



Introduction to the Clinical Practice Guidelines for the Assessment and Treatment of Patients with Depressive Disorders

Magellan Health Services Clinical Practice Guideline Task Force

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Overview

Effective March 31, 2009, Magellan Behavioral Health has re-adopted the American Psychiatric Association's (APA) *Practice Guideline for the Treatment of Patients With Major Depressive Disorder Second Edition*¹ and the 2005 update of that document entitled *Guideline Watch: Practice Guideline for the Treatment of Patients With Major Depressive Disorder, 2nd Edition*² to serve as an evidence-based framework for practitioners' clinical decision-making with adult patients who have a major depressive disorder. The APA guideline is one of the most comprehensive, evidence-based clinical practice guideline (CPG) for this disorder and is widely used. Therefore, adoption of this guideline provides an excellent source of evidenced-based treatment information, and since the guideline is accepted by other managed behavioral health care organizations, it reduces the burden on practitioners serving multiple organizations.

This introduction, the APA Guideline, and the APA Guideline Watch for Major Depressive Disorder (MDD) are designed for use with patients manifesting symptoms of unipolar depression. Patients presenting with depressive symptoms should be screened for possible bipolar depression, since accurate diagnosis is critical to appropriate and effective treatment.³ For patients with known or suspected bipolar depression, see the Magellan-adopted guideline for bipolar disorder, which consists of the APA's *Practice Guideline for the Treatment of Patients with Bipolar Disorder, Second Edition*⁴ and the associated Guideline Watch,⁵ both of which are available on the APA Web site.

The APA depression guideline covers the main areas of psychiatric management of patients with this disorder, covering topics from clinical features and epidemiology to various aspects of treatment approach and planning. Nonetheless, the behavioral health field is rapidly evolving and there have been continued developments since the APA Guideline (2000) and Guideline Watch (2005) were published. This introduction provides a brief overview of major developments in the clinical literature and in Federal policy with literature review through January 2009. The reader is encouraged to review other sources that may incorporate ongoing clinical developments, such as medication selection, safety, and management.^{6,7,8,9,10,11,12,13} The Magellan introduction also includes a section regarding ongoing concerns about antidepressant medications and suicidality in children, adolescents, and adults^{14,15,16,17,18,19} and on treatment of depression in special populations, such as women, elder adults, and non-Caucasian populations.

As with all CPGs, the adopted guideline and this introduction are intended to augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to this practice guideline should be noted in the member's treatment record, documenting the clinical reasoning used in making the exception. Magellan periodically requests clinical files from providers in order to monitor compliance with adopted guidelines. Clear documentation of the rationale for exceptions to the guideline's recommendations should be documented in the member's treatment record whenever there is evidence of deviation from the guideline.

Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval of specific medications or devices, and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings that are issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

Obtaining Copies of the APA Guideline & Guideline Watch

The APA's *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* and *Guideline Watch* may be viewed on the Internet at:

http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Or

Copies may be ordered through American Psychiatric Publishing, Inc. (APPI) at www.appi.org, by calling (800) 368-5777, or by U.S. Mail at:

American Psychiatric Publishing, Inc.
1000 Wilson Blvd., Suite 1825
Arlington, VA 22209-3901

Providing Feedback on the Guidelines

Magellan welcomes feedback on adopted clinical practice guidelines. All suggestions and recommendations are taken into consideration in our review.

Comments may be submitted to:

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Magellan Updates to the APA Guideline & Guideline Watch

Antidepressant Medications and Augmenting Agents

The 2000 APA Guideline cites the imminent availability of reboxetine as well as the use of moclobemide. Practitioners should note, however, that neither medication is available in the United States. In U.S. trials, Pharmacia could not demonstrate a difference between reboxetine and placebo. In addition, moclobemide has not been marketed in the U.S.

New antidepressants and new preparations of established antidepressants have been introduced since the publication of the APA Guideline, namely Paxil-CR (controlled release), Prozac weekly preparation, Effexor XR (extended-release), Pristiq (Desvenlafaxine succinate, the major active metabolite of venlafaxine), Lexapro (escitalopram oxalate), Cymbalta (duloxetine), and Emsam (selegiline), which was approved for use as a transdermal antidepressant^{20, 21} (Pharmaceutical Business

Review Online, 2008). Prozac weekly appears to offer a more convenient way for some patients to take this antidepressant medication.^{20,21} Duloxetine, a new antidepressant, is unique in also having an indication for neuropathic pain associated with diabetic peripheral neuropathy.^{22,23,24,25,26,27} This is an interesting dual indication in need of further study since chronic pain from a variety of etiologies is often co-morbid with depression and often responds to antidepressants. The need for a medication to treat both syndromes is made apparent by the high co-morbidity of physical symptoms with depression (69 percent) and the higher costs and utilization incurred by such dually afflicted patients.^{28,29}

Studies also have been published on the role, relative effectiveness and innovative means of administration of various current antidepressants and augmenting agents, as well as new medications in clinical trials.^{30,31,32,33,34,35,36,37}

Selegiline (Eldepryl), a monoamine oxidase inhibitor or MAOI, has been prescribed for the treatment of Parkinson's disease for many years. In February 2006, the Food and Drug Administration (FDA) approved Emsam (selegiline), the first transdermal patch for use in treating major depression.^{20,21} The once-a-day patch works by delivering selegiline through the skin and into the bloodstream. At its lowest strength, Emsam can be used without the dietary restrictions that are needed for all oral MAO inhibitors that are approved for treating major depression. In November 2007, the FDA approved the atypical antipsychotic Abilify (aripiprazole) as an add-on for patients whose major depressive disorder is not relieved by antidepressants alone (Correll, 2008). Also, since publication of the adopted APA Guideline and Guideline Watch, an FDA Alert was issued notifying health care professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis (FDA Alert June 16, 2008). Additionally, an FDA Alert was issued with new safety information on the antidepressant Norpramin (desipramine hydrochloride). This notification specified that extreme caution should be used when Norpramin is given to patients who have a family history of sudden death, cardiac dysrhythmias and cardiac conduction disturbances with the warning that seizures precede cardiac dysrhythmias and death in some patients (FDA Alert December 2, 2009).

Medication Algorithms

Studies that employ structured medication algorithms seem to improve outcomes by providing not only medication choice guidance, but also providing structure for frequency of visits, standardized assessments, and a clinical coordinator who provides patient and family education.^{6,7,8,9,10,11,12,13,38,39}

Such studies demonstrate improved outcomes over usual care. It should be noted that these studies, conducted with populations receiving public benefits with fewer exclusion criteria, did not achieve positive response percentages as high as typical studies of depression treatment. Such lower response rates are probably closer to what can be expected in representative patient populations.

Lithium Prophylaxis and Augmentation

As of the publication of the APA MDD guideline revision, antidepressant medications were cited as the primary choice for depression prophylaxis in patients at risk for recurrences. Some studies have indicated that lithium should be added to this group of medication choices, particularly in patients

with a high suicidal risk and/or a family history of bipolar disorder. One open study demonstrated a dramatic decrease in hospital admissions and hospital days on lithium prophylaxis.⁴⁰ Additionally, there were no suicides in the lithium group, along the lines of other studies that have demonstrated a suicide protective effect of lithium.

A systematic review of the literature also found substantial evidence supporting the role of lithium as an augmentation agent in the treatment of treatment-resistant depression.⁴¹ This review covered literature published between 1966 and 2003, and found that 50 percent of patients responded positively to lithium augmentation within two to six weeks. The authors declared that this augmentation strategy is the one most supported by the literature at this time.

One large meta-analysis of studies relating to suicidality among depressed and schizophrenic patients noted a marked decrease in suicide rates when lithium was used either alone or as an augmenting agent with any antipsychotic or antidepressant medication.⁴² It was felt that lithium led to a significant reduction in both impulsivity and aggressive behaviors across all diagnostic groups, possibly due to its serotonergic effects. It was noted in some studies that suicidal behaviors increased if the patient stopped taking lithium.

In terms of other antidepressants, evidence exists showing that nefazodone carries a higher risk of hepatotoxicity than other antidepressants,^{43,44} which has led to the inclusion of a warning in its listing in the Physician's Desk Reference (FDA Medwatch 2006). The warning indicates that life-threatening hepatic failure has been reported following the use of this medication.

The warning recommends that this medication not be used in patients with active liver disease or elevated serum transaminases. Practitioners are urged to heed this caution when selecting this medication. It should be noted that this medication is now only available in a generic preparation.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The selective serotonin reuptake inhibitor (SSRI) revolution has provided effective medications with fewer bothersome side effects, but clearly, there are still adverse effects that need to be monitored and addressed. Sexual side effects are possible with all antidepressants. A study of citalopram and paroxetine suggests the surprising finding that the occurrence of sexual side effects is only associated with duration of the depression as opposed to factors such as dose or blood level.⁴⁵ Furthermore, it was found that direct questioning for sexual side effects yields a much higher percentage of positive responses than waiting for a spontaneous patient report. Unlike side effects such as headache, diarrhea, or nausea, sexual side effects usually persist throughout medication treatment. This supports the recommendation that clinicians should ask specifically for these and other likely side effects at all contacts, rather than waiting for a spontaneous report or only asking open-ended questions.

Studying of the efficacy and acceptability of the SSRIs continues as treatment parameters and guidelines for depressive disorders are proposed and evaluated. A systematic review of six randomized trials of SSRIs (paroxetine, sertraline and citalopram) or placebo treatment have supported current recommendations for six to eight months of antidepressant treatment following

initial recovery, but provided no guidance for longer treatment (Deshauer et al. 2008). Another large systematic re-examination of 29 published and 11 unpublished clinical trials with 6,391 patients treated with paroxetine or placebo for acute major depression showed that paroxetine was not superior to placebo in terms of the proportion of study participants discontinuing treatment for any reason, but did exert a modest antidepressant effect relative to placebo (Barbui et al. 2008).

The APA Guideline indicates that thyroid hormone supplementation may be beneficial to enhance the effectiveness of antidepressants even in euthymic patients. While there is support in the literature for augmentation by T₃ of the therapeutic effect of tricyclic antidepressants in treatment-resistant patients, there are very few studies for use of T₃ as an augmenting agent with the SSRIs—now the first-line antidepressant agents used in depressive disorders. A clinical trial evaluated the antidepressant efficacy and safety of liothyronine sodium (triiodothyronine) when administered concurrently with the SSRI, sertraline, in patients with major depression not known to be treatment-resistant at the onset of treatment. Study findings showed that liothyronine enhanced the antidepressant effect of sertraline, whereby response and remission rates were 20 percent higher than in the sertraline and placebo group (Cooper-Kazaz et al. 2007).

Antidepressants and Suicidal Behavior

In recent years, national attention has focused on a possible link between treatment of patients with depression using antidepressant medication and induction or worsening of suicidal thinking and behavior (suicidality) in children, adolescents, and adults.

The FDA raised the visibility of a possible link when in 2004, it issued an analysis of existing data and testimony suggesting a greater risk of suicidal behavior during the first few months of treatment for children taking antidepressants.⁴⁶ The average risk for children taking the drugs was found to be 4 percent, twice the placebo risk of 2 percent.^{6,47}

The FDA identified specific drugs in its 2004 analysis and eventually directed manufacturers of all antidepressants to include a boxed warning and expanded warning statements alerting clinicians to an increased risk of suicidal thinking and behavior in children and adolescents being treated with these agents.^{46,47,48}

The FDA also expressed concern regarding possible links between antidepressants and suicidality in adults, stating that adults treated with antidepressants, particularly for depression, should be watched closely for worsening of depression and/or increases in suicidality, especially when antidepressants were started for the first time or when doses were changed.^{49, 50}

This heightened concern for the link between antidepressants and suicidality has triggered new areas of research. Two additional analyses using collected DNA samples from participants in the level 1 (citalopram) treatment arm of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study were conducted to determine the genetic influence on the propensity to develop suicidal thoughts or behaviors during antidepressant treatment. One DNA analysis showed that among male participants, risk of emergence of suicidality was associated with two single nucleotide polymorphisms (SNPs) that flanked CREB1 gene that were previously implicated in a measure of

anger expression (Perlis et al. 2007). Another DNA analysis showed that markers within GRIK2 and GRIA3 genes were associated with treatment emergent suicidal ideation during citalopram therapy (Laje G et al. 2007). The researchers indicated that, if replicated, these findings would suggest that pharmacogenetic testing could facilitate the identification of a small subset of individuals at greater suicide risk during short-term antidepressant therapy.

Concurrent with the advisories described above, several clinical studies have contributed to the uncertainty concerning antidepressants and suicidality. A Swedish study found evidence for a decreased suicide rate in people taking SSRIs. The authors reviewed post-mortem toxicology results on almost 15,000 victims of suicide in Sweden in 1992-2000 and found a protective effect from most SSRIs.⁵¹ In a large-scale 2006 American study of 82,285 episodes of treatment for depression with antidepressants between 1992 and 2003, including 5,107 episodes involving patients age 17 or younger, suicide risk was compared between patients treated with newer antidepressants, including the 10 antidepressants listed in the 2004 FDA advisory, and other (older) antidepressants. The authors found that only for those treated with older drugs [tricyclic antidepressants (TCAs) and trazodone] the risk was higher in the first month of treatment compared with the second to sixth months of treatment. There was no evidence of greater risk in the first month of treatment for the newer drugs included in the FDA advisory.¹⁶ A study of multiple national databases for the period 1985 – 1999 found that SSRI prescription rates were inversely associated with suicide rates.⁵²

Additionally, other studies pointed out that TCAs are not a better alternative to serotonergic agents, due to the sudden unexplained death (SUD) risk in adolescents, and due to the higher risks of suicide by overdose.⁵³

To address possible under-prescribing of antidepressants in response to the uncertainties in the clinical literature and the FDA advisories, the American Psychiatric Association and American Academy of Child and Adolescent Psychiatry issued a statement summarizing findings suggesting that the suicide rate for patients age 10 to 19 decreased by 25 percent over the prior decade in which SSRI prescriptions increased substantially.⁵⁴

Further, the Treatment for Adolescents with Depression Study (TADS), a multi-center project investigating the effectiveness of four treatments among adolescents with MDD, concluded that a combination of fluoxetine and cognitive behavioral therapy offered the most favorable risk/benefit ratio.⁵⁵ The research studied a cohort of 439 adolescents, ages 12 to 17, treated with fluoxetine alone, CBT alone, placebo alone, or CBT with fluoxetine. No suicides occurred in the group. The authors concluded that medical management with fluoxetine, including careful monitoring for adverse events, and with CBT as an add-on, should be made more widely available rather than discouraged.⁵⁵

Recommendations

In the absence of evidence from clinical literature, FDA advisories, or other credible sources, determining that the risk of increased suicidality for patients with depression treated with antidepressants makes their use inadvisable, Magellan's position remains that clinical evidence strongly supports the use and effectiveness of antidepressant medications in the treatment of depression in all age groups, and that careful, frequent, and proactive monitoring for changes in

status that could indicate suicidality is crucial to preserving the safety of these patients.^{46,47,48,49} When there is a current or past history of suicidality, such monitoring should occur at every session. In addition, Magellan recommends that patients who miss appointments be contacted by the clinician, especially when there are reasonable grounds for concern about the patients' safety.

Specifically, Magellan recommends following the cautions of the APA Guideline Watch,² FDA Advisories,⁴⁶⁻⁴⁹ and the joint APA-AACAP publication, *PhysiciansMedGuide*,⁵⁴ such that prescribing physicians, other clinicians involved in the care of patients taking antidepressants, and patients and their families stay alert and watchful for warning signs of possible increased suicidality and take prompt action if any adverse effects are observed.

In addition, Magellan has developed a clinical practice guideline that addresses suicidal behavior in more detail than the depression guideline introduction: the Magellan Clinical Practice Guideline for Assessing and Managing the Suicidal Patient.⁵⁶

Clinicians are urged to be familiar with the recommendations in these documents and to check for changes in FDA advisories and other communications frequently, since the recommendations and warnings may change swiftly as new clinical evidence becomes available.

Psychotherapy

The APA Guideline briefly discusses the choice of specific psychotherapies in the treatment of major depression. The guideline concludes that cognitive behavioral therapy and interpersonal therapy are the psychotherapeutic approaches that have the best documented efficacy in the literature for the specific treatment of MDD and that rigorous studies evaluating the efficacy of psychodynamic psychotherapy have not been published. The guideline indicates that when psychodynamic psychotherapy is used as a specific treatment, in addition to symptom relief, it is frequently associated with broader long-term goals.

Researchers in the Netherlands studied the predictive value of object relations for therapeutic alliance and outcome in psychotherapy for depression, and asserted that these concepts of psychodynamic theory are widely used by clinicians to understand the etiology of symptoms in patients. They rated the object relational functioning (ORF) of 81 patients by using the Developmental Profile. They drew the patient sample from a randomized clinical trial comparing antidepressant treatment versus short-term psychodynamic supportive therapy. The overall maturity of ORF measured at baseline was higher in patients who showed a better treatment response and the adaptive level of individuation appeared to be specifically predictive of outcome. Also, patients with a recurrent depression showed less mature levels of ORF, lower adaptive levels and a higher score on the symbiotic level. Researchers found no association between ORF and therapeutic alliance during treatment but growth of alliance was related to positive outcome (Van et al. 2008).

Combination Pharmacotherapy and Psychotherapy Treatment

The APA Guideline and Guideline Watch state that combination psychotherapy and pharmacotherapy may be a useful initial treatment choice for some patients.^{1,2} Multiple studies have shown that the combination of medications with structured psychotherapies can improve acute phase recovery rates.

One study evaluated a specialized form of CBT called Cognitive-Behavioral Analysis System Therapy (CBAST), used alone or in combination with nefazodone,⁵⁷ and found a treatment response rate of 70 percent in the combination treatment group, but only 40 percent in the CBAST-alone group. In the maintenance phase (beginning after 28 weeks of treatment), the CBAST group experienced a reduced recurrence rate (10 percent) compared to a non-medicated group receiving monthly evaluations only (30 percent).⁵⁷ In addition, a meta-analysis of 16 clinical trials concluded that when combination therapy is continued past 12 weeks, it is associated with a reduction in the number of dropouts from treatment.⁵⁸ Such findings suggest a positive effect on patient adherence with the entire treatment plan, including medications.

Researchers on the team of the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Study indicated that accumulated research findings show that 60 percent of adolescents with depression will show an adequate clinical response to an initial treatment trial with an SSRI drug. In this clinical trial, adolescents who did not respond to an adequate initial trial of an SSRI, the combination of CBT and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine, and resulted in fewer side effects (Brent et al. 2008). Similarly, combination treatment showed superior results for patients with MDD who were hospitalized in Germany. An intensive treatment program for severely depressed inpatients was studied comparing the efficacy of intensive interpersonal psychotherapy plus pharmacotherapy (i.e., sertraline as first-line or amitriptyline as second-line agents) versus clinical management and pharmacotherapy. The patients who received the adjuvant interpersonal psychotherapy had better response rates (70 percent versus 51 percent), remission rates (49 percent versus 34 percent) and relapse rates (3 percent versus 25 percent) than the clinical management group (Schramm et al., 2007).

Other studies suggest that during maintenance phase treatment, a higher level of symptom variability is associated with shorter time to relapse, and continuation of pharmacotherapy alone or in combination with interpersonal therapy can reduce this variability more than interpersonal therapy alone, thus prolonging the time to relapse.⁵⁹

However, other studies have found either conflicting evidence or variations on the theme. One study suggests that patients with a history of childhood abuse had no significantly greater response to combination treatment when compared to psychotherapy alone.⁶⁰ Additionally, two papers suggest an alternative approach called sequential therapy, which is using pharmacotherapy in the acute phase of depression followed by CBT alone focused on residual symptoms or with an antidepressant in the residual phase. It was found that sequential therapy yielded a reduction in the recurrence rate for depression.⁶¹

The use of functional neuroimaging techniques, including fluorine-18-fluorodeoxyglucose positron emission tomography (PET) has been the focus of recent clinical investigation in helping to delineate regional differences in metabolic activity between depressed and non-depressed subjects and in studying cerebral activity following both psychological and pharmacological interventions. One study compared patterns of cerebral metabolism in depressed patients following treatment for 16 weeks with CBT or venlafaxine. Authors reported that responders to either treatment modality demonstrated reduced metabolism in the ventrolateral and dorsomedial prefrontal cortices, changes that have previously differentiated depressed and euthymic states in major depression (Kennedy et al. 2007).

Treatment-Resistant Depression (TRD)

It has been estimated that one-third of patients experience only a partial response to medication and that one-fifth experience no response.⁶²

There is disagreement in the literature about the criteria for TRD, but some researchers recommend including those who have had no response to two or more antidepressants of different pharmacologic classes at six weeks of adequate dosages, and those with only a partial response by 12 weeks, in treatment-resistant criteria.^{62,63}

A staging system may assist clinicians in understanding where a patient is located along a sequential treatment algorithm. The patient can be assessed as being in Stages 0 to 5, with 0 indicating no adequate trials, and 5 indicating two adequate trials, plus two adequate trials of augmentation, plus a failure of ECT.⁶³

One universal criterion for diagnosing TRD is the failure of a certain number of *adequate* trials of antidepressants. *Adequate* encompasses definitions of both duration of the trial and daily dosage.

Before determining that a given patient has TRD, it is important for the clinician to re-evaluate the accuracy of the depression diagnosis and rule out co-morbid medical or psychiatric conditions that could explain the lack of response to treatment. In the event that the diagnosis of TRD is accurate, clinical literature provides increasing evidence for an algorithm-based approach.^{1,2}

Effective treatment of TRD is the subject of a long-term study, the STAR*D study, which consists of sequenced interventions for depression with patients who do not achieve remission of symptoms after the first, second, and subsequent adequate treatment regimens.

In STAR*D's Level 1, all participants were treated initially with citalopram (Celexa) administered in either primary care or psychiatric settings. Thirty percent of the 2,876 patients achieved remission within six to seven weeks using an average of five to six visits.⁶⁴

In STAR*D's Level 2, patients who did not achieve remission in Level 1, were invited to choose from among seven treatment alternatives, with four consisting of switching to a different medication (either sertraline, bupropion-SR, or venlafaxine-XR) or to cognitive-behavioral therapy, and three

consisting of augmenting the citalopram with either bupropion-SR or buspirone.^{12,13} Of the 727 patients who received switched medications, 25 percent became symptom-free within 14 weeks. Of the 565 patients who received an augmenting agent, about one-third became symptom free within 14 weeks. Of note: while both augmenting agents produced similar rates of remission, the augmentation with bupropion-SR led to fewer symptoms, greater symptom relief, and lower side effects compared with augmentation with buspirone.^{12,13}

In STAR*D's Level 3, patients who did not experience remission in Level 2 were given the choice of switching medications (with subsequent random assignment to either mirtazapine or nortriptyline), or augmenting the existing medications from Level 2. In the switching group, the two medications were about equally effective and worked at about the same rate, with 10 percent to 20 percent of patients becoming symptom free within 14 weeks. Side effect profiles were similar for the medications.⁶⁵

While the overall cumulative remission rate for participants in the STAR*D study was 67 percent, those requiring greater numbers of treatment steps to remission also had a greater likelihood of relapse.⁶⁶ The results from the STAR*D study, which was not placebo-controlled, continue to be analyzed and their implications for treatment of depression discussed.⁶⁷

Because the STAR*D's study design incorporated participant choice, the trial offered a unique opportunity to identify socio-demographic and clinical factors associated with participants' choice of second-step treatment. One follow-up analysis showed that few participants were willing to accept *all* possible second-step treatments (Wisniewski et al. 2007). The acceptance of cognitive therapy was associated primarily with socio-demographic characteristics (higher education level and a family history of mood disorder) and was unrelated to the degree of improvement or intolerance to citalopram. However, only 29 percent of participants were willing to accept cognitive therapy—a rate that was substantially lower than anticipated. The acceptance of a switch strategy versus an augmentation strategy was primarily driven by participants' experience in the initial treatment. Specifically, participants in primary care settings and those who experienced a greater side effect burden or a lower reduction in symptom severity with citalopram were more likely to accept a switch strategy as compared with an augmentation strategy. Also, those with a concurrent drug abuse and recurrent MDD were less likely to accept a switch strategy (Wisniewski et al. 2007).

Researchers also determined that, after an unsatisfactory response to citalopram, patients in the STAR* D trial who consented to random assignment to either cognitive therapy or alternative pharmacologic strategies had generally comparable outcomes (Thase et al. 2007). The pharmacologic augmentation was more rapidly effective than the cognitive therapy, whereas switching to cognitive therapy was better tolerated than switching to a different antidepressant.

Another analysis of the STAR*D study revealed that clinical, demographic and treatment history were of little value in recommending one medication versus another as a second step for MDD (Rush et al. 2008). These findings indicated that participants were most likely to remit in the second step when they had less Axis I psychiatric disorder comorbidity, less social disadvantage, and had at least a response to citalopram in the first step. Similarly, another STAR*D report revealed that remission was less likely and took longer to occur in patients with anxious depression than in those

with non-anxious depression following antidepressant treatment (Fava et al. 2008). A different STAR*D report showed that, while age at onset of illness was not distinctive as a depressive subgroup or associated with a different treatment response, earlier onset was associated with multiple indicators of greater illness burden across a wide range of indicators (Zisook et al. 2007).

Other findings from the STAR*D study focused on predictors of attrition during initial treatment for major depression where researchers found approximately one-quarter of participants who entered the study dropped out before their 12-week visit. Of these, approximately one-third discontinued treatment after only the baseline visit (Warden et al. 2007). Here it was noted that immediate attrition was associated with younger age, less education, and higher perceived mental health functioning. Attrition later in treatment was associated with younger age, less education, and African American race. However, experience with one episode of depression was associated with less attrition. As a result of their findings, researchers have suggested that in clinical trials and actual practice there may be specific points in time that provide opportunities to engage and encourage patients at high risk of dropping out of treatment.

Additionally, results from the full set of genotyped individuals from the STAR*D study suggested that a new marker (rs1954787) in the GRIK4 and HTR2A genes was associated with treatment response and remission due to their coding for kainic acid-type glutamate receptor (KA1) where the glutamate system may play an important role in modulating response to SSRIs (Paddock et al. 2007).

Results from an earlier study of TRD suggested that nortriptyline might have a special advantage in allowing accurate measurement of an adequate trial, since there is a reliable therapeutic range of blood levels that objectively defines adequate dosage. This study included patients with TRD and co-morbid medical conditions, and found that in patients with low to moderate medical co-morbidity, nortriptyline produced a 42 percent positive response when adequate blood levels were achieved and maintained.⁶⁸

A 2004 review article discussed the different definitions of TRD in the literature and reviewed the studies on the various approaches, including switching antidepressants, augmenting antidepressants, and combining antidepressants.⁶⁹ This article, along with others, discussed the favorable observations of including atypical or second-generation antipsychotics in this group of augmentation agents.⁷⁰ They also suggest that calling these agents “dopamine-5-HT antagonists” rather than antipsychotics will make them more acceptable to this population of patients.

Further clinical reviews, a meta-analysis of controlled studies and a clinical trial on the efficacy of augmenting standard antidepressants with atypical antipsychotics have been published (Mahmoud et al. 2007, Papakostas et al. 2007, Philip et al. 2008, Shelton et al. 2008). These findings supported the utility of augmenting standard antidepressants with atypical antipsychotic agents (i.e., risperidone, olanzapine, aripiprazole and quetiapine) in patients with refractory depression. Researchers indicated that the rate of discontinuation due to adverse events was higher among patients treated with atypical antipsychotics than with placebo as augmenting agents. Findings revealed that the side effect burden may be significant and could include extrapyramidal side effects, sedation, hyperprolactinemia, weight gain and metabolic syndrome. Additionally, authors noted that the data supporting the augmentation effects of ziprasidone is much more limited. The articles concluded

that these preliminary data suggest the need for additional clinical trials comparing atypical antipsychotic augmentation with traditional antidepressant augmentation regimens, and in more advanced TRD when there have been multiple prior treatment failures.

Having a co-morbid personality disorder may also contribute to TRD. One study from New Zealand reported on 30 patients with both MDD and borderline personality disorder (BPD).⁷¹ The researchers found that Prozac was more effective than nortriptyline (response rate 67 percent versus 27 percent) and suggested that SSRIs had evidential and theoretical advantages over noradrenergic or dopaminergic medications in this population. They also noted that the borderline patients with depression improved slowly, but by six months had achieved reductions in depressive symptoms and improvements in social functioning equal to patients with no personality disorders. Also of note in this study was the improvement in BPD patients of self-directedness and less blaming of others. Other articles describe the efficacy of Dialectical Behavior Therapy (DBT) in the treatment of patients with BPD.⁷² Such findings suggest that if the patient with TRD also has BPD, the addition of DBT to the medication regimen may be productive.

Alternative Treatments

Phototherapy or light therapy has been used for seasonal depressive syndromes since the 1980s. The treatment is administered through the use of light boxes, considered Class III medical devices by the FDA and available without prescription. The APA Guideline treats light therapy as first-line treatment for seasonal affective disorder (SAD) and an adjunct to pharmacotherapy for other depressive disorders.¹ A meta-analysis of 20 studies conducted by the APA found significant effect sizes for bright light treatment of SAD.⁷³ A multi-center trial of 96 patients with moderate to severe SAD found light therapy equal to fluoxetine in remitting symptoms after eight weeks (Lam 2006) with earlier response onset and fewer adverse effects.⁷⁴ Light therapy may be particularly useful for patients with mild to moderate depression who, through necessity or preference, are not candidates for pharmacotherapy, e.g., pregnant and postpartum women.⁷⁵ Clinicians who recommend the use of phototherapy are cautioned to present other treatments in addition, such as pharmacotherapy and psychotherapy, especially with patients who have moderate to severe forms of MDD. Clinicians also should advise their patients of the potential exclusion from insurance coverage of the actual light box, which is sometimes excluded from medical insurance benefits.

The APA Guideline and Guideline Watch indicate that St. John's Wort (SJW) has shown efficacy in mild to moderate depression comparable to low-dose tricyclics.^{1,2} Several studies, including placebo-controlled, double-blind studies of SJW or hypericum extracts compared with citalopram, fluoxetine, paroxetine, and sertraline have suggested that standardized preparations of SJW or hypericum extracts dosed at 600 to 1800 mg per day are as effective, or more effective, at achieving symptom reduction or remission for patients with MDD of moderate severity.^{76,77,78,79} SJW extracts have been found to be better tolerated, with fewer adverse effects, than antidepressant medications.^{76,77,78,79,80}

Several studies, however, have demonstrated equivocal results.^{1,2,81,82,83} Further, lack of product standardization, potential for interactions with prescribed antidepressants such as MAOIs, and potential for reduced effectiveness of cytochrome P450 (CYP) enzymes metabolizing CYP 3A4

substrates (estimated at about 50 percent of all marketed medications), leads to a conclusion that clinicians should exercise caution if recommending the use of SJW or hypericum extracts.^{1,2,84}

Observations of altered dehydroxyepiandrosterone (DHEA) secretion in middle-aged depressed men and women and the mood-elevating properties of this hormone have led to research of DHEA as a monotherapy for depression. A study using a double-blind randomized placebo-controlled design found that DHEA was successful in treating minor and major depression of a moderate severity in both middle-aged men and women.⁹⁰ Due to its 50 percent response rate, the authors recommend that it not be a front-line treatment, but be reserved for those who fail to respond to initial traditional antidepressant trials or those who do not want a traditional antidepressant. A small open-label study found that DHEA at 100 to 400 mg/day was superior to placebo in relieving depressive symptoms and dysthymia among HIV-positive adults.⁹¹ Further research is needed to determine if this treatment can become a proven part of the depression treatment armamentarium.

Corticotropin-releasing hormone (CHR) is implicated in the pathogenesis of several psychiatric disorders, including major depression. A study was conducted to evaluate the safety and efficacy of CP-316,311, a selective nonpeptide antagonist of corticotropin-releasing hormone type 1 (CRH₁) receptors, in the treatment of recurrent major depression where it was compared to sertraline or placebo. Although CP-316,311 was safe and well-tolerated in the study population, it failed to demonstrate efficacy in the treatment of depression (Binneman et al. 2008).

Somatic Treatments - Neurostimulation

The adopted APA Guideline Watch briefly discusses somatic therapies used in the treatment of major depression and indicates that ECT has the most compelling evidence for effectiveness compared to other neurostimulation techniques—i.e., repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST) and vagus nerve stimulation (VNS)—where the evidence is not yet sufficient enough to recommend their use in routine clinical practice. The Guideline Watch also notes that while unilateral ECT is associated with fewer cognitive effects, it appears to have less overall efficacy than bilateral ECT.

Repetitive transcranial magnetic stimulation (rTMS) is a treatment for depression that, if efficacious, could offer some potential advantages over ECT since it does not require anesthesia, can be administered in outpatient settings, and has less severe cognitive side effects. Since publication of The APA Guideline Watch the FDA has approved an rTMS device. This market clearance was specifically for the treatment of major depression in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dosage and duration in the current episode (FDA Market Notification October 8, 2008). One small study demonstrated that rTMS may be a useful adjunct in younger populations, but not for older adults with TRD.⁸⁵ A more recent randomized double-blind controlled trial concluded that rTMS has substantial treatment efficacy for patients with TRD. The rTMS protocol found to be effective consisted of three trains of low-frequency rTMS to the right prefrontal cortex of 140 seconds' duration at 1 Hz daily, followed immediately by 15 trains of five seconds' duration of high-frequency left-side rTMS at 10 Hz.⁸⁶ It remains a question whether this technique will be useful as a treatment option, since there are issues of the clinical importance/durability of the treatment effect

and definitions of optimal parameters (e.g., coil placement, stimulus frequency and intensity) that have yet to be resolved (Carpenter 2006).

In 2005, the FDA approved the use of vagus nerve stimulation (VNS), which involves implantation in the neck of a device that emits a mild electrical pulse to the left vagus nerve at specified frequencies and intervals. At this time, Magellan has determined that VNS remains investigational due to insufficient evidence that it is as safe and effective as existing somatic treatments, including electroconvulsive therapy. VNS had previously been used in the treatment of epilepsy, and subsequently was approved for use as an “adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.”⁸⁷ The device has been studied with patients who have major depression or who are in the depressive phase of bipolar illness, with varying results.⁸⁸ One author has recommended that patients have at least one year of VNS before concluding whether the device is helping (Corcoran CD, 2006). Side effects from the implantation of the device and from the presence of the device have been noted, including voice alteration, dyspnea, neck or throat pain, and headache.⁸⁹

Magnetic seizure therapy combines aspects of both ECT and rTMS by inducing a seizure using the device borrowed from rTMS. The primary benefit of MST over ECT is its ability to produce focal stimulation and target appropriate areas of the cortex for optimization of antidepressant effects. Research on MST is in very early stages of development for treatment of depression (Carpenter 2007) Deep-Brain Stimulation (DBS) is approved by the FDA for treatment of dystonia, essential tremor and tremor in Parkinson’s Disease. While DBS is considered an improved alternative to ablative neurosurgical procedures, there is considerable surgical risk associated with implantation of the electrodes. DBS is still in the investigational phase for the treatment of extremely severe refractory depression (Carpenter 2007, Mayberg et al. 2005, Marangell et al. 2007).

Dysthymia and Minor Depression (MiDD)

There is a substantial literature suggesting that psychotherapies such as cognitive-behavioral or interpersonal therapy, as well as antidepressant medications and other somatic treatments that are effective for MDD are also effective for two related conditions, Dysthymia and Minor Depressive Disorder (MiDD).¹ Antidepressant medications have been demonstrated as efficacious in many patients with these disorders, with one study demonstrating a more rapid rate of improvement using an SSRI in MiDD when compared to placebo.⁹²

Medical/Behavioral Integration

The prevalence rates of depression have been found to be 3.5 percent in the general population, 6 percent in primary care offices, and 12 percent in medical inpatient settings; the majority of patients with MDD are treated in primary care.^{93,94} In one study of emergency department admissions, 30 percent of patients at four emergency rooms reported depression.⁹⁵

Furthermore, patients with several chronic medical conditions, such as chronic pain, fibromyalgia, chronic fatigue, diabetes and diabetic neuropathy, coronary disease, stroke, and asthma⁹³⁻¹⁰⁸ are at higher risk for MDD and are, on average, three times more likely to be non-compliant with medical treatments.^{93, 109} Evidence demonstrating the relative safety of depression treatments in the medically ill population has been accumulating.¹¹⁰⁻¹¹⁴

Important to the discussion on safety of depression treatments in medically ill patients is the recent interest in studying the use of antidepressant drugs and their relationship to weight gain and glucose homeostasis. Findings from a very large nested case-control study (n=165,958) using patients with depression being treated with antidepressants, affirmed that recent long-term use of antidepressants in moderate to high daily doses was associated with an 84 percent increase in the risk of diabetes. Andersohn et al., reported that this association was present for both tricyclic antidepressants and SSRIs. Antidepressant treatment for shorter periods or with lower daily doses was not associated with an increased risk. The recent use of other antidepressants (i.e., bupropion, reboxetine, venlafaxine, nefazodone, mirtazapine and trazodone) was also associated with an 80 percent increase risk of diabetes. For these drugs, researchers indicated that the dose or duration effect could not be detected due to their smaller numbers in the sample (Andersohn et al. 2009).

Similarly, evaluating the effectiveness of treatments for depressive symptoms in patients with coronary artery disease (CAD) continues to be an important area of focus for clinical inquiry. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) clinical trial demonstrated the efficacy of citalopram administered in conjunction with weekly clinical management for major depression among patients with CAD and found no evidence of added value of interpersonal psychotherapy (IPT) over clinical management. The authors noted that, based on these results and those of previous published trials - specifically, the Enhancing Recovery in Coronary Heart Disease (ENRICH) and the Sertraline Antidepressant Heart Attack Trial (SADHART) studies, citalopram or setraline plus clinical management should be considered as a first-step for patients with CAD and major depression (Lespérance et al. 2008, Berkman et al. 2003, Glassman AH et al. 2002).

Another cardiac study focused on assessing the influence of depression on mortality following a coronary event. A clinical trial on the effects of depression on decreased heart rate variability (HRV), a predictor of mortality, was conducted to determine the influence of both sertraline and improvement in mood on HRV. Using Holter electrocardiogram recordings, results showed that both sertraline treatment and symptomatic recovery from depression were associated with increased HRV. Researchers note that further study is needed to understand the role of depression and its treatments in post-acute coronary syndrome HRV recovery (Glassman et al. 2008).

More recently, a clinical review on the effectiveness of depression screening and treatment on patient outcomes was published with equivocal findings (Thombs et al. 2008). The authors indicated that clinical guidelines promulgated by the American College of Cardiology and the American Heart Association recommend that screening and treatment of depression be considered in patients with cardiovascular disease (CVD). The findings of this systematic review showed that depression treatment with medication or CBT in patients with CVD is associated with only modest improvement in depressive symptoms but no improvement in cardiac outcomes. No clinical trials have assessed whether screening for depression improves depressive symptoms or cardiac outcomes in patients with CVD. Researchers suggested that these findings did not provide evidence for *or* against the recommendations that depression should be evaluated or that screening for depression be considered as part of standard care for patients with CVD (Thombs et al. 2008).

For the reasons cited throughout this section, it is important for all clinicians treating patients with depression to be aware of the effects of general medical and behavioral comorbidity, and for treatment plans to address medical and behavioral needs or to foster integration and coordination of care among medical and behavioral health providers.

Remission as the Goal of Treatment

It is stated in the APA Guideline and in a number of studies that treatment to remission of symptoms is the preferred outcome during the acute phase of depression treatment to optimize functioning and to better protect against relapse and recurrence.¹¹⁵ Both the APA *Guideline Watch for the Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 2nd Edition* and the Institute for Clinical Systems Improvement (ICSI) *Health Care Guideline: Major Depression in Adults in Primary Care, Twelfth Edition*, recommend long-term maintenance treatment with antidepressants in order to prevent relapse and recurrence of depression. The ICSI Guideline specifies that the dosage of antidepressant drug resulting in a therapeutic response should be the dose that is used for the maintenance phase (i.e., six to 12 months for the first depressive episode, three years for the second episode, and indefinitely for a second episode with complicating factors or for a third/subsequent episode). Complicating factors for depression may include rapid recurrence of episodes, advanced age (older than 60 years) at the onset of a major depressive episode, severity and family history (Institute for Clinical Systems Improvement, 2009). Getting patients to the point of remission can be challenging, and determining the best treatment approaches to achieve the lowest rates of relapse and recurrence has been the focus of many studies. There is some evidence that suggests that cognitive behavioral therapy for depression may be effective in reducing the incidence of recurrence when it is targeted toward residual symptoms that are not completely cleared with the use of anti-depressant medication.⁶¹

Special Populations

Women

Since the APA Guideline was published, newer studies have shed light on the rapidly evolving specialized area of women and depression, some focusing on postpartum depression,¹¹⁶ some on depression associated with peri- and post-menopausal status,^{7,117} some on gender differences in

antidepressant response,^{118,119} and others on the vital area of fetal/newborn risk and antidepressant treatment.¹²⁰⁻¹²³ Two studies showed that women who took paroxetine (Paxil) during the first three months of pregnancy were about 1.5 to 2 times as likely to have a baby with a heart defect as women who received other antidepressants or women in the general population, causing the FDA to advise clinicians to discuss potential risk of birth defects with women taking Paxil who may become pregnant.¹²⁴ Some studies have also focused on the different phenomenology of depression in women, finding that women have more sleep disturbances, psychomotor retardation, anxiety, somatization, appetite disturbances, and yet less agitation.¹²⁵

Premenstrual Dysphoric Disorder (PMDD)

Between 3 percent and 8 percent of women experience premenstrual dysphoric symptoms, and an additional percentage of women may have sub-threshold symptoms.⁹⁴ Structured tools and diaries are available to assist women and their treating clinicians in assessing symptom presence and severity over the entire cycle.¹²⁵ It has been demonstrated that patients with PMDD are at increased risk for development of MDD and postpartum depression. There have been reports that SSRIs are effective in reducing both the physical and behavioral symptoms of PMDD whether administered intermittently during the premenstrual phase or continuously. More research is needed to help guide clinicians in deciding how to make this choice.¹²⁵

Depression and Antidepressants during Pregnancy

It is known that the rate of depression increases during late pregnancy.¹²⁵ Risk factors for depression during pregnancy include a prior mood disorder, less education, single status, unemployed, marital discord or dissatisfaction, inadequate psychosocial support, unwanted pregnancy, and being in a second or subsequent pregnancy. Recurrence in women who discontinue antidepressant medication at conception or early pregnancy has been estimated at 75 percent.

Depression itself during pregnancy affects the woman in ways that pose risks for developing fetuses. Effects on the woman include decreased appetite, poor weight gain, and self-medication with nicotine, alcohol, or other drugs, all things that can lead to problems for the fetus.¹²⁵ These untreated depression risks should be weighed against potential risks of fetal exposure to antidepressant medication. Antidepressants with substantial studies looking at potential risk to the fetus include citalopram, fluoxetine, paroxetine, sertraline, nefazodone, venlafaxine, and the tricyclics. In a review of multiple large studies, one researcher found no evidence of increases in major congenital malformations because of SSRI exposure.¹²⁵ However, the study did find evidence of associated earlier delivery, lower birth weight, and lower Apgar scores with antidepressant exposure during the third trimester.¹²⁵ More recently, similar findings were also published in a large study examining data on infants born with and without birth defects. Researchers discovered that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories of birth defects (Alwan et al. 2007). These findings suggested that the literature does not support that there are long-term adverse consequences of in-utero exposure to SSRIs, venlafaxine, or the tricyclics. Additionally, a prospective, naturalistic design through pregnancy study evaluated the effects of prenatal antidepressant exposure and maternal depression on infant gestational age at birth and risk of pre-term birth. The findings of this prospective study

showed that antidepressant exposure, independent of depressed mood, adversely affects gestational age at birth and that this effect may be possibly be dose-related (Suri et al. 2007).

In 2008, the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin on the use of psychiatric medications during pregnancy and lactation. It is recommended for practitioners to review this guideline if considering initiating treatment, or maintaining treatment, on any person who is pregnant. This guideline indicated that lithium exposure may be associated with an increased risk for cardiac malformations by a factor of 1.2 to 7.7, and for overall congenital malformations by a factor of 1.5 to 3. Also specified in the guideline was that neonatal lithium toxicity can result in flaccidity and lethargy, and poor suck reflexes. Additionally, the guideline suggested that echocardiogram examination of the fetus should be considered for women exposed to lithium during the first trimester (ACOG practice bulletin; no. 92, 2008; Vega 2008).

Two studies cited by the FDA in its public health advisory, as noted above, found a substantially higher risk of birth defects in babies when their mothers took Paxil (paroxetine) during the first trimester of pregnancy.¹²⁴ Similarly, the aforementioned ACOG practice bulletin indicated that, while women with depression may be considered for medical therapy during pregnancy on an individual basis based on the severity of illness, paroxetine should be avoided, if possible. The bulletin based this cautionary note on evidence of congenital cardiac malformation, anencephaly, and omphalocele with use of this medication during early pregnancy (ACOG practice bulletin; no. 92, 2008; Vega 2008). Clearly the risks and benefits of Paxil use in women who are trying to conceive or who may have an unplanned pregnancy must be weighed carefully and discussed, and an alternative to Paxil use sought if possible. Short-term consequences in the form of neonatal withdrawal syndromes are possible and more research is needed to elucidate these findings.

In 2009, the APA and ACOG collaborated to review the literature on fetal and neonatal outcomes associated with depression and antidepressant treatment during childbearing in order to provide clinicians with a comprehensive overview of the scientific data. Their published joint report (*The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists*) addressed maternal and neonatal risks of both depression and antidepressant exposure and proposed treatment algorithms for periconceptional and antenatal management. This report noted that both depression, as well as antidepressant treatment, confer risks and may be associated with adverse birth outcomes such as fetal growth changes and shorter gestation periods. The authors also cautioned that the available research has not yet controlled for confounding factors that may influence birth outcomes, e.g., maternal illness, poor prenatal care, problematic health behaviors including the use of alcohol, drugs and nicotine, and the use of multiple medications for other conditions (Yonkers et al. 2009).

Other important findings from the literature highlighted in the APA/ACOG report indicated the following: (1) Neonates born to mothers with a depressive disorder have an increased risk for irritability, less activity and attentiveness, and fewer facial expressions compared with those born to mothers without depression. (2) Several studies reported fetal malformations in association with first-trimester antidepressant exposure, but there was no specific pattern of defects for individual medications or class of agents. (3) The association between paroxetine and cardiac defects was more often found in studies that included all malformations, rather than clinically significant

malformations. (4) Late gestational use of SSRI antidepressants was associated with transitory neonatal signs and an increased low risk for persistent pulmonary hypertension in the newborn. (5) Most of the studies did not show an association between tricyclic antidepressant use in pregnancy and structural malformations, but they were associated with increased perinatal complications such as jitteriness, irritability and convulsion in neonates (Yonkers et al. 2009; Barclay 2009).

It is important to note that the APA/ACOG report also delineated treatment algorithms supporting their recommendations for women contemplating pregnancy and for those who are currently pregnant. Tapering and discontinuing medication for those with mild or no depressive symptoms (e.g., six months or longer) may be appropriate for women considering becoming pregnant, but not for those women with a history of severe or recurrent depression. Women who are pregnant and psychiatrically stable on medications may be able to continue on their regimen after consultation with their psychiatrist and obstetrician/gynecologist. Tapering may be appropriate for pregnant women who are not at high risk for relapse and are not experiencing symptoms.

The APA/ACOG report stressed that pregnant women with recurrent depression or symptoms despite their medication would benefit from psychotherapy to replace or augment their regimen. Additionally, pregnant women with severe depression should remain on medication with alternative treatment and monitoring in place should the patient refuse medication. The report emphasized that clinicians should support pregnant women who are depressed and want to avoid medication. In these instances, non-psychiatric clinicians should consider consultations with a psychiatrist to determine if a trial of psychotherapy alone is reasonable. Lastly, the report recognized that it is common to diagnose untreated depression during pregnancy or encounter patients who have discontinued their medications but are symptomatic. In these instances, if possible, the physician should avoid the first trimester use of antiepileptic agents since they are teratogens, and also the newer antipsychotic and antidepressant agents that have not been on the market for at least a decade until reproductive safety information is available (Yonkers et al. 2009; Barclay 2009).

Postpartum Depression (PPD) and Antidepressants during Breastfeeding

The APA Guideline cites the prevalence, symptoms, and risks of postpartum depression.^{1,2} The Edinburgh Postnatal Depression Scale, a self-report screening tool, has been found to significantly increase detection of PPD compared with routine examination, especially in primary care settings.¹²⁵ Research on treatment for PPD has increased since the publication of the APA Guideline with more evidence found to support the use of venlafaxine, sertraline, fluvoxamine, and fluoxetine, as well as the use of psychotherapy, specifically interpersonal psychotherapy, and support groups in which women's partners also attend. Some evidence has been found for the efficacy of estrogen augmentation (estradiol) as monotherapy or an adjunct to antidepressant therapy, yet no benefit has been found for the use of synthetic progestogens.¹²⁵

A significant proportion of women with PPD refuse treatment with antidepressants because of fear of harm to their infant during breastfeeding. Most antidepressants do pass into breast milk, with estimated infant daily dosages from 0.1 percent to 6.2 percent of maternal dosage. However, one reviewer notes very few reports of adverse effects to nursing infants exposed to psychotropic

medications.¹²⁵ Some data suggest that sertraline and paroxetine are most concentrated in hind milk, which when discarded can substantially reduce the amount of antidepressant the infant receives.¹²⁵

Since the prevalence of PPD is so high, estimated at 13 percent, more knowledge about the amount of antidepressant that is transferred to infants during breast-feeding and the associated risks is needed. A review of 57 studies found evidence to support a conclusion that nortriptyline, paroxetine, and sertraline may be the preferred choices in these situations when the mother is breast-feeding.¹²³

Maternal and Offspring Depression

The APA Guideline briefly discusses positive family history of depression and its impact on the clinical course of the patient's own illness. Specifically, a positive history will increase the chance that a patient's own illness will be recurrent and that the patient may not fully recover between episodes. Since release of the APA Guideline, more has been published about the children of depressed parents.

Maternal depression is a risk factor for child psychopathology where offspring have high rates of anxiety, disruptive and depressive disorders that begin early, and often continue into adulthood causing impairment (Weissman et al. 2006). The STAR*D-Child study was an ancillary study to the STAR*D trial where it was initiated about a year after the adult segment began. This trial enrolled 151 mother-child (ages 7 to 17 years) pairs in eight primary care and 11 psychiatric outpatient clinics across seven regional centers in the United States. The purpose was to assess the children whose depressed mothers were being treated with medication as part of the STAR*D trial. Results revealed that remission of maternal depression after three months of medication treatment was significantly associated with either reductions in the children's diagnoses and symptoms, or remaining free of psychiatric diagnosis (Weissman et al. 2006). The findings from the one-year follow-up to the STAR*D-Child study also showed decreases in the number of children's psychiatric symptoms that were significantly associated with decreases in maternal depression severity (Pilowsky et al. 2008). Researchers proposed that these findings support the importance of vigorous treatment for depressed mothers in primary care or psychiatric clinics, and suggest the utility of evaluating the children, especially children whose mothers continue to be depressed. Authors suggested that a reduction in stress associated with maternal remission may reverse the long-standing symptoms in children who are likely to be genetically vulnerable (Weissman et al. 2006).

Another related study evaluated an interpersonal psychotherapy program specifically designed for mothers with major depression who were also caring for children with psychiatric disorders. Here again, the mothers who received the customized treatment (i.e., IPT-MOMS) versus treatment as usual (psycho-educational materials and referral information) showed reduced symptoms and improved functioning at the three- and nine-month follow-ups, with some evidence that their ill child also showed clinical improvement (Swartz et al. 2008).

Recurrent Depression

The long-term treatment of recurrent depression is an important focus of psychiatric research and is particularly important for women who often prefer psychotherapy regimes during childbearing years

or for other medical reasons. A study of 233 women ages 20 to 60 years of age with recurrent depression, who were seeking non-pharmacologic management of their illness, was conducted to determine the efficacy of weekly, twice-weekly or monthly interpersonal therapy (IPT). The women were treated in the acute phase of their episode with weekly IPT or, if required, weekly IPT plus an SSRI antidepressant until they achieved remission. Researchers concluded that when IPT alone is effective in bringing about a remission of symptoms, it is also effective as a maintenance treatment. Also IPT in the maintenance phase delivered at weekly or twice-monthly intervals is no more effective in maintaining remission than IPT delivered on a monthly basis. Additionally, the authors noted when IPT alone is not effective in the acute treatment phase, it is generally not effective in maintaining remission (Frank et al. 2007).

Menopause and Hormone Replacement Therapy

In women with a history of mood disorders, the developmental changes from pre-menopause to peri-menopause, and peri-menopause to post-menopause are each associated with significant increased risk for depression.¹²⁵

Various studies, including a 2001 expert consensus guideline on women and depression, have suggested that hormone therapy be considered in peri-menopausal and post-menopausal women experiencing an MDD.^{7,117} However, the studies have been marred by methodological flaws, such as using different types of estrogens and hormone combinations, including women at different stages of peri-menopause and menopause, and including women with a range of mood disturbances.¹²⁵ In addition, since hormone replacement therapies have been associated with increased risk for serious medical illness, such as cancer, the decision whether to include hormone replacement in the treatment plan is best made with consideration of the cost/benefit ratio of risk from hormonal therapy versus risk from depression, and in consultation with the patient's gynecologist.

There continues to be interest in the association of major depression and osteoporosis, but the reported findings to date are inconsistent. One study investigated the relationship between cortisol levels and bone mineral density (BMD) among premenopausal women between the ages of 26 and 56 years with major depression and healthy women who were matched for age and body mass index. Study findings showed that plasma cortisol levels were significantly higher in the depressive patients than in the controls, osteocalcin was lower and C-telopeptide (CTx) were higher in the patients than in the controls. Also, lumbar and femur bone mineral density (BMD) were negatively correlated with cortisol levels in the depressed patients group. Authors noted that major depression had important effects on BMD and bone turnover markers, and suggested that depression should be considered among risk factors for osteoporosis in premenopausal women (Abdurrahman et al. 2007).

Sexual Dysfunction

The APA Guideline cites sexual side effects such as the loss of libido in men and anorgasmia in both sexes as complications of any antidepressant medication, but more common with SSRIs. The guideline discusses the use of sildenafil, yohimbine or neostigmine for arousal or erectile dysfunction and sildenafil, cyproheptadine or amantadine for orgasm dysfunction in men. Since publication of the guideline, use of phosphodiesterase (PDE) inhibitors in women for the treatment of such sexual

side effects of antidepressants is under clinical investigation. One clinical trial of 49 women reported that flexible doses of sildenafil starting at 50 mg adjustable to 100 mg before sexual activity versus placebo was associated with a reduction in the adverse sexual side effects of selective and non-selective serotonin reuptake inhibitors (Nurnberg et al. 2008).

Older Adults

Some authors estimate that 2 million adults age 65 or older have major depression and another 5 million in this age group are affected by depressive symptoms. This latter group becomes even more significant in light of findings that even minor depression in post-stroke patients, a predominantly older group, can lead to significantly increased mortality.¹⁰²

In long-term care settings, depression may affect 20 percent of patients. Older adults are less likely to be diagnosed with depression and less likely to receive treatment than are their younger cohorts. Elderly persons of color are even less likely to be accurately diagnosed or to receive treatment. Furthermore, in low-income elderly, nearly 25 percent diagnosed with depression do not receive drug therapy, and more than 21 percent diagnosed with depression do not receive either psychotherapy or an antidepressant, despite having health insurance.¹²⁶

Regarding the choice of pharmacotherapy or psychotherapy, or a combination for older adults, a meta-analysis found only modest effect sizes for treatment with either pharmacotherapy or psychotherapy, and concluded that treatment choice is best based on collaborative consideration of contra-indications, co-morbidities, treatment access, and patient preferences.¹²⁷ Since depression is a common disorder in the elderly and it is often associated with cognitive deficits and physical pain, researchers have focused on antidepressant agents that can alleviate these symptoms. A clinical trial of duloxetine versus placebo in elderly patients demonstrated that the drug improved cognition, depression and some pain measures, and was safe and well-tolerated in patients over age 65 with recurrent MDD (Baskin et al. 2007).

Regarding ECT, a review article of 121 studies concluded that ECT is effective in the acute treatment of late-life depression and is generally safe.¹²⁸ However, the authors pointed out that only four of the 121 studies used a randomized design; so important questions still remain about ECT's effectiveness relative to medications, its longer term efficacy, and its use in patients with cognitive impairment.

Researchers studying the effects of care management of depression have indicated that depressed older patients are much more likely to present and be managed in a primary care setting. Using data from the Prevention of Suicide in Primary Care Elderly, Collaborative Trial (PROSPECT) and data from the National Death Index (NDI), authors noted that older primary care patients with major depression in practices that implemented care management of depression were less likely to die over a five-year period than were patients with major depression in usual care practices. Since this effect was limited to deaths due to cancer, the authors stress that further investigation is warranted (Gallo et al. 2007).

Another important study looked at hope and hopelessness during the dying process¹²⁹ and found that the end-of-life-process is becoming more prolonged and more shaped by human choice. It further found that in the dying elderly, hopelessness is a more reliable indicator of depression than depressed mood, is a stronger predictor of suicide, and is more often linked to cardiac mortality in those with coronary disease. The authors suggested that clinicians go beyond competence evaluations and depression treatments to offer hope to patients through providing timely and thorough palliative care that reduces symptoms, invite family and friends into the ICU or nursing home, facilitate patient life review by guiding them in writing biographies and dictating stories, and foster the strengthening of relationships and reconciliation with friends and family.¹²⁹

African Americans

In a review of 24 studies on the evaluation and treatment of African Americans with depression, one analysis found that, for this population specifically, major depression may be under-diagnosed and inadequately managed due to barriers such as lack of familiarity with clinical presentation in this group, access problems, and competing clinical demands of co-morbid medical disorders.¹³⁰ It is especially important that in any patient-caregiver dyad in which the parties are of different ethnic, cultural, or racial origin, particular attention is paid to possible misinterpretation of clinical signs and symptoms based on differences in presentation, treatment preferences, treatment response, and disease course.

Children and Adolescents

The APA guidelines include scant information regarding assessment and treatment of depressive disorders in children and adolescents, and the associated Guideline Watch includes a section on antidepressants and suicide risk in this population.¹³² The American Academy of Child and Adolescent Psychiatry (AACAP) has issued practice parameters for assessment and treatment of depression in this population that were originally published in 1998 and revised in 2007.¹³¹ Other literature on etiology, assessment, and treatment of depression in this population have been published.¹³²⁻¹⁴⁶ In late 2007, The Guidelines for Adolescent Depression in Primary Care (GLAD-PC) Steering Group published Guidelines for Adolescent Depression in Primary Care to assist primary care physicians in all phases of clinical management of adolescent depression. These evidence-based guidelines also include ongoing tracking of outcomes and specific steps to be taken in instances of partial or no improvement after an initial treatment program has begun (Zuckerbrot et al. 2007; Cheung et al. 2007).

More recently, a meta-analysis of 27 randomized controlled trials was conducted to assess the efficacy and risk of reported suicide ideation/attempt of antidepressants for the treatment of pediatric MDD, obsessive-compulsive disorder (OCD) and non-OCD anxiety disorders. The conclusions showed that relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Researchers also indicated that the benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity and study conditions (Bridge et al. 2007).

An earlier meta-analysis of 23 placebo-controlled clinical trials, including data from 4,582 children and adolescents with MDD, OCD, generalized anxiety, attention-deficit hyperactivity disorder, and social anxiety disorder who were prescribed SSRIs, concludes that there is a modestly increased risk for suicidal behavior in these patients when antidepressant drugs are used.¹⁷ In a matched, case control study of nearly 5,500 Medicaid beneficiaries, the authors found that for children and adolescents with depression severe enough to warrant inpatient care, antidepressant drug treatment was significantly associated with suicide attempts and suicide deaths.¹⁹

Following the FDA's Black Box Warning on antidepressant use in children and adolescents in 2004, the rate of prescription of antidepressants for children and adolescents dropped by 20 percent, leading several professional organizations to issue a statement in support of combination treatment (medication and psychotherapy) for children and adolescents with depression.⁵⁴ Since that time, further analysis of a large pediatric national integrated claims data base has been conducted showing that the FDA advisory was associated with significant reduction in aggregate rates of diagnosis and treatment of depression. Pediatricians and non-pediatrician primary care physicians accounted for the largest reduction in new diagnoses. Among patients with depression, the proportion receiving no antidepressant increased to three times the rate predicted by the pre-advisory trend, and SSRI prescription fills were 58 percent lower than predicted by the trend. Additionally, there was no evidence of a significant increase in use of treatment alternatives—psychotherapy, atypical antipsychotics and anxiolytics (Libby et al. 2007). While more research is needed, it is clear that every clinician who treats children and adolescents who have been prescribed an antidepressant—whether or not he or she is the prescribing clinician—should be especially vigilant for signs of increased suicidal ideation, intent, or behavior on the part of these patients. Furthermore, discussion with the patient, family, and/or primary custodian regarding the clinical signs that may indicate increased suicide risk is essential.

Prevention

Studies have shown that depression tends to aggregate in families,¹³⁴⁻¹⁴⁶ and the incidence of depression among offspring of adults with depression has been found to be as high as 45 percent.¹³² Children with at least one first-degree relative with depression have been found to have a three-fold increased risk of developing MDD.¹³³ Also, childhood depression is generally under-identified.¹³⁸ Only about 25 percent of depressed offspring of parents with depression receive treatment,¹¹¹ and those children have a higher mean total of annual health care costs than their peers.¹⁴⁶ Efforts to prevent depression have focused mainly on adults. However, a growing body of literature supports the effectiveness of prevention programs for children who are at risk for depression, including children who are the offspring of parents with depression.^{143,147-152}

Providing information to depressed parents on risks of depression and ways to foster resilience in their children has been found to increase behavioral and attitudinal changes in their children.^{145,147} In addition, increasing children's understanding of parental depression has also been found to promote resilience.¹⁴⁸

Prevention of a first depressive episode appears to be possible in high-risk adolescents, defined as those adolescents ages 13 to 18 with subsyndromal symptoms of depression but not MDD, and who also have a parent who received treatment for MDD in the past year. In one study, 49 high-risk adolescents received 15 weekly sessions of CBT, and 49 received no intervention. During the subsequent 15 months, 29 percent of non-treated adolescents experienced a first episode of MDD versus 9 percent who had CBT.¹⁵³

A meta-analytic review of 19 studies on the efficacy of preventive interventions in reducing the number of depressive disorders was conducted and revealed that prevention of new cases of depression may be possible. Findings revealed no systematic differences between target populations or types of prevention (universal, selective or indicated). The results also showed that the number of patients needed to treat to prevent one case of depressive disorder was 22 and that prevention based on interpersonal psychotherapy may be more effective than prevention based on CBT (Cuijpers et al. 2008).

Other psychiatric prevention studies have been conducted in medically ill patients in an effort to evaluate current strategies to reduce episodes of concurrent depression. One study of non-depressed post-stroke patients investigated the use of escitalopram in double-blind trial, and problem-solving therapy in an open trial, in order to determine their effects on prevention of depression within the first year after the event. The results showed that 7.2 stroke patients would need to be treated with escitalopram or 9.1 patients with problem-solving therapy to prevent one case of depression (Robinson et al. 2008). Similarly, a prospective study of patients being treated for head and neck cancer (HNC) showed that use of a prophylactic antidepressant (citalopram) may prevent some cases of MDD during the first 16 weeks following initiation of cancer therapy. Study findings also suggested that some mitigation in the expected decline in quality-of-life typically during HNC therapy may have been achieved and psychological health better retained (Lydiatt et al. 2008). Prevention of recurrence is critically important in depressive disorders as the APA Guideline emphasizes that on average 50 percent to 85 percent of patients with a single episode of depression will have at least one more episode. This risk of recurrence increases over time and with each subsequent depressive episode. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study examined the safety and efficacy of venlafaxine extended release (ER) in the preventing recurrence of depression. Study results showed that an additional 12 months of maintenance with venlafaxine ER was effective in preventing recurrence of depression in patients who had been responders to venlafaxine ER after acute (10 weeks), continuation (six months) and initial maintenance (12 months) therapy. This study provides new direction because while the APA guideline indicates that maintenance therapy is essential for recurrent depression, the optimal duration, choice of antidepressants and use of supplemental CBT for maintenance treatment remains a focus of clinical research (Keller et al. 2007).

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