Pharmacologic Management of Difficult-to-Treat Depression in Clinical Practice

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Objective: **This article reviews the concept of difficult-to-treat depression and outlines some principles of pharmacologic management.** ***Methods:*** **The authors conducted a MEDLINE review for the years 1999 to 2004, using the key words refractory, resistant, and difficult-to-treat depression.** ***Results:*** **Only a small body of evidence-based literature exists to guide the management of difficult-to-treat depression. Nevertheless, clinicians often need to make treatment decisions in the absence of clear data. Depression should not be considered resistant, refractory, or difficult to treat in the absence of trials in which an appropriate drug is given in a dosage and duration sufficient to produce a response. Nevertheless, inadequate antidepressant trials are a relatively common phenomenon. Nonresponse may also result from pharmacokinetic or pharmacogenomic factors. Principals for assessing difficult-to-treat depression include preventing pseudo-resistant cases, recognizing that finding the best treatment option is a process, developing a systematic step-by-step approach, and preserving hope. A review of the literature demonstrated a two-step approach for managing difficult-to-treat depression. The first step is to evaluate for factors that contribute to nonresponse, such as comorbid medical and psychiatric conditions. The second step involves using the four classical strategies for enhancing antidepressant efficacy: optimization, augmentation, combination, and switching.** ***Conclusion:*** **Advances have been made in the treatment of depression, but a great deal more research needs to be done. It is hoped that new alternatives and promising developments in methods will contribute to the improved management of what we now call difficult-to-treat depression.** (***Psychiatric Services*** **56:1005–1011, 2005)**

The introduction of new antidepressants and specific psychotherapies has enhanced the treatment and reduced the suffering and burden associated with depression. Approximately 50 to 70 percent of patients with major depression respond partially to currently used antidepressants within eight weeks (1), and up to 80 percent respond after two years (2,3).

Response with partial remission is an important achievement, but it should not be the final goal of antidepressant treatment or of any medical treatment. It is remarkable that only about half the persons who respond to an antidepressant achieve complete remission (4). Moreover, 30 to 50 percent of patients who receive antidepressants do not respond within eight weeks, and 20 percent remain persistently depressed beyond two years.

Two groups of patients with depression present a particular challenge: patients who do not respond to at least one antidepressant trial and those who respond but have residual symptoms. Traditionally, depressive disorders that did not respond to several antidepressant trials were called resistant, refractory, or, more recently (and perhaps more appropriately from a clinician's perspective), difficult-to-treat depression (4). In traditional scientific literature, response without remission was not included as resistant or refractory depression (5). However, from the perspective of patients, failure to achieve remission is not a satisfactory outcome, because persistent depressive symptoms are associated with poor functioning, low quality of life, and increased risk of relapse (6–8).

This article reports the results of a review of recent literature on difficult-to-treat depression.

Methods

To review the concept of difficult-to-treat depression and to outline some principles of pharmacologic management, we conducted a MEDLINE review using the key words refractory, resistant, and difficult-to-treat depression and covering the years 1999 to 2004. Randomized clinical trials and review papers were selected.

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Results

Definitions

An adequate antidepressant trial is defined as a trial in which an appropriate drug is given in a dosage and duration sufficient to produce a response (9). Nowadays, four to six weeks is considered an adequate trial period to see clinical response, although recent research suggests that longer periods of up to eight or 12 weeks may be needed to achieve remission. An adequate dosage is a more relative concept. Clinically, it is defined as the minimum dosage that would produce the expected effect or the maximum dosage that a patient can tolerate until the expected effect is achieved. Higher dosages of antidepressants, within the therapeutic range, generally increase the likelihood of response (9).

We would not consider depression resistant, refractory, or difficult to treat in the absence of adequate trials, as defined above. Nevertheless, inadequate antidepressant trials are a relatively common phenomenon. Thirty to 60 percent of patients referred for an evaluation of treatment resistance probably have received inadequate trials with antidepressants (10,11).The term "pseudo-resistance" has been used to describe nonresponse to treatment that is inadequate in dosage and duration (12). Clinicians do not titrate up to the higher ranges of antidepressant dosages for various reasons—for example, adverse effects, fears of overdose or other toxicity, lack of confidence in higher dosages, and therapeutic nihilism—which may lead to nonresponse.

Nonresponse may also result from pharmacokinetic or pharmacogenomic factors. Some patients are known to be rapid metabolizers, a genetic characteristic that requires the use of higher than usual antidepressant dosages to achieve therapeutic plasma levels of the drug (13).

There is no consensus in the literature about the definition of treatment resistance or refractoriness. In a review of ten years of literature, Souery and colleagues (14) found more than 15 separate definitions. One can approach these concepts from a categorical or a dimensional perspective. The categorical approach is based on the use of cutoff points. For example, Souery and colleagues (15) proposed that depression should be considered resistant when two adequate trials of different antidepressants have failed, and Nierenberg and colleagues (16) suggested a higher threshold that consisted of nonresponse to three or more adequate trials, one of which must have been a tricyclic.

The dimensional perspective places a greater emphasis on levels of resistance and specifying the treatments to which the depression does not respond, rather than viewing resistance as an intransitive phenomenon. Thase and Rush (17) proposed five stages of treatment resistance on the basis of adequate clinical trials of specified antidepressants. Stage 1 requires the use of an antidepressant from one major class. Stage 2 involves a trial with an antidepressant from a class that is distinct from that used in stage 1. Stage 3 entails a tricyclic antidepressant trial. Stage 4 calls for a monoamine oxidase inhibitor (MAOI) trial. Stage 5 suggests a course of bilateral electroconvulsive therapy (ECT). The staging model assumes that higher stages of resistance are more difficult to treat, but its predictive value with respect to treatment outcome has not been systematically validated (5).

The concepts of resistant and refractory depression sometimes are confused with chronic depression, a term that should be used when the duration of illness (generally two years or longer) rather than treatment response is the key issue. A depression that is resistant to treatment may be chronic, but a chronic depression is not necessarily resistant to treatment—for example, it may be that no treatment was attempted. A resistant depression also may remit spontaneously, further differentiating the concepts of treatment resistance and chronicity.

According to Rush and colleagues (18), difficult-to-treat depression "includes depression that inherently does not respond satisfactorily to one or more treatments that are optimally delivered (treatment-resistant depression) and also depression treated under circumstances precluding the optimal delivery of potentially effective treatments. Such circumstances include the use of subtherapeutic doses, nonadherence, intolerable side effects that prevent an adequate dose or duration of treatment, and concurrent axis I, II, or III conditions that reduce the likelihood of remission for adherence, pharmacokinetic, or pharmacodynamic reasons."

Assessment principles

Preventing pseudo-resistant cases. A heretofore untreated depression could become difficult to treat in the near future. For this reason it is very important that the clinician approach new cases as potential difficult-to-treat depressions. Each antidepressant trial should be introduced systematically, with close attention to attaining an adequate dosage and duration of treatment and to maintaining adherence. Transitory initial side effects should be managed carefully, so as not to cause nonadherence or become obstacles to achieving an adequate dosage and duration of a medication trial.

The process of finding the best treatment option. Many times the patient arrives with the idea that the doctor will provide "the" right drug. In fact, on the basis of randomized clinical trials, most antidepressants within a class are equivalent in efficacy for groups of patients. The challenge is that one cannot predict treatment response or adverse reactions for the individual patient. Therefore, finding the best treatment option for a specific case is a process in which each step provides information for the next trial.

Developing a systematic step-by-step approach. Although the literature provides insufficient evidence to clearly guide a pharmacologic strategy, one can develop a rationale for steps in the choice of medications. The class of medication, side-effect profile, history of individual or family treatment response, and type of depression may serve as guides for developing a systematic pharmacologic treatment approach.

Preserving hope. Therapeutic optimism is invaluable for a successful treatment outcome. Fortunately, each year we have new treatments for

depression, and the future promises even more effective options. Advances in molecular biology and genetics may create new treatment approaches in the near future. We have good reasons to inspire hope for desperate and hopeless patients and their families.

Managing difficult-to-treat depression

Evaluating factors that contribute to nonresponse. We recommend a two-step approach for managing difficult-to-treat depression. The first step is to evaluate for factors that contribute to nonresponse, such as comorbid medical and psychiatric conditions (19). Endocrinopathies (especially thyroid disease and Cushing syndrome), infectious diseases (postviral syndromes, HIV, and tuberculosis), neoplasia (pancreatic cancer), and neurologic diseases (cerebrovascular accident and Parkinson's disease) are among the causes of depression that could contribute to unsatisfactory antidepressant response. Drugs used to treat medical conditions also may cause iatrogenic depression (corticosteroids, efavirenz, and interferon alpha).

A number of studies show that comorbid psychiatric conditions are associated with poor response to antidepressant treatment (20,21). Comorbid panic disorder (21) or obsessive-compulsive disorder (22), substance abuse (23,24), and personality disorder (25) are among the conditions associated with poor outcome of treatment for depression.

Enhancing antidepressant efficacy. The second step involves using the four classical strategies for enhancing antidepressant efficacy: optimization, augmentation, combination, and switching.

Optimization of both the dosage and the duration of an antidepressant trial is essential to achieve treatment response. However, finding the best antidepressant dosage for an individual patient is not always straightforward, because there is wide interindividual variation in pharmacokinetics and pharmacodynamics. A clear relationship between the dosage and the response has not been well established for most antidepressants. Therapeutic blood concentrations are well defined and serve as a guide to appropriate dosing for nortriptyline, imipramine, and desipramine but not for other antidepressants. In the absence of therapeutic blood concentrations, it is difficult for clinicians to know when nonresponse to an antidepressant is due to pharmacokinetic factors, such as rapid metabolism, which may require using a dosage above the upper limits of the recommended therapeutic range. For tricyclic antidepressants, it is not unusual to administer a dosage in the high end of the therapeutic range but find plasma concentrations that are barely therapeutic (26). For drugs without therapeutic blood concentrations, a sign that of rapid metabolism might be the use of a high antidepressant dosage in the absence of any treatment response or side effect (5).

A number of studies show that having a comorbid psychiatric condition, such as panic disorder, substance abuse, or personality disorder, is associated with poor response to antidepressant treatment.

Optimizing duration of antidepressant treatment is also challenging. Although it is well known that some patients will respond only late in the course of an antidepressant trial (beyond four to six weeks), there is often pressure in a clinical setting to switch drugs rather than wait for a response when a treatment is not working. Frequent medication changes before completion of an adequate trial are common in antidepressant treatment.

Augmentation, the second strategy for enhancing efficacy, refers to the addition of another medication with the purpose of enhancing the effect of an antidepressant drug. This strategy is particularly attractive for patients with partial response, because it allows them to maintain the improvement already achieved and the opportunity to rapidly achieve additional positive effects (27). The most well-studied augmentation strategy is the addition of lithium to a tricyclic antidepressant. Adding lithium to a tricyclic is associated with a 50 to 60 percent response rate (28). Other common augmentation strategies are not well supported by studies but employ the addition of thyroid hormones (thyroxin [T4] or triiodothyronine [T3]), pindolol, or buspirone. T3 augmentation appears to exert greater effects than does T4 (28), whereas controlled studies with buspirone augmentation have reported mixed results (27) and pindolol has shown no benefits among patients resistant to antidepressants (29,30).

Combining two antidepressants is a frequently used strategy with only a small body of supporting literature, consisting mainly of open trials, small randomized trials, or crossover studies. The rationale for combining antidepressants is that two drugs with different mechanisms of action could have complementary, synergistic, or additive effects compared with each drug used alone. Although there are many possible combinations, we review only a few of the more commonly used strategies.

Open studies and anecdotal reports of the combination of a tricyclic and an MAOI are encouraging (31–33), although no controlled studies confirm these findings. Clinicians tend to avoid this combination because of the risk of a hypertensive crisis. Nevertheless, the combination is generally safe if low dosages of both drugs are started simultaneously or if a low dosage of an MAOI is added to an ongoing tricyclic trial (34,35).

Adding a selective serotonin reup-

take inhibitor (SSRI) to a noradrenergic tricyclic (36) or vice versa (37) is another combination. A prospective study that compared desipramine plus fluoxetine with either drug alone found that the combination was associated with significantly higher remission (27). Although this study did not specifically examine resistant patients, the patients who did not respond to a single drug (50 percent of the sample) showed the same trend of favorable response to the combination.

Bupropion plus SSRI is a popular combination, although supported only by uncontrolled studies. The rationale for this combination is the presumed complementary effect of the noradrenergic and dopaminergic stimulation by bupropion added to the serotoninergic stimulation by the SSRI. The presence of residual symptoms of anergy after an adequate trial of an SSRI is thought to predict a response to this strategy (38).

Use of an alpha-2 antagonist plus an SSRI is another approach. Controlled studies of yohimbine (39), mianserin (40), and mirtazapine (41) have shown beneficial effects from the addition of an alpha-2 antagonist to an SSRI among patients who have depression and do not respond to SSRI monotherapy.

Antipsychotics are sometimes added to antidepressants. Antipsychotics have been combined with tricyclics since the mid-1970s, when investigators observed that patients with delusional depression responded poorly to tricyclic monotherapy (42) but had a 92 percent response rate to a combination of perphenazine with imipramine (43). More recently, Ostroff and Nelson (44) have suggested that risperidone might be useful as augmentation among patients who respond poorly to SSRIs. Shelton and colleagues (45) conducted a double-blind study of nonresponders to fluoxetine monotherapy and found greater improvement among those who received fluoxetine plus olanzapine. Papakosta and colleagues (46) conducted a study of 20 patients with major depressive disorder who did not respond to six weeks of an SSRI and found that ten responded, five of whom attained remission, after six weeks of augmentation with ziprasidone, with a considerable proportion of overall improvement occurring within one week of adding ziprasidone.

A psychostimulant may be combined with an antidepressant. Ayd and Zohar (47) identified five uncontrolled studies in which a stimulant was added to an antidepressant (mostly tricyclics) among persons who did not respond to monotherapy. The response rate was up to 78 percent when a stimulant was combined with an MAOI (48). Despite the absence of controlled studies, some experts acknowledged dramatic benefits with selected patients (49).

Switching is the fourth strategy for enhancing efficacy. A change from one antidepressant to another is usually based on the lack of a satisfactory response or the presence of significant side effects. In fact, there is no convincing evidence-based approach to guide such a switch. The choice of a second antidepressant usually is based on factors similar to those in the initial drug selection: side-effect profile, past antidepressant response, family history of antidepressant response, premorbid personality, and depressive subtype (34). The most commonly used initial antidepressants are SSRIs. Consequently, most studies report the switch from an SSRI to another antidepressant (27). We will review the most common switch strategies.

One strategy is to switch from an SSRI to a tricyclic. The rationale for this strategy is that switching from a selective serotoninergic antidepressant to a dual-action serotoninergic and noradrenergic antidepressant reaches a wider spectrum of neuroreceptors and may improve efficacy. This idea originated from the observation that tricyclics are more effective in severe depression than SSRIs (50–52). Peselow and colleagues (53) used a small sample with a crossover double-blind design and showed that 73 percent of 15 patients responded to imipramine after not responding to paroxetine. In a larger study with a similar design, 44 percent of 117 patients with chronic depression who did not respond to sertraline responded to imipramine (54). In an open trial of nortriptyline among 92 patients with depression who did not respond to monotherapy with various drugs (including SSRIs), Nierenberg and colleagues (55) showed that approximately 40 percent responded and the disease remitted in 12 percent of the patients after six weeks of receiving nortriptyline. One major limitation of switching from an SSRI to a tricyclic is the likelihood of increased side effects.

A switch from an SSRI to a serotonin norepinephrine reuptake inhibitors is another strategy. There is some evidence that patients who do not respond to an SSRI will respond to venlafaxine. Poirier and Boyer (56), in a double-blind randomized study, compared venlafaxine with paroxetine among 122 patients who did not respond to two previous antidepressant trials; two-thirds of those previous trials included an SSRI. The venlafaxine and paroxetine groups had, respectively, 52 and 33 percent response rates and 42 and 20 percent remission rates. In a multicenter open study, Kaplan (57) found that 58 percent of 152 patients who did not respond to at least one previous antidepressant (not specifically an SSRI) had at least 50 percent improvement when they were switched to venlafaxine.

Another strategy is to switch from an SSRI to bupropion. Although this strategy is commonly used, almost no literature supports it. Clinicians often try buproprion after an SSRI for patients who have depression and anergy and psychomotor retardation. This selection is based on the idea that combined noradrenergic and dopaminergic stimulation is effective for these symptoms (38). In a small open study of 18 participants, McGrath and colleagues (58) showed that 28 percent of those who did not respond to a 40 mg dosage of fluoxetine showed a 50 percent improvement in response to bupropion.

Some patients are switched from one SSRI to another. When switching antidepressants, the usual clinical recommendation is to switch to another class of antidepressants. There are some studies that have examined a switch from one SSRI to another, but most of these studies are open label and include a mix of patients with

either nonresponse or intolerance (59–61). However, in these studies it is not clear whether the response is caused by the second SSRI or other factors. Between 42 and 63 percent of patients respond after switching to another SSRI. Joffe and colleagues (62) published the only report in which the study investigated only patients who were resistant to previous SSRI treatment. In this open study 51 percent of 55 patients who were resistant to a first SSRI trial had a marked or complete response after five weeks of receiving a second SSRI.

Another strategy is to switch from SSRI to mirtazapine. In a randomized clinical trial, Thase and colleagues (63) showed that mirtazapine was not superior to an SSRI among patients who did not respond to an eight-week SSRI trial. In an open-label study, Fava and colleagues (64) found that 48 percent of 69 patients who were resistant to various SSRIs responded to mirtazapine.

A switch to an MAOI is another strategy. Several case reports and open studies as well as one double-blind study indicated that MAOIs are effective in about 50 percent of patients who are resistant to tricyclics (65). No studies used an MAOI among patients who were resistant to SSRIs. Although the risk of a hypertensive crisis limits the use of MAOIs, this class of drug remains an important tool for treating resistant depression.

Another strategy is switching to ECT. Studies from the 1960s and 1970s support the idea that ECT is effective for approximately 40 percent of patients who did not previously respond to adequate courses of tricyclics and MAOIs (66,67). More recent clinical experience and the preliminary results of the studies by the Consortium for Research in ECT suggest that the benefits of ECT are superior to those of drug switching or augmentation algorithms (68–70). An important meta-analytic study showed that ECT is more effective than drug therapy (71). In a short-term study, Folkerts and colleagues (72) found that ECT was markedly superior to paroxetine among patients with resistant depression.

Discussion and conclusions

Difficult-to-treat depression is a common clinical challenge and often requires making treatment decisions that are based on little systematic evidence. The literature is sparse and based mainly on open trials and case reports, with few double-blind randomized trials. There are several reasons for a dearth of evidence to support clinical decisions in the management of treatment-resistant depression. First, clinical practice poses multiple treatment scenarios that cannot be covered by specific research trials. Quite often patients have had multiple drug trials at inadequate dosages or of insufficient duration. They may not remember which antidepressants they have already taken. This diversity of clinical situations makes it difficult to know whether the results of a randomized, double-blind clinical trial are applicable to an individual patient, with his or her own unique biography, life events, and treatment history. Second, many antidepressant studies are funded by pharmaceutical companies that may not be entirely neutral in interpreting results and may not publish clinical trials that are unfavorable to their own product. Third, individual patients sometimes respond to a specific dosage or a drug combination that defies the available evidence base. Such a unique treatment response is simply not accounted for in large clinical trials that test for group rather than individual responses.

Nevertheless, much has been done in recent years for patients who have difficult-to-treat depression. Novel nonpharmacologic approaches—such as vagus nerve stimulation, repetitive transcranial magnetic stimulation, and magnetic seizure therapy (73)—are being developed, although they require further study before being incorporated into clinical practice. A prospective multisite study, sponsored by the National Institute of Mental Health and known as Sequenced Treatment Alternatives for Relief of Depression (STAR*D), is investigating sequential randomized controlled trials of antidepressants among outpatients with nonpsychotic major depression. With its original methodologic design, this very large and ambitious project promises to provide a more systematic evidence base for a sequence of next best-treatment steps in depression (74).

Another promising area of investigation is the pharmacogenetics of antidepressant drugs. Pharmacogenetic studies may address either pharmacokinetic or pharmacodynamic effects. Genetic variants of the cytochrome P450 enzymes affect the metabolism of antidepressants and may cause clinically relevant variations in plasma drug concentration or half-life. Studies have looked at allelic variants of the genes that encode for CYP2D6 and CYP3A4, liver enzymes involved with the metabolism of many psychotropics, including antidepressants (75). Only a few studies have been performed in clinical settings, and they have tended to focus on polymorphisms of the CYP2D6 gene or inhibitors of the CYP2D6 enzyme, factors that affect the metabolism of tricyclic antidepressants and may contribute to toxic or subtherapeutic plasma concentrations (76–80). However, future research may lead to the identification of pharmacogenetic factors that help to tailor antidepressant therapy to the individual patient and lead to better treatment response or tolerability.

A number of studies have reported on pharmacogenetic markers that affect antidepressant pharmacodynamics. For the most part, these studies have hypothesized the effects on antidepressant efficacy caused by functional variation in neurotransmitter receptors and transporter proteins, such as the serotonin transporter gene (75). It has been suggested that future studies may profitably target the autonomic nervous system and end-organs as predictors of antidepressant side effects and treatment nonadherence (81).

Hopefully, these and other more technical avenues of study, which are outside the scope of this review, will bring new answers for old questions, benefit many patients, and narrow the space occupied by difficult-to-treat depression. ♦

Acknowledgment

The authors thank Steven Roose, M.D., for his advice and contributions.

References

1. O'Reardon J, Amsterdam J: Overview of treatment-resistant depression and its management, in Treatment-Resistant Mood Disorders. Edited by Amsterdam J, Hornig M, Nierenberg A. Cambridge, UK, Cambridge University Press, 2001
2. Keller MB, Shapiro RW, Lavori PW, et al: Recovery in major depressive disorder: analysis with the life table and regression models. Archives of General Psychiatry 39:905–910, 1982
3. Paykel E: Epidemiology of refractory depression, in Refractory Depression: Current Strategies and Future Directions. Edited by Nolen W, Zohar J, Roose S, et al. New York, John Wiley and Sons, 1994
4. Kupfer DJ, Charney DS: Difficult-to-treat depression. Biological Psychiatry 53:633–634, 2003
5. Fava M: Diagnosis and definition of treatment-resistant depression. Biological Psychiatry 53:649–659, 2003
6. Lewis L, Hoofnagle L: Treatment-resistant depression: the patient perspective. Biological Psychiatry 53:635–639, 2003
7. Judd LL, Akiskal HS, Maser JD, et al: Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. Journal of Affective Disorders 50:97–108, 1998
8. Van Londen L, Molenaar RP, Goekoop JG, et al: Three- to 5-year prospective follow-up of outcome in major depression. Psychological Medicine 28:731–735, 1998
9. Thase ME: New approaches to managing difficult-to-treat depressions. Journal of Clinical Psychiatry 64(suppl 1):3–4, 2003
10. Keller MB, Klerman GL, Lavori PW, et al: Treatment received by depressed patients. JAMA 248:1848–1855, 1982
11. Scott J, Eccleston D, Boys R: Can we predict the persistence of depression? British Journal of Psychiatry 161:633–637, 1992
12. Nierenberg AA, Amsterdam JD: Treatment-resistant depression: definition and treatment approaches. Journal of Clinical Psychiatry 51:39–47, 1990
13. Vormfelde SV, Bitsch A, Meineke I, et al: Non-response to maprotiline caused by ultra-rapid metabolism that is different from CYP2D6? European Journal of Clinical Pharmacology 52:387–390, 1997
14. Souery D, Lipp O, Massat I, et al: The characterization and definitions of treatment-resistant mood disorders, in Treatment-Resistant Mood Disorders. Edited by Amsterdam J, Hornig M, Nierenberg A. Cambridge, UK, Cambridge University Press, 2001
15. Souery D, Amsterdam J, de Montigny C, et al: Treatment resistant depression: methodological overview and operational criteria. European Neuropsychopharmacology 9: 83–91, 1999
16. Nierenberg AA, Feighner JP, Rudolph R, et al: Venlafaxine for treatment-resistant unipolar depression. Journal of Clinical Psychopharmacology 14:419–423, 1994
17. Thase ME, Rush AJ: When at first you don't succeed: sequential strategies for antidepressant nonresponders. Journal of Clinical Psychiatry 58(suppl 13):23–29, 1997
18. Rush AJ, Thase ME, Dube S: Research issues in the study of difficult-to-treat depression. Biological Psychiatry 53:743–753, 2003
19. Hall RC, Gardner ER, Popkin MK, et al: Unrecognized physical illness prompting psychiatric admission: a prospective study. American Journal of Psychiatry 138:629–635, 1981
20. Coryell W, Endicott J, Andreasen NC, et al: Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. American Journal of Psychiatry 145:293–300, 1988
21. Fawcett J, Kravitz HM: Anxiety syndromes and their relationship to depressive illness. Journal of Clinical Psychiatry 44:8–11, 1983
22. Hollander E, Mullen L, DeCaria CM, et al: Obsessive compulsive disorder, depression, and fluoxetine. Journal of Clinical Psychiatry 52:418–422, 1991
23. MacEwan GW, Remick RA: Treatment resistant depression: a clinical perspective. Canadian Journal of Psychiatry 33:788–792, 1988
24. Worthington J, Fava M, Agustin C, et al: Consumption of alcohol, nicotine, and caffeine among depressed outpatients: relationship with response to treatment. Psychosomatics 37:518–522, 1996
25. Pfohl B, Stangl D, Zimmerman M: The implications of DSM-III personality disorders for patients with major depression. Journal of Affective Disorders 7:309–318, 1984
26. Amsterdam JD, Brunswick DJ, Mendels J: Reliability of commercially available tricyclic antidepressant levels. Journal of Clinical Psychiatry 41:206–207, 1980
27. Nelson JC: Managing treatment-resistant major depression. Journal of Clinical Psychiatry 64(suppl 1):5–12, 2003
28. Joffe RT, Singer W: A comparison of triiodothyronine and thyroxine in the potentiation of antidepressants. Psychiatry Research 32:241–252, 1990
29. Moreno FA, Gelenberg AJ, Bachar K, et al: Pindolol augmentation of treatment-resistant depressed patients. Journal of Clinical Psychiatry 58:437–439, 1997
30. Perez V, Soler J, Puigdemont D, et al: A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Archives of General Psychiatry 56:375–379, 1999
31. Pandy AC, Calarco MN, Grunhaus LJ: Combined monoamine oxidase inhibitor TCA treatment in refractory depression, in Refractory Depression. Edited by Amsterdam J. New York, Raven Press, 1991
32. Razani J, White KL, White J, et al: The safety and efficacy of combined amitriptyline and tranylcypromine antidepressant treatment: a controlled trial. Archives of General Psychiatry 40:657–661, 1983
33. White K, Simpson G: Combined MAOI-tricyclic antidepressant treatment: a reevaluation. Journal of Clinical Psychopharmacology 1:264–282, 1981
34. Charney D, Berman R, Miller H: Treatment of depression, in Textbook of Psychopharmacology, 2nd ed. Edited by Schatzberg A, Nemeroff C. Washington, DC, American Psychiatric Press, 1999
35. Bakish D, Hooper C: Conventional and second generation monoamine oxidase inhibitors in treatment-resistant depression, in Treatment-Resistant Mood Disorders. Edited by Amsterdam J, Hornig M, Nierenberg A. Cambridge, UK, Cambridge University Press, 2001
36. Weilburg JB, Rosenbaum JF, Biederman J, et al: Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. Journal of Clinical Psychiatry 50:447–449, 1989
37. Seth R, Jennings AL, Bindman J, et al: Combination treatment with noradrenalin and serotonin reuptake inhibitors in resistant depression. British Journal of Psychiatry 161:562–565, 1992
38. Shelton RC, Tomarken AJ: Can recovery from depression be achieved? Psychiatric Services 52:1469–1478, 2001
39. Cappiello A, McDougle CJ, Malison RT, et al: Yohimbine augmentation of fluvoxamine in refractory depression: a single-blind study. Biological Psychiatry 38:765–767, 1995
40. Dam J, Ryde L, Svejso J, et al: Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. Pharmacopsychiatry 31:48–54, 1998
41. Carpenter LL, Yasmin S, Price LH: A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biological Psychiatry 51:183–188, 2002
42. Glassman AH, Kantor SJ, Shostak M: Depression, delusions, and drug response. American Journal of Psychiatry 132:716–719, 1975
43. Nelson JC, Bowers MB Jr: Delusional unipolar depression: description and drug response. Archives of General Psychiatry 35:1321–1328, 1978
44. Ostroff RB, Nelson JC: Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. Journal of Clinical Psychiatry 60:256–259, 1999
45. Shelton RC, Tollefson GD, Tohen M, et al: A novel augmentation strategy for treating resistant major depression. American Journal of Psychiatry 158:131–134, 2001
46. Papakostas GI, Petersen TJ, Nierenberg AA, et al: Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. Journal of Clinical Psychiatry 65:217–221, 2004
47. Ayd FJ, Zohar J: Psychostimulant (amphetamine or methylphenidate) therapy for chronic and treatment-resistant depression, in Treating Resistant Depression. Edited by Zohar J, Belmaker RH. New York, PMA Publishing, 1987

48. Fawcett J, Kravitz HM, Zajecka JM, et al: CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. Journal of Clinical Psychopharmacology 11:127–132, 1991

49. Price L, Carpenter L, Rasmussen S: Drug combining strategies, in Treatment-Resistant Mood Disorders. Edited by Amsterdam J, Hornig M, Nierenberg A. Cambridge, UK, Cambridge University Press, 2001

50. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study: Danish University Antidepressant Group. Psychopharmacology 90:131–138, 1986

51. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study: Danish University Antidepressant Group. Journal of Affective Disorders 18: 289–299, 1990

52. Thase ME, Entsuah AR, Rudolph RL: Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. British Journal of Psychiatry 178:234–241, 2001

53. Peselow ED, Filippi AM, Goodnick P, et al: The short- and long-term efficacy of paroxetine HCl: A. Data from a 6-week double-blind parallel design trial vs imipramine and placebo. Psychopharmacological Bulletin 25:267–271, 1989

54. Thase ME, Rush AJ, Howland RH, et al: Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Archives of General Psychiatry 59:233–239, 2002

55. Nierenberg AA, Papakostas GI, Petersen T, et al: Nortriptyline for treatment-resistant depression. Journal of Clinical Psychiatry 64:35–39, 2003

56. Poirier MF, Boyer P: Venlafaxine and paroxetine in treatment-resistant depression: double-blind, randomised comparison. British Journal of Psychiatry 175:12–16, 1999

57. Kaplan EM: Efficacy of venlafaxine in patients with major depressive disorder who have unsustained or no response to selective serotonin reuptake inhibitors: an open-label, uncontrolled study. Clinical Therapy 24:1194–1200, 2002

58. McGrath P, Fava M, Steward J, et al: Bupropion for SSRI-resistant depression. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, Dec 10–14, 2000

59. Thase ME, Blomgren SL, Birkett MA, et al: Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. Journal of Clinical Psychiatry 58:16–21, 1997

60. Brown WA, Harrison W: Are patients who are intolerant to one SSRI intolerant to another? Psychopharmacological Bulletin 28:253–256, 1992

61. Zarate CA, Kando JC, Tohen M, et al: Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? Journal of Clinical Psychiatry 57:67–71, 1996

62. Joffe RT, Levitt AJ, Sokolov ST, et al: Response to an open trial of a second SSRI in major depression. Journal of Clinical Psychiatry 57:114–115, 1996

63. Thase M, Kremer C, Rodrigues H, et al: Mirtazapine versus sertraline after SSRI non-response. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, Dec 10–14, 2000

64. Fava M, Dunner DL, Greist JH, et al: Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. Journal of Clinical Psychiatry 62:413–420, 2001

65. Nolen W, Hoencamp E, Haffmans P, et al: Classical and selective monoamine oxidase inhibitors in refractory major depression, in Refractory Depression: Current Strategies and Future Directions. Edited by Nolen W, Zohar J, Roose S, et al. New York, John Wiley and Sons, 1994

66. Thiery M: Clinical trial of the treatment of depressive illness: report to the Medical Research Council by its Clinical Psychiatry Committee. British Medical Journal 5439:881–886, 1965

67. Avery D, Lubrano A: Depression treated with imipramine and ECT: the DeCarolis study reconsidered. American Journal of Psychiatry 136:559–562, 1979

68. Petrides G, Fink M, Husain MM, et al: ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. Journal of ECT 17:244–253, 2001

69. Kellner CH, Fink M: The efficacy of ECT and "treatment resistance." Journal of ECT 18:1–2, 2002

70. Pearlman C: Electroconvulsive therapy in clinical psychopharmacology. Journal of Clinical Psychopharmacology 22:345–346, 2002

71. UK ECT Review Group: Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 361:799–808, 2003

72. Folkerts HW, Michael N, Tolle R, et al: Electroconvulsive therapy vs paroxetine in treatment-resistant depression—a randomized study. Acta Psychiatrica Scandinavica 96:334–342, 1997

73. Schlaepfer T, Kosel M: Novel physical treatments for major depression: vagus nerve stimulation, transcranial magnetic stimulation, and magnetic seizure therapy. Current Opinion in Psychiatry 17:15–20, 2004

74. Fava M, Rush AJ, Trivedi MH, et al: Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psychiatric Clinics of North America 26:457–494, 2003

75. Malhotra AK, Murphy GM, Kennedy JL: Pharmacogenetics of psychotropic drug response. American Journal of Psychiatry 161:780–796, 2004

76. Bertilsson L, Dahl ML, Dalen P, et al: Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. British Journal of Clinical Pharmacology 53:111–122, 2002

77. Sachse C, Brockmoller J, Bauer S, et al: Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. American Journal of Human Genetics 60:284–295, 1997

78. Marez D, Legrand M, Sabbagh N, et al: Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies, and evolution. Pharmacogenetics 7:193–202, 1997

79. Raimundo S, Fischer J, Eichelbaum M, et al: Elucidation of the genetic basis of the common "intermediate metabolizer" phenotype for drug oxidation by CYP2D6. Pharmacogenetics 10:577–581, 2000

80. Johansson I, Lundqvist E, Bertilsson L, et al: Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. Proceedings of the National Academy of Sciences of the United States of America 90:11825–11829, 1993

81. Blakely RD: Physiological genomics of antidepressant targets: keeping the periphery in mind. Journal of Neuroscience 21: 8319–8323, 2001