1

Evidence-based pharmacotherapy of major depressive disorder

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Major depressive disorder (MDD) is estimated by the World Health Organization to be the fourth leading cause of loss of disability-adjusted life years. In the National Comorbidity Survey, MDD is the most common mental illness and is one of the most common and disabling of all illnesses (Kessler *et al.*, 1994). The lifetime risk for MDD is 10–25% in women and 5–12% in men, and at any point its prevalence is 5–9% in women and 2–3% in men. Given the widespread and disabling nature of the illness, MDD is of great public health concern.

The first useful antidepressants, imipramine and isoniazid, were serendipitously found to have antidepressant properties in the 1950s. These discoveries – coupled with the observation that reserpine, which depletes monoamines, induced depression – led to the development of the monoamine hypothesis of depression. This led to the rational development of drugs which affect central nervous system monoamines, primarily norepinephrine (noradrenaline), serotonin (5-HT), and dopamine.

The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) formed the foundation for several decades of pharmacologic treatments for depression, although their side-effects (including lethality in overdose in the case of TCAs, and strict dietary restriction to avoid hypertensive crises in the case of MAOIs) limited their utility and tolerability. Pharmaceutical research focused on the development of drugs with improved tolerability and safety. Next-generation drugs such as trazodone, a 5-HT_2-receptor antagonist, were an incremental improvement, but not until the arrival to the market in 1988 of the first selective serotonin reuptake inhibitor (SSRI), fluoxetine (Prozac), did the use of antidepressants markedly change. Several other SSRIs followed, including paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro).

Antidepressants are not effective for all patients. In clinical practice, 40–50% of episodes do not completely respond to initial antidepressant drug therapy. Response to antidepressant medication is also delayed, with weeks to months until remission for those who do respond. Many patients are only partially responsive to treatment, and residual symptoms are responsible for significant morbidity and loss of function. A further generation of antidepressants was developed with effects on multiple neurotransmitter systems in the hope that drugs with effects on multiple neurotransmitter sites would be effective for a higher percentage of patients or have a more rapid onset of response. These so-called dual-action and triple-action antidepressants include venlafaxine (Effexor), nefazodone (Serzone), mirtazapine (Remeron), duloxetine, and bupropion (Wellbutrin). Reversible monoamine oxidase inhibitors (RIMAs) such as moclobemide and brofaromine were also developed, and may have an improved safety profile compared to earlier-generation non-reversible MAOIs. Conflicting data exist regarding the success of these latest-generation drugs in improving depression treatment beyond existing drugs.

For the purposes of this chapter, we searched MEDLINE and PsychLit for all controlled trials published in English between January 1981 and January 2004 in which adults with MDD were randomly assigned to receive medication, placebo, or active comparator drugs, and all meta-analyses of psychopharmacotherapy for MDD. The number of published randomized controlled trials (RCTs) of antidepressants for the acute treatment of MDD is too vast to allow for discussion of each study individually.

In order to recommend first-line treatment for MDD, we examined meta-analyses of RCTs of antidepressant drugs for MDD as a statistical means of weighing the relative efficacy of antidepressants that have not been compared directly. This was done both to evaluate the acute effectiveness of multiple antidepressant agents in MDD and to determine what recommendations are to be made for continuation and maintenance treatment of MDD with antidepressants. Meta-analysis increases the power to show a difference between treatment groups, in effect by increasing the sample size. This can reduce type II error; that is, the failure to find a difference when one actually exists. Because placebo response rates in antidepressant trials tend to be very high – thus causing many positive trials of active drugs to have small effect sizes – meta-analysis of multiple trials may be used to determine whether drug–placebo differences are meaningful.

The literature on evidence-based treatment for first-line antidepressant treatment failures is, to this date, quite limited. Few randomized, parallel-group trials of such treatments have been published; limited evidence from open trials will be reviewed.

What is the first-line pharmacotherapy of MDD?

All marketed antidepressants are effective in the treatment of depression. In determining which of these antidepressants can be recommended as first-line treatment for major depression, however, several factors are important. Does an antidepressant have demonstrable response and remission rates? Is the time to remission and recovery more rapid for a given antidepressant or class of antidepressant? Does superiority in terms of adverse events lead fewer patients to discontinue their medications, and thus lead to a greater percentage of responders at endpoint? To what extent should the safety of a drug – in overdose or due to side-effects – have an impact on prescribing? Do drugs differ in the response rates for different subtypes of depression (e.g., melancholic or psychotic) or in patients with comorbid conditions (e.g., anxiety disorders, substance abuse), or who differ in sex or age?

Randomized controlled efficacy trials generally use a straightforward, simple design to answer a basic question. As these studies tend to exclude patients with significant medical or psychiatric comorbidity, however, they offer only incomplete information about a drug's effectiveness in an unselected clinical population. Many studies exclude patients with active or recent substance abuse, even though the rate of comorbid substance abuse in mood disorders is substantial, thus limiting how generalizable the results are to actual clinical practice.

An essential task in recommending first-line treatment is to determine whether an individual antidepressant or class of antidepressant has superior efficacy compared to others. Meta-analyses of multiple antidepressant trials can improve the ability to distinguish between the relative equivalences of different antidepressants or classes of antidepressants. The methodology of the meta-analysis is important in interpreting the results, as the results can only be as good as the criteria for deciding which studies are analyzed. Only double-blind, parallel-group studies ought to be included. All available studies that meet criteria for data quality must be included, and not merely those with favorable results. Dosages of the medications in an individual study, for example, must be adequate (and comparable, in a comparator trial) or the results will not be interpretable.

SSRIs in MDD

The most widely prescribed antidepressants are the SSRIs. Most, though certainly not all, SSRI trials have shown superiority of active drug over placebo in the treatment of MDD. These studies generally fail to demonstrate a clear dose–response curve, suggesting that increasing SSRI dose beyond what is minimally effective does not increase response (although in some cases dropout rates are greater with

higher dosages), although a meta-analysis of fixed- versus variable-dose trials of SSRIs found a 7–10% increased response rate for increased dosages (Baker *et al.*, 2003). It also appears that higher doses of SSRIs may have higher effect sizes, suggesting again that some dose–response relationship does exist for SSRIs (Khan *et al.*, 2003).

A Cochrane Collaboration meta-analysis identified 98 trials comparing SSRIs to other antidepressants, with a total of 5044 SSRI-treated patients, and failed to detect any clinically significant difference in efficacy between drugs (Geddes *et al.*, 2003). SSRIs also demonstrate efficacy for depression, without clear evidence of superiority over older drugs when studied in particular patient subgroups. A smaller meta-analysis including 365 SSRI-treated geriatric depressed patients found SSRIs and TCAs to be equally efficacious (Wilson *et al.*, 2003). Similarly, a meta-analysis which included 18 antidepressant studies, including six with SSRIs, in medically ill patients noted efficacy for multiple classes, but did not find one to be superior (Gill and Hatcher, 1999, 2003).

A well-designed meta-analysis funded by Eli Lilly compared fluoxetine to TCAs. Thirty trials (16 USA and 14 non-USA) and 4120 patients (3447 USA and 673 non-USA) were included in the study. The criteria for study inclusion in the analysis included adequate TCA and fluoxetine dosing, double-blind design, and the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). Analyses were performed separately for studies conducted in the USA versus elsewhere. The effect size (−0.30) for fluoxetine compared to placebo was small for the main outcome measure, 50% decrease in HAM-D. There was not a statistically significant difference favoring fluoxetine versus TCAs overall. The European trials, comparing fluoxetine to newer TCAs, showed a non-significant trend in favor of the TCAs, while the US trials, comparing fluoxetine to older TCAs, showed a non-significant trend in favor of fluoxetine.

One recent study attempted to assess the effectiveness, rather than the efficacy, of SSRIs in clinical practice. The ARTIST trial showed a non-significant trend in favor of the randomized 573 depressed patients in a primary care practice to open-label treatment with one of three SSRIs (paroxetine, fluoxetine, and sertraline). Over the 9-month trial, patients in all three groups improved, but the three groups did not differ statistically in degree of improvement. This supports the findings of a Cochrane Collaboration meta-analysis of individual trials of SSRIs (Geddes *et al.*, 2002).

One area where SSRIs may demonstrate benefit over older medications is in tolerability. A Cochrane Collaboration review that identified 136 randomized trials in which SSRIs and tricyclic antidepressants were compared among depressed patients found a modest but significant difference favoring SSRIs in terms of dropouts (Barbui *et al.*, 2003). Accordingly, the SSRIs have advantages in terms of safety and

tolerability compared to many newer and older agents, and their place as a primary treatment choice for major depression is not disputed.

Dual- and triple-action agents and RIMAs in MDD

The most recent generation of antidepressants (which includes bupropion, mirtazapine, and venlafaxine) has proved effective for major depression in both outpatient and inpatient settings in placebo-controlled and comparator trials. Whether these newer-generation dual-action agents improve response compared to SSRIs is unclear, although there are some interesting data suggesting that this might be the case.

An early meta-analysis of double-blind, placebo-controlled trials of imipramine, bupropion, trazodone, and fluoxetine published between 1980 and 1990 found no difference in effect size for any of the antidepressants, suggesting equivalence between these antidepressants (Workman and Short, 1993). Although the criteria for study interpretability, however, did not include minimum dosages, the results are consistent with other analyses.

A meta-analysis funded by Wyeth, the manufacturer of venlafaxine, pooled eight trials of venlafaxine compared to SSRIs or SSRIs and placebo. After treatment with venlafaxine ($n = 851$), SSRIs (fluoxetine, paroxetine, fluvoxamine; $n = 748$) or placebo (four studies; $n = 446$), the study found remission rates (defined as HAM-D17 < 7) of 45% (382/851) for venlafaxine, 35% (260/748) for SSRIs, and 25% (110/446) for placebo ($P < 0.001$). The odds ratio for remission was 1.50 (1.3–1.9), favoring venlafaxine versus SSRIs (Thase *et al.*, 2001). Venlafaxine separated from placebo at week 2, while this only occurred at week 4 for SSRIs.

The study has several important limitations. First, previous non-responders to SSRIs were not excluded from any of the studies; as previous non-response to an SSRI would likely have predicted non-response to the study SSRI, this would have been an important exclusion criterion. Second, the difference in response was only true for venlafaxine doses greater than 150 mg/day; at 75 mg/day there was no difference in remission rates with venlafaxine compared to SSRIs. Third, two studies were 6 weeks in duration and the remainder 8 weeks. Whether the ultimate response rates over a longer period would have been more similar cannot be known.

Overall, no clear benefit for dual- and triple-action agents or RIMAs can be found in larger meta-analyses (Freemantle *et al.*, 2000). A meta-analysis using a modified intent-to-treat design compared older, newer, and alternative treatments for multiple depressive disorders (including major depression), and found equivalent benefit for older and newer antidepressants (Williams *et al.*, 2000). For MDD, there was equivalent effectiveness between the newer agents (SSRIs, serotonin norepinephrine reuptake inhibitors, RIMA, norepinephrine reuptake inhibitors,

5-HT_2-receptor antagonists, and dopamine reuptake inhibitors) and older agents (first-generation TCAs, tetracyclic antidepressants, second-generation TCAs, trazodone, and non-reversible MAOIs). Fifty-four percent of the patients randomly assigned to receive a newer antidepressant and 54% of those assigned to receive an older antidepressant experienced at least a 50% improvement in depressive symptoms (relative benefit, 1.0: confidence interval (CI) 0.97–1.06). The authors found an overall dropout rate of 30% across these studies, suggesting that actual clinical care must address the tendency of patients to stop their antidepressants. They rightfully point out that large "effectiveness" trials in actual clinical practice will be necessary to determine whether there are meaningful differences between drugs.

There have been several notable attempts to examine effectiveness in clinical practice. The Texas Medication Algorithm Project (TMAP) compared the use of expert consensus guidelines for the treatment of multiple psychiatric disorders, including MDD (Crismon *et al.*, 1999). There were several methodological problems in the design of the studies. Most significantly, there was no randomization to treatment. Instead different sites (primarily outpatient treatment centers) implemented the guideline algorithms with treatment-as-usual at control sites. The study is also limited in that it was implemented in a public sector, primarily indigent population; this aspect of the design may underestimate the effectiveness of all treatments.

A large National Institute of Mental Health (NIMH)-funded effectiveness study, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, will attempt to clarify what differences there are between treatments in clinical practice. STAR*D will enroll up to 4000 depressed outpatients in open treatment with citalopram; those who fail to respond will then be randomized to various "next-step" interventions. STAR*D will provide data which will examine SSRI and second-line treatment efficacy in MDD, and attempt to fill gaps in information guiding current treatment (Fava *et al.*, 2003).

Depressive subtypes, comorbidity, and demographics

It has been suggested that certain antidepressants are more effective than others in different subpopulations of patients. If this is indeed the case, then recommendations for first-line treatment should bear this in mind. We examined the published data regarding the differential effects of different antidepressants on medical comorbidity, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) axis I and II comorbidity (including anxiety disorders), subtypes of depression (e.g., atypical, melancholic), and demographics such as sex and age. There have been no robust predictors of response in MDD; studies that suggest that one treatment

may be preferable to another for given populations of patients are too small and underpowered to dictate treatment recommendations.

Medical comorbidity

Significant medical comorbidity often excludes patients from participating in randomized trials of antidepressants for MDD. When the medical risk of the drugs themselves was considered high, as it was with TCAs, general recommendations were to avoid using antidepressants in the medically ill (Koenig *et al.*, 1989). Newer drugs are expected to be safer for use in this population; analysis of randomized trials suggests benefit for all antidepressants for the treatment of MDD in this subgroup of patients (Gill and Hatcher, 2003).

A retrospective review of TCA treatment of medically ill patients with TCAs by a psychiatric consultation service found poor tolerability of the drug (30% dropouts due to side-effects) and limited response (40% responded) (Popkin *et al.*, 1985). Even though this was only a retrospective chart review, the study reinforced the impression that TCAs were not useful in medically ill patients.

A Cochrane Collaboration meta-analysis of the antidepressant treatment of medically ill patients, however, comes to a different conclusion (Gill and Hatcher, 2003). The study examined 18 RCTs of antidepressants in medically ill subjects (six of SSRIs, three of atypical antidepressants, and nine of tricyclics). There was substantial benefit to antidepressant treatment, with 52% responding to antidepressant overall compared to 30% responding to placebo (13 studies, odds ratio (OR) 0.37, 95% CI 0.27–0.51). There was a small but statistically significant increase in dropout rates for drug compared to placebo for TCAs and SSRIs (OR 1.66, 95% CI 1.14–2.40); for one study of mianserin there were fewer dropouts in the treatment group. The authors noted that there was a small increased treatment effect of TCAs over SSRIs, but that TCAs had a somewhat increased dropout rate.

A limitation of the Cochrane meta-analysis is that none of the studies analyzed included patients without significant medical illness as a comparator group. A naturalistic study which included both medically ill and healthy patients examined the effects of axis III comorbidity in the treatment of treatment-resistant depression with nortriptyline, and concluded that medical illness did not have an impact on the effectiveness of the drug compared to subjects without medical illness (Papakostas *et al.*, 2003).

Although the data suggest that response to antidepressants may not be impeded by the presence of medical illness, drug safety and tolerability are still concerns in treating MDD in the medically ill. It is worth avoiding orthostatic hypotension in the frail elderly, for instance, and drugs with these prominent side-effects should be avoided. It is also the case that large-scale trials comparing antidepressants in the

medically ill population are lacking, so one antidepressant cannot be recommended over any other because of effectiveness.

Axis II comorbidity

A large study found that axis II personality disorder comorbidity had no effect on therapeutic outcome in the antidepressant treatment of acute MDD. A total of 635 patients with major depression and dysthymia were treated blindly with imipramine or sertraline (Russell *et al.*, 2003). The prevalence of axis II disorders was 46%; there was no clear impairment in the percentage of responders (>50% drop in HAM-D scores, HAM-D score <15, and Clinical Global Impression (CGI) improvement score of 1 or 2) or remitters (HAM-D score <7 and CGI improvement score of 1 or 2) compared to the subjects without any axis II disorder. There was a non-significant trend towards longer time to remission in the axis II group (10 versus 12 weeks, $P = 0.052$). Subjects with two or more axis II disorders did have a lower response rate, however (62% versus 47%, $P = 0.009$). A smaller study, comparing fluoxetine to nortriptyline, also found that having an axis II disorder did not predict worse outcome (Mulder *et al.*, 2003).

A meta-analysis of the impact of axis II personality disorders on outcome in major depression concluded that antidepressants are as effective in the presence of personality disorders as in their absence (Mulder, 2002). Antidepressant treatment should not be withheld because of the presence of an axis II personality disorder, at least for acute episodes of depression.

Anxiety disorder comorbidity

Comorbid anxiety disorders (but not anxiety symptoms) may predict poorer response to antidepressant treatment for MDD (Walker *et al.*, 2000). No study has prospectively studied the effectiveness of antidepressants with comorbid anxiety disorders in a randomized, double-blind trial. While many antidepressants have shown efficacy for major depression and anxiety disorders, there remains a gap in our knowledge about how to treat patients who present with both disorders. Even as logic would lead one to recommend the use of an antidepressant with efficacy for both disorders individually, there are not enough data to make this recommendation.

Major depressive subtypes

Limited and contradictory information is available to determine if one subtype of depression responds more robustly to one antidepressant versus another. For atypical depression, MAOIs appear in early studies to be more effective than TCAs (Liebowitz *et al.*, 1988). A total of 119 patients were randomized to phenelzine, imipramine, or placebo, with response rates of 71%, 50%, and 28% respectively

(Liebowitz *et al.*, 1988). In later studies SSRIs appear as effective as MAOIs (Pande *et al.*, 1996). In a more recent study, however, fluoxetine was not superior to imipramine in this subtype of depression (McGrath *et al.*, 2000). As MAOIs, TCAs, and SSRIs have not been directly compared (and are not likely to be compared) in an adequately powered trial, and no meta-analysis exists, one cannot with certainty recommend one antidepressant over another for major depression with atypical features.

Few data are available to determine whether one antidepressant or class is preferable to another for more severe and melancholic forms of depression. It is difficult to compare studies due to the lack of a standard definition of severe depression. Using inpatients as a subgroup, one large meta-analysis found TCAs to have a small amount of benefit over SSRIs (Geddes *et al.*, 2002). The authors caution, however, that this difference may be due to chance, and amounts to only 1 HAM-D point. Another meta-analysis found that, while depressed inpatients responded somewhat better to TCAs compared to SSRIs, SSRIs were moderately more tolerable (Anderson, 1998, 2000). This is significant, as the TCA with the highest likelihood of superior efficacy, amitriptyline, is one of the TCAs with the lowest tolerability due to adverse effects. While it is not certain whether one antidepressant is superior for more severe forms of depression, it has become clear that placebo–drug difference increases directly with increased severity (Khan *et al.*, 2002). The more severely ill the patients were who were included in trials, the more likely the drug would be found effective. Higher depression rating scale scores predicted a greater decrease in scores in the treatment group, while higher depression rating scale scores predicted smaller decreases in the placebo group.

Demographics: sex

A small, but statistically significant, increase in response was found to imipramine versus sertraline, an SSRI, for men compared to women in one study of MDD. The results suggest that SSRIs may be preferable to TCAs in premenopausal women (Kornstein *et al.*, 2000). This finding, however, has not been replicated. Wohlfarth *et al.* (2004) found no difference in response to TCAs by sex in a meta-analysis. Quitkin *et al.* (2003) published a meta-analysis of placebo-controlled trials of TCAs, MAOIs, and fluoxetine, and found no differential effect based on age or sex (Quitkin *et al.*, 2002). A small but statistically significant effect favoring MAOIs for women was found, but the authors could not conclude that this effect was clinically significant. Parker *et al.* (2003), in two naturalistic studies of antidepressant treatment of MDD (one retrospective, one prospective) did not find a meaningful difference in response to SSRI or TCA by sex, although there was a trend to better SSRI response in younger subjects and better TCA response in older ones (Parker *et al.*, 2003).

Age

Several studies had found that antidepressants are effective in the elderly (Feighner and Cohn, 1985; Cohn *et al.*, 1990; Bondareff *et al.*, 2000; Schneider *et al.*, 2003). There does not appear to be clear benefit to one versus another in older patients, in spite of the expectation that side-effects of TCAs would limit their usefulness in this group. A meta-analysis of randomized, double-blind studies of antidepressant treatment in the elderly confirms this (Wilson *et al.*, 2003). The authors concluded with caution that, while low-dose treatment with TCAs, ostensibly to reduce the incidence of adverse events in this population, was more effective than placebo in the elderly. They could not, however, recommend this as a treatment strategy as it had not itself been studied prospectively.

How long should pharmacotherapy of MDD continue?

The ideal length of time to continue antidepressant treatment after the resolution of an acute episode has not been definitively determined. In practice this is generally dependent on whether the acute episode is recurrent and – since the older the patient, the more likely that the episode is recurrent – on the age of the patient (American Psychiatric Association, 2000). It is also important to note whether the episode has resolved completely, or whether there are continued or residual symptoms of depression. Residual symptoms after treatment of an episode may predict recurrence (Judd *et al.*, 1998).

Most antidepressants have been studied in continuation after a depressive episode has resolved, and all appear – at least over 4–12 months – better at preventing relapse than placebo (Weihs *et al.*, 2002). Responders to drug are randomized to continue with active drug versus placebo for months to years, and a survival analysis – usually time to relapse or time to given score on a depression rating scale – is performed. Several patterns have emerged which may guide treatment decisions. From these data emerges the recommendation that antidepressants be continued at least 4–6 months after the resolution of an acute episode (American Psychiatric Association, 2000).

It may be the case that antidepressant treatment should be more prolonged. Major depression tends to be a recurrent illness, and the most robust predictor of relapse is having had a previous episode (Keller *et al.*, 1983; Roy-Byrne *et al.*, 1985; Coryell *et al.*, 1991; Maj *et al.*, 1992; Simpson *et al.*, 1997; Mueller *et al.*, 1999). Longitudinal, naturalistic follow-up data of patients who recover from an index episode of major depression found that 85% of subjects had a recurrence over the 15 years of the study, and that even in those who remained well for 5 years there was a 58% risk of relapse (Mueller *et al.*, 1999). The authors suggest that, while there were several predictors of who had a greater likelihood of relapse (female sex,