GUIDELINE WATCH: PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER, 2ND EDITION

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Since the publication in 2000 of the APA's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder,* 2nd Edition (1), two important safety concerns have emerged (hepatotoxicity with nefazodone and suicide risk with antidepressants), and two new antidepressants have been approved for use (escitalopram and duloxetine). This watch describes these developments as well as evidence that has accrued since 2000 in other areas related to the treatment of major depressive disorder.

ANTIDEPRESSANTS AND OTHER SOMATIC TREATMENTS

Hepatotoxicity with nefazodone

The guideline recommends the serotonin modulator nefazodone as an effective medication for the treatment of depression. However, before initiating or continuing treatment with nefazodone, consideration should be given to the recent reports of life-threatening hepatic failure in patients treated with nefazodone (2–8). These reports have led the Food and Drug Administration (FDA) to change the drug's labeling, adding a black box warning of possible liver failure leading to death and/or a need for transplant and contraindicating the drug in patients who

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The American Psychiatric Association (APA) practice guidelines are developed by expert work groups using an explicit methodology that includes rigorous review of available evidence, broad peer review of iterative drafts, and formal approval by the APA Assembly and Board of Trustees. APA practice guidelines are intended to assist psychiatrists in clinical decision making. They are not intended to be a standard of care. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available. Guideline watches summarize significant developments in practice that have occurred since publication of an APA practice guideline. Watches may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent the opinion of the authors and approval of the Executive Committee but not policy of the APA. This guideline watch was published in September 2005. Suggested citation: Fochtmann lJ, Gelenberg AJ: *Guideline Watch: Practice Guideline for the Treatment of Patients With Major Depressive Disorder,* 2nd Edition. Arlington, VA: American Psychiatric Association, 2005. Available online at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

were withdrawn from it because of evidence of liver injury. According to the warning, the reported rate of liver failure resulting in death or transplant in the United States is about 1 case per 250,000–300,000 patient-years of nefazodone treatment. This represents a rate of about three to four times the estimated background rate of liver failure and is probably an underestimate. There are no known predictors of the development of liver toxicity and failure with nefazodone; toxicity and failure have been reported in individuals early in the course of treatment as well as in persons receiving stable dosages for many months. The FDA warns that patients with preexisting liver disease should not be treated with nefazodone and that patients should be advised to immediately report symptoms that may indicate liver dysfunction, such as jaundice, anorexia, gastrointestinal complaints, and malaise. The warning is available at http://www.fda.gov/medwatch/SAFETY/2002/serzone_deardoc.pdf.

Suicide risk and antidepressants

Because patients with major depressive disorder are at greater risk of suicide, the guideline indicates that they should be assessed for suicide risk initially and over the course of treatment. The guideline also notes that "the risk of suicide in some patients recovering from major depressive disorder increases transiently as they develop the energy and capacity to act on self-destructive plans made earlier in the course of their illness" (1). The guideline describes factors associated with an increased risk of suicide in patients with major depressive disorder but notes that "the ability to predict suicide attempts and completed suicide is poor, with both many false positives (i.e., patients who appear more likely to make attempts or complete suicide but who do not) and false negatives (i.e., patients who appear less likely to make attempts or complete suicide but who do)" (1). With respect to children and adolescents, the guideline recommends caution when basing treatment decisions on adult data. All of these general principles remain true.

Recent research has raised concern about the safety of antidepressant use for children and adolescents and has led the FDA to add additional warnings, including a black box warning, to the labeling of all antidepressant medications (9). Although the APA practice guideline focused on treatment of adults, not children and adolescents, discussion of this research is appropriate in this watch. In 23 short-term (4- to 16-week) trials involving more than 4,400 patients receiving nine antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others), suicidal thinking or behavior was observed in 78 individuals. The average risk of suicidal thinking or behaviors was 3.8% for participants receiving a drug compared with 2.1% for those given placebo, suggesting an approximately twofold increase in risk (10). Consequently, in the new labeling, the FDA notes that pooled analyses of placebo-controlled antidepressant trials (available at http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm) have shown an increased risk of suicidal thinking or behavior in children and adolescents with major depressive disorder, obsessive-compulsive disorder, and other psychiatric disorders. However, it is important to note that no suicides occurred in any of these trials. Furthermore, according to the Centers for Disease Prevention and Control, suicidal thinking and suicide attempts are common among adolescents, occurring respectively in about 17% and 8.5% of adolescents each year. As a result of such attempts, only 0.002% of girls and 0.012% of boys ultimately die (11), highlighting the fact that suicidality (i.e., suicidal thoughts and behaviors) and suicide are not equivalent.

Although the studies reviewed by the FDA showed some variations among antidepressants, it was not clear whether the increase in suicidal thinking or behavior was specific to particular antidepressants, extended to adults, or occurred with longer-term antidepressant use (i.e., beyond several months). Thus, the FDA labeling change recommends that "all pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases" (9). To facilitate this, the FDA suggests an increased frequency of face-to-face contacts (i.e., weekly for the first 4 weeks, biweekly for the next 8 weeks), with prescriptions written for "the smallest quan-

tity of tablets consistent with good patient management, in order to reduce the risk of overdose." The FDA also recommends that patients be screened for bipolar disorder before antidepressant therapy is initiated. Medication guides that will accompany prescriptions of antidepressant medications are intended to alert families and caregivers of pediatric and adult patients to the need to monitor patients for the emergence of agitation, irritability, hostility (aggressiveness), impulsivity, anxiety, panic attacks, insomnia, akathisia, hypomania, mania, or unusual changes in behavior so that such symptoms can be reported immediately to health care professionals.

When signs or symptoms are observed that suggest an increased suicide risk, recommendations are available for assessing and managing suicidal behaviors in children and adolescents from the American Academy of Child and Adolescent Psychiatry (12) and in adults from the APA (13).

As with all decisions about treatment for individuals with psychiatric illnesses, the choice to initiate antidepressant therapy must balance the potential risks of treatment against the potential therapeutic benefit and the risks of untreated illness (14–16). The risks of untreated depression, including suicide and other suicidal behaviors, are high and have been clearly delineated in youths and in adults (1, 12, 13, 17). In adults, the evidence for antidepressant efficacy is also clear, as reviewed in the APA guideline.

In children and adolescents, the issue has been confounded by a smaller number of clinical trials as well as by negative trials. Positive evidence includes the studies of fluoxetine that led to its receiving an FDA indication for treatment of depression in children and adolescents and the recent Treatment for Adolescents With Depression Study (TADS) sponsored by the National Institute of Mental Health. This large, yearlong community effectiveness trial (18) of youths with moderate to severe major depressive disorder found that by 12 weeks of treatment, rates of response to fluoxetine alone (60.9%) were greater than those with either placebo (35%) or cognitive behavior therapy (CBT) alone (43.2%). In combination with CBT, fluoxetine was associated with an even greater response rate (71%)—twice that seen with placebo. Furthermore, clinically significant suicidal thinking, which was observed in 29% of study subjects prior to treatment, improved in all groups.

In addition to this direct evidence of antidepressant efficacy from clinical trials, the national decreases in youth suicide and overall suicide rates, during a period when the prescribing of antidepressants has increased, might provide indirect evidence for an overall preventive effect of antidepressant treatment on suicide (14, 19, 20).

Because additional information on the issue of antidepressants and suicide risk is likely to emerge, readers are urged to seek updates on the Web sites of the FDA (http://www.fda.gov), the American Academy of Child and Adolescent Psychiatry (http://www.aacap.org), and the APA (http://www.psych.org).

Availability of new antidepressants

Two new antidepressants, escitalopram and duloxetine, have been approved by the FDA since publication of the guideline. Escitalopram, the active *S*-enantiomer of citalopram, is an SSRI antidepressant that has FDA approval for acute and maintenance treatment of major depressive disorder. Evidence from randomized, clinical trials suggests that escitalopram is superior to placebo in the short-term treatment of depression (21), with efficacy and tolerability comparable to that of other antidepressants, including venlafaxine (22, 23) and citalopram (21, 24).

Duloxetine, a dual serotonin-norepinephrine reuptake inhibitor, has also been approved for the treatment of depression. Randomized, clinical trials show duloxetine to be more efficacious than placebo (25–28) and comparable in efficacy to SSRI antidepressants (27, 28). The drug is generally well tolerated, with reported adverse effects of treatment (e.g., nausea, dry mouth, dizziness, somnolence, insomnia, constipation, and asthenia) varying across studies but typically being infrequent at total oral daily doses of 40–120 mg. In addition to ameliorating core symptoms of depression, duloxetine exhibits efficacy relative to placebo in treating painful

physical symptoms (26, 28–31) and anxiety in depressed individuals (32). It also appears to ameliorate pain in the absence of depression (31), and it is FDA indicated for the management of pain associated with diabetic peripheral neuropathy.

Since publication of the guideline, the combination of fluoxetine and olanzapine has received FDA approval on the basis of a randomized, clinical trial supporting its use (33). Although the combination product (brand name Symbyax) is indicated for the treatment of episodes of bipolar depression, combined treatment with fluoxetine and olanzapine has also been found useful in treating episodes of major depression with psychotic features (34) and in treatment-resistant depression (35, 36).

Reboxetine, a selective norepinephrine reuptake inhibitor that was noted in the guideline to be possibly close to receiving approval, is not currently approved for use. Atomoxetine, another selective norepinephrine reuptake inhibitor, has recently become available but is approved for the treatment of attention deficit hyperactivity disorder. Although the possibility of using atomoxetine, either alone or in combination with an SSRI, for the treatment of depression has prompted interest among clinicians, the drug does not have an FDA indication for this use, and data on its use in the treatment of depression are limited (37–39). In addition, the FDA has just added a bolded warning to atomoxetine's labeling noting that the medication should be discontinued in patients who develop jaundice or laboratory evidence of liver injury (http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01335.html).

The evidence cited here on new medications is based on premarketing research. Clinicians are cautioned that real-world experiences after a drug is approved often bring unexpected findings, including less efficacy in some circumstances and unanticipated adverse events.

St. John's wort

Since publication of the guideline, results from additional meta-analyses and well-designed trials of St. John's wort have become available. Although some additional randomized, controlled trials have shown St. John's wort to be superior to placebo (40–42) or to comparator antidepressants (43, 44) in treating mild to moderate depression, other large trials have shown it to be no better than placebo (45–47) or comparator antidepressants in efficacy (42, 46–50). Several factors continue to confound interpretation of the literature, including trial length, adequacy of comparison treatment, and the reliability, stability, and comparability of *Hypericum* preparations. The most recent meta-analysis noted a trend for decreasing effect sizes in trials of St. John's wort over time, suggesting that it may be less effective in treating depression than previously thought (51). Although St. John's wort is generally well tolerated in clinical trials, increasing attention has been given to its tendency to compromise the effectiveness of other medications (e.g., cyclosporine, HIV protease inhibitors, oral contraceptives, digoxin, warfarin, and theophylline) by interactions mediated through cytochrome P450 enzymes (e.g., CYP3A4, CYP2C9, CYP1A2, CYP2C19) and transport protein P-glycoproteins (52–56).

Other somatic treatments

Evidence for the efficacy of electroconvulsive therapy (ECT) in treating major depressive episodes, already compelling at the time the guideline was published, has been strengthened by additional findings. Recent meta-analyses have highlighted the superior efficacy of ECT relative to sham treatment and also relative to pharmacotherapies for depression (57, 58). In depressed patients who received an acute course of ECT, data from the Consortium for Research in ECT have shown that thrice-weekly bilateral ECT is associated with rapid initial response and high rates of sustained response and remission (59). In comparison with bilateral ECT, right unilateral ECT has been associated with fewer cognitive effects (60, 61), particularly in autobiographical memory (62). However, as with bilateral ECT, cognitive effects vary with the extent to which the electrical stimulus exceeds the seizure threshold (60). In addition, the overall efficacy of unilateral ECT appears to be less than that with bilateral ECT (57). Several ad-

ditional studies highlight the diminished efficacy of barely suprathreshold electrical stimulation with right unilateral electrode placement (60, 61, 63) and a corresponding need to administer right unilateral ECT at stimulus intensities that are at least six times the initial seizure threshold (64). Additional details on the clinical use of ECT in the treatment of major depression can be found in the 2001 revision of the APA's *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging* (64).

Although other somatic treatments, including repetitive transcranial magnetic stimulation, magnetic seizure therapy, and vagal nerve stimulation, have also been studied over the past 5 years, evidence is not yet sufficient to recommend their use in routine clinical practice.

PSYCHOTHERAPY AND OTHER PSYCHOSOCIAL TREATMENTS

Recent studies have provided additional support for the efficacy of a number of psychosocial treatment approaches, including problem-solving treatment (65, 66), group psychoeducation (65), and the cognitive behavioral analysis system of psychotherapy (67). Additional meta-analyses have suggested that among psychotherapeutic approaches, other bona fide psychotherapies have efficacy comparable with CBT for treating depression (68, 69), although more research with CBT has been done. Given the evidence for the benefits of exercise in older depressed adults (70, 71), exercise may also be of value in other subgroups of patients with major depression.

Psychotherapy combined with pharmacotherapy

As noted in the guideline, studies examining combination treatment with psychotherapy and pharmacotherapy have shown mixed results. Although this has continued to be true in subsequently published studies (66, 67, 72, 73), a recent meta-analysis suggested that a combination of psychotherapy and pharmacotherapy is more effective than pharmacotherapy alone (74). Combination therapy may be particularly useful in improving treatment adherence (73, 74) and might be of some use in targeting particular symptoms or patient subgroups (75–77).

CONTINUATION AND MAINTENANCE TREATMENT

At the time the guideline was published, much data suggested the importance of continuation and maintenance treatment in individuals at high risk of recurrent depression, although the majority of studies on this practice examined the use of tricyclic antidepressants. Several more recent studies have confirmed the benefits of continuation and maintenance treatment with antidepressants in other classes (e.g., sertraline, venlafaxine, and mirtazapine) in decreasing the likelihood of recurrence (78–82).

Supplementing the earlier data on continuation and maintenance psychotherapy, most (83–87) but not all (88) additional studies of CBT support its use either alone or in addition to pharmacotherapy in decreasing depressive recurrence.

Inadequate response to treatment

Given the clinical importance of treatment nonresponse, it is not surprising that a number of studies and meta-analyses have examined strategies for augmenting antidepressant therapy. Although no consistently effective approach has emerged (89), pharmacotherapeutic approaches with some recent positive results include augmentation with thyroid hormone (particularly in women) (90), lithium (91, 92), buspirone (93), and lamotrigine (94). Addition of a benzodiazepine may also be helpful in some individuals after a careful weighing of potential advantages and disadvantages (95). Some studies have suggested that adjunctive treatment with omega-3 fatty acids is efficacious (96–98), although a single study using omega-3 fatty acid monotherapy showed no benefit (99). Evidence on the use of estradiol augmentation in peri-

menopausal or postmenopausal women is mixed (100, 101), and other potentially negative health effects of estrogen treatment are emerging. The possible adjunctive use of mifepristone in treating psychotic depression has also generated interest recently, although data are sparse (102, 103).

Modafinil has been used increasingly in depressed patients, either as an augmenting agent or to counteract symptoms of fatigue resulting from depression or sedation from other agents. Evidence for the efficacy of modafinil is limited and comes primarily from small or uncontrolled trials (104–107). A single randomized trial showed a brief period of improvement in fatigue after initiating adjunctive treatment with modafinil but no augmenting effect on depressive symptoms relative to placebo (108).

Some additional evidence suggests that response may be enhanced by increasing the dosage of antidepressant medication, although an increase in side effects may also be observed (109–111).

In terms of the choice of antidepressant medication, some studies (111–114) and meta-analyses (115–118) suggest that greater efficacy is seen with medications that act on more than one neurotransmitter system (e.g., venlafaxine and mirtazapine), although this is not invariably the case (119, 120). Despite the fact that tricyclic antidepressants are no longer typically used as first-line agents because of problems with tolerability and toxicity, they are efficacious (120–125) and may still be indicated in individuals whose illness has not responded to other treatments.

Gender may also play a role in response to and tolerability with specific antidepressants, but findings across studies are inconsistent (126–132).

As noted in the guideline, there is some evidence that addition of cognitive-behavior psychotherapy may be beneficial for patients who have had only a partial response to pharmacotherapy. However, more recent findings have been mixed, with some (87, 133) but not all (88) studies showing adjunctive psychotherapy to be beneficial. One study suggests that in women, outcomes with combined treatment may not be as good as outcomes using sequential treatment with initial interpersonal psychotherapy followed by pharmacotherapy in nonresponders (134). Although the full implications of this finding are unclear, the sequential treatment approach merits further study and may be of particular relevance to women in the childbearing years.

TREATMENT OF DEPRESSION IN OLDER ADULTS

A number of recent randomized, controlled trials have examined the treatment of depression in older adults. Comparisons of several SSRIs with the tricyclic antidepressant nortriptyline show better tolerability with SSRIs in this group of patients (135–137). Although the efficacies of nortriptyline and SSRIs generally appear to be comparable (135, 136), some data suggest that nortriptyline may be more effective in severely depressed individuals (137). An additional randomized, controlled outpatient trial showed comparable efficacy for two SSRIs, sertraline and fluoxetine, in the acute treatment of major depression (138).

Maintenance antidepressant therapy is associated with a lesser likelihood of relapse in older adults (139, 140). These data extend the findings of Reynolds et al. (141), discussed in the guideline, which showed antidepressant medication (nortriptyline) or interpersonal therapy to be effective maintenance therapy for elderly patients with recurrent major depressive disorder.

In the PROSPECT study (142), in which elderly patients were treated in primary care practices with facilitation by case managers, interventions included treatment with an antidepressant (typically citalopram) and interpersonal psychotherapy (for patients who declined antidepressant). Compared with treatment as usual, intervention was associated with more rapid and more prominent reductions in suicidal ideation and depressive symptoms, and the beneficial impact on depression extended throughout the 12-month study period. Although not all patients in the intervention group continued to receive treatment for depression throughout the study period, a greater proportion of intervention patients received ongoing treatment compared with the treatment-as-usual group, strengthening the observation that maintenance treatment is beneficial in depressed older adults.

Several studies have compared antidepressant treatment, nonpharmacological treatments, or combined treatments in older adults. Blumenthal et al. (143) found comparable rates of response in older depressed patients randomly assigned to treatment with sertraline, aerobic exercise, or combination treatment. After 10 months, greater sustained benefit was seen in the exercise-alone group, whereas response rates in the sertraline-alone and sertraline-plus-exercise groups were comparable (71). Thompson et al. (144) showed combination treatment with desipramine and CBT to be better than desipramine alone, comparable to CBT alone, and of particular benefit in elderly outpatients who were severely depressed. These findings supplement those of Reynolds et al. (141), who showed a trend for superior acute response with combined nortriptyline and interpersonal therapy. With maintenance treatment, either therapy was effective in rapid responders to treatment, but combined treatment was superior in patients who had a mixed or delayed response to initial therapy (139). In addition, combination therapy was more effective in maintaining social adjustment than either therapy alone (145).

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