRIs (Beasley et al., 1993; Ottevanger, 1995). Anderson performed a meta-analysis on 102 randomized controlled trials that included a total of 10,706 subjects (Anderson, 2000). Patients were stratified based on age (adult <65 years, and elderly >65 years), in- and out-patient status, and level of depression severity. In agreement with other studies (Beasley et al., 1993; Bowden et al., 1993; Ottevanger, 1995; Pande and Sayler, 1993), the analysis indicated that there were insignificant differences in efficacy between the SSRIs and TCAs in the total patient population and in all the subgroups analyzed. Although TCAs demonstrated greater efficacy in hospitalized patients, this benefit was not observed in patients with more severe forms of depression. Overall, the available information to date suggests similar efficacy rates between TCAs and SSRIs, with some differences in depression subtypes.

3.3. Comparisons between SSRIs

Several randomized controlled studies have examined the clinical differences among the SSRIs in treating severely depressed MDD patients. In one study, Flament and colleagues (Flament et al., 1999) randomly assigned 286 psychiatric outpatients, 87 of which were subtyped as severely depressed with or without melancholia, to receive either sertraline (50–100 mg/day) or fluoxetine (20–40 mg/day). Mean baseline HAMD scores were similar for the two treatment groups, (sertraline, 27.4 and fluoxetine, 27.5). Although there was no statistical difference in efficacy between the two treatment groups, when analyzed by subgroups, the sertraline-treatment group showed a greater proportion of responders compared to fluoxetine in treating severe depression with (59% versus 44%) or without melancholia (59% versus 41%). In particular, the analysis showed that significant differences existed in favor of sertraline in patients with low anxiety in the melancholia and severe depression subgroups ($p < 0.05$). However, multiple tests of significance were performed, which may have resulted in increased type I errors. A pooled analysis of data from five double-blind studies of treatment duration

12–32 weeks compared sertraline ($n = 547$, 50–150 mg/day) versus fluoxetine ($n = 541$, 20–60 mg/day) in the treatment of anxious and severe depression (Feiger et al., 2003). The treatment response rate for all patients was similar for sertraline and fluoxetine, however further post-hoc analysis of the high severity subgroup (mean HAMD = 28) indicated that the sertraline treatment group exhibited a larger endpoint improvement than fluoxetine, with CGI-I response rates of 88% versus 71% ($p = 0.03$), for sertraline and fluoxetine, respectively.

Other studies suggest there may be differences in efficacy between the various SSRIs. A post-hoc analysis of pooled data from three similarly designed, randomized, double-blind, placebo-controlled trials ($n = 1321$) compared escitalopram (10–20 mg/day) and citalopram (20–40 mg/day) in the treatment of moderate-to-severely depressed patients (MADRS score $\geqslant 22$ at baseline) (Gorman et al., 2002). When only the severely depressed patients (MADRS score $\geqslant 30$) were analyzed ($n = 506$), escitalopram ($n = 169$) demonstrated significantly greater improvement in MADRS scores as early as week 1 and at endpoint compared to either citalopram ($n = 171$) or placebo ($n = 166$). Response rates were 56% for escitalopram and 41% for citalopram (Llorca et al., 2005). The suggested superiority of escitalopram over citalopram in the treatment of severely depressed patients has recently been confirmed in a prospective study (Moore et al., 2005). Outpatients with MADRS scores $\geqslant 30$ (mean = 36) at baseline were randomized to receive 8 weeks treatment with either escitalopram 20 mg/day ($n = 138$) or citalopram 40 mg/day ($n = 142$). Patients treated with escitalopram experienced a statistically greater improvement in MADRS score compared with citalopram (-22.4 versus -20.3, $p < 0.05$), and were more likely to respond to treatment (76.1% versus 61.3%, $p < 0.01$). Recently, Kennedy et al. (2006) conducted a meta-analysis of all randomized double-blind studies in major depression in which escitalopram was compared with other SSRIs or venlafaxine. The final sample was comprised of 2687 patients treated with escitalopram ($n = 1345$), other SSRIs including sertraline, fluoxetine, paroxetine and citalopram ($n = 1102$) and venlafaxine XR ($n = 240$). Escitalopram was superior to the other SSRIs and comparable to venlafaxine in efficacy including measures of response and remission. These findings were not only also true in severe depression, but as severity of depression increased, the advantage of escitalopram was even more robust.

3.4. Summary

There is substantial evidence to support the use of SSRIs in the treatment of severe depression. Although several trials indicate a possible advantage of TCA relative to SSRI therapy in patients hospitalized for depression, other studies show comparable efficacy between the classes. Conclusions regarding the superior safety and tolerability of SSRIs are less equivocal, with TCA therapy more likely

to produce anticholinergic and cardiovascular events and treatment discontinuations. The few available comparisons of SSRIs in severe depression suggest marginal advantages for sertraline relative to fluoxetine and escitalopram relative to citalopram. The SSRIs remain the initial treatment of choice for the majority of severe depression cases.

4. Newer generation antidepressants

4.1. Serotonin-norepinephrine reuptake inhibitors and norepinephrine-serotonin reuptake inhibitors (NSRIs)

4.1.1. Venlafaxine

It has been suggested that compounds that inhibit reuptake of both serotonin and norepinephrine – but lack the anticholinergic effects of TCAs – may have an efficacy advantage compared with single-action antidepressants in treating MDD subtypes, particularly melancholia (Gutierrez et al., 2003; Kienke and Rosenbaum, 2000). Venlafaxine is one such agent that appears to be efficacious especially in doses >150 mg/day across a range of depression subtypes (Benkert et al., 1996; Clerc et al., 1994; Costa e Silva, 1998; Guelfi et al., 1995; Zanardi et al., 2000).

In a 4-week study (Guelfi et al., 1995) the efficacy and safety of venlafaxine (150–375 mg/day) was evaluated in 93 severely depressed inpatients (mean baseline MADRS scores $\geqslant 25$ and mean baseline HAMD = 28.2 for the venlafaxine group and 28.6 for the placebo group). As early as day 4, statistically significant improvement in MADRS scores in the venlafaxine-treated group over placebo was observed, with MADRS response rates of 65% for venlafaxine and 28% for placebo.

In a number of clinical studies examining the treatment of MDD, venlafaxine has been shown to be clinically comparable and, in some studies but not others, superior to SSRIs. In a randomized, double-blind comparative study of 68 hospitalized patients with melancholic depression (mean baseline HAMD $\geqslant 29$ and MADRS $\geqslant 34$ scores) (Clerc et al., 1994), venlafaxine (200 mg/day) was found to be superior to fluoxetine (40 mg/day), resulting in greater improvement in HAMD scores (-18.0 versus -12.4, $p = 0.027$) and MADRS scores (-22.8 versus -15.7, $p = 0.028$) after six weeks of treatment. At week 4, there were significantly more responders in the venlafaxine group (76%) than in the fluoxetine group (47%) on the MADRS, HAMD (76% versus 41%), and CGI-I (76% versus 47%), and at six weeks, the venlafaxine group continued to have a higher, although statistically insignificant, proportion of responders than the fluoxetine group for HAMD, MADRS, and CGI-I. Although a placebo control was not included, the response rates for venlafaxine were similar to those in a previous placebo-controlled study by Guelfi and colleagues (Guelfi et al., 1992).

In contrast, a larger, multicenter, randomized, double-blind study of venlafaxine ($n = 196$, 75–150 mg/day) versus fluoxetine ($n = 186$, 20–40 mg/day) showed no difference between the two drugs in outpatients with major depres-

sion (mean baseline HAMD $\geqslant 30$ and MADRS $\geqslant 34$) after 8 weeks of treatment (Costa e Silva, 1998). A global response ($\geqslant 50\%$ decrease in HAMD or MADRS score and CGI-I of 1 or 2) was observed in 86.8% with venlafaxine and 82.0% with fluoxetine, and remission rates (HAMD $\leqslant 8$) were 60.2% in each group. Similarly, in adult outpatient (Nemeroff and Thase, in press) and geriatric outpatient (Schatzberg and Cantillon, 2000) studies of patients with major depression ($n \approx 300$/study), venlafaxine exhibited no advantage compared to fluoxetine. Recently, we completed a paroxetine CR (final dose 75 mg/day) versus venlafaxine (final dose 375 mg/day) comparison in outpatients with major depression. Although primarily designed to assess transporter occupancy during treatment with these two antidepressants, efficacy measures were obtained. Venlafaxine had a slight numeric but not statistically significant advantage compared to paroxetine CR (Simon et al., 2005b).

A pooled analysis of remission rates (HAMD $\leqslant 7$) from eight randomized, double-blind studies of MDD comparing venlafaxine ($n = 851$) and three selective SSRIs, fluoxetine, paroxetine, and fluvoxamine ($n = 748$) or placebo (four studies, $n = 446$), report significantly higher remission rates with venlafaxine than with comparison SSRIs or placebo (Thase et al., 2001). Final remission rates were 45% for venlafaxine, 35% for the SSRIs over all, and 25% for placebo ($p < 0.001$ for all comparisons, venlafaxine versus SSRIs, venlafaxine versus placebo, and SSRIs versus placebo). However, there were several limitations to the individual trials included in this analysis, such as varying study duration and design, population type, and dose ranges, as well as lack of placebo in half of the studies, that limit, in part, conclusions from this analysis (Burke, 2004). Moreover, it remains unclear whether the small differences observed, even if statistically significant, are clinically meaningful.

Subsequently, 33 Wyeth-sponsored studies comparing venlafaxine and SSRIs have been subjected to a pooled analysis (Nemeroff et al., 2003). Venlafaxine was superior to SSRIs as a class and to fluoxetine, but not superior to paroxetine or sertraline. Alternative statistical analysis found venlafaxine to be superior in efficacy to fluoxetine and paroxetine (Thase et al., 2005), although the minimal dose allowed of the antidepressants precludes any firm conclusions. In addition, a number of safety concerns have arisen concerning venlafaxine, including TCA-like lethality in overdose (Buckley and McManus, 2002; Cheeta et al., 2004), and cardiovascular side effects including QT prolongation (Blythe and Hackett, 1999) and reduced heart rate variability (Davidson et al., 2005).

4.1.2. Milnacipran

There are several reports demonstrating the efficacy of the NSRI milnacipran in individuals with moderate to severe depression with or without endogenous features (Clerc, 2001; Guelfi et al., 1998; Lecrubier et al., 1996; Lopez-Ibor et al., 1996; Macher et al., 1989). In 58 severely depressed, hospitalized patients with a MADRS $\geqslant 25$, milnacipran (100 mg/day) treatment produced a significant reduction in mean MADRS scores (44.5% versus 23.0%) and mean HAMD scores (57.0% versus 21.0%) from baseline compared to placebo (Macher et al., 1989). This study was included in a meta-analysis of three multicenter, placebo-controlled trials, which supported the positive results of the efficacy of milnacipran in hospitalized patients with major depression (Lecrubier et al., 1996). In the overall analysis, milnacipran (100 mg/day) was significantly more effective than placebo based on improvement in both MADRS and HAMD scores.

There is some evidence that milnacipran may have greater efficacy than SSRIs in patients with severe MDD (Clerc, 2001; Guelfi et al., 1998; Lopez-Ibor et al., 1996). In one study (Clerc, 2001), 113 severely depressed patients (baseline MADRS = 37) were randomized to milnacipran ($n = 57$, 100 mg/day) or fluvoxamine ($n = 56$, 200 mg/day) for 6 weeks; milnacipran treatment led to significantly greater improvement in both MADRS and HAMD scores than fluvoxamine treatment. At endpoint, response rates in the ITT population were 78.9% in milnacipran-treated patients compared with 60.7% for those individuals receiving fluvoxamine. Response rates, as measured by a 50% reduction in the 24-item HAMD scores, were 70.2% versus 57.1% for milnacipran and fluvoxamine, respectively. Another study comparing milnacipran (100 and 200 mg/day) with fluoxetine (20 mg/day) in 289 inpatients with endogenous depression (baseline MADRS = 32) revealed a significant difference in favor of milnacipran (100 mg/day) as early as 4 weeks (Guelfi et al., 1998). The percentage of MADRS responders at endpoint (12 weeks) was 64% and 55%, respectively, for those individuals receiving milnacipran or fluoxetine.

In a meta-analysis evaluating efficacy of milnacipran compared to fluoxetine and fluvoxamine, milnacipran showed higher response rates than fluoxetine or fluvoxamine (milnacipran, 64% versus SSRIs, 50%) (Lopez-Ibor et al., 1996). Remission rates were also higher with milnacipran than with SSRIs (39% versus 28%). Overall incidence of adverse events was similar between the treatment groups. Milnacipran is not approved for the treatment of major depression in the US. There is evidence that it is effective in fibromyalgia (Vitton et al., 2004) and perhaps other chronic pain states (Briley, 2004). Recently, our group reported that a particular polymorphism of the norepinephrine transporter gene was associated with an antidepressant response to milnacipran but not fluvoxamine (Yoshida et al., 2004).

4.1.3. Duloxetine

Clinical trials of duloxetine, a dual NE/5HT reuptake inhibitor, in severely depressed patients have yet to be presented. However, in patients with MDD (baseline HAMD $\geqslant 15$), results from six double-blind, placebo- and/or operator-controlled multicenter clinical trials of 1755 patients demonstrated significant efficacy of duloxetine (60 mg/

day) in four of six of the studies compared to placebo ($p < 0.05$) (Mallinckrodt et al., 2003; Nemeroff et al., 2002). Duloxetine was evaluated for the treatment of major depression (baseline HAMD $\geqslant$ 15) in an 8-week, randomized, double-blind, placebo- and paroxetine-controlled multicenter trial (Goldstein et al., 2004). At endpoint, the response rate (50% reduction in mean HAMD scores) for duloxetine 80 mg/day (51%, $n = 86$) was significantly greater than placebo (31%, $n = 89$). In contrast the response rates for duloxetine 40 mg/day (44%, $n = 86$) and paroxetine 20 mg/day (40%, $n = 87$) were not significantly greater than placebo.

The efficacy and tolerability of duloxetine in acute (8 weeks) and long-term (6 months) treatment of major depression (baseline HAMD $\geqslant$ 15) were investigated in a randomized, placebo- and paroxetine-controlled trial (Detke et al., 2004). Following an 8-week acute treatment phase, patients who had $\geqslant$30% reduction from baseline HAMD scores were allowed to continue on the same blinded treatment during the continuation phase. After the acute phase, the response rates (50% reduction in mean HAMD scores) in patients receiving duloxetine 80 mg/day (70%, $n = 95$) and 120 mg/day (77%, $n = 93$) were significantly superior to that of the placebo group (47%, $n = 93$), and the response of paroxetine 20 mg/day patients (82%, $n = 86$) was also significantly greater than placebo. At the end of the continuation phase, patients receiving duloxetine 80 mg/day ($n = 70$), duloxetine 120 mg/day ($n = 75$), and paroxetine 20 mg/day ($n = 70$) had a significantly longer time to loss of response (maintenance of $\geqslant$30% reduction in HAMD) compared with placebo ($n = 58$). Studies on the efficacy of duloxetine in more severely depressed patients are clearly warranted.

4.2. Summary

In general, the newer generation antidepressants appear to be valuable treatment options for severe depression. Similar to the research comparing TCAs and SSRIs, there are venlafaxine data suggesting a treatment advantage relative to SSRIs, studies indicating comparable efficacy, and potential safety concerns related to venlafaxine, especially in overdose. Although not available in the US, milnacipran has shown superior efficacy in comparison trials of severe depression involving fluoxetine and fluvoxamine. To date no clinical trials of duloxetine in the treatment of severe depression have been published, but the agent has shown efficacy comparable to paroxetine in MDD studies. Additional research will help establish the place of these agents in the treatment of severe depression.

4.3. Other novel pharmacotherapies

The efficacy and safety of various atypical antidepressants, such as bupropion, mirtazapine, nefazodone, and trazodone, as well as the reversible MAOI, moclobemide,

also have been evaluated in the treatment of severe depression.

4.3.1. Mirtazapine

In several studies, mirtazapine has been shown to be as effective as TCAs in the treatment of severe depression (Benkert et al., 2002; Gorman, 1999; Kasper, 1995; Kasper et al., 1997). A meta-analysis of five randomized, double-blind studies involving 405 severely depressed patients (mean baseline HAMD = 29) concluded that mirtazapine and amitriptyline were equally effective in reducing symptoms of depression (Kasper et al., 1997). After 4 weeks of treatment, 49% versus 43%, respectively, of the patients responded to mirtazapine compared to those treated with amitriptyline. Of those patients classified as remitters (total HAMD $\leqslant$ 7), 39.0% were mirtazapine-treated (mean dose at endpoint 43 mg/day) and 37.8% were amitriptyline-treated (mean dose at endpoint 180 mg/day). Eighty-nine percent of the mirtazapine- and 87% of the amitriptyline-treated severely depressed patients completed the entire study period. Drug-related side effects were implicated as a reason for premature termination in 6% of the mirtazapine- and 9% of the amitriptyline-treated patients.

Several double-blind, uncontrolled studies comparing mirtazapine with SSRIs have been conducted in patients with severe depression with or without melancholia (Benkert et al., 2000; Leinonen et al., 1999; Wheatley et al., 1998). In one study, mirtazapine ($n = 66$, 15–60 mg/day) was found to be significantly more effective than fluoxetine ($n = 67$, 20–40 mg/day) in severely depressed patients (HAMD $\geqslant$ 26) in reducing HAMD total scores at weeks 3 and 4 ($p = 0.006$). However, by week 6, this difference was only of borderline statistical significance ($p = 0.054$) (Wheatley et al., 1998). In another study comparing mirtazapine ($n = 137$, 15–60 mg/day) with citalopram ($n = 133$, 20–60 mg/day), no significant differences were observed between the groups after 8 weeks of treatment (Leinonen et al., 1999). Mirtazapine ($n = 78$, 15–60 mg/day) was compared to venlafaxine ($n = 79$, 75–375 mg/day) in hospitalized severely depressed, melancholic patients (HAMD $\geqslant$ 25) (Guelfi et al., 2001). Although not statistically significant, there was a slight numerical advantage with those subjects treated with mirtazapine at endpoint on HAMD (62% versus 52%) and MADRS (64% versus 58%) scores. Another study comparing the efficacy and tolerability of mirtazapine ($n = 126$, mean daily dose at endpoint 34 mg) and paroxetine ($n = 120$, mean daily dose at endpoint 33.6 mg) in elderly patients ($\geqslant$65 years old) with major depression revealed that mirtazapine displayed a more rapid onset of action than did paroxetine (28% versus 13% responded at 2 weeks) (Schatzberg et al., 2002).

4.3.2. Bupropion

The atypical antidepressant bupropion has been shown to be effective in the treatment of severely depressed outpatients (Fabre et al., 1983; Merideth and Feighner, 1983;

Pitts et al., 1983; Reimherr et al., 1998). In one placebo-controlled study, reductions in HAMD scores were significantly greater in the treatment group, and CGI improvement scale-determined response rates were significantly better for bupropion (61%) than for placebo (28%) (Fabre et al., 1983). Another placebo-controlled study of 59 hospitalized depressed, non-psychotic patients (baseline HAMD $\geqslant$ 30) found that bupropion treatment resulted in a significant reduction in HAMD scores compared with placebo as early as day 5, which was maintained throughout the 4-week study (Pitts et al., 1983). Pooled data from seven randomized, double-blind, controlled studies of major depressive disorder showed that remission rates with bupropion ($n = 348$, 60 mg/day) and SSRIs (fluoxetine, sertraline, and paroxetine) were similar and consistent across trials (bupropion, 47.1%, SSRIs, 47.3%), and the remission rate with bupropion was superior to placebo (36.1%, $p < 0.01$) (Thase et al., 2003).

4.3.3. Nefazodone

The efficacy of nefazodone for the treatment of chronic depression was demonstrated in a 12-week multicenter trial in which chronically depressed (HAMD > 20) non-psychotic outpatients received nefazodone, cognitive-behavioral psychotherapy, or both (Keller et al., 2000). The response rate (50% reduction from baseline HAMD) was 48% for patients receiving nefazodone ($n = 226$, mean final dose 466 ± 166 mg/day) and 48% for patients receiving psychotherapy alone ($n = 228$). Of interest, the response rate was 73% for patients receiving combination therapy ($n = 227$, nefazodone mean final dose 460 ± 139 mg/day). While nefazodone produced effects more rapidly than did psychotherapy in the first 4 weeks, psychotherapy had a greater effect during the second part of the trial, and by week 12, the efficacy of the two treatments was similar. The effects of combination therapy became apparent and significantly greater than either treatment alone after 4 weeks, which suggests that when administered together, the treatments continue to have independent rather than synergistic mechanisms of action.

4.3.4. Trazodone

A controlled release form of the atypical antidepressant trazodone was evaluated in a 6-week open study of 549 outpatients with different sub-types of depression, including recurrent depressive episode (Saletu-Zyhlarz et al., 2003). Doses were fixed at 50 mg/day for 3 days and were increased to 100 mg/day for days 4–6 and 150 mg/day for days 6–14. After 2 weeks, doses were adjusted as needed for efficacy and tolerability. Mean HAMD scores improved significantly from baseline 20.6 to 7.6 at endpoint. Tolerability of trazodone was very good, with only 6.7% of patients reporting adverse events, mostly fatigue, mild nausea, and vertigo, and a 3.7% drop-out rate, an improvement over previous studies of conventional (immediate-release) trazodone tablets (Fisher et al., 1993; Moon et al., 1990). Most patients in this study, however, were considered mod-

erately depressed, and the role of trazodone treatment in severely depressed patients remains unclear.

4.3.5. Moclobemide

There are several reports indicating that moclobemide has comparable efficacy compared to TCAs in the treatment of severe depression (Angst et al., 1995). A meta-analysis comparing the efficacy of moclobemide ($n = 238$, mean daily dose 453 mg) and imipramine ($n = 248$, mean daily dose 159 mg) reported similar efficacies in all subgroups, including the severely depressed (HAMD $\geqslant$ 28), and those with psychosis (Angst et al., 1995). Moclobemide clearly possesses a superior side effect profile than the non-reversible MAOIs (Stabl et al., 1995), partly because it does not require dietary restrictions and, therefore, may increase compliance (Da Prada et al., 1988).

4.4. Summary

A number of other agents have shown promise as monotherapy against severe depression. The efficacy of mirtazapine in treatment trials has been comparable to TCAs and citalopram and somewhat better than fluoxetine and venlafaxine. Depression studies involving bupropion suggest a level of efficacy that is similar to that available from SSRIs. Nefazodone and trazodone have shown benefit in the treatment of depression subtypes including chronic and recurrent varieties but have not been well studied in severe depression. The effect of moclobemide in severe depression has been judged as comparable to the TCAs. These medications broaden the options available to clinicians when first-line treatments prove ineffective or intolerable.

5. Non-pharmacologic treatments

A substantial number of depressed patients either are chronic non-responders or medication intolerant, which has led to the pursuit of non-pharmacologic therapies, such as ECT, TMS, VNS, (Janicak et al., 2002; Rush et al., 2000) and DBS (Mayberg et al., 2005).

5.1. Electroconvulsive therapy

ECT generally is considered to be the most effective treatment for severe depression, and may be particularly effective for patients with melancholia and refractory depression (Broquet, 1999; McDonald et al., 2004; Sackeim et al., 2001a; Sonawalla and Fava, 2001). A meta-analysis of randomized and non-randomized controlled trials comparing efficacy of ECT versus traditional antidepressants ($n = 892$, mean $n = 69$ per trial) revealed a significant superiority of ECT over TCAs, MAOIs, and an SSRI, paroxetine (Pagnin et al., 2004). The patient groups were quite heterogeneous in terms of diagnostic subtypes, and there was no specific evaluation for severe depression. Another meta-analysis of 18 randomized controlled trials ($n = 1144$) confirmed that ECT was significantly more

effective than pharmacotherapy (TCAs, MAOIs, or paroxetine) (2003). ECT does not have long-lasting efficacy, with a rate of relapse that exceeds 50% in the year following cessation of treatment. As such, the APA recommends antidepressant therapy during the post-ECT period (Sackeim et al., 2001a), although considerable data now support the use of maintenance ECT.

A double-blind, placebo-controlled trial randomized 84 patients with unipolar major depression who completed an open ECT treatment phase (mean pre-ECT HAMD = 35.3) to placebo ($n = 29$), nortriptyline ($n = 27$), or combination nortriptyline and lithium ($n = 28$) (Sackeim et al., 2001a). Without active treatment, virtually all remitted patients relapsed within 6 months of stopping ECT. Monotherapy with nortriptyline had limited efficacy (60% relapse rate), while the combination with lithium was more effective (39% relapse rate). Common adverse events associated with ECT include temporary confusion, memory impairment, and headache (Sonawalla and Fava, 2001), however, various modifications to its administration have greatly lessened the risk of complications. In addition, a thorough medical examination is required to evaluate the risk of cardiovascular and neurologic adverse events associated with ECT (2000b).

5.2. Transcranial magnetic stimulation

Repetitive TMS (rTMS) is a non-invasive method that is thought to exert its putative antidepressant properties through the use of single or repetitive pulses of electrical currents which generate magnetic energy over focused areas of the brain. TMS has been shown to modify regional cerebral blood flow, with cortical excitability being increased or decreased, depending on the stimulation frequency (Bohning et al., 2000; Catafau et al., 2001). Preliminary results from several studies have shown that when compared with ECT, rTMS was more favorable in the treatment of more severely ill, treatment-resistant depressed patients (Grunhaus et al., 2000; Pridmore, 2000). However, in a 4-week randomized, prospective trial of severely depressed patients (mean baseline HAMD = 32), rTMS and ECT treatment had comparable response rates (rTMS, 46% versus ECT, 56%) (Janicak et al., 2002). Our assessment of the literature (Schlaepfer et al., 2003) suggested that there is still insufficient positive findings to conclude that rTMS is effective in the treatment of depression. However, a number of treatment trials sponsored by the National Institute of Mental Health and by Neuronetics, Inc. are currently ongoing.

There is some evidence to suggest that single transcranial magnetic stimulation (sTMS) as an add-on therapy may be effective in treating severely depressed non-psychotic inpatients (Conca et al., 2000). Twelve patients receiving either citalopram or trazodone also received sTMS for 4 weeks. At endpoint, 8 patients (67%) were identified as sTMS responders (50% reduction in HAMD). However, a study of 41 patients with major depression (mean baseline HAMD$_{21}$ = 32.3) reported that rTMS as

an add-on strategy to either citalopram, milnacipran, mirtazapine, or reboxetine treatment found no evidence of an additional antidepressant effect (Hausmann et al., 2004). Additional adequately powered, placebo-controlled randomized trials are clearly needed to define the role of TMS in the treatment of depression.

5.3. Vagus nerve stimulation

VNS, in which the vagus nerve is stimulated by electrical signals from an implanted pacemaker-like pulse generator, has been shown to be an effective therapy for treatment-resistant epilepsy (Ben-Menachem et al., 1994; Handforth et al., 1998) and is under investigation as an alternative for treatment-resistant depression (Goodnick et al., 2001; Marangell et al., 2002; Sackeim et al., 2001b). In a multisite, open-label study of 30 patients (mean baseline HAMD$_{28}$ = 38, MADRS = 34) with treatment-resistant depression (failing ⩾2 medications), nearly 40% of the patients (all maintained on their current medication regimen) were responders (⩾50% reduction in HAMD or MADRS scores) after 10 weeks of treatment (Rush et al., 2000). A long-term follow-up study (9 months) of this same group of patients showed that 91% of the responders continued in remission (Marangell et al., 2002). When this same study was expanded to 60 patients, approximately one-third of the population responded acutely and maintained this response rate over 9 months (Sackeim et al., 2001b). Recently, the US Food and Drug Administration (FDA) approved VNS for the treatment of refractory depression.

5.4. Deep brain stimulation

The placement of stimulating electrodes within the CNS for the treatment of refractory neuropsychiatric disorders is a field in its infancy, but there is already evidence to suggest its efficacy in refractory depression (Greenberg and Rezai, 2003). Recently, Mayberg and colleagues (Mayberg et al., 2005) demonstrated the benefits of DBS in a small series of severely depressed, treatment-refractory patients.

5.5. Summary

Although ECT may be indicated for some patients in whom severe depression is accompanied by psychosis or suicidality, the non-pharmacologic therapies discussed here generally are not considered first-line interventions for severe depression. They can be, however, valuable options for patients whose depression proves to be resistant to pharmacological treatment and those who cannot tolerate pharmacotherapy. Electroconvulsive therapy is seen as the most effective acute intervention for severe depression, although the associated relapse rate is high and administration is complex relative to standard pharmacotherapy. To date results with rTMS as monotherapy and as an add-

on treatment in severe depression have been mixed, with research continuing. Vagus nerve stimulation has demonstrated utility in the treatment of treatment-resistant patients and has received FDA approval for that indication. Deep brain stimulation is an emerging modality that similarly has shown promise in refractory severe depression. In addition to their value as options for treatment-resistant depression, these strategies provide additional avenues for patients who cannot tolerate traditional pharmacotherapy.

6. Combination and augmentation therapy

Combined antidepressant therapy may be an effective alternative for the treatment of severely depressed and treatment-resistant patients (Hirschfeld, 1999). In addition, augmentation therapy (i.e., the use of a combination of an antidepressant and a second medication that is not by itself an effective antidepressant, but is effective when added to an antidepressant) represents a very active avenue of investigation. In fact, there is a growing view in the field that many patients, particularly those with severe or refractory depression, require more than one pharmacological strategy to attain remission, not unlike the standard of care for the treatment of hypertension or neoplastic disease. Combined pharmacotherapy and psychotherapy also has shown benefit in patients with severe, chronic, or refractory depression (Keller et al., 2000; Segal et al., 2002; Thase et al., 1997), although a detailed assessment of the available evidence for this treatment strategy is beyond the scope of this review.

6.1. Antidepressants

A retrospective, uncontrolled study reported that seven of 20 severely depressed patients who demonstrated a poor or partial response to fluoxetine responded when a heterocyclic antidepressant was added (Zajecka et al., 1995). Additionally, five (71%) of the responders to the combination therapy had previously failed to respond to monotherapy with the heterocyclic agent.

A preliminary four-week, open trial comparing the combination of desipramine and fluoxetine in 14 inpatients with major depression to the response of 52 inpatients who had been previously treated with desipramine alone demonstrated the response to the combined therapy to be more rapid and more robust (Nelson et al., 1991). The most substantial difference observed was the remission rate at four weeks, which was considerably higher in the combined treatment group compared to desipramine monotherapy (71% versus 14%, $p = 0.0002$). In a double-blind trial, inpatients with non-psychotic unipolar major depression (mean baseline MADRS > 32) treated with combination fluoxetine (20 mg/day) and desipramine ($n = 13$) were found to be significantly more likely (53.8%) to remit (defined as 75% improvement in MADRS score and a final score $\leqslant 9$) than those treated with fluoxetine ($n = 14$) (7.1%). There

were no patients treated with desipramine ($n = 12$) alone that achieved remission, as defined in this study (Nelson et al., 2004). However, a modest non-significant correlation of desipramine plasma levels and depression remission was observed in the combined-treatment group. The small sample size and short duration of the study leaves the possibility that longer treatment could have resulted in higher remission rates, especially for the single drug arms of the study.

6.2. Lithium

Some evidence indicates that lithium augmentation of antidepressant therapy in non-responsive, severely depressed patients is effective in improving response rates (De Montigny et al., 1983; De Montigny et al., 1981). In a group of severely depressed inpatients (mean baseline HAMD = 26, MADRS = 36) non-responsive to monotherapy with mirtazapine ($n = 50$) or imipramine ($n = 50$), the treatment strategy of imipramine plus lithium was more effective than the same strategy with mirtazapine and lithium (76% versus 53% responders, respectively) (Bruijn et al., 1998).

Similar effects were seen with combination desipramine and lithium therapy in 14 patients with severe major depression (mean total HAMD = 32.8) (Cappiello et al., 1998). Four (28.6%) of the patients receiving combination therapy had a marked response, and in responders, HAMD scores decreased by 73% following 4 weeks of combination therapy.

6.3. Triiodothyronine

Another strategy reported to accelerate the antidepressant response of medications and/or convert antidepressant non-responders to responders is the combination of thyroid hormone, triiodothyronine (T_3), with antidepressants. A meta-analysis of six placebo-controlled trials for unipolar depressive disorder suggested significant effects for T_3 in accelerating TCA response (Altshuler et al., 2001). The effects were more pronounced during the first week of treatment. In addition, the meta-analysis also revealed that women may be more likely than men to benefit from this approach. In contrast, in spite of results of earlier studies, the addition of T_3 to augment SSRI response has not been shown to be effective in two large recent studies (Appelhof et al., 2004; Ninan and Nemeroff, in preparation).

6.4. Buspirone

Additionally, there is evidence that buspirone may potentiate the antidepressant effects of SSRIs (Appelberg et al., 2001). Initial non-responders ($n = 102$) to citalopram or fluoxetine had a significantly greater reduction in MADRS score with buspirone addition compared with placebo, especially in a subgroup of patients with initially high MADRS scores (>30) (Appelberg et al., 2001).

6.5. Atypical antipsychotics

Augmentation with atypical antipsychotics in antidepressant non-responders showed some promising results in small pilot trials (Barbee et al., 2004). Patients ($n = 8$) with major depression without psychotic features, who were non-responsive to at least one SSRI (either fluoxetine or paroxetine), benefited dramatically from the addition of the atypical antipsychotic risperidone to continued administration of the SSRI (Ostroff and Nelson, 1999). All eight patients remitted within one week of the addition of risperidone. Another report by Tani and colleagues (Tani et al., 2004) describes risperidone augmentation for five inpatients with MDD who had partially responded to 100–300 mg milnacipran after 6–11 weeks, but remained hospitalized with persistent symptoms. Three patients reported improved sleep after one day of 1 mg risperidone, followed by improved mood and complete remission within 4–12 weeks. Two patients responded more slowly to augmentation (4–21 days), but also were discharged fully recovered. Two large controlled studies have now provided evidence that risperidone augmentation increases the number of days well compared to placebo in SSRI non-responders (Nemeroff et al., 2004; Keitner et al., 2005). Other trials involving olanzapine (Parker et al., 2005; Shelton et al., 2001), ziprasidone (Papakostas et al., 2004) and aripiprazole (Simon and Nemeroff, 2005a) support augmentation strategies for patients who did not respond to antidepressant treatment.

6.6. Dopamine agonists

Dopamine agonists have gained attention for their possible antidepressant effects. In a 6-week double-blind, placebo-controlled study, 21 patients with DSM-IV bipolar II disorder, depressive phase treated with lithium or valproate were randomly assigned to treatment with flexibly dosed pramipexole ($n = 10$) or placebo ($n = 11$) (Zarate et al., 2004). Response, defined as >50% decrease in MADRS from baseline, occurred in 60% of patients taking pramipexole and 9% taking placebo ($p = 0.02$). In another study, 22 outpatients with DSM-IV non-psychotic bipolar disorder were randomly assigned to receive placebo ($n = 10$) or flexibly dosed pramipexole ($n = 12$) for 6 weeks (Goldberg et al., 2004). All patients had previously been non-responsive to antidepressant treatment with concomitant mood stabilizers and all continued their maintenance doses of mood stabilizers during the study. Eight (67%) of 12 patients taking pramipexole and 2 (20%) of 10 taking placebo had an improvement of $\geqslant 50\%$ in their HAMD scores. In both studies, discontinuations were greater in the placebo-treated groups. While preliminary, these studies suggest that augmenting mood stabilizers with pramipexole may be effective for antidepressant treatment-resistant bipolar depression.

6.7. Summary

Combined antidepressant and augmentation therapies have demonstrated efficacy in partial responders and patients with severe, refractory, and chronic depression. Tricyclic and heterocyclic antidepressants have been combined with SSRIs, and augmentation agents have included lithium, T_3, buspirone, atypical antipsychotics, and dopamine antagonists. These strategies provide valuable options when response to initial monotherapy or antidepressant switches proves unsatisfactory.

7. Discussion

Considerably more research is warranted to improve the definition, diagnosis, and treatment of severe depression. Complicating this issue is the presence of specific depression subtypes (such as melancholic, atypical, or psychotic depression), each of which likely responds more favorably to different pharmacological interventions. Moreover, much of the existing treatment data comes from subgroup analyses and retrospective studies. These realities underscore the need for prospective randomized, controlled trials of severe depression in prospectively defined patient populations to better characterize disease subtypes and identify optimal treatment approaches. In addition to studies geared toward elucidating the heterogeneity of severe depression, randomized, controlled trials of combination and augmentation therapies would help reveal whether such strategies might offer advantages beyond their current role as alternatives to monotherapy.

Given the lack of a clear consensus on differences in efficacy between TCAs and SSRIs, the SSRIs' more favorable adverse effect profile still renders them the drug of first choice. Because the SSRIs differ as to their potency at differing monoamine transporters, it is likely that individual patients may respond preferentially to one SSRI compared to another. In addition, there is some evidence that TCAs and SNRIs may be more effective than SSRIs in hospitalized or melancholic patients. Combination antidepressant/psychotherapy (see Craighead and Nemeroff, 2005 for review) and combination antidepressant therapy as well as augmentation therapy should also be considered. For highly resistant individuals, ECT, VNS, and other novel non-pharmacologic therapies should be utilized.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al., 2003) is beginning to provide data (Rush et al., 2006; Trivedi et al., 2006) on strategies for addressing failed antidepressant intervention, although this trial includes only outpatients with non-psychotic depression. Alternate insight may be gleaned through review of treatment strategies for psychotic and non-psychotic MDD that were developed in connection with the Texas Medication Algorithm Project (Trivedi et al., 2004). These algorithms, which advocate as first-line approaches antidepressant monotherapy for non-psychotic MDD and combination pharmacotherapy

for psychotic MDD, hint at the complexity of treating severe depression.

Until there is a universal consensus on the definition of severe depression and how treatment success is defined, confusion will remain in guiding clinical practice.

Disclosure statement

Acknowledgments

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