Introduction to Magellan’s Adopted Clinical Practice Guideline
For the Assessment and Treatment of Patients
With Major Depressive Disorder
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Magellan Clinical Practice Guideline: Major Depressive Disorder

Magellan Health, Inc. Clinical Practice Guideline Task Force

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Purpose of This Document

Magellan Healthcare has adopted the American Psychiatric Association’s (APA) Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition (2010) to serve as an evidence-based framework for practitioners’ clinical decision-making with adults who have unipolar depression. The APA guideline is among the most comprehensive, evidence-based clinical practice guidelines (CPGs) for this disorder, and is widely used. It incorporates the rapidly evolving developments in pharmacotherapy and somatic treatments, as well as developments in other areas of clinical management for patients with major depressive disorder (MDD). The APA guideline covers most areas of psychiatric management of patients with this disorder, including topics from clinical features and epidemiology to numerous aspects of treatment approach and planning. Since this guideline is broadly accepted by managed behavioral health care organizations (MBHOs), this adoption will minimize the burden on practitioners participating in multiple MBHOs.

This introduction and the APA guideline are 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. For patients with known or suspected bipolar depression, please 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 and the associated Guideline Watch, both of which are available on the APA website.

As with all guidelines, this adopted guideline and Magellan’s Introduction augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to the treatment guideline are noted in the member’s record. Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval for specific medications or devices and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

Content of This Adopted Guideline

The APA 2010 major depressive disorder guideline covers the assessment and treatment of major depressive disorder. It summarizes treatment recommendations and describes elements of psychiatric management in the formulation and implementation of a treatment plan. The guideline examines specific clinical features influencing the treatment plan, e.g., psychiatric factors,
demographic and psychosocial variables, and co-occurring general medical conditions. It provides a review and synthesis of available evidence regarding the efficacy of various treatments, including acute phase somatic treatment, specific psychotherapies, psychotherapy combined with pharmacotherapy, continuation treatment and maintenance treatment.

**Additional Recommendations Based on Recent Literature Review**

The APA guideline is based on a literature review through May 2009. Magellan conducted a further review of the clinical literature on assessment and treatment of major depressive disorder published through February 2015. Key relevant recommendations from this more recent review are included and summarized below. Magellan encourages providers to become familiar with this information, as well as the information in the APA guideline.

**Executive Summary**

(Discussion of changes/new information in this updated guideline)

**Disease Definition, Natural History, and Course and Epidemiology**

A recent study examined data from a study of male-female, adult, white, dizygotic twin pairs (n=1057) to delineate risk factors that may contribute to a higher rate of major depression in one sex over the other. Of the 1057 twin pairs, both members in 12 pairs had episodes of major depression in the past year, while only one of the members had episodes of major depression in 208 pairs. In the 208 pairs discordant for major depression, episodes of major depression were present in female members in 62% of the pairs, while present in male members in only 38% of the pairs. In two waves of personal interviews at least 1 year apart, researchers studied how 20 risk factors differed in how they are associated with major depression in males and females. Acute stressors, e.g., lack of achievements at work, played a stronger etiologic role in major depression in males, whereas personality and failures in interpersonal relationships played the stronger etiologic role in females.

**DSM-5 Changes for Major Depressive Disorder**

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5™) refers to major depressive disorder as the classic condition in depressive disorders, characterized by episodes of at least 2 weeks’ duration, including changes in affect and cognition. Single episodes are possible, although in most cases, the disorder is a recurrent one. The bereavement exclusion is eliminated from the DSM-5. Ordinary grief is not an illness, but grieving persons are not immune to major depressive disorder. According to Pies, bereavement is a common trigger for major depressive disorder and some bereaved patients will benefit from cognitive, supportive or grief-oriented psychotherapies. Others, e.g., more severely depressed patients or suicidal patients, may require treatment with medication and/or psychotherapy. He cautioned that normal grief not be medicalized, while major depression should not be normalized simply because it may occur in the context of bereavement.
Antidepressant Medications

The fourth member of the SNRI class to receive FDA approval for major depressive disorder is levomilnacipran (Fetzima®), approved on July 25, 2013 by the FDA. The efficacy of levomilnacipran sustained release in moderate to severe major depressive disorder was investigated in a 10-week randomized, double-blind, placebo controlled trial. Patients (n=563) were randomized to receive placebo or once-daily levomilnacipran (75 mg), with the dose increasing to 100 mg, if good tolerance was discerned, on day 12 through the end of the study. Study results showed that patients treated with levomilnacipran had significantly greater decrease from baseline in mean Montgomery Asberg Depression Rating Scale (MADRS) score from week 3 onward than those receiving placebo. Additionally, patients receiving levomilnacipran had significantly greater improvement on Hamilton Rating Scale for Depression (HDRS) from baseline to week 10. Compared with placebo, response and remission rates were significantly greater for levomilnacipran compared with placebo. Treatment emergent adverse events (i.e., hyperhidrosis, constipation, diarrhea, tachycardia, palpitations, and hypertension) occurred in the levomilnacipran group with at least twice the frequency of the placebo group. Nine patients reported serious adverse events in the placebo group, compared to four patients in the levomilnacipran group. Withdrawals due to adverse events occurred in 6.5% of the placebo group and 9.4% of the levomilnacipran group; the most common adverse event in the placebo group was suicidal ideation while nausea and vomiting were the most common in the levomilnacipran group. Researchers concluded that evidence from this study suggest that levomilnacipran sustained release is a welcome addition as a treatment for major depressive disorders. There are no published studies comparing levomilnacipran to other antidepressants for the treatment of major depressive disorders.

On September 30, 2013, the FDA approved vortioxetine (Brintellix®), a so-called “serotonin modulator and stimulator” for the treatment of major depressive disorder. The FDA news release noted that six randomized placebo controlled clinical studies demonstrated vortioxetine’s effectiveness in treating depression and in decreasing the likelihood of patients becoming depressed after treatment of a major depressive episode. In a recent 8-week randomized, double-blind, duloxetine-referenced study, Mahableshwarkar et al. evaluated the efficacy, safety, and tolerability of this new antidepressant in patients (n=614) with major depressive disorder. In this study, patients were randomized to receive placebo, vortioxetine 15 mg, vortioxetine 20 mg, or duloxetine 60 mg once daily during the study period. Improvement from baseline in MADRS total score was not significantly greater than placebo at week 8 in the vortioxetine 15 mg group; however, patients in the vortioxetine 20 mg group demonstrated significantly greater decrease from baseline in the MADRS at 8 weeks than those in the placebo group. The active reference, duloxetine, had the greatest decrease from baseline at 8 weeks. Importantly, 36% of patients in the placebo and vortioxetine 15 and 20 mg groups reported treatment emergent adverse events compared to 53% of those in the duloxetine group. Researchers concluded that vortioxetine 20 mg/day significantly reduced the MADRS total scores after 8 weeks of treatment with both the 15- and 20-mg doses well tolerated.

Augmenting and Combining Treatments

The APA guideline cautions that when compared with other strategies for antidepressant nonresponders, augmentation with a second-generation antipsychotic carries risks which should be considered: weight gain and other metabolic complications, hyperprolactinemia, tardive dyskinesia, neuroleptic malignant syndrome, QTc prolongation and high cost of many agents. A recent post hoc
analysis of data from patients (n=292) with major depressive disorder, enrolled in a 52-week open-label study, examined the safety, tolerability and effectiveness of long-term treatment with aripiprazole adjunctive to either bupropion, SSRIs, or SNRIs. When aripiprazole was added to either bupropion or an SSRI/SNRI, the Clinical Global Impression Scale (CGIS) showed improvement in depressive symptoms over 52 weeks. Aripiprazole augmentation with bupropion had a safety profile comparable to that of augmentation with SSRIs/SNRIs and was not associated with any unexpected adverse events. In participants receiving aripiprazole augmentation with bupropion, rates of akathisia were no higher than with aripiprazole adjunctive to SSRI/SNRIs. Seizures, one of the neurologic side effects reported with bupropion, were not reported in this group, but patients with a significant history of seizure disorder were excluded. An increase in weight occurred in all groups, without an apparent association between type of antidepressant and extent of weight gain. Aripiprazole combinations with bupropion or SSRI/SNRI were not associated with exacerbation of sexual dysfunction. Researchers concluded that the addition of aripiprazole augmentation to antidepressant therapy results in improvements in depression symptoms and sexual function, and is not associated with any unexpected adverse events. The tolerability of adjunctive aripiprazole was similar between bupropion and SSRI/SNRI.

An 8-week double-blind placebo-controlled study tested whether the addition of creatine monohydrate (creatine) to escitalopram in the treatment of patients with major depressive disorder would lead to more rapid onset of antidepressant effects and greater treatment response. Women (n=52) with major depressive disorder were randomly assigned to receive escitalopram plus creatine or escitalopram plus placebo with results measured by changes in the Hamilton Depression Rating Scale (HAM-D) score. Greater improved depressive symptoms were evidenced in the group receiving creatine augmentation as early as week 2, and were maintained until the end of treatment. Researchers suggested further studies to replicate this finding in a larger sample and with a longer observation period.

Treatment Strategies for Depression with Psychotic Features

Acknowledging that previous research has not demonstrated the efficacy of psychotherapy for major depression with psychotic features, Gaudiano et al. conducted an open trial of a new behavioral intervention that combined elements of Behavioral Activation (BA) and Acceptance and Commitment Therapy (ACT) with pharmacotherapy. The new intervention, Acceptance-based Depression and Psychosis Therapy (ADAPT) was developed by Gaudiano et al. and its preliminary effects were tested in this study. Delivered in weekly individual sessions for up to six months and integrating both BA and ACT, the therapy focuses on improving functioning by implementing acceptance and mindfulness-based coping strategies. Four phases of therapy include (1) Rapport Building - building a therapeutic alliance – therapist elicits short-term behavioral treatment goals linked with the patient’s values, highlighting discrepancies between values and behaviors linked with symptoms, (2) Behavioral Activation – developing a behavioral activation plan - therapist teaches patient to monitor mood and activities, explaining the role of avoidance in influencing mood; teaches patient to monitor avoidance patterns prior to attempting to change them, (3) Acceptance and Mindfulness – implementation of behavioral activation strategies and psychoeducation – therapist teaches patient to defuse from negative thoughts, increase willingness to experience distress, practice mindfulness techniques, (4) Relapse Prevention – ensuring that patient has a clear plan post-ADAPT treatment based on clinical needs and patient preferences – focuses on improved functioning and quality of life rather than symptom reduction. All patients (n=14) received pharmacotherapy, involving antidepressant medication, as well as antipsychotic and other medications as appropriate. Researchers noted that this is the first study to demonstrate the
feasibility, credibility, acceptability, and potential efficacy of psychotherapy in conjunction with pharmacotherapy for the treatment of patients with psychotic depression. Results showed large and sustained reductions in depressive and psychotic symptoms following an acute episode as well as significant improvements in psychosocial functioning over time. The majority of patients showed clinically significant changes in symptoms, and 55% of those who completed the study were in remission for depression and psychosis through follow-up. Researchers suggested future randomized controlled studies examining the effects of pharmacotherapy alone versus pharmacotherapy plus ADAPT to better understand the efficacy of ADAPT for major depression with psychotic features.\textsuperscript{10}

**Antidepressants and Suicidal Ideation and Behaviors**

In a recent population-based cohort study, Cheung et al. investigated the association between antidepressant use and risk of suicide in incident antidepressant users in relation to time since beginning therapy.\textsuperscript{11} Researchers conducted this study using the Dutch Integrated Primary Care Information database of patient records from more than 600 Dutch practitioners between 1994 and 2012. The study population included patients (n=27,712) with an incident antidepressant prescription and included data from the date of first antidepressant drug prescription until first attempted or completed suicide or end of study period on February 1, 2012. More women than men were included in this group. Patients using SSRIs were younger than those using TCAs, and the largest group of patients with a diagnosis of depression used SSRIs. Findings showed that history of self-harm and psychotropic drug use, i.e., antipsychotics, anxiolytics, and hypnotics and sedatives were the strongest factors associated with the risk of suicide. Significant associations with suicide were not evident in patients with current use of SSRIs or other antidepressants compared to those with past use of antidepressants. Patients receiving TCAs at a high dose compared to low dose had higher risk of suicide, but in patients treated with SSRIs, significant differences were not observed between high and low doses. Researchers summarized that no evidence was found for increased risk of suicide or suicidal attempts in the first weeks of treatment in patients who were treated with SSRIs, TCAs, or other antidepressants when compared with patients previously treated with antidepressants.\textsuperscript{11}

In a recently published cohort study using a primary care database including patients (n=238,963) aged 20 to 64 years with a first diagnosis of depression, researchers assessed the associations between different antidepressant treatments and the rates of suicide, attempted suicide, and self-harm (Coupland et al, 2015). Patients whose mean age was 39.5 included in this study had their first diagnosis of depression between January 2000 and August 2011 and were followed up until the earliest of leaving the practice, death or end of follow-up in August 2012. Results showed similar rates of suicide and attempted suicide or self-harm during treatment with SSRIs and TCAs and related antidepressants. The antidepressants associated with the highest rates of suicide and attempted suicide or self-harm were mirtazapine, venlafaxine and trazodone. Researchers acknowledged that estimates were imprecise due to the small number of suicide events. Increased rates of suicide events occurred in the first 28 days of starting and stopping antidepressants, but researchers pointed out that periods when patients were not taking antidepressants likely reflected the absence of current depression or less severe depression. Researchers suggested careful monitoring of patients taking antidepressant drugs, especially during early treatment with antidepressants, and when discontinuing the treatment.
The Antidepressant Pharmaceutical Pipeline

A study by Nagele et al. tested the antidepressant effects of nitrous oxide, an agent with a similar mechanism of action as ketamine.\textsuperscript{12} Patients with treatment-resistant depression (n=20) were randomly assigned to inhalation over one hour of either a mix of 50% nitrous oxide/50% oxygen (active treatment) or 50% nitrogen/50% oxygen (placebo). One week after the first treatment, patients returned and were switched in the crossover study, receiving either the treatment or placebo. They were assessed at pretreatment, 2 hours after each treatment, and 24 hours after each treatment. The primary outcome measure was change in the HDRS score 24 hours after treatment. Results showed significant improvement in depressive symptoms at 2 hours and 24 hours after receiving active treatment compared with placebo. Several patients even showed lower HDRS scores when they had the second treatment one week later. Researchers noted that compared with ketamine, nitrous oxide had a similarly rapid onset of antidepressant action while patients receiving nitrous oxide did not have the psychotomimetic side effects that occur with ketamine (delusions, illusions, hallucinations). They concluded that although this study provides evidence of nitrous oxide’s antidepressant effects in patients with treatment resistant depression, larger studies are required to determine optimal dosing strategies and to evaluate risks and benefits of this treatment in diverse populations of patients with treatment resistant depression.\textsuperscript{12} The FDA has not approved the use of nitrous oxide in the treatment of depression.

Agomelatine (trade names Valdoxan, Melitor or Thymanax) is a novel antidepressant approved for use in the European Union in 2009.\textsuperscript{13} Taylor et al. indicated that it “is thought to act through a combination of antagonist activity at 5\textsubscript{HT}2\textsubscript{C} receptors and agonist activity at melatonergic MT\textsubscript{1}/MT\textsubscript{2} receptors” (Taylor et al, page 1). Further, they indicated the uniqueness of agomelatine among antidepressant drugs, as it lacks an ability to interfere with the neuronal reuptake of serotonin, norepinephrine, or dopamine. In a recent systematic review and meta-analysis of published and unpublished studies, researchers identified 20 trials evaluating the efficacy of agomelatine in the acute treatment of adult participants (n=7640) meeting the criteria for major depressive disorder. These randomized, double blind, and controlled (placebo and/or other antidepressant) studies showed that agomelatine is moderately more effective than placebo and has similar efficacy to standard antidepressants (outcome measures included the HDRS and the MADRS). This meta-analysis suggests an effect size for agomelatine of 0.24 compared to placebo, which researchers noted is small in absolute terms and is smaller than the effect size (0.31) calculated from other reviews of trials of other antidepressants. In this study, participants randomized to agomelatine were less likely to discontinue treatment due to adverse effects than those receiving other antidepressants and no more likely to discontinue than those randomized to placebo. Researchers concluded that with agomelatine’s unique pharmacological mode of action combined with good tolerability as evidenced in these studies, it is an effective antidepressant with similar efficacy to standard antidepressants.\textsuperscript{13} The FDA has not approved agomelatine for use in treating depression.

Clinical trials are currently studying the safety and efficacy of fixed-dose brexpiprazole as adjunctive therapy in the treatment of adults with major depressive disorder with and without anxious distress. Brexpiprazole is a serotonin-dopamine activity modulator (SDAM), acting as a partial agonist at 5\textsubscript{HT}1\textsubscript{A} and dopamine D2 receptors, and an antagonist at 5-HT2A and noradrenaline alpha 1B/2C receptors. It is a novel compound with a close structural analogue of aripiprazole. In one randomized, placebo-controlled phase of a recent study including patients (n=379) with major depressive disorder, those receiving adjunctive brexpiprazole (2 mg/d) had significant improvement in MADRS mean scores compared with placebo at 6-week endpoint.\textsuperscript{14}
Other Somatic Treatments

In a recent non-blinded, randomized controlled trial performed in Sweden, researchers randomly assigned patients (n=56) with unipolar or bipolar depression who had responded to a course of ECT to receive one of two treatments: (1) 29 treatments of continuation ECT with pharmacotherapy or (2) pharmacotherapy alone for one year. Pharmacotherapy consisted of antidepressants, lithium, and antipsychotics. This study tested whether relapse prevention with continuation electroconvulsive therapy plus pharmacotherapy is more effective than pharmacotherapy alone after a course of ECT for depression. Results found that the one-year relapse rate was greater in the pharmacotherapy alone group (61%) compared with 32% in the ECT plus pharmacotherapy group. The six-month relapse rates were 36% in the pharmacotherapy alone group, compared with 29% in the ECT plus pharmacotherapy group. Additionally, one suspected suicide by intoxication occurred in the pharmacotherapy alone group. Researchers suggested further studies to define indications for continuation ECT, pharmacotherapy, and the combination of the treatments.

The APA guideline discusses the association of ECT with cognitive effects noting that only rarely do patients report persistent cognitive disruption following ECT. Cusin et al. discussed studies suggesting that the administration of an ultrabrief pulse to induce the seizure causes fewer cognitive adverse effects. In a recent randomized controlled trial of brief and ultrabrief pulse right unilateral ECT, participants (n=102) with major depressive disorder were randomly assigned to receive ultrabrief (at 8 times seizure threshold) or brief (at only 5 times seizure threshold) pulse right unilateral ECT. This study tested whether ultrabrief pulse right unilateral ECT results in fewer cognitive side effects than brief pulse right unilateral ECT when given at doses which achieve comparable efficacy. In this study, the dosage of ultrabrief pulse ECT increased to a dose level likely to achieve comparable efficacy to brief-pulse ECT. Results showed that when ultrabrief pulse ECT was given at a higher dosage than brief pulse ECT (8 versus 5 times seizure threshold), ultrabrief pulse ECT had comparable efficacy to brief-pulse ECT. Increasing the dosage also diminished its overall cognitive advantage.

A recent systematic review and meta-analysis of randomized, double-blind and sham-controlled trials investigated response, remission, and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) for primary major depression. The trials used HF-rTMS over the left dorsolateral prefrontal cortex (DLPFC) with a focus on treatment-resistant cases. Analysis of data from 29 randomized control trials including subjects (n=1371) with major depression found this neuromodulation technique to be significantly more effective than sham rTMS both in response and remission rates. HF-rTMS was just as effective as an augmentation strategy as a monotherapy for major depression when used for treatment resistant depression (or in patients with less resistant depression). HF-rTMS was equally effective in subjects with primary unipolar major depression and in mixed samples with unipolar and bipolar major depression. Researchers suggested that future studies shift away from establishing the efficacy of current stimulation protocols against sham rTMS, but instead focus on new ways of improving its therapeutic effects, tolerability and availability. They suggested new protocols and devices, e.g., theta burst stimulation, H-coil, and the targeting of alternative brain regions, such as dorsomedial, ventrolateral and ventromedial prefrontal cortices.

Shafi et al. reported the effects of low field magnetic stimulation (LFMS) in a large group of stably medicated, depressed patients (n=63) with either bipolar depression of major depressive disorder. The single, 20-minute treatment was applied in a double-blind, sham-controlled design.
with change in mood assessed immediately after treatment using a visual analog scale (VAS), the Hamilton Depression Rating Scale (HDRS-17) and the Positive and Negative Affect Schedule scales. Results demonstrated substantial improvement in mood ten to fifteen minutes after LF-rTMS treatment relative to sham treatment. Authors suggest a need for further exploration of the benefit from combining neuromodulation techniques with conventional behavior and/or pharmacologic therapy.19

**Psychosocial Treatments**

A recent study compared mindfulness-based cognitive therapy (MBCT) with both cognitive psychological education (CPE) and treatment as usual (TAU) in preventing relapse to major depressive disorder.20 Patients (n=255) currently in remission following at least three previous major depressive episodes were randomized to one of the three treatment conditions (Williams et al., 2014). Researchers noted that past studies had not compared MBCT with an active psychological treatment, preventing knowledge about whether the beneficial benefits of MBCT are attributable to the learning of mindfulness meditation skills rather than nonspecific factors such as group support. CPE, following the same group format as MBCT, included no training in meditation and provided a control treatment. Researchers compared the outcomes of both CPE and MBCT with those of TAU and examined how variables, e.g., number of prior episodes of depression, age of first onset of major depressive disorder, history of suicidal ideation or behavior, adversity in childhood and adolescence are associated with outcomes of MBCT. Time to relapse to major depression was the main outcome of the trial which found that treatment group generally had no significant main effect on risk of relapse. However, for persons with high childhood trauma scores, the raw rates of relapse for MBCT, CPE, and TAU were 41%, 54%, and 65%, respectively, and for those with no history of childhood trauma, relapse risk was not reduced by MBCT compared with TAU. Researchers suggested that MBCT is superior to both an alternative psychological treatment and TAU in preventing recurrence of depression over 12 months when severity of childhood trauma is considered. Other than this, there were no general differences in outcome according to the allocated treatment. They concluded that their findings support the body of evidence that psychological interventions may help prevent future episodes of major depression, especially for those at highest risk of relapse.20

A current systematic review provided an overview of recent randomized studies describing the effectiveness and efficacy of sole individual psychotherapy (IPT) in comparison with other forms of psychotherapy and/or pharmacotherapy.21 Eight studies were reviewed including patients (n=1233) with major depressive disorder out of which 854 patients completed treatment in outpatient facilities. Treatments included usual care consisting of communication with a physician for appropriate treatment, IPT, Cognitive Behavioral Analysis System of Psychotherapy, CBT, pharmacotherapy plus clinical management, IPT plus nefazodone, IPT plus placebo, placebo plus clinical management, or pharmacotherapy (i.e., nefazodone, nortriptyline hydrochloride, or venlafaxine hydrochloride). Findings include: (1) the efficacy of IPT and CBT appeared to be equal, (2) the efficacy of IPT and nortriptyline were similar, (3) IPT combined with nefazodone had a higher efficacy than sole nefazodone, (4) pharmacotherapy combined with clinical management appeared to have higher efficacy than IPT alone, and (5) IPT and Cognitive Behavioral Analysis System of Psychotherapy were comparable in efficacy. Researchers concluded that differences between treatment effects were very small and insignificant. They recommended psychotherapeutic treatment such as IPT and CBT and/or pharmacotherapy as first-line treatments for adult outpatients, suggesting consideration of individual preferences of patients in choosing a treatment.21
In a later study comparing the efficacy of psychodynamic therapy with CBT in the outpatient treatment of major depression, adults (n=341) with major depression were randomly assigned to 16 sessions (within 22 weeks) of individual manualized CBT or short-term psychodynamic supportive therapy. Results showed that less than 25% of patients reached remission within 22 weeks of treatment, with no significant difference in rates between the two groups. One-year follow-up rates of remission were 34.7% and 26.8% in the CBT and psychodynamic therapy groups, respectively. Researchers indicated that these findings extend the evidence base of psychodynamic therapy for depression, but that many patients encountered in psychiatric outpatient clinics require more than time-limited treatment in order to reach remission.

**Combination Pharmacology and Psychotherapy Treatments**

In a recent trial assessing the efficacy of combining cognitive therapy (CT) with antidepressant medication (ADM), researchers randomly assigned adult outpatients (n=452) with chronic or recurrent major depressive disorder to ADM treatment alone or CT combined with ADM treatment. Treatment continued up to 42 weeks. Patients in both treatment groups received personalized antidepressant therapy; most received SSRIs or SNRIs while some switched to tricyclic antidepressants or monoamine oxidase inhibitors. CT occurred in 50-minutes sessions held twice weekly, weekly, and monthly during the first 2 weeks, acute treatment, and continuation treatment, respectively. Outcome measures were the Hamilton Rating Scale for Depression and the Longitudinal Interval Follow-up. Results of this study included: (1) high remission rates in both groups, not differing significantly based on treatment group, and (2) no significant difference in recovery rates for patients with low-severity major depressive disorder in the two treatment groups, but higher rates of recovery in the combined group for patients with high-severity depression. Researchers concluded that combined medication treatment with cognitive therapy enhances rates of recovery compared to medication treatment alone, but this effect may be limited to patients with severe nonchronic depression.

A recent meta-analysis of randomized trials compared the effects of treatment with antidepressant medication to the effects of combined pharmacotherapy and psychotherapy in adults with a depressive or anxiety disorder. Researchers analyzed the results of 52 studies (3,623 patients) of which 32 studies involved depressive disorders. Treatments included antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs) and psychotherapies (e.g., CBT, IPT, and psychodynamic therapies). Evidence from this study found combined treatment was more effective than pharmacotherapy alone in major depression, OCD, and panic disorder. The effect size of difference between the two groups was not associated with baseline severity of depression. Researchers found clear evidence that combined treatment with psychotherapy and antidepressant medication is significantly more effective than treatment with antidepressant alone for major depression, panic disorder, and OCD. Analysis of the study results also showed that psychotherapy and pharmacotherapy may be additive, and not interfering with each other while contributing similarly to the effects of combined treatments. In conclusion, researchers summarized that results support the use of combined treatment, rather than psychotropic medication alone.

**Complementary and Alternative Treatment**

A recent meta-analysis of 13 randomized trials compared the effects of combined acupuncture and antidepressant medications to antidepressants alone in the treatment of adults (n=1046) with major depressive disorder. Results indicated greater therapeutic efficacy of the combination
treatment than of SSRI treatment alone. Authors suggested that acupuncture combined with antidepressant medication has an early onset of action, is effective, and well tolerated over a 6-week treatment period. They suggested the need for further high quality, randomized clinical trials evaluating the clinical benefit and long-term effectiveness of acupuncture in the treatment of depression.25

The APA Guideline notes that data supports modest improvement in mood symptoms for patients with major depressive disorder who engage in aerobic exercise or resistance training, and that regular exercise reduces the prevalence of depressive symptoms in the general population. A recent study, Treatment with Exercise Augmentation for Depression (TREAD), examined whether exercise was associated with fewer and less-severe symptoms associated with major depressive disorder (Rethorst et al, 2013). Adults, ages 18-70 years (n=122), with major depressive disorder who had a partial response to an SSRI were randomized to a "low dose" group that engaged in 40-60 minutes of aerobic exercise per week or a "high dose" group engaging in 150 minutes of aerobic exercise per week for 12 weeks. Results showed that patients in the high-dose group were more likely to have fewer and less-severe symptoms of major depressive disorder, higher recovery rates, and longer remission than those in the low-dose group. Aerobic exercise also was associated with reducing blood levels of pro-inflammatory cytokines, which are elevated in some depressed patients. Rethorst and Trivedi provided recommendations, e.g., assessment of the patient's overall health and ability to participate in regular exercise, advising patients on the benefits of exercise related to depression, assistance to patients with problem-solving techniques and creating atmosphere of support (Psychiatric News, 2014).

**Depression and Pregnancy**

In a recent article reviewing recent studies of relapse of major depression in women who continue or discontinue antidepressant medication during pregnancy, Guille and Epperson noted conflicting results from two recent studies.26 27 28 A study by Cohen et al. demonstrated women (recruited from psychiatric treatment centers) with a history of recurrent major depression who discontinued antidepressant treatment during pregnancy or just before conception were five times as likely to have a relapse compared with women who continued medication during pregnancy. Another prospective study of pregnant women (recruited from community- and hospital-based obstetric clinics) with a history of depression found no difference in risk of major depressive episode in women who discontinued antidepressant treatment compared with those who continued with the medication. Guille and Epperson suggested that the conflicting results may be attributable to these divergent populations; individuals from the psychiatric centers had more severe depression and comorbid psychiatric illness. They also noted in both studies, women with at least four previous episodes of depression had greater risk of relapse of depression during pregnancy.26

**Depression and Older Adults**

A recent study evaluated whether adding methylphenidate to treatment with citalopram improves antidepressant response in older outpatients diagnosed with major depression.29 In this 16-week randomized double-blind placebo-controlled trial, patients (n=143) whose mean age was 70.1 with major depression of moderate severity and who were free of psychotropic medications for two or more weeks were assigned to one of three treatment groups: methylphenidate plus placebo, citalopram plus placebo, or citalopram plus methylphenidate. Mean doses were 32 mg and 16 mg for citalopram and methylphenidate, respectively. Improvement in depression severity in the combined citalopram and methylphenidate group was significantly higher than in the other two
groups. There were no differences in cognitive improvements or number of side effects in the
groups. Researchers concluded that a citalopram and methylphenidate combination demonstrates a
higher rate of remission compared with either drug alone.\textsuperscript{29} Yager commented that based on these
findings, carefully selected depressed seniors may benefit from combining a selective serotonin
reuptake inhibitor with methylphenidate, and that further studies are needed including
antidepressants other than citalopram in the combination treatment.\textsuperscript{30}

**Healthcare Effectiveness data and Information Set (HEDIS) Measures**

The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of performance measures
developed and maintained by the National Committee for Quality Assurance (NCQA). HEDIS
measures that include major depressive disorder diagnosis are: Follow-Up after Hospitalization for
Mental Illness (FUH) and Antidepressant Medication Management (AMM).

Both of these measures focus on processes, rather than on outcome measures. The FUH measure
requires that patients with major depressive disorder treated in an acute inpatient setting receive a
follow-up visit within 30 days of discharge, preferably within the first 7 days after the discharge.
The AMM measure requires that patients with major depressive disorder who are 18 years of age
and older, diagnosed with a new episode of major depression, and treated with antidepressant
medication should remain on an antidepressant medication for at least 12 weeks and should
receive continuous therapy for at least 180 days (six months).

**Disease Definition, Natural History, and Course and Epidemiology**

Since publication of the APA guideline, the National Survey on Drug Use and Health (NSDUH)
reported that in 2011, 6.6 percent of adults aged 18 or over experienced at least one major
depressive episode (MDE) and 8.3 percent of adolescents experienced at least one MDE.\textsuperscript{31} The
percentage of adults with past year MDE was higher among women than among men (8.3 percent
vs. 4.7 percent) and the percentage having MDE was lower among women aged 50 or older (5.8
percent) than women aged 18 to 25 (11.0 percent) or those aged 26 to 49 (10 percent). Percentages
among adults varied by race/ethnicity in 2011: native Hawaiians or other Pacific islanders (3.2
percent), Asians (4.0 percent), Hispanics (4.6 percent), Blacks (5.6 percent), Whites (7.3 percent),
American Indians or Alaska natives (7.4 percent), and persons reporting two or more races (8.3
percent). In 2011, the percentage having past year MDE was higher among unemployed persons
(8.5 percent) and persons employed part-time (8.1 percent) than those employed full-time (5.0
percent). Among adults aged 18 or over with MDEs in the past year, 68.1 percent received
treatment (saw or talked to a medical doctor or other professional, or used prescription
medication). The NSDUH estimated that in 2013, 10.7 percent of adolescents experienced at least
one MDE in the past year and 7.7 percent had MDE with severe impairment in the past year.\textsuperscript{32}

A report from the Substance Abuse & Mental Health Services Administration (SAMHSA) shows that
the onset of puberty is associated with an increase in depression among adolescents, particularly
among adolescent girls.\textsuperscript{33} Results showed that 12 percent of girls aged 12 to 17 experienced a MDE
in the past year compared with 4.5 percent of their male peers. Between the ages of 12 and 15, the
percentage of girls who experienced MDE tripled (from 5.1 to 15.2 percent).

A later study examined data from a study of male-female, adult, white, dizygotic twin pairs
(n=1057) to delineate risk factors that may contribute to a higher rate of major depression in one
sex over the other.² Of the 1057 twin pairs, both members in 12 pairs had episodes of major depression in the past year, while only one of the members had episodes of major depression in 208 pairs. In the 208 pairs discordant for major depression, episodes of major depression were present in female members in 62% of the pairs, while present in male members in only 38% of the pairs. In two waves of personal interviews at least 1 year apart, researchers studied how 20 risk factors differed in how they are associated with major depression in males and females. Acute stressors, e.g., lack of achievements at work, played a stronger etiologic role in major depression in males, whereas personality and failures in interpersonal relationships played the stronger etiologic role in females.²

**DSM-5 Changes for Major Depressive Disorder**

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) refers to major depressive disorder as the classic condition in depressive disorders, characterized by episodes of at least 2 weeks’ duration, including changes in affect and cognition. Single episodes are possible, although in most cases, the disorder is a recurrent one. The bereavement exclusion is eliminated from the DSM-5. Ordinary grief is not an illness, but grieving persons are not immune to major depressive disorder.³⁴ According to Pies (2013), bereavement is a common trigger for major depressive disorder and some bereaved patients will benefit from cognitive, supportive or grief-oriented psychotherapies. Others, e.g., more severely depressed patients or suicidal patients, may require treatment with medication and/or psychotherapy. He cautioned that normal grief should not be medicalized, and neither should major depression be normalized simply because it occurs in the context of bereavement."³⁴

**Antidepressant Medications**

The APA guideline indicates that an antidepressant medication is recommended as an initial treatment for patients with mild to moderate major depressive disorder and should be provided for those with severe major depressive disorder unless electroconvulsive therapy (ECT) is planned (APA, 2010). The guideline notes that the initial selection of an antidepressant medication is largely based on tolerability, safety, cost, patient preference and history of prior medication treatment. Based on these considerations, it lists the following second-generation antidepressants as first-line pharmacotherapeutic options for treatment: selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action selectively targeting neurotransmitters, e.g., mirtazapine and bupropion. The APA guideline’s list of currently available SSRIs includes fluoxetine, sertraline, paroxetine, paroxetine extended release, fluvoxamine, citalopram and escitalopram. Since publication of the guideline, the US Food and Drug Administration (FDA) approved another SSRI, vilazodone hydrochloride, for the treatment of MDD in adults, on January 24, 2011.³⁵ SNRIs listed in the guideline include the following FDA antidepressants: venlafaxine, desvenlafaxine and duloxetine. The fourth member of the SNRI class to receive FDA approval for major depressive disorder is levomilnacipran, approved on July 25, 2013 by the FDA.

The efficacy of levomilnacipran sustained release in moderate to severe major depressive disorder was investigated in a 10-week randomized, double-blind, placebo controlled trial.⁵ Patients (n=563) were randomized to receive placebo or once-daily levomilnacipran (75 mg), with the dose increasing to 100 mg, if good tolerance was discerned, on day 12 through the end of the study. Study results showed that patients treated with levomilnacipran had significantly greater decrease
from baseline in mean MADRS score from week 3 onward. Additionally, patients receiving levomilnacipran had significantly greater improvement on the HDRS from baseline to week 10. Compared with placebo, response and remission rates were significantly greater for levomilnacipran compared with placebo. Treatment-emergent adverse events (i.e., hyperhidrosis, constipation, diarrhea, tachycardia, palpitations, and hypertension) occurred in the levomilnacipran group at least twice the frequency of the placebo group. Nine patients reported serious adverse events in the placebo group, compared to four patients in the levomilnacipran group. Withdrawals due to adverse events occurred in 6.5% of the placebo group and 9.4% of the levomilnacipran group; the most common adverse event in the placebo group was suicidal ideation while nausea and vomiting were the most common in the levomilnacipran group. Researchers concluded that evidence from this study suggest that levomilnacipran sustained release is a welcome addition as a treatment for major depressive disorders.5

On September 30, 2013, the FDA approved vortioxetine, a so-called “serotonin modulator and stimulator” for the treatment of major depressive disorder.6 In their news release, they noted that six randomized placebo controlled clinical studies demonstrated vortioxetine’s effectiveness in treating depression and in decreasing the likelihood of patients becoming depressed after treatment of a major depressive episode. In a recent 8-week randomized, double-blind, duloxetine-referenced study, Mahableshwarkar et al. evaluated the efficacy, safety, and tolerability of this new antidepressant in patients (n=614) with major depressive disorder.7 In this study, patients were randomized to receive placebo, vortioxetine 15 mg, vortioxetine 20 mg, or duloxetine 60 mg once daily during the study period. Change from baseline in MADRS total score was not significantly greater than placebo at week 8 in the vortioxetine 15 mg group; however, patients in the vortioxetine 20 mg group demonstrated significantly greater decrease from baseline in the MADRS at 8 weeks than those in the placebo group. Change from baseline in the vortioxetine 15 mg group was greater than placebo but not statistically significant. The active reference, duloxetine, had the greatest decrease from baseline at 8 weeks. Importantly, 36% of patients in the placebo and vortioxetine 15 and 20 mg groups reported treatment emergent adverse events compared to 53% of those in the duloxetine group. Researchers concluded that vortioxetine 20 mg/day significantly reduced the MADRS total scores after 8 weeks of treatment and both the 15- and 20-mg doses were well tolerated.7

The APA guideline cites several analyses that show no significant evidence of the superiority of any antidepressant over SSRIs in the treatment of MDD. A later meta-analysis of 26 studies (n=5,858) comparing venlafaxine with SSRIs in the treatment of MDD showed that it had superior response and remission rates compared with fluoxetine, but there were no significant differences in efficacy compared with other SSRIs.36 However, there were only a small number of studies comparing venlafaxine with SSRIs other than fluoxetine and researchers concluded that the evidence with regard to comparisons with SSRIs other than fluoxetine is inadequate. In another meta-analysis of data from 234 studies (n=1,000), including 118 randomized controlled trials, direct and indirect comparisons of second-generation antidepressants found no substantial differences in efficacy for the treatment of MDD.37 Researchers concluded that current evidence does not warrant recommending a particular second-generation antidepressant based on differences in efficacy, suggesting that differences in onset of action and adverse events be considered when choosing an antidepressant medication. The APA guideline notes that studies have shown that the efficacy of other second generation antidepressants, e.g., bupropion and mirtazapine, in treating MDD is comparable to that of the SSRIs. A new and reformulated antidepressant agent, hydrobromide salt of bupropion (Aplenzin), received approval on April 23, 2008 by the FDA for the treatment of depression in adults.38 It is available as extended-release tablets and provides patients who require
the maximum allowable dose of bupropion with a single tablet, once-daily option. Patients treated with high doses of bromide-containing pharmacotherapy have a risk of developing bromism and studies are needed to determine whether hydrobromide salt of bupropion has a lower risk for inducing seizures.

The APA guideline section titled "Formulation and Implementation of a Treatment Plan: Acute Phase" examines the use of older and less commonly prescribed antidepressant classes including the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) which are effective treatments for MDD and have comparable efficacy to other classes of antidepressants. When patients do not respond to first-line pharmacotherapies, these older drugs may be prescribed but their use is limited due to side effects and/or dietary restrictions in the case of the MAOIs. An FDA Alert (December 2009) was issued with new safety information on the tricyclic antidepressant desipramine specifying that extreme caution should be used when desipramine is given to patients who have a family history of sudden death, cardiac dysrhythmias and cardiac conduction disturbances. The Alert warns that seizures precede cardiac dysrhythmias and death in some patients. The APA guideline notes that the newer transdermal formulation of selegiline (the first FDA-approved transdermal patch for treatment of major depression) is advantageous over orally administered MAOIs as it can be used without the dietary restrictions that are needed for all oral MAOIs that are approved for treating major depression. Since publication of the guideline, more interest revived in the use of MAO inhibitors in the treatment of major depressive disorder, but a disadvantage of the selegiline patch is its high cost.

Although antidepressants are a mainstay of depression treatment, their efficacy is limited. The APA guideline reports that response rates in trials generally range from 50 percent to 75 percent of patients and that greater efficacy relative to placebo may be seen in individuals with severe depressive symptoms as compared with those with mild to moderate symptoms. In a review of four meta-analyses of efficacy trials submitted to the FDA and an analysis of STAR*D (Sequenced Treatment Alternatives to Relieve Depression), researchers suggested that antidepressants are only marginally efficacious compared to placebos. They cautioned that clinical trial investigators sometimes fail to report the negative results for the pre-specified primary outcome measure while highlighting the positive results of a secondary or new measure, concluding that a reappraisal of the current recommended standard of care of depression may be warranted.

### Augmenting and Combining Treatments

The combination of two antidepressants as a strategy to improve the efficacy of antidepressants was examined in a systematic review and meta-analysis comparing a combination of antidepressants with a single antidepressant from the beginning of the treatment of major depressive disorder in adults (n=250). Results of the study showed that mirtazapine plus SSRI was superior to a SSRI alone for remission, but not for response and tricyclic antidepressant plus SSRI was superior to SSRI alone both for remission and response. Although this study suggested that combined antidepressants may be more efficient in the treatment of major depressive disorder than monotherapy, placebo-controlled, short and long-term studies are necessary to assess the efficacy and tolerability of antidepressant combinations.

The APA guideline cites two studies suggesting that the combination of olanzapine and fluoxetine is not significantly more effective than continued therapy with nortriptyline or venlafaxine. In a later meta-analysis of data from five clinical studies in patients with treatment resistant MDD (n=1,146)
who had at least one historical antidepressant treatment failure during the current episode along with failing a prospective antidepressant therapy during the study lead-in period, results showed rapid, symptomatic improvement with olanzapine/fluoxetine combination therapy. Researchers found that the olanzapine/fluoxetine combination is superior to fluoxetine or olanzapine alone in producing early improvement in patients with MDD who have had prior inadequate response to antidepressants. They suggested that although the absence of rapid onset of response is highly predictive for overall response failure, the presence of rapid onset of response is not predictive for overall outcome.

Quetiapine XR received approval by the FDA on December 7, 2009 for use as an adjunctive treatment for depression. In a pooled analysis of two large, randomized, placebo-controlled studies (n=919) of extended release quetiapine fumarate adjunctive to antidepressant therapy, i.e., amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine, the anti-psychotic was found to be significantly more effective than placebo in patients with MDD who had an inadequate response to ongoing antidepressant treatment. Improvement in depressive symptoms was seen as early as one week. The study also investigated the influence of demographic and disease-related factors on responses, demonstrating that improvement in symptoms of MDD with quetiapine XR was not a result of the severity of depression, adjunctive antidepressant, gender or age. Compared with placebo, the percentage of patients withdrawing from the study due to adverse effects, i.e., somnolence and sedation, was higher in the quetiapine XR treated group than in the placebo group.

For patients with MDD who have not responded to more than two medication trials, even when there are no psychotic symptoms, the APA guideline emphasizes the augmentation of antidepressant therapy with second-generation antipsyhiotic medications, e.g., aripiprazole. Nelson et al. 2012) evaluated the efficacy of adjunctive aripiprazole in patients with minimal response to prior antidepressant therapy, pooling data from three randomized, double-blind, placebo-controlled trials (n=1,038). The findings of this study challenge the traditional clinical practice of favoring augmentation in partial responders and switching to another antidepressant in minimal responders. Researchers found that the time to response and remission were significantly shorter for patients receiving aripiprazole plus antidepressant than those receiving adjunctive placebo plus antidepressant. In a study using data from the 2009, 2010 and 2011 US National Health and Wellness Survey (NHWS) databases, Kalsekar et al. compared the levels of health-related quality of life in patients with depression (n=426) using aripiprazole plus antidepressant to patients using olanzapine, quetiapine, risperidone, or ziprasidone in combination with an antidepressant for treatment of depression. Based on the results of the study, researchers suggested that general health domain and mental health domain scores are higher among those treated with aripiprazole relative to those treated with other atypical antipsychotics, even after adjustment for demographic and health characteristics between the groups.

The APA guideline cautions that when compared with other strategies for antidepressant nonresponders, augmentation with a second-generation antipsychotic carries risks: weight gain and other metabolic complications, hyperprolactinemia, tardive dyskinesia, neuroleptic malignant syndrome, QTc prolongation and high cost of many agents. A recent post hoc analysis of data from patients (n=292) with major depressive disorder, enrolled in a 52-week open-label study, examined the safety, tolerability and effectiveness of long-term treatment with aripiprazole adjunctive to either bupropion, SSRIs, or SNRIs. When aripiprazole was added to either bupropion or an SSRI/SNRI, the CGIS showed improvement in depressive symptoms over 52 weeks. Aripiprazole augmentation with bupropion had a safety profile comparable to that of augmentation with
SSRIs/SNRIs and was not associated with any unexpected adverse events. In participants receiving aripiprazole augmentation with bupropion, rates of akathisia were no higher than with aripiprazole adjunctive to SSRI/SNRIs. Seizures, one of the neurologic side effects reported with bupropion, were not reported in this group, but patients with a significant history of seizure disorder were excluded. An increase in weight occurred in all groups, without an apparent association between type of antidepressant and extent of weight gain. Aripiprazole combinations with bupropion or SSRI/SNRI were not associated with exacerbation of sexual dysfunction. Researchers concluded that the addition of aripiprazole augmentation to antidepressant therapy results in improvements in depression symptoms and sexual function, and is not associated with any unexpected adverse events. The tolerability of adjunctive aripiprazole was similar between bupropion and SSRI/SNRI.

Augmentation of antidepressant medications can utilize other non-antidepressant agents such as lithium, thyroid hormone and stimulants. The APA guideline discusses their use for adjunctive treatment of depression. Bauer et al. questioned whether the response to lithium augmentation represents true augmentation resulting from synergistic effects or whether the response is simply owed to the antidepressant effect of lithium itself. They suggested that a randomized, double-blind study investigating the effects of lithium alone and comparing them with the effects of lithium in combination with an antidepressant is warranted. However, the authors referred to augmentation of antidepressants with lithium as the best-evidenced augmentation therapy in the treatment of depressed patients not responding to standard antidepressants. They suggested that effective lithium doses continue in combination with the antidepressant for at least 12 months after remission.

An 8-week double-blind placebo-controlled study tested whether the addition of creatine monohydrate (creatine) to escitalopram in the treatment of patients with major depressive disorder would lead to more rapid onset of antidepressant effects and greater treatment response. Women (n=52) with major depressive disorder were randomly assigned to receive escitalopram plus creatine or escitalopram plus placebo with results measured by changes in the HDRS score. Greater improvement of depressive symptoms was evident in the group receiving creatine augmentation as early as week 2 and was maintained until the end of treatment. Researchers suggested further studies to replicate this finding in a larger sample and with a longer observation period.

Treatment Strategies for Depression with Psychotic Features

The APA guideline discusses electroconvulsive therapy or pharmacotherapy as effective first-line treatments for psychotic depression and notes that the combination of an antipsychotic and antidepressant medication rather than treatment with either component alone provides better response. In a later systematic review and meta-analysis, the largest study to-date evaluating the comparative efficacy of antidepressant-antipsychotic combinations versus monotherapy with either drug class alone, Farahani and Correll (2012) reviewed eight randomized, placebo-controlled acute-phase studies in adults (n=762) comparing antidepressant-antipsychotic combined treatment with antidepressant and antipsychotic monotherapy. Evidence from the study supports antidepressant-antipsychotic combination treatment, e.g., amitriptyline + perphenazine, nortriptyline + perphenazine, venlafaxine + quetiapine, rather than monotherapy, e.g., amitriptyline, amoxapine, venlafaxine, with either an antipsychotic or antidepressant for the acute management of psychotic depression. Researchers also reported that some studies have shown that first generation antipsychotics given in combination with tricyclic antidepressants did not provide
superior efficacy compared to TCA monotherapy. In one study, researchers reported that first generation antipsychotics remained nonsignificant and only the addition of a second generation antipsychotic (quetiapine) was superior to antidepressant monotherapy (but only when added to venlafaxine). Researchers suggested additional studies are warranted to assess the effectiveness of different combinations.

Acknowledging that previous research has not demonstrated the efficacy of psychotherapy for major depression with psychotic features, Gaudiano et al. conducted an open trial of a new behavioral intervention that combined elements of Behavioral Activation (BA) and Acceptance and Commitment Therapy (ACT) with pharmacotherapy for the treatment of patients with psychotic depression. The new intervention, Acceptance-based Depression and Psychosis Therapy (ADAPT) was developed by Gaudiano et al. and its preliminary effects were tested in this study. Delivered in weekly individual sessions for up to six months and integrating both BA and ACT, the therapy focuses on improving functioning by implementing acceptance and mindfulness-based coping strategies. Four phases of therapy include (1) Rapport Building - building a therapeutic alliance – therapist elicits short-term behavioral treatment goals linked with the patient’s values, highlighting discrepancies between values and behaviors linked with symptoms, (2) Behavioral Activation – developing a behavioral activation plan - therapist teaches patient to monitor mood and activities, explaining the role of avoidance in influencing mood; teaches patient to monitor avoidance patterns prior to attempting to change them, (3) Acceptance and Mindfulness – implementation of behavioral activation strategies and psychoeducation – therapist teaches patient to defuse from negative thoughts, increase willingness to experience distress and practice mindfulness techniques, (4) Relapse Prevention – ensuring that patient has a clear post-ADAPT treatment plan based on clinical needs and patient preferences – focuses on improved functioning and quality of life rather than symptom reduction. Pharmacotherapy, involving antidepressant medication, as well as antipsychotic and other medications as appropriate, was provided to all patients. Researchers noted that this is the first study to demonstrate the feasibility, credibility, acceptability, and potential efficacy of psychotherapy in conjunction with pharmacotherapy for the treatment of patients with psychotic depression. Results showed large and sustained reductions in depressive and psychotic symptoms following an acute episode as well as significant improvements in psychosocial functioning over time. The majority of patients showed clinically significant changes in symptoms and 55% of those who completed the study were in remission for depression and psychosis through follow-up. Researchers suggested future controlled research on the efficacy of psychotherapy for major depression with psychotic features.

Antidepressants and Suicidal Ideation and Behaviors

The APA guideline notes the controversy about the risk of suicidal ideas and behaviors after initiation of antidepressant treatment and cautions that in making decisions about treatment of children, adolescents and young adults, the potential increase in suicidal thinking and behavior resulting from treatment as well as the potential negative effects of untreated depression deserve consideration. To help determine what impact antidepressants have on the course of depression and suicidal thought and behavior in different age groups, Gibbons et al. (2012) performed person-level meta-analysis or integrative data analysis of randomized placebo-controlled studies of patients with depression (n=9,185 [7,477 adults, 960 geriatric patients, 708 youths]) treated with fluoxetine and venlafaxine. Results of these analyses clarified the relationship between suicidal thoughts and behavior and antidepressant treatment, and suggested that adults and geriatric patients who do not have improvement in depressive symptoms remain at higher suicide risk. Adults treated with fluoxetine, immediate-release venlafaxine or extended-release venlafaxine and...
geriatric patients treated with fluoxetine had decreased suicidal thoughts and behavior relative to control patients receiving placebo. For all adult trials, the effect of antidepressant medication on suicide risk was mediated by decreases in depressive symptoms. For youths, no significant effects of treatment with fluoxetine on suicidal thoughts and behavior were found although depressive symptoms decreased. Researchers summarized their findings that treatment with fluoxetine and venlafaxine decreased suicide risk in adult and geriatric patients and that treatment with fluoxetine was not shown to increase the risk of suicidal thoughts or behavior in youths.

In a later population-based cohort study, Cheung et al. investigated the association between antidepressant use and risk of suicide in incident antidepressant users in relation to time since beginning therapy. Researchers conducted this study using the Dutch Integrated Primary Care Information database of patient records from more than 600 Dutch practitioners between 1994 and 2012. The study population included patients (n=27,712) who had received an antidepressant prescription and included data from the date of first antidepressant drug prescription until first attempted or completed suicide or end of study period on February 1, 2012. More women than men were included in this group. Patients using SSRIs were younger than those using TCAs, and the largest group of patients with a diagnosis of depression used SSRIs. Findings showed that history of self-harm and psychotropic drug use, i.e., antipsychotics, anxiolytics, and hypnotics and sedatives were the strongest factors associated with the risk of suicide. No significant associations with suicide were found in patients with current use of SSRIs or other antidepressants compared to those with past use of antidepressants. Patients receiving TCAs at a high dose compared to low dose had higher risk of suicide, but in patients treated with SSRIs, no significant differences were observed between high and low doses. Researchers summarized that no evidence was found for increased risk of suicide or suicidal attempts in the first weeks of treatment in patients who were treated with SSRIs, TCAs, or other antidepressants when compared with patients previously treated with antidepressants.

In a recently published cohort study using a primary care database including patients (n=238,963) aged 20 to 64 years with a first diagnosis of depression, researchers assessed the associations between different antidepressant treatments and the rates of suicide, attempted suicide, and self-harm (Coupland et al, 2015). Patients whose mean age was 39.5 included in this study had their first diagnosis of depression between January 2000 and August 2011 and were followed up until the earliest of leaving the practice, death or end of follow-up in August 2012. Results showed similar rates of suicide and attempted suicide or self-harm during treatment with SSRIs and TCAs and related antidepressants. The antidepressants associated with the highest rates of suicide and attempted suicide or self-harm were mirtazapine, venlafaxine and trazodone. Researchers acknowledged that estimates were imprecise due to the small number of suicide events. Increased rates of suicide events occurred in the first 28 days of starting and stopping antidepressants, but researchers pointed out that periods when patients were not taking antidepressants likely reflected the absence of current depression or less severe depression. Researchers suggested careful monitoring of patients taking antidepressant drugs, especially during early treatment with antidepressants and also when discontinuing the treatment.

The Antidepressant Pharmaceutical Pipeline

Many patients with major depressive disorders who are taking existing antidepressants have low remission rates, delayed onset of action, as well as relapses. New therapeutic agents that may be more effective are being investigated to treat this disorder. Current first-line antidepressant agents modulate components of the monoamine neurotransmitter system, likely accounting for their
similar efficacy profiles of depression therapeutics. Many of the agents in development for major depressive disorder are classified as monoaminergic and include “triple-reuptake inhibitors.” Triple-reuptake inhibitors (TRIs) inhibit the serotonin transporter, the norepinephrine transporter and the dopamine transporter. Murrough et al. questioned whether the addition of dopaminergic modulation in the pharmacodynamic profile of the next generation of antidepressants may result in enhanced efficacy compared to SSRIs or SNRIs. Novel agents in development for potential treatment of depression represent marked departures from existing therapies which act to increase in concentration of monoamines, i.e., serotonin and norepinephrine, at the nerve synapse. More rapid acting innovative agents including those targeting the hypothalamic-pituitary-adrenal axis, the melatonin system, the inflammatory system, hippocampal neurogenesis and the glutamate system are currently the interest of scientific inquiry.

Magellan has reviewed the literature and evaluated published research studies on the use of ketamine in the treatment of treatment-resistant depression. Ketamine is a high-affinity, noncompetitive N-Methyl-D-aspartate (NDMA)-glutamate receptor that is theorized to be instrumental in the neurobiology of depression. Ketamine has demonstrated antidepressant-like properties but the exact biologic mechanism underlying its antidepressant activities is unclear. Ketamine has been employed in clinical practice as a nonbarbiturate adjunct to anesthesia and procedural sedation for use in human and veterinary medicine. It is also used illicitly in order to intensify social experiences by giving a reported sense of physical closeness, empathy and euphoria. Small randomized, placebo-controlled studies have been conducted including patients with major depressive episodes where intravenous treatment with ketamine in sub-anesthetic doses, i.e., 0.5mg/kg, has been studied. Preliminary evidence from these studies demonstrated robust effects for ketamine, but the duration of the therapeutic effect was very short term. Investigators have concurred that the sustainability of ketamine’s antidepressant effect and its long-term safety in repeated exposure in patient’s remains unknown, e.g., risk of severe psychosis and more dissociate and psychotomimetic effects. Much research now focuses on what can prevent post-ketamine relapse. Other clinical studies are examining augmentation of ketamine with other glutamate-modulating agents, i.e., riluzole, to prevent relapse. Magellan considers the use of ketamine in the treatment of refractory depression highly investigational. Future studies should test ketamine’s antidepressant effect beyond a single administration, and characterize its longer-term safety profile.

A later study tested the antidepressant effects of nitrous oxide, an agent with a similar mechanism of action as ketamine. Patients with treatment-resistant depression (n=20) were randomly assigned to inhalation over one hour of either a mix of 50% nitrous oxide/50% oxygen (active treatment) or 50% nitrogen/50% oxygen (placebo). One week after the first treatment, patients returned and were switched in the crossover study, receiving either the treatment or placebo. They were assessed at pretreatment, 2 hours after each treatment, and 24 hours after each treatment. The primary outcome measure was change in the HDRS score 24 hours after treatment. Results showed significant improvement in depressive symptoms at 2 hours and 24 hours after receiving active treatment compared with placebo. Several patients even showed lower HDRS scores when they had the second treatment one week later. Researchers noted that compared with ketamine, nitrous oxide had a similarly rapid onset of antidepressant action while patients receiving nitrous oxide did not have the psychotomimetic side effects that occur with ketamine (delusions, illusions, hallucinations). They concluded that although this study provides evidence of nitrous oxide’s antidepressant effects in patients with treatment resistant depression, larger studies are required to determine optimal dosing strategies and to evaluate risks and benefits of this treatment in...
Agomelatine, a novel antidepressant approved for use in the European Union, does not possess an ability to interfere with the neuronal reuptake of serotonin, norepinephrine, or dopamine. In a recent systematic review and meta-analysis of published and unpublished studies, researchers identified 20 trials with adult participants (n=7640) meeting the criteria for major depressive disorder in published literature. These randomized, double blind, and controlled (placebo and/or other antidepressant) studies showed that agomelatine is moderately more effective than placebo and has similar efficacy to standard antidepressants (outcome measures included the HDRS and the MADRS). This meta-analysis suggests an effect size for agomelatine of 0.24 compared to placebo, which researchers noted is small in absolute terms and is smaller than the effect size (0.31) calculated from other reviews of trials of other antidepressants. Participants randomized to agomelatine were less likely to discontinue treatment due to adverse effects than those receiving other antidepressants and no more likely to discontinue than those randomized to placebo. Researchers concluded that with agomelatine’s unique pharmacological mode of action combined with good tolerability as evidenced in these studies, it is an effective antidepressant with similar efficacy to standard antidepressants. The FDA has not approved agomelatine for use in treating depression.

Clinical trials are currently studying the safety and efficacy of fixed-dose brexpiprazole as adjunctive therapy in the treatment of adults with major depressive disorder with and without anxious distress. Brexpiprazole is a serotonin-dopamine activity modulator (SDAM), acting as a partial agonist at 5HT1A and dopamine D2 receptors, and an antagonist at 5-HT2A and noradrenaline alpha 1B/2C receptors. It is a novel compound with a close structural analogue of aripiprazole. In one randomized, placebo-controlled phase of a recent study including patients (n=379) with major depressive disorder, those receiving adjunctive brexpiprazole (2 mg/d) had significant improvement in mean scores compared with placebo at 6-week endpoint.

Other Somatic Treatments

Electroconvulsive therapy (ECT) is considered the gold standard for treatment of depression that has not responded to two or more adequate pharmacologic trials. According to the APA guideline, ECT has the highest rates of response and remission of any other form of antidepressant treatment and the proportion of patients with MDD who respond to ECT is greater than the proportion of patients who respond to antidepressant medication. The APA guideline recommends ECT as a viable treatment option when pharmacotherapy and psychotherapy have failed, when affective, psychotic or catatonic symptoms accompany major depressive disorder, and in situations where rapid relief is required, e.g., suicide risk or deteriorating medical conditions. The guideline states that ECT therapy is a first-line treatment for patients who prefer it and who have previously shown a positive response to the treatment.

Petrides et al. reviewed a study by the Consortium for Research in Electroconvulsive Therapy (CORE), the first large randomized controlled trial including patients with unipolar depression (n=531), showing that continuation ECT and combination pharmacotherapy were equally effective in preventing relapse following response to acute ECT. Authors concluded that both continuation ECT and maintenance ECT are under-used despite more than 70 years of positive clinical
experience. A new clinical trial, Prolonging Remission in Depressed Elderly (PRIDE) builds upon this research and tests whether combined pharmacotherapy and maintenance ECT will be more effective in maintaining remission in depressed older adults than pharmacotherapy alone.\textsuperscript{57}

In a recent non-blinded, randomized controlled trial performed in Sweden, researchers randomly assigned patients (n=56) with unipolar or bipolar depression who had responded to a course of ECT to receiving one of two treatments: (1) 29 treatments of continuation ECT with pharmacotherapy or (2) pharmacotherapy alone for one year. Pharmacotherapy consisted of antidepressants, lithium, and antipsychotics.\textsuperscript{15} This study tested whether relapse prevention with continuation electroconvulsive therapy plus pharmacotherapy is more effective than pharmacotherapy alone after a course of ECT for depression. Results found that the one-year relapse rate was greater in the pharmacotherapy alone group (61%) compared with 32% in the ECT plus pharmacotherapy group. The six-month relapse rates were 36% in the pharmacotherapy alone group, compared with 29% in the ECT plus pharmacotherapy group. Additionally, one suspected suicide by intoxication occurred in the pharmacotherapy alone group. Researchers suggested further studies to define indications for continuation ECT, pharmacotherapy, and the combination of the treatments.\textsuperscript{15}

The APA guideline discusses the association of ECT with cognitive effects noting that only rarely do patients report persistent cognitive disruption following ECT. Cusin et al. discussed studies suggesting that the administration of an ultrabrief pulse to induce the seizure causes fewer cognitive adverse effects.\textsuperscript{16} In a recent randomized controlled trial of brief and ultrabrief pulse right unilateral ECT, participants (n=102) with major depressive disorder were randomly assigned to receive ultrabrief (at 8 times seizure threshold) or brief (at only 5 times seizure threshold) pulse right unilateral ECT.\textsuperscript{17} This study tested whether ultrabrief pulse right unilateral ECT results in less cognitive side effects than brief pulse right unilateral ECT when given at doses which achieve comparable efficacy. In this study, the dosage of ultrabrief pulse ECT increased to a dose level likely to achieve comparable efficacy to brief-pulse ECT. Results showed that when ultrabrief pulse ECT was given at a higher dosage than brief pulse ECT (8 versus 5 times seizure threshold), ultrabrief pulse ECT had comparable efficacy to brief-pulse ECT. Increasing the dosage also diminished its overall cognitive advantage.\textsuperscript{17}

Based on an extensive review of the literature and evaluation of published research studies in peer-reviewed clinical journals, Magellan considers transcranial magnetic stimulation (TMS) used in the treatment of refractory depression to be an established treatment. There is a considerable amount of published research data to support an improvement in net health outcome – specifically, an antidepressant effect using high-frequency repetitive transcranial magnetic stimulation (rTMS) administered to the left dorsolateral prefrontal cortex. This determination is based on an evaluation of the research findings where the evidence supported TMS’s effect on health outcomes, its safety and efficacy against existing alternative treatments, and its ability to demonstrate that benefits outweigh the risks. Similarly, the adopted APA guideline discusses the extensive clinical research findings for TMS and interprets these data as generally supporting the use of high-frequency TMS over the left dorsolateral prefrontal cortex while stipulating that lesser degrees of treatment resistance may be associated with a better acute response to TMS.

Current available research evidence on rTMS is now sufficient to meet all of Magellan’s technology assessment criteria. The FDA Advisory Panel has cleared the transcranial magnetic stimulation device (the \textit{NeuroStar TMS Therapy System} device manufactured by Neuronetics, Inc.) for the treatment of depression. The FDA noted that this device is specifically indicated for the treatment of
Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. The NeuroStar TMS Therapy has not been studied in patients who have not received prior antidepressant treatment.

Research findings have demonstrated a significant rTMS treatment effect for the aforementioned subset of depressed patients along with compelling evidence that rTMS outcomes are comparable or better than pharmacotherapy alternatives. In addition, sham controls used in more recent clinical trials have been significantly improved to adequately mimic the somatosensory experience of rTMS and through use of masking procedures for rTMS administrators and patients to the acoustic signals produced by stimulations. Also, more recent research studies have shown better rTMS outcomes due to recognition of the need for optimized treatment parameters – i.e., application of rTMS with increased dosage, intensity of pulses, length/spacing of treatments and use of magnetic resonance imaging (MRI) for proper scalp placement of coil and use of new coil geometries, e.g., H-coil, angled coil.

Further study is still necessary in order to confirm the durability of rTMS compared to ECT. Additionally, continued research is needed on the application of rTMS as a rescue or augmenting strategy in the treatment of depression, along with further investigation of alternative and newer approaches, e.g., unilateral right-sided, sequential bilateral, accelerated regimens, deep TMS, for specific indications. Research is also needed in order to more fully understand the use of brain imaging, genetic, electroencephalographic or other predictors of response in order to better determine the length of treatment in patients not responding adequately to rTMS. Substantial published clinical evidence reviewed by Magellan and evaluated against the technology assessment criteria, supports rTMS for the treatment of refractory major depression as an established treatment when used as a monotherapy for adult patients with refractory Major Depression who have demonstrated treatment-resistance to pharmacotherapy, i.e., failure of at least one antidepressant agent at effective dose and duration.

Since publication of the APA guideline, there has been a significant increase in the acceptance and utilization of TMS as a treatment modality for depression and another medical device has been developed and approved for use in TMS. In January 2013, the FDA cleared the Brainsway H-Coil Deep TMS System, developed by Brainsway Ltd., an Israeli manufacturer, for treatment of depression in patients who fail to respond to therapeutics during a depression episode. This decision was based on the results of an international, multi-site, double-blind, controlled trial where the company reported its deep TMS system was safe and effective in this patient population. The FDA approval for this indication is actually broader than the indication specified by this agency for approval of the NeuroSTAR Therapy System.

A recent systematic review and meta-analysis of randomized, double-blind and sham-controlled trials investigated response, remission, and dropout rates following high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) for primary major depression. The trials used HF-rTMS over the left dorsolateral prefrontal cortex (DLPFC) with a focus on treatment-resistant cases. Analysis of data from 29 randomized control trials including subjects (n=1371) with major depression found this neuromodulation technique to be significantly more effective than sham rTMS both in response and remission rates. HF-rTMS was just as effective as an augmentation strategy as a monotherapy for major depression when used for treatment resistant depression (or in patients with less resistant depression). Effectiveness was equally effective in subjects with primary unipolar major depression or in mixed samples with unipolar and bipolar major
Researchers suggested that future studies shift away from establishing the efficacy of current stimulation protocols against sham rTMS, but instead focus on new ways of improving its therapeutic effects, tolerability and availability. They suggested new protocols and devices, e.g., theta burst stimulation, H-coil, and the targeting of alternative brain regions, such as dorsomedial, ventrolateral and ventromedial prefrontal cortices.\textsuperscript{18}

Shafi et al. reported the effects of low field magnetic stimulation (LFMS) in a large group of stably medicated, depressed patients (n=63) with either bipolar depression of major depressive disorder.\textsuperscript{19} The single, 20-minute treatment was applied in a double-blind, sham-controlled design with change in mood assessed immediately after treatment using a visual analog scale (VAS), the HDRS-17 and the Positive and Negative Affect Schedule scales. Results demonstrated substantial improvement in mood ten to fifteen minutes after LF-rTMS treatment relative to sham treatment. Authors suggest a need for further exploration of the benefit from combining neuromodulation techniques with conventional behavior and/or pharmacologic therapy.\textsuperscript{19}

Based on an extensive review of the literature relating to deep brain stimulation (DBS) for the treatment of treatment-resistant depression, Magellan considers DBS as an investigational procedure.\textsuperscript{67} The APA guideline names deep brain stimulation (DBS) as one of the stimulation treatments, along with vagus nerve stimulation, TMS and other electromagnetic stimulation therapies, to be compared with electroconvulsive therapy. DBS involves surgically implanting a neurostimulator under the skin to deliver continuous electrical stimulation to targeted areas in the brain where electrodes are implanted bilaterally. Despite the advantages of DBS to the alternative of ablative neurosurgery, the neurosurgical procedure to implant the stimulation device is associated with considerable risk including intracranial hemorrhage, infection, compromised oculomotor function, substantial reduction in energy levels and death. Additionally, the battery may need replacement every one to three years depending on the stimulation parameters. Currently, there is growing, but still limited, empirical data published from well-designed and sham-controlled studies of DBS in the treatment of refractory depression that can determine whether benefits outweigh the risks. More recent long-term follow-up studies on DBS for refractory have shown promising results in sustained clinical and functional improvements. However, there are no published studies which directly compare DBS to the established existing treatment alternatives of ablative surgery, pharmacotherapy, psychotherapy, cognitive-behavioral therapy, behavioral therapy, combined (pharmacotherapy and psychosocial) treatment or ECT. Therefore, Magellan considers deep brain stimulation as a treatment for treatment-resistant depression to be an investigational procedure at this time.\textsuperscript{67}

In VNS therapy, a mild electrical pulse is applied to the left vagus nerve via an implantable device positioned under the skin of the neck during an outpatient surgery with the patient under either general anesthesia or regional cervical block. The adopted APA guideline indicates that Vagal Nerve Stimulation (VNS) may be a treatment strategy to address nonresponse in cases of significant treatment resistance and after several attempts of switching antidepressants, augmentation or ECT. However, the APA guideline stipulates that this recommendation has a degree of clinical confidence supported by very limited data and recommended only on the basis of individual circumstances. Based on a review of the literature and evaluation of published research studies in peer-reviewed clinical journals, Magellan considers VNS used in the treatment of refractory depression to be an investigational treatment.\textsuperscript{68} This determination results from an evaluation of the research findings where the evidence did not support VNS’s effect on health outcomes, its safety and efficacy against existing alternative treatments; and its ability to demonstrate that benefits outweigh the risks. On July 15, 2005, the Centers for Devices and Radiological Health (CDRH) of the FDA notified the
manufacturer, Cyberonics, Inc., that its device was approved for use for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode. Further, they must not have had an adequate response to four or more adequate antidepressant treatments. This approval allowed Cyberonics, Inc. to begin commercial distribution of the device for this intended use. While the technology of VNS appears promising, evidence thus far remains limited, i.e., only one randomized, sham-controlled study published since FDA approval, and does not yet clearly demonstrate that this is an established adjunctive treatment for refractory depression. Therefore, Magellan has determined that VNS for the treatment of treatment-resistant depression remains investigational at this time.

**Psychosocial Treatments**

The APA guideline cites studies suggesting: 1) that behavioral interventions may be preferable to cognitive techniques for patients with more severe depression, and 2) that CBT has "significant protective effect," lowering relapse in patients with five or more prior depressive episodes. In a later meta-analysis including six randomized controlled trials, Piet and Hougaard (2011) evaluated the effect of mindfulness-based cognitive therapy (MBCT) for prevention of relapse or recurrence among patients (n=593) with recurrent major depressive disorder in remission. MBCT is a psychological therapy, utilizing CBT methods, enhanced by mindfulness and mindfulness meditation. It focuses on an awareness of thoughts and feelings, which may interrupt automatic cognitive processes that can trigger a depressive episode. Researchers compared MBCT to controls, including treatment as usual (TAU), placebo plus clinical management (PLA), and maintenance antidepressant medication (MADM). Results showed that the relapse rate of MBCT was significantly lower, compared to TAU and PLA, in participants with three or more previous episodes of major depressive disorder and was comparable to the rate of participants with three or more previous episodes treated with antidepressant medications. Researchers concluded that, based on the results of studies in the meta-analysis, the use of MBCT is a low cost treatment for relapse prevention in recurrent major depressive disorder in remission and they suggest future research is needed to investigate the differential effects of MBCT for patients with low and high risk of relapse.

A later study compared MBCT with both cognitive psychological education (CPE) and treatment as usual (TAU) in preventing relapse to major depressive disorder. Patients (n=255) currently in remission following at least three previous major depressive episodes were randomized to one of the three treatment conditions. Researchers noted that past studies had not compared MBCT with an active psychological treatment, preventing knowledge about whether the beneficial benefits of MBCT are attributable to the learning of mindfulness meditation skills rather than nonspecific factors such as group support. CPE, following the same group format as MBCT, included no training in meditation and provided a control treatment. Researchers compared the outcomes of both CPE and MBCT with those of TAU and examined how variables, e.g., number of prior episodes of depression, age of first onset of major depressive disorder, history of suicidal ideation or behavior, adversity in childhood and adolescence are associated with outcomes of MBCT. Time to relapse to major depression was the main outcome of the trial, which found that treatment group generally had no significant main effect on risk of relapse. However, for persons with high childhood trauma scores, the raw rates of relapse for MBCT, CPE, and TAU were 41%, 54%, and 65%, respectively, and for those with no history of childhood trauma, relapse risk was not reduced by MBCT compared with TAU. Researchers suggested that MBCT is superior to both an alternative psychological treatment and TAU in preventing recurrence of depression over 12 months when severity of childhood trauma is considered. Other than this, there were no general differences in outcome according to the allocated treatment. They concluded that their findings support the body...
of evidence that psychological interventions may help prevent future episodes of major depression, especially for those at highest risk of relapse.20

The APA guideline notes the behavioral activation element of CBT may be as efficacious (or more efficacious) as CBT as a whole, especially for more severely depressed patients. In a case study of treatment failure with a depressed breast cancer patient, Hopko et al. suggested recommendations to reduce failure rates in behavior therapy.70 Basic behavioral principles and applications, e.g., shaping, fading, emotional validation and within-session reinforcement of adaptive social behaviors, were suggested as enhancing the therapeutic relationship and resulting in treatment compliance by the patient with major depressive disorder.

Since publication of the APA guideline, Cuijpers et al. conducted a meta-analysis examining the effects of interpersonal psychotherapy (IPT) for depression.71 Included in the meta-analysis were 38 studies including patients (n=4,356) with a unipolar depressive disorder or an elevated level of depressive symptoms. The studies compared IPT with one of the following: a control condition, e.g., usual care, placebo, a different psychotherapy; pharmacotherapy; IPT plus pharmacotherapy or pharmacotherapy alone. Findings of this meta-analysis included: (1) IPT was moderately more effective compared with usual care, placebo, or a different psychotherapy, (2) combination treatment with IPT and pharmacotherapy was more efficacious than pharmacotherapy alone, (3) maintenance IPT combined with pharmacotherapy reduced relapse rate significantly compared with pharmacotherapy alone, (4) placebo plus IPT was more effective than placebo alone in decreasing relapse rates, and (5) SSRI pharmacotherapy had greater efficacy than IPT. Researchers did not find that IPT had greater efficacy than other psychotherapies, including CBT; they concluded that IPT and CBT seem equally effective overall and are considered the best psychological treatments for depression. They noted that the superior effect of combination treatment over pharmacotherapy alone suggests that IPT has an additional effect beyond the effects of pharmacotherapy, concluding that the study found clear indications for the efficacy of IPT for unipolar depression.

A current systematic review provided an overview of recent randomized studies describing the effectiveness and efficacy of sole individual IPT in comparison with other forms of psychotherapy and/or pharmacotherapy.21 Eight studies were reviewed including patients (n=1233) with major depressive disorder out of which 854 patients completed treatment in outpatient facilities. Treatments included usual care consisting of communication with a physician for appropriate treatment, IPT, Cognitive Behavioral Analysis System of Psychotherapy, CBT, pharmacotherapy plus clinical management, IPT plus nefazodone, IPT plus placebo, placebo plus clinical management, or pharmacotherapy (i.e., nefazodone, nortriptyline hydrochloride, or venlafaxine hydrochloride). Findings include: (1) the efficacy of IPT and CBT appeared to be equal, (2) the efficacy of IPT and nortriptyline were similar, (3) IPT combined with nefazodone had a higher efficacy than sole nefazodone, (4) pharmacotherapy combined with clinical management appeared to have higher efficacy than IPT alone, and (5) IPT and Cognitive Behavioral Analysis System of Psychotherapy were comparable in efficacy. Researchers concluded that differences between treatment effects were very small and insignificant. They recommended psychotherapeutic treatment such as IPT and CBT and/or pharmacotherapy as first-line treatments for adult outpatients, suggesting consideration of individual preferences of patients in choosing a treatment.21

The APA guideline advises that, based on findings from meta-analyses of both short-term and long-term psychodynamic psychotherapy, individuals with depressive symptoms may benefit from this therapy. The guideline suggests that further research with more rigorous study designs is needed.
In a later meta-analysis, Jakobsen et al. (2012) compared the benefits and harms of psychodynamic therapy by analyzing five trials randomizing participants (n=365) who received antidepressants as co-intervention. The benefits and harms of psychodynamic therapy plus antidepressants versus “no intervention” or sham plus antidepressant were compared. The results of this review with meta-analysis showed that psychodynamic therapy added to antidepressants may benefit patients with major depressive disorder, but that the treatment effect may be small. Researchers suggested the need for randomized trials with low risk of bias, with low risk of random errors and with longer follow-up to assess both benefits and harms.

In a later study comparing the efficacy of psychodynamic therapy with CBT in the outpatient treatment of major depression, adults (n=341) with major depression were randomly assigned to 16 sessions (within 22 weeks) of individual manualized CBT or short-term psychodynamic supportive therapy. Results showed that less than 25% of patients reached remission within 22 weeks of treatment, with no significant difference in rates between the two groups. In the severely depressed subgroup receiving additional pharmacotherapy, noninferiority of psychodynamic therapy relative to CBT was not demonstrated for differences in remission rates and follow up measures. Researchers indicated that many patients encountered in psychiatric outpatient clinics required more than time-limited treatment in order to reach remission.

Studies cited in the APA guideline suggested that problem-solving therapy may have advantages over usual care for home-bound geriatric patients with depressive symptoms and that problem-solving therapy was superior to supportive psychotherapy for depressed geriatric patients. In a later study to examine whether problem solving therapy reduces disability more than supportive therapy in older patients with depression and executive dysfunction, participants (n=221) were randomized to problem solving therapy or supportive therapy. Patients in the problem solving model were guided to set goals, determine ways to reach goals, create an action plan and evaluate whether they had accomplished their goals. The supportive therapy included encouraging patients to talk about their depression and contributing life events while the therapists actively listen and offer support focusing on participants’ problems or concerns. This study found that problem solving therapy was more effective than supportive therapy in reducing disability in older patients with major depression and executive dysfunction. This advantage was greater in patients with greater cognitive impairment and higher number of previous episodes. Researchers reported that this reduction in disability paralleled reduction in depressive symptoms.

Group therapy has been shown to have benefits in the acute treatment of major depressive disorder. The APA guideline cites findings from studies of group CBT as well as group IPT. Some of those findings are: group CBT was more beneficial than group supportive therapy; group CBT showed promise in lowering relapse risk; group mindfulness based cognitive therapy was effective as an augmentation strategy compared to treatment as usual in reducing relapse rates; group CBT was ineffective in treating dysthymic disorder and IPT may have benefit as both a preventive intervention as well as a treatment for postpartum depression. In a later randomized controlled trial, including women with postnatal depression (n=50), that compared outcomes from group IPT with “treatment as usual” (TAU), Mulcahy et al. (2010) found that women with postnatal depression who had received group IPT improved more in terms of mean depressive scores than women who had received TAU, e.g., antidepressant medication, individual psychotherapy, community support groups, etc. Patients receiving group IPT also had significant improvement in terms of marital functioning and perceptions of the mother-infant relationship compared to TAU participants.
A systematic review and meta-analysis was conducted to determine the efficacy of brief psychotherapy, i.e., ≤ 8 sessions, for the treatment of depression.\textsuperscript{75} Two systematic reviews and a meta-analysis of 15 randomized controlled trials of brief psychotherapy, encompassing patients with depression (n=1,716), were identified. Brief psychotherapies were found to be more efficacious than control, e.g., TAU, telephone case management, usual care, waitlist control. Researchers concluded that brief CBT and problem solving therapy are efficacious in treating the acute-phase of depression and suggested that brief psychotherapies present an attractive treatment alternative for implementation in the primary care environment. They pointed out that this review was aimed at determining the overall efficacy of brief psychotherapies rather than comparing the effectiveness of brief vs. standard-duration psychotherapies.

In a systematic review and meta-analysis of computer-based psychological treatment for depression, researchers evaluated the overall effectiveness of computer-based treatments for depression.\textsuperscript{76} The selected trials including participants (n=2,996) with depression randomized to active computer-based intervention group, e.g., CBT-based program, or control group, e.g., TAU, waitlist control. The results of the review and meta-analysis supported the efficacy and effectiveness of computer-based psychological treatment for depression. The review found that computer-supported interventions yielded better outcome, along with greater retention, and the researchers suggested that support may include regular mail, automated email, reminder emails, phone calls or in person interviews.

**Combination Pharmacology and Psychotherapy Treatments**

The APA guideline cites two meta-analyses that confirm the benefits of combining pharmacotherapy and psychotherapies in the treatment of major depressive disorders. The studies showed that the advantages of combined psychotherapy and pharmacotherapy are greater among studies of patients with more severe symptoms and among those with more chronic depressive disorders. A later comprehensive meta-analysis of studies comparing pharmacotherapy to the combination of pharmacotherapy and psychotherapy examined whether combined treatment is more effective than pharmacotherapy alone.\textsuperscript{77} Twenty-five randomized trials including patients (n=2,036) with major depressive disorder as well as dysthymia were included in the study. The studies examined cognitive behavioral therapy, interpersonal psychotherapy, psychodynamic therapy or problem solving treatment and most were individual psychotherapies. Researchers found clear indications that a combined treatment including psychotherapy is more effective than pharmacotherapy alone in treating depression. However, the combined treatment was not more effective, compared with pharmacotherapy, i.e., SSRIs, TCA and other medications, alone in patients with dysthymia. Another finding was that the dropout rate was significantly lower in the combined treatment group compared to pharmacotherapy suggesting that most patients prefer psychotherapy. No association was found between the effect size and the severity of depression. Researchers suggested more research is needed to examine further the effectiveness of psychotherapy in dysthymic disorder.

DSM-5 includes both “chronic major depressive disorder” and “dysthymic disorder” into a single classification, “persistent depressive disorder,” focusing on chronicity as a significant factor in treatment outcome.\textsuperscript{78} The FDA has not indicated any medications for the treatment of chronic depression,\textsuperscript{79} but a current clinical trial is investigating desvenlafaxine for the treatment of people with chronic depression.\textsuperscript{80} In a randomized, controlled trial of duloxetine versus placebo for the treatment of patients (n=57) with non-major chronic depression, Hellerstein et al. found that
participants receiving treatment with duloxetine showed better outcome on core depression symptoms, severity of illness and patient-reported improvement over placebo.79 Response and remission rates favored duloxetine treatment, but social functioning measures did not. Researchers suggested augmenting medication with psychotherapies such as CBT, ITP or behavioral activation therapy if medication alone does not lead to significant improvement in psychosocial functioning. They pointed out that the chronicity of depression is a major factor in poor outcome, regardless of severity, and stressed the need for future studies of both short-term and long-term treatment of chronic depressive disorder.

In a recent trial assessing the efficacy of combining cognitive therapy (CT) with antidepressant medication (ADM), researchers randomly assigned adult outpatients (n=452) with chronic or recurrent major depressive disorder to ADM treatment alone or CT combined with ADM treatment.23 Treatment continued up to 42 weeks. Patients in both treatment groups received personalized antidepressant therapy; most received SSRIs or SNRIs while some switched to tricyclic antidepressants or monoamine oxidase inhibitors. CT occurred in 50-minute sessions held twice weekly, weekly, and monthly during the first 2 weeks, acute treatment, and continuation treatment, respectively. Outcome measures were the HDRS and the Longitudinal Interval Follow-up. Results of this study included: (1) high remission rates in both groups, not differing significantly based on treatment group and (2) no significant difference in recovery rates for patients with low-severity major depressive disorder in the two treatment groups, but higher rates of recovery in the combined group for patients with high-severity depression. Researchers concluded that combined medication treatment with cognitive therapy enhances rates of recovery compared to medication treatment alone, but this effect may be limited to patients with severe nonchronic depression.23

A recent meta-analysis of randomized trials compared the effects of treatment with antidepressant medication to the effects of combined pharmacotherapy and psychotherapy in adults with a depressant or anxiety disorder.24 Researchers analyzed the results of 52 studies (3,623 patients) of which 32 studies involved depressive disorders. Treatments included antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs) and psychotherapies (e.g., CBT, IPT, and psychodynamic therapies). Evidence from this study found combined treatment was more effective than pharmacotherapy alone in major depression, OCD, and panic disorder. The effect size of difference between the two groups was not associated with baseline severity of depression. Researchers found clear evidence that combined treatment with psychotherapy and antidepressant medication is significantly more effective than treatment with antidepressant alone for major depression, panic disorder, and OCD. Analysis of the study results also showed that psychotherapy and pharmacotherapy may be additive, and not interfering with each other while contributing similarly to the effects of combined treatments. In conclusion, researchers summarized that results support the use of combined treatment, rather than psychotropic medication alone.24

**Combination ECT and Psychotherapy Treatments**

Although ECT is one of the most effective treatments for major depressive disorder, relapse rates are significant. In a systematic review of the combined use of electroconvulsive therapy and depression specific psychotherapy for depression, Mc Clintock et al. investigated the efficacy of augmenting ECT with psychotherapy to prolong remission.51 They conducted a systematic review of studies investigating combinations in the acute and continuation phase of treatment for major depressive disorder. Authors cited past studies that reported beneficial effects of the combined use of ECT and psychotherapy in the treatment of depression, but they also pointed out the limitations of the studies: methodological concerns, lack of comparative control group or control condition.
limited data). Authors noted that the cognitive sequelae of ECT is a major challenge to combining ECT and psychotherapy and proposed mitigating the challenge by ensuring that both treatments are administered at optimum levels, e.g., ECT administered with ultrabrief pulse waveform and psychotherapeutic treatment provided on days when ECT is not administered, allowing the patient to regain adequate cognitive function. Based on advances in ECT and evidence-based psychotherapies, e.g., CBT and IPT, they concluded that combined use of ECT and psychotherapy warrants further investigation in the treatment and management of patients with major depressive disorder.

**Complementary and Alternative Treatment**

The APA guideline addresses the use of complementary and alternative treatments, e.g., St John’s Wort, S-adenosyl methionine, omega-3 fatty acids, light therapy and acupuncture in treating major depressive disorder. Although St. John’s Wort has been commonly prescribed in Europe as a treatment for mild to moderate depression, it has not been approved by the FDA for treating depression. Some studies supporting the efficacy of St. John’s Wort in patients with mild-to-moderate depression have limitations which may negatively affect the conclusions. Chen et al. 2011 reanalyzed data from a 2002 study by the Hypericum Depression Trial Study Group to investigate whether patients (n=207) who believed they were receiving hypericum, sertraline or placebo obtained greater improvement, independent of treatment. Findings of this study showed that patient beliefs about which treatment they received had a stronger association with clinical outcome than the actual medication that they received. Among those who believed they received placebo, clinical improvement was small regardless of the treatment actually received; among those who guessed hypericum, improvement was large regardless of the treatment actually received; and among those who thought they received sertraline, patients who received placebo or sertraline had large improvements, but those who received hypericum had significantly less improvements. The APA guideline discusses the potential for drug-drug interactions when using St. John’s Wort. According to Soloman et al, the main caveat to prescribing St. John’s Wort is its potential for drug interactions and its tendency to reduce the serum levels of many pharmaceuticals.

Although the APA guideline acknowledges that some data supports the efficacy and tolerability of S-adenosyl methionine (SAMe) in patients with major depressive disorder, the guideline states that the data is not sufficient to make a recommendation for its use as monotherapy or as augmentation therapy. In a study after publication of the guideline, Papakostas et al. conducted a randomized, double-blind, placebo-controlled trial to examine the efficacy, safety and tolerability of SAMe as augmentation of SSRIs or SSNIs for patients (n=73) with major depressive disorder who were antidepressant non-responders. Remission rates for antidepressant plus SAMe treated patients versus antidepressant plus placebo treated patients were 25.8 versus 11.7 percent and response rates were 36.1 percent versus 17.6 percent respectively. Researchers suggested the results of this study provide preliminary evidence suggesting that SAMe can be an effective, relatively well tolerated and safe adjunctive treatment strategy for antidepressant non-responders and that it justifies larger scale, adequately powered tests of efficacy, tolerability and safety. The activity and metabolism of SAMe involves methylation whose byproduct is S-adenosyl homocysteine which is then converted to homocysteine. Results of a later study to characterize the impact of SAMe on homocysteine and potential risk of adverse cardiovascular effects found no significant increase in total homocysteine after treatment with SAMe. Researchers noted limitations of their findings, e.g., relatively small patient sample and short-term (six-week) trial, concluding that further
Omega-3 polyunsaturated fatty acids (PUFA) are generally recommended as an adjunctive therapy for mood disorders, but the APA guideline advises that more evidence is required to establish a definitive role in the acute treatment of major depressive disorder. The guideline also indicates that adjunctive eicosapentaenoic acid (EPA) or the combination of EPA and docosahexaenoic acid (DHA) appears most useful than DHA alone in the treatment of major depressive disorder. Sublette et al., in a later meta-analysis (2011) tested the hypothesis that EPA is the effective component in PUFA treatment of major depressive episodes.\(^6\) Included in the meta-analysis were 15 randomized, double-blinded, placebo-controlled studies involving participants (n=916) whose primary complaint was depressive episode. Results of the meta-analysis found no evidence that DHA is acutely effective against depression, instead finding that it may, in fact, block beneficial effects of EPA at about a 1:1 dose ratio. Researchers acknowledged that current studies support the use of omega-3 supplements containing at least 60 percent EPA and that further studies are needed to evaluate the long-term efficacy and health effects of PUFA in depression.

The APA guideline cites studies supporting L-methylfolate, the biologically active form of folate, as a modest adjunctive strategy for major depressive disorder. After publication of the guideline, Papakostas et al. reported on the outcome of two randomized, double-blind, placebo-controlled separate trials of L-methylfolate as an adjunct to a SSRI in the treatment of patients (n=148 in first trial and n=75 in second trial) with major depressive disorder.\(^7\) The trials were identical except that in the first trial the dosage of L-methylfolate was at 7.5 mg/day whereas in the second trial it was at 15.0 mg/day. Researchers found that there was no difference between placebo and adjunctive L-methylfolate at 7.5 mg/day. Adjunctive L-methylfolate at 15 mg/day showed significantly greater efficacy compared with continued SSRI therapy plus placebo. Researchers concluded that 15 mg/day of adjunctive L-methylfolate may be an effective and safe augmentation strategy for patients with major depressive disorder. They suggested the need for additional studies further clarifying the antidepressant role of L-methylfolate and its efficacy for long-term use.

Studies are cited in the APA guideline providing some evidence supporting light therapy for patients with seasonal affective disorder and non-seasonal major depressive disorder that has not responded to antidepressant medication. Studies cited also suggest that greater intensity of light is associated with efficacy and that light therapy may augment the antidepressant benefits of partial sleep deprivation. The APA guideline states that in general, light therapy is both a low-risk and low-cost option for the treatment of major depressive disorder. To examine factors associated with light therapy use and adherence, Roecklein et al. (2012) reviewed data from a web survey of individuals (n=40) who had been diagnosed with a disorder for which light therapy had been indicated.\(^8\) The data, including social, cognitive and behavioral variables, was analyzed to learn whether these variables were associated with the actual use of light therapy. In this study, light therapy self-efficacy and social support were positively associated with self-reported use of light therapy. Researchers expressed surprise that some individuals choose not to use light therapy, even after a previous winter of successful treatment, given that the side effects are mild. They concluded that interventions, e.g., motivational enhancement therapy or motivational interviewing, that manipulate motivational, cognitive and behavioral factors, may increase light therapy use rates.

The APA guideline acknowledges that acupuncture’s efficacy is somewhat difficult to assess partly due to the variation in techniques used as well as limited descriptions of methodology and
diagnosis. The guideline cites a meta-analysis whose results showed that acupuncture was not associated with any benefits in treating major depressive disorder in terms of response or remission rates. After publication of the APA guideline, Wu et al. (2012) reviewed published studies including systematic reviews and two meta-analyses examining clinical applications of acupuncture for depression, including monotherapy and augmentation. Authors cautioned that there are limitations in current studies of acupuncture for depression: limitations of acupuncture sham controls; differential effects on depression with different acupuncture treatment protocols, insufficient systematic training and supervision of treatment providers; and methodological limitation. Based on this meta-analysis, authors suggested that acupuncture augmentation in antidepressant non-responders has not received adequate study. They reported that manual acupuncture was found to reduce the side effects of antidepressants in major depressive disorder. Citing the lack of reports on acupuncture for preventing recurrence after recovery from a depressive episode, authors recommended further investigation.

A recent meta-analysis of 13 randomized trials compared the effects of combined acupuncture and antidepressant medications to antidepressants alone in the treatment of adults (n=1046) with major depressive disorder. Results indicated greater therapeutic efficacy of the combination treatment than of SSRI treatment alone. Authors suggested that acupuncture combined with antidepressant medication has an early onset of action, is effective, and well tolerated over a 6-week treatment period. They suggested the need for more high quality, randomized clinical trials evaluating the clinical benefit and long-term effectiveness of acupuncture in the treatment of depression.

The APA Guideline notes that data supports modest improvement in mood symptoms for patients with major depressive disorder who engage in aerobic exercise or resistance training, and that regular exercise reduces the prevalence of depressive symptoms in the general population. A recent study, Treatment with Exercise Augmentation for Depression (TREAD), examined whether exercise was associated with fewer and less-severe symptoms associated with major depressive disorder (Rethorst et al, 2013). Adults, ages 18-70 years (n=122), with major depressive disorder who had a partial response to an SSRI were randomized to a “low dose” group that engaged in 40-60 minutes of aerobic exercise per week or a “high dose” group engaging in 150 minutes of aerobic exercise per week for 12 weeks. Results showed that patients in the high-dose group were more likely to have fewer and less-severe symptoms of major depressive disorder, higher recovery rates, and longer remission than those in the low-dose group. Aerobic exercise also was associated with reducing blood levels of pro-inflammatory cytokines, which are elevated in some depressed patients. Rethorst and Trivedi provided recommendations, e.g., assessment of the patient’s overall health and ability to participate in regular exercise, advising patients on the benefits of exercise related to depression, assistance to patients with problem-solving techniques and creating atmosphere of support (Psychiatric News, 2014).

Depression and Pregnancy

The APA guideline discusses the unique treatment considerations of major depressive disorder during pregnancy, noting the risks of untreated depression as well as the limited body of research that informs safety of antidepressants. Studies have shown that women treated with antidepressants during pregnancy are potentially at risk for a host of poor obstetrical and fetal outcomes, but the risks may be confused by confounding factors and study design limitations. Chaudron cautioned that women who stop their antidepressants during pregnancy are at higher risk for relapse compared with women who maintain their antidepressant treatment across the
pregnancy.\textsuperscript{90} Untreated depression during pregnancy may be related to poor obstetrical outcomes, e.g., low birth weight, preterm delivery, postpartum depression and neonatal effects, e.g., increased risk for irritability and less activity or attentiveness.\textsuperscript{91}

Determining the impact of antidepressants on the fetus is difficult, as there are many potentially confounding factors, e.g., severity of maternal depression; maternal substance use; and comorbid medical and mental illnesses.\textsuperscript{90} Some studies show associations between antidepressant use and outcomes, while other studies do not.\textsuperscript{90} Some studies have shown evidence that preterm birth is significantly higher among women who used antidepressants, e.g., SSRIs and TCAs, but other studies do not support this association. Only modest difference in mean gestational duration of one week or less was evidenced in studies finding an effect for antidepressants on gestational age. Studies have found no association between SNRI/NRI use and malformations and there is conflicting associations for TCA and SSRI use and malformations. At the request of the FDA (2005), paroxetine’s pregnancy category was changed from C to D due to a potential risk of cardiac malformations to the fetus when a woman is treated with paroxetine in the first trimester of pregnancy.\textsuperscript{92} In some studies, SSRIs have been associated with persistent pulmonary hypertension (PPHN) in babies of mothers who used a SSRI antidepressant in later pregnancy, but other studies do not show any association. In 2006 the FDA issued the following warning: “Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN).”\textsuperscript{93} Based on later studies, the FDA issued a revision of the warning indicating that it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. The small potential risk of PPHN that may be associated with SSRI use in pregnancy must be weighed against the substantial risks associated with under-treatment or the lack of treatment of depression in pregnancy.\textsuperscript{94}

In a recent article reviewing recent studies of relapse of major depression in women who continue or discontinue antidepressant medication during pregnancy, Guille and Epperson noted conflicting results from two recent studies.\textsuperscript{27, 28} A study by Cohen et al. demonstrated women (recruited from psychiatric treatment centers) with a history of recurrent major depression who discontinued antidepressant treatment during pregnancy or just before conception were five times as likely to have a relapse compared with women who continued medication during pregnancy.\textsuperscript{26} Another prospective study of pregnant women (recruited from community- and hospital-based obstetric clinics) with a history of depression found no difference in risk of major depressive episode in women who discontinued antidepressant treatment compared with those who continued with the medication. Guille and Epperson suggested that the conflicting results may be attributable to these divergent populations; individuals from the psychiatric centers had more severe depression and comorbid psychiatric illness. They also noted that, in both studies, women with at least four previous episodes of depression had greater risk of relapse of depression during pregnancy.\textsuperscript{26}

A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists addressed the maternal and neonatal risks of both depression and antidepressant use during pregnancy and developed algorithms for pregnant patients with MDD who are both taking and not taking antidepressants. These algorithms are meant to guide decision-making related to the management of depression during pregnancy. In this report, authors stated that women with severe depression characterized by suicide attempts, loss of weight or functional incapacitation continue on their medication.
The APA guideline discusses psychotherapy, e.g., IPT and CBT, as a part of the treatment plan for major depressive disorder during pregnancy. Electroconvulsive therapy is also recommended for the treatment of depression during pregnancy.

**Bereavement and Depressive Episodes**

The bereavement exclusion was omitted from the DSM-5. Ordinary grief is not an illness, but grieving persons are not immune to major depressive disorder. According to Pies, bereavement is a common trigger for major depressive disorder and some bereaved patients will benefit from cognitive, supportive or grief oriented psychotherapies. Others, e.g., those more severely depressed or suicidal patients, may require treatment with medication and/or psychotherapy. He cautioned that, "We must not ‘medicalize’ normal grief. But neither must we ‘normalize’ major depression simply because it occurs in the context of bereavement.” The DSM-5 notes that both physicians and grief counselors recognize that the duration of bereavement lasts 1-2 years. It also indicates that careful consideration is required when a major depressive episode occurs in addition to the normal response to a significant loss.

**Depression and Older Adults**

Given the aging of the population, late-life depression becomes an important public health issue. The APA guideline notes that it is common for major depressive disorder to be undiagnosed and untreated among older adults, and it may be erroneously regarded as expected or an inevitable part of aging, and therefore untreated. A meta-analysis selecting randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for the treatment of major depressive disorder in patients (n=20,572) aged > 65 years or ≥ 55 years was conducted to examine the efficacy of antidepressants for the treatment of major depressive disorder in elderly patients. Results of this meta-analysis suggested that antidepressants are efficacious in the treatment of late-life major depressive disorder (aged 55 or older), but not more effective than placebo in older late-life depression (aged 65 or older). Researchers suggested that executive dysfunction in older patients with depression has been associated with a lower probability of antidepressant response; other possible explanations suggested for the differences in late-life and older late-life responses to antidepressants included: white matter hyperintensities, medical comorbidity, chronicity, and subtherapeutic doses of antidepressants. Researchers suggested further studies of factors moderating antidepressant response in late life.

A recent study evaluated whether adding methylphenidate to treatment with citalopram improves antidepressant response in older outpatients with major depression. In this 16-week randomized double-blind placebo-controlled trial, patients (n=143) whose mean age was 70.1 with major depression of moderate severity and who were free of psychotropic medications for two or more weeks were assigned to one of three treatment groups: methylphenidate plus placebo, citalopram plus placebo, or citalopram plus methylphenidate. Mean doses were 32 mg and 16 mg for citalopram and methylphenidate, respectively. Improvement in depression severity in the combined citalopram and methylphenidate group was significantly higher than in the other two groups. There were no differences in cognitive improvements or number of side effects in the groups. Researchers concluded that a citalopram and methylphenidate combination demonstrates a higher rate of remission compared with either drug alone. Yager commented that these findings suggest that carefully selected depressed seniors may benefit from combining a selective serotonin reuptake inhibitor with methylphenidate.
Men and Women: Efficacy and Safety of Antidepressant Treatment

In an umbrella review to determine whether clinically relevant differences in efficacy and safety of commonly prescribed medications exist between men and women, Gartlehner et al. reviewed a pooled analysis of eight randomized studies on patients (n=>3,500) with major depressive disorder, finding similar remission rates for men (36 percent) and women (36 percent) treated with fluoxetine, fluvoxamine or paroxetine. Men and women treated with venlafaxine also achieved the same remission rate (45 percent). Men treated with paroxetine experienced higher rates of medication-related sexual dysfunction than women.

Healthcare Effectiveness Data and Information Set (HEDIS) Measures

The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of performance measures developed and maintained by the National Committee for Quality Assurance (NCQA). HEDIS measures that include major depressive disorder diagnosis are: Follow-Up after Hospitalization for Mental Illness (FUH) and Antidepressant Medication Management (AMM).

Both of these measures focus on processes, rather than on outcome measures. The FUH measure requires that patients with major depressive disorder treated in an acute inpatient setting receive a follow-up visit within 30 days of discharge, preferably within the first 7 days after the discharge. The AMM measure requires that patients with major depressive disorder who are 18 years of age and older, diagnosed with a new episode of major depression, and treated with antidepressant medication should remain on an antidepressant medication for at least 12 weeks and should receive continuous therapy for at least 180 days (six months).

Obtaining Copies of the Guideline


Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. We take all suggestions and recommendations into consideration in our ongoing review of guidelines. Comments may be submitted to:

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