Magellan HEALTHCARE℠

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

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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 (APA, 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 healthcare 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 should be 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 2017. 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)

Epidemiology

The 2015 National Survey on Drug Use and Health (NSDUH) estimated that in 2015, 16.1 million adults aged 18 years or older (representing 6.7% of this age group) experienced at least one major depressive episode (MDE) in the past year (Substance Use and Mental Health Services [SAMHSA]), 2016). The definition of a MDE included a "period of 2 weeks or longer in the past 12 months when they experienced a depressed mood or loss of interest or pleasure in daily activities, and they had at least some additional symptoms, such as problems with sleep, eating, energy, concentration, and self-worth" (SAMHSA, 2016, p. 34). The NSDUH also estimated that in 2015, almost two thirds of adults aged 18 years or older with a past-year MDE had an MDE with severe impairment, including "severe problems with their ability to manage at home, manage well at work, have relationships with others, or have a social life (SAMHSA, 2016, p. 34). Between 2005 and 2015, the percentage of adults aged 18 years or older who had a past-year MDE, as well as the percentage of adults with a past year MDE with severe impairment, remained stable.

The NSDUH provided additional estimates as follows (SAMHSA, 2016):
- Adults aged 18 to 25: 3.6 million young adults aged 18 to 25, representing 10.3% of this age group, had a past-year MDE; and 2.2 million young adults aged 18 to 25, representing 6.5% of this age group, had a past-year MDE with severe impairment.
- Adults aged 26 to 49: 7.3 million adults aged 26 to 49, representing 7.5% of this age group, had a past-year MDE; and 4.8 million g adults aged 26 to 49, representing 4.9% of this age group, had a past-year MDE with severe impairment.
- Adults aged 50 or older: 5.2 million adults aged 50 or older, representing 4.8% of this age group, had a past-year MDE; and 3.2 million young adults aged 50 or over, representing 3.0% of this age group, had a past-year MDE with severe impairment.

The NSDUH also provided estimates for the treatment of depression in adults aged 18 or over who had a past year MDE as follows (SAMHSA, 2016):
- Adults 18 years or older: 10.8 million adults with a past-year MDE, representing 67.2% of this age group, received treatment in the past year for depression; and 7.5 million adults with a past-year MDE along with severe impairment, representing 72.7% of this age group, received treatment in the past year for depression.
- Adults 18 to 25: 1.7 million adults 18 to 25 with a past-year MDE, representing 46.8% of this age group, received treatment in the past year for depression; and 1.2 million young

adults with a past-year MDE along with severe impairment, representing 52.0% of this age group, received treatment in the past year for depression.

- Adults 26 to 49: 4.9 million adults 26 to 49 with a past-year MDE, representing 67.4% of this age group, received treatment in the past year for depression; and 3.4 million young adults with a past-year MDE along with severe impairment, representing 72.0% of this age group, received treatment in the past year for depression.
- Adults 50 or over: 4.2 million adults 50 or older with a past-year MDE, representing 80.9% of this age group, received treatment in the past year for depression; and 2.8 million adults 50 or over with a past-year MDE along with severe impairment, representing 87.9% of this age group, received treatment in the past year for depression.

In a recent study, utilizing data from the World Health Organization (WHO) World Mental Health Surveys and including 23 community epidemiological surveys administered in 21 countries, authors examined prevalence and treatment of MDD (Thornicroft et al., 2016). This included the following: 12-month prevalence of major depressive disorder (MDD) in adults aged 18 years or older; proportion of those with MDD who were aware of their problem and who wanted to receive care; proportion of those wanting care who received care; and proportion of treatment meeting minimal standards (Thornicroft et al, 2016). Results found an average percentage of 4.6% of respondents meeting 12-month criteria for MDD (based on DSM-IV/Composite International Diagnostic Interview [CIDI] MDD), with prevalence higher in higher income countries than in lower income countries. Among those with 12-month MDD, 56.7% recognized the need for treatment, with greater recognition in higher income than lower income countries. A large percentage (71.1%) of individuals recognizing a need for treatment visited a service provider at least once for their emotional problems. Treatment proportions were greater in high income than lower income countries. Of those receiving treatment, 41% met criteria for minimally adequate treatment. The percentage was lower (16.5%) for all individuals with 12-month MDD. **Authors concluded that there is a large "treatment gap" for individuals with MDD** (Thornicroft et al., 2016, p. 3). They also noted that a perceived need for treatment in only 56.7% of persons who had access to acceptable treatment; in low-/lower-middle-income countries, the proportion was only 34.6%. Authors suggested the need to both decrease the treatment gap and scale up the quality of treatment to meet criteria for evidence-based treatment (Thornicroft et al., 2016).

The 2015 National Survey on Drug Use and Health estimated that in 2015, 3.0 million adolescents aged 12 to 17 (representing 12.5% of this age group) experienced at least one major depressive episode (MDE) in the past year (SAMHSA, 2016). Persons were defined as having an MDE if they had a "period of 2 weeks or longer in the past 12 months when they experienced a depressed mood or loss of interest or pleasure in daily activities, and they had at least some additional symptoms, such as problems with sleep, eating, energy, concentration, and self-worth" (SAMHSA, 2016, p. 38). The NSDUH also estimated that in 2015, more than two-thirds (70.7%) of adolescents aged 12 to 17 with a past-year MDE had severe impairment, including "severe problems with their ability to do chores at home, do well at work or school, get along with their family, or have a social life" (SAMHSA, 2016, p. 38). The NSDUH also reported that between 2005 and 2015, the percentage of adolescents aged 12 to 17 who had a past year MDE and the percentage of adolescents with a past year MDE along with severe impairment, **increased** (SAMHSA, 2016). A recent study examining national trends in depression treatment of adolescents and young adults found that the increase in prevalence was larger among non-Hispanic whites than minorities, and among adolescent girls than boys (Mojtabia et al., 2016).

The NSDUH also provided estimates for the treatment of depression in youth aged 12 to 17 who had a past-year MDE. In 2015, 1.2 million youths with a past-year MDE (39.3% of this age group)

received treatment in the past year for depression; and 945,000 youths who had a past-year MDE with severe impairment (72.7% of this age group) received treatment in the past year for depression (SAMHSA, 2016). Mojtabia et al., concerned about the growing numbers of adolescents and young adults who receive no treatment for their MDE, called for outreach effort in school, counseling services, and pediatric practices to improve detection and management of depression in this group (Mjotabia et al., 2016).

Researchers have attempted to find genetic sequences that link to depression with the hopes that genetic markers representing the inherited sequence of DNA may help identify individuals that are likely to benefit from specific treatment with the least adverse events (McMahon, 2015). The author suggested that "more progress can be made if we can develop models that incorporate clinical, genetic, and other biomarker data that can be applied to more biologically valid clinical subtypes of depression" (McMahon, p. 698). In a recent, large randomized, prospective, trial, Schatzberg et al. examined genetic variation of the ABCB1 gene (Schatzberg et al., 2015). Researchers noted that ABCB1 variation has been associated with efficacy and side effects in small sample studies, but there had been no tests of ABCB1 genetic effects in large trials or in patients with cognitive impairment. This study "examined ABCB1 genetic variants as predictors of remission and side effects in this clinical trial that also incorporated cognitive assessment. Researchers examined 10 ABCB1 single-nucleotide polymorphisms (SNPS) in patients (n=683) with MDD who had received treatment for at least two weeks. Of these, almost 600 individuals had completed eight weeks of treatment with escitalopram, sertraline, or extended release venlafaxine. Assessment of antidepressant efficacy utilized the Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR) and a rating scale for frequency, intensity, and burden of side effects. A battery of 13 tests assessed general and emotional cognition. Patients were from the International Study to Predict Optimized Treatment in Depression (iSPOT-D) cohort that provided DNA. Researchers found that a common variation for the ABCB1 gene (SNP rs10245483) predicted high rate of response and lower side effects to specific antidepressants. The presence of cognitive impairment did not lessen the predictive power of the SNP for either response or side effects (Schatzberg et al., 2015).

Cai et al. analyzed DNA sequences from saliva samples of Chinese women with recurrent MDD (5,303) and Chinese women without depression (n=5337), recruited by the China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) consortium, to identify genetic sequences linked to MDD (Cai et al., 2015). This study found two genetic sequences that seemed to be linked to depression. One of the genome-wide significant loci was near the SIRT1 gene and the other "in an intron of the LHPP gene" (Cai et al., p. 588). At the SIRT1 locus, an increased genetic signal was associated with melancholia. Authors suggested that MDD is highly polygenic, with future discoveries of more loci likely. Others have noted, "The hope is that as more genetic links are found, they will flag up groups of proteins known to work together to affect certain cellular functions: these 'pathways' could be investigated as drug targets, and for their potential to make diagnosis of depression more definitive" (Ledford, 2015).

In a recent study, authors discussed the difficulty in identifying single candidate genes associated with MDD as "complex psychiatric illnesses are under polygenic influence and are associated with interactions between genetic variants and environmental exposures" (Kupfer et al., 2014). They discussed studies that examined a combination of genetic, molecular, and neuroimaging measures to identify relations among genes, molecules, neural systems, and behavior in major depressive disorder, noting how these studies "could increase our understanding of the underlying pathophysiological processes and prediction of treatment response" (Kupfer et al., p. 221).

Individualizing Treatment

In a review of the literature for treatment of major depression, Culpepper et al. discussed how an understanding of neurobiology provides a basis for individualizing treatment (Culpepper et al., 2015). Authors noted how the effectiveness of all antidepressants is similar in first-line therapy, although only about one-third of patients improve with first-line treatment. For patients not responding to initial treatment, they **suggested** switching to a drug whose mechanism of action is different or adding another drug whose mechanism of action is based on potential molecular targets, e.g., 12-transmembrane region transporter, 7 transmembrane region G-protein linked receptors, 4 transmembrane region ligand-gated ion channel, 6-transmembrane region voltage gated ion channel, or an enzyme. Culpepper et al. discussed how individualizing drug selection in the initial treatment, as well as in treatment-refractory depression, can improve outcomes. With the knowledge that symptom domains correlate somewhat with malfunctioning brain circuits, treatment that restores neurotransmitter activity in the circuits with impaired information processing may restore function (Culpepper et al., 2015). Authors **suggested** that application of neurobiology principles to treatment selection influences decisions to switch antidepressants, add another antidepressant medication, or augment with another pharmacologic agent or a nonpharmacologic treatment (Culpepper et al., 2015).

Measurement-based care is another form of individualized care, allowing treatment decisions for major depression based on changes in psychopathology and side effects. A recent randomized controlled trial investigated the effect of measurement-based care compared with standard treatment on time to response and remission in patients with depression (Guo et al., 2015). In this trial, outpatients (n=120), 18-65 years of age, were randomized to 24 weeks of either measurement-based care utilizing guideline and rating scale based decisions or standard treatment including decisions by clinicians. Pharmacotherapy included paroxetine (20-60 mg/day) or mirtazapine (15-40 mg/day). Measurement of depressive symptoms included the Hamilton Depression Rating Scale (HAM-D) and the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR). Results found that time to response and time to remission was significantly shorter in patients receiving measurement-based care than those in the standard treatment group. Researchers noted that dosages of antidepressants were higher from week 2 to week 24 in the measurement-based care group, which had more treatment adjustments, than in the standard treatment group, and **suggested** that the most critical time for fine-tuning the treatment approach is between 1 and 3 months. They concluded that measurement-based care is more effective in treating patients with moderate to severe major than standard treatment (Guo et al., 2015).

Depression Screening in the Emergency Department (ED)

A recent study evaluated the test-retest reliability of the Computerized Adaptive Testing – Depression Inventory (CAT-DI) for assessment of depression at an academic emergency department (ED) (Beiser et al., 2016). The development goal of CAT-DI, based on multidimensional item response theory (IRT), was decreased patient and clinician burden while increasing measurement precision. Unlike traditional measurement fixing the number of items administered, CAT allows the number of items to vary, reducing the number of items needed to measure depression. Questions "tap every domain, subdomain, and facet of an underlying disorder" (Beiser et al., p. 1039). This study measured test-retest reliability of the CAT-DI for assessment of depression in an ED setting where an estimated 8 to 32% of patients present for depression. A random sample of adults patients (n=101) were screened twice with the CAT-DI, using tablet computers, during their ED visit; the second test was administered 1-3 minutes after the end of the first testing. Questions inquired about how they were feeling during the initial and repeated

administration of the test, with questions on the second test based on previous responses on the first test and a given patient's severity level. Researchers assessed test-retest reliability and found **consistent results between the two testing sessions**. Based on test scores, 79% of patients were free of depression, while 14% had mild depression; 4% had moderate depression, and 3% had severe depression. Researchers concluded that the CAT-DI "provided reliable screening results among ED patients. Concerns about whether changes in item presentation during repeat testing would affect test-retest reliability were not supported" (Beiser et al., p. 1039). Researchers found no evidence of bias, and scores were highly correlated between the two tests. They reported that test-retest reliability exceeded the reported reliability for the fixed-length PHQ-9. Recognizing that items providing good discrimination of high and low levels of depression in psychiatric settings and in a general ED may not be the same, they stated the need for examining differential item functioning between the two settings to determine items that may be less useful in the ED for the assessment of depression (Beiser et al., 2016).

Depression Treatment in Primary Care

A recent randomized controlled trial evaluated practice nurse-led proactive care for chronic depression in primary care (Buszewicz et al., 2016). Although chronic depression is associated with high use of primary care services, high mortality, and increased psychological morbidity, investigation of these patients as a distinct group is rare. Trial participants (n=558) aged 18 or over, with evidence of recurrent and/or chronic depression and a baseline Beck Depression Inventory (BDI-II) of 14 or above, were randomized by telephone to general practitioner (GP) treatment as usual or to proactive care involving regular scheduled follow-up appointments with trained nurses over a 24-month period. Proactive care included 10 appointments, most of which were face to face. Although there was no significant improvement in depression score (BDI-II) or quality of life (EuroQuol EEQ-5D) in the intervention group at 24 months, there was a significant improvement in functional impairment in the group, measured by the Work and Social Activity Schedule (WSAS). Researchers concluded that "although overall improvements in depressive symptoms were small and non-significant for patients receiving the intervention, there were significant improvements in work and social functioning" (Buszewicz et al., p. 379). They also **suggested** that the improved levels of functioning were a result of the nurses' focus and approach on practical goals and problem-solving (Buszewicz et al., 2016).

A recent study investigated the relationship between primary care mental health integration (PCMHI) staffing characteristics in the Department of Veterans Affairs (VA) health system and the quality-of-care processes among VA patients who had received a diagnosis of depression by primary care physicians (PCPs) or PCMHI providers (Levine et al., 2016). Implementation of VA policies that require primary care mental health integration began in 2007 and require all VA medical centers and large community-based outpatient clinics to have services including "care management and collocated collaborative care components" (Levine et al., p. 1). The requirements include "routine monitoring of medication effectiveness, adherence, and treatment needs, provided by a care manager in coordination with PCPs" and "mental health practitioners working in the primary care clinic setting, with shared responsibility for evaluation and treatment of mental health conditions" (Levine et al., p. 1). Using data obtained from the VA Corporate Data Warehouse (CDW), this study examined whether PCMHI provider staffing affected performance on indicators of depression care quality at the facility level. Depression treatment measures across the facilities for patients (n=279,199) with a new episode of depression and at a primary care or PCMHI clinic encounter were calculated. Results found that higher facility staffing ratios resulted in a greater percentage of patients receiving psychotherapy treatment, but not with higher rates of medication use. Authors noted that primary care providers often prescribe antidepressant medications without

specialty prescriber input and psychiatrists often have a supervisory/consultative role in collaborative care models. Higher proportions of PCMHI social worker staffing were "positively correlated with the percentage of patients with adequate antidepressant treatment continuation" (Levine et al., p. 1).

Another randomized controlled trial, Patients, Providers, and Clinics Together (PACT), examining the effectiveness of collaborative care for depression in three public sector primary care clinics serving Latinos, found culturally relevant collaborative care that accommodates patient treatment preferences for depression significantly improves depression, quality of life, and satisfaction outcomes (Lagomasino et al, 2016). Improved quality of care indicators included the proportion of patients receiving either psychotherapy or antidepressant medication. Systematic random sampling in waiting rooms and referrals of clinic patients by primary care providers resulted in participants (n=400) who completed a baseline assessment and were randomly assigned to a collaborative care group or to an enhanced usual care control group. The collaborative care group received education about depression and its treatments from social workers, functioning as depression care specialists. They were allowed to choose to receive psychotherapy, antidepressant medication or both. If psychotherapy was the choice, the depression care specialists provided the 12-week CBT intervention. The depression care specialists also communicated with primary care providers about adherence to medication, side effects and treatment response. The control group received an educational pamphlet about depression and its treatment as well as a list of mental health resources. A letter stating that they screened positive for depression was available for sharing with their primary care providers. Participants receiving collaborative care for depression "had reduced depressive symptomatology, increased satisfaction with overall and emotional health care, and a much higher likelihood of receiving a minimum level of adequate depression care, compared with patients in enhanced usual care" (Lagomasino et al, p. 5). The greatest effect on quality of care was an increase in psychotherapy visits, provided in Spanish.

A sample of adults from the 2008-2012 NSDUH included 17,700 respondents meeting the criteria for a major depressive episode in the past 12 months, of whom 8,900 (61.5%) received treatment for depression from general providers, specialty mental health providers only, or from both types of providers (Kuramoto-Crawford et al., 2016). The breakdown was 21% from general providers, 19% from specialty mental health providers only, and 19% from both. This study compared individuals receiving care from both primary care and specialty mental health providers with those receiving care from only one of the provider types to provide "characterization of persons who receive treatment from both general medical providers (GMPs and specialty mental health providers (SMHPs)" (Kuramoto-Crawford et al., p. 758). This study found that adults receiving care from both types of provider were younger and more highly educated, had more suicidal ideation and functional impairment, and had more access to psychiatrists providing patient care than those who received care from GMPs only. This highlights the need for continuing education and training for the prevention of suicide in primary care (Kuramoto-Crawford et al., 2016). Of those receiving care from both types of provider, more were females, had higher education, more general medical comorbidities, and more functional impairment than those who received care only from a SMHP. Authors concluded that efforts to "understand differences in depression care in specialty mental health and general medical settings may help improve the provision of mental health services as health care reform continues" (Kuramoto et al., p. 758). Collaborative care for depression in primary care settings, along with the increased role of mental health care in patient-centered medical home projects, is a part of the move toward coordination and integration of behavioral health care and primary health care (Kuramoto et al., 2016).

Antidepressant Medications

The APA guideline recommends an antidepressant medication for the initial treatment of patients with mild to moderate major depressive and those with severe major depressive disorder unless electroconvulsive therapy (ECT is planned (APA, 2010). Selection of an antidepressant should consider tolerability, safety, cost, patient preference and history of prior medication treatment. First line pharmacotherapeutic options for treatment include second-generation antidepressants: **selective serotonin reuptake inhibitors (SSRIs)**, i.e., citalopram, escitalopram fluoxetine, fluvoxamine, paroxetine, sertraline; **serotonin norepinephrine reuptake inhibitors (SNRIs)**, i.e., duloxetine, desvenlafaxine, levomilnacipran and venlafaxine; **norepinephrine-dopamine reuptake inhibitors (NDRIs**), i.e., bupropion; and **atypical antidepressants**, i.e., trazodone, mirtazapine, nefazonde, vortioxetine, and vilazodone. First-generation antidepressants include the older and less commonly prescribed classes including the **tricyclic antidepressants (TCAs)**, e.g., amitriptyline, imipramine, and nortriptyline; and **monoamine oxidase inhibitors (MAOIs)**, e.g., phenelzine and tranyleypromine. The use of these drugs is limited although they may be beneficial when patients do not respond to first line pharmacotherapies. Caution may be required in prescribing and treatment due to harmful side effects.

Noting that it takes several weeks before an antidepressant is fully effective and that a significant percentage of people may not respond to a prescribed antidepressant, the FDA advises continuation of the medication for several weeks before switching to a different antidepressant or adding another medication. Common side effects of antidepressants may include nausea and vomiting, weight gain, diarrhea, sleep disturbances and sexual problems, and some antidepressants can have serious risks, e.g., suicidal thinking or suicidal behavior, birth defects, and high blood pressure leading to a stroke or other complications (FDA, 2016).

A recent observational, retrospective analysis evaluated antidepressant prescription claims of insured patients (n=54,107) with MDD who had a prescription for an antidepressant filled during 2013, to determine the most commonly prescribed antidepressant medications along with their most common dosages (Treviño et al., 2016). From most prescribed to least prescribed, the most commonly prescribed medications were SSRIs, SNRIs, serotonin antagonist and reuptake inhibitors (SARIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Doses of the most frequently prescribed drugs generally were within established guidelines, e.g., APA guidelines and Centers for Medicare and Medicaid Services (CMS). Authors reported "an incidental finding from the study sample derivation was that approximately 80% of patients who were diagnosed as having MDD filled an

antidepressant medication within the study period" (Treviño et al., p.3). This finding correlated with findings of past studies reporting that 73.8 and 75.3 % of patients with MDD received antidepressant medication in 1998 and 2007, respectively. Authors concluded that encouraging findings showed that "most physicians followed treatment guidelines" while also indicating a need for further research to investigate cases where guidelines are not being met for some drug prescribing (Treviño et al., 2016).

Augmenting and Combining Treatments

Patients with MDD who do not achieve adequate response to first-line antidepressant treatment (approximately 50% of patients with MDD) may benefit from switching antidepressants, adding another antidepressant, or adding adjunctive therapy with an atypical antipsychotic (Sussman et al., 2017). Even among those responding to initial treatment, only 50-65% of patients achieve remission (Singh et al., 2017). A recent study discussed the STAR*D (Sequenced Treatment

Alternatives to Relieve Depression) trial which found that "bupropion, sertraline, and venlafaxine are comparable in terms of therapeutic effectiveness following unsuccessful treatment with citalopram" (Singh et al., p. 81). Authors, in this current study, tried to determine whether treatment with one of the drugs was more cost-effective relative to others. They found that although costs of the medications differed significantly, there were no significant differences in the pairwise comparisons of total costs and cost effectiveness of the three medications. They emphasized the importance of other factors considered in choosing an antidepressant over another: preference of the clinician, family history, or treatment of most evident cardinal symptoms (Singh et al., p. 81).

For treatment-resistant depression, the STAR*D study found a small decrease in remission rates from first-line initial treatment, e.g., SSRI or SNRI, to the next course of treatment including a dissimilar antidepressant or a combination of antidepressants (Thase, 2016). Author noted, "Chances for recovering from an episode of major depressive disorder become progressively smaller as the number of fail treatment trials mount" (Thase, p. 181). Thase reported that the trials in STAR*D suggested, "Patients who received adjunctive therapies were more likely to remit than those who were switched to another course of antidepressant monotherapy" (Thase, p. 181). The author noted that the most widely used form of adjunctive treatment for MDD appears to be treatment with second-generation antipsychotics, e.g., aripiprazole, olanzapine, and quetiapine. The efficacy of aripiprazole, olanzapine, and quetiapine in treatment of depression is "observed at doses that are only one-fourth to one-half those used to treat acute schizophrenia or mania" (Thase, p. 181) which **suggests** the effects may not be "directly tied to their antipsychotic effects" (Thase, p. 181). Author noted the need for answers to the following concerns: how long the second-generation antipsychotic should be continued; the relative efficacy compared with older standards, e.g., lithium; and whether this treatment is cost effective. Thase stated, "At present, there is no better proven strategy for treatment-resistant depression, given that multiple positive, placebo-controlled studies have been conducted for adjunctive therapy with five second-generation antipsychotics: aripiprazole, brexpiprazole, olanzapine, risperidone, and quetiapine" (Thase p. 183). He further stated that second-generation antipsychotics "should indeed by thought of as one of the gold standards for treating antidepressant nonresponders" although potential benefits must be carefully balanced against both the higher cost of these medications and the several manageable but real risks" (Thase p. 183). Consideration of the risks of adverse events, e.g., weight gain and extrapyramidal symptoms, when augmenting antidepressants with antipsychotic treatment in patients is advised (Thase, 2016).

A recent randomized prospective open-label multi-center study compared the efficacy and safety of aripiprazole versus bupropion augmentation for the treatment of patients (n=103) with major depressive disorder unresponsive to SSRIs (Cheon et al., 2017). Over a six-week treatment period, patients were randomized to receive an SSRI plus aripiprazole (2.5-20 mg/day) or an SSRI plus bupropion (150-300 mg/day) augmentation. Results found reductions in MADRS scores at six weeks were not significantly different in the two groups, and the scores were much improved compared to baseline scores in both groups. Researchers **suggested** that aripiprazole augmentation therapy and bupropion combination therapy with SSRI have comparative efficacy and tolerability in the treatment of MDD (Cheon et al., 2017).

On July 13, 2015, the U.S. Food and Drug Administration (FDA) approved an atypical antipsychotic, brexpiprazole, to treat schizophrenia and as add-on to an antidepressant medication to treat patients with major depressive disorder (FDA, 2015). The FDA News Release reported the results of two six-week trials comparing brexpiprazole combined with an antidepressant to placebo plus an antidepressant for patients (n=1046) for whom an antidepressant alone was not adequate in

treating their symptoms. These trials found adjunctive oral brexpiprazole (2 or 3 mg once per day) plus antidepressant was more effective than placebo plus antidepressant in improving depressive symptoms. Brexpiprazole has a Boxed Warning about an increased risk of death associated with off-label use in treating older people with dementia-related psychosis. The Boxed Warning also includes an alert about an increased risk of suicidal thinking and behavior in children, adolescents, and youth who are taking antidepressants (FDA, 2015).

A recent trial randomized patients (n=379) with MDD and inadequate response to antidepressants to treatment with an antidepressant plus brexpiprazole 2 mg/d or to an antidepressant plus placebo for six weeks to determine efficacy, tolerability, and safety of adjunctive brexpiprazole (Thase et al., 2015). Results of this randomized, placebo-controlled study found adjunctive brexpiprazole reduced the mean score on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Sheehan Disability Scale (SDS) greater from baseline to week six compared with placebo. The study found adjunctive brexpiprazole well tolerated, with weight gain and akathisia the most frequently reported treatment emergent adverse effects (Thase et al., 2015). Another randomized, double-blind placebo-controlled trial randomized patients (n=677) with MDD and inadequate response to antidepressants to brexpiprazole 1 mg, brexpiprazole 3 mg, or placebo for six weeks adjunctive to antidepressant to determine efficacy, tolerability, and safety of adjunctive brexpiprazole (Thase et al., 2015). Results found that adjunctive brexpiprazole 3 mg reduced mean score on the MADRS compared with placebo, while adjunctive brexpiprazole 1 mg did not reduce the score significantly. Both brexpiprazole 1 mg and 3 mg showed greater reductions from baseline to week six than placebo in SDS mean scores. This study found adjunctive brexpiprazole at both 1 mg and 3 mg dosage well tolerated (Thase et al., 2015).

Another randomized, double-blind, placebo-controlled trial compared the efficacy of ziprasidone as an adjunct to escitalopram with adjunctive placebo in adult patients (n=139) with MDD who had not responded to eight weeks of flexible dosing of escitalopram (Papakostas et al., 2015). Results found that adjunctive ziprasidone had greater antidepressant efficacy than adjunctive placebo based on response rates of the HAM-D. Although more patients discontinued adjunctive ziprasidone than placebo (due principally to sedation, anxiety, agitation, and insomnia), more serious adverse events were equal with ziprasidone and placebo (Papakostas et al., 2015). Among patients treated with adjunctive ziprasidone, two serious events occurred, i.e., hospitalization due to suicidal ideation and hospitalization due to a fall. Serious adverse events in the group treated with adjunctive placebo also had two serious adverse events, i.e., hospitalization for treatment-emergent viral meningitis and hospitalization for pneumonia. Another atypical antipsychotic under investigation as an adjunctive treatment for patients who inadequately respond to standard antidepressant therapy is cariprazine (Durgam et al., 2016). In another recent randomized, double-blind, placebo-controlled study including patients (n=810) with MDD and inadequate antidepressant response, patients were randomized to adjunctive cariprazine 1-2 mg/d, adjunctive cariprazine 2-4.5 mg/d, or adjunctive placebo for eight weeks (Durgam et al., 2016). Stable doses of antidepressant treatment, i.e., sertraline, citalopram and escitalopram, continued during the eight-week treatment period. Results found that treatment with cariprazine 2-4.5 mg/d resulted in greater reduction in MADRS total score at week eight than placebo or the lower dose of cariprazine. Adverse events in both dosage groups of those treated with cariprazine were akathisia, insomnia, and nausea; however, in all three groups, changes in metabolic parameters, vital signs and ECG parameters were significantly similar (Durgam et al., 2016).

Treatment Strategies for Psychotic Depression

The APA practice guideline recommends Electroconvulsive Therapy (ECT) or pharmacology as first-line treatment for psychotic depression (APA, 2010). Many patients prefer pharmacologic treatment instead of ECT. The guideline recommends combination of an antipsychotic and an antidepressant, rather than either component alone, to provide better response in the treatment of psychotic depression. Although clinical trials indicate greater efficacy of the combination treatment based on HAM-D scales, Østergaard et al. noted in a new study that the HAM-D scales were not subjected to validation, clinical and psychometric, in relation to psychotic depression and covered only a fraction of the psychotic symptoms in psychotic depression (Østergaard et al., 2014). Acknowledging no established psychometric instrument dedicated to measurement of severity in psychotic depression, authors investigated a new rating scale covering both the psychotic and the depressive domains of psychotic depression, i.e., the Psychotic Depression Assessment Scale (PDAS), to determine whether it "could detect differences in effect between two psychopharmacological treatment regimens" (Østergaard et al., p. 69). They compared its performance to that of the HAM-D, using data from the Study of Pharmacotherapy of Psychotic Depression (STOP-PD). They addressed the following: whether measured responses to treatment regimens were similar across the PDAS and the HAM-D; whether the PDAS and HAM-D were sensitive to differences in the effects of different drug combination on severity of psychotic depression; and the proportion of patients still psychotic at end of participation in the STOP-PD. The investigation found that the PDAS and HAM-D distinguished between the effect of different combinations of treatment in psychotic depression, and effect sizes of the rating scales were similar, although slightly lower for the PDAS than for the HAM-D. Of the patients included in the STOP-PD, 45% continued to experience at least probable psychotic symptoms at the end of the trial, underscoring "the importance of including items that assess psychotic symptoms in rating scales for psychotic depression" (Østergaard et al., p. 74). Authors indicated the need for further study of the PDAS while noting, "measurement of severity and treatment response in *psychotic depression* should take both *psychotic and depressive* symptoms into account (Østergaard et al., p. 74).

Antidepressants and Suicidal Ideation and Behavior

Barbui and Patten reported the results of a propensity score-matched cohort study by Miller et al., (Miller et al., 2014) based on data from a large clinical population of patients (n=162,625) with depression who received initial treatment of citalopram, sertraline or fluoxetine (Barbui and Patten, 2014). Patients were divided into two age groups: 10-24 or 25-64, with patients in each group assigned to either modal or higher-than-modal doses of the drugs. Results showed that patients receiving higher doses of drugs in the 10-24 age groups had a rate of deliberate self-harm (DSH) almost twice as high as the patients in the modal dose group**.** In the age 25-64 group, this effect was not detected. Authors considered the fact that most individuals who engage in DSH do not commit suicide and that if the study was replicated employing completed suicide instead of deliberate self-harm, the findings may be different. Authors argued that this study "may have at least partially captured DSH as a consequence of impulsivity linked to borderline personality traits, rather than suicidality as a consequence of adverse effects of antidepressant exposure" (Barbui and Patten, p. 330). They also noted that in the study population, nearly 20% of individuals began treatment with high-dose antidepressants that could have been related to the severity of depression or previous suicide ideas, identifying patients at greater risk for DSH for reasons other than higher dose of antidepressant. Authors noted that the findings of the Miller et al. study have implications for clinical practice, and suggest that antidepressant treatment "should not be started with greater than modal doses" (Barbui and Patten, p. 331). Dose change or dose escalation was not a focus of the Miller study. In another review of the Miller study, Petersen and Nazareth **suggested**

"the jury is still out on whether antidepressants are indeed likely to enhance suicidation in younger people receiving high doses of selective serotonin reuptake inhibitors. In any circumstances, the study by Miller et al. highlights close clinical monitoring of young people with severe and potential acute psychiatric problems" (Petersen and Nazareth, 2015).

The Antidepressant Pharmaceutical Pipeline

Past studies have shown that in addition to the monoaminergic system, the glutamatergic system is targeted for treating major depressive disorder (Schoevers et al., 2016). Schoevers et al. noted that those studies found short-term success within hours of rapid intravenous infusion, but at seven days post-infusion, effects were not significantly different between ketamine and placebo. A recent review of literature including 88 small, uncontrolled studies, obtained information including number of individuals receiving ketamine, study types and sizes, dosing regimens, and effects of treatment for depression. Studies included intravenous ketamine, oral ketamine, intranasal ketamine, sublingual ketamine and intramuscular ketamine. In one study, patients (n=4) receiving up to 1.25 mg/kg oral ketamine for two weeks showed depression relief. Another study found that patients (n=2) showed significant improvements after one oral dose of 0.5 mg/kg, with the improvement lasting 1-2 weeks. In another study, patients (n=14) were administered daily oral ketamine (0/5 me/kg over 28 days), with eight patients completing the trial and showing significant improvement in depression with few side effects. Two patients with chronic suicidal ideation and two prior suicide attempts, both of whom received 3 mg/kg, sustained remission from suicidal ideation. In another study, 10 mg sublingual ketamine was administered once, or every 2, 3, or 7 days for a total of 20 doses in 26 patients of whom 20 showed improved mood. Authors concluded that results of these small, uncontrolled studies suggest that oral ketamine may be well tolerated; however long-term consequences have not been systematically studied. They discussed potential misuse of ketamine warranting monitoring and cautioned that although side-effects of oral ketamine appear milder than that reported in intravenous studies, a hospital setting is necessary for ketamine administration. Authors further cautioned that more studies are needed examining long-term effects of repeated use of ketamine (Schoevers et al., 2016). **Magellan continues to consider the use of ketamine in the treatment of depression highly investigational** (Magellan Health, 2013).

The results of a systematic review and meta-analysis of ketamine and other N-methyl-D-aspartate (NMDA) receptor antagonists found that "the antidepressant efficacy of ketamine, and perhaps D-cycloserine and rapastinel, holds promise for future glutamate-modulating strategies" (Newport et al., 2015). They also tempered enthusiasm about ketamine's use due to limited clinical trial data demonstrating only a "transient benefit" (Newport et al., p. 950). Authors also noted that high-dose D-cycloserine and rapastinel "behave as classic partial agonists within a low (weak agonist activity) to moderate (relative antagonist activity) dose range but at especially high doses exhibit full agonist activity via GluN2C glycine binding sites activation. These agents are certainly worthy of further scrutiny" (Newport et al., p. 961). Authors **suggested** other ionotropic receptors within the glutamatergic system, e.g., AMPA and kainate receptors, metabotropic glutamate receptors, and glutamate transporters (Newport et al, 2015).

A systematic review and meta-analysis of 20 studies examined the potential role of cytokines in the treatment of depression in participants (n=5063) using trials of chronic inflammatory conditions where a secondary outcome measure was depressive symptoms (Kappelmann et al., 2016). Authors noted, "cytokine-mediated communication between the immune system and the brain has been implicated in the pathogenesis of depression" and that "major depression is common (one in four) in individuals after interferon treatment, a potent inducer of cytokines, in patients affected by

hepatitis C virus" (Kappelmann et al., p. 1). Studies included randomized controlled trials of anti-cytokine drugs vs. placebo, as well as non-randomized and non-placebo trials in patients with several conditions, e.g., psoriasis, Crohn's disease, atopic dermatitis, and rheumatoid arthritis. Results of the studies showed that anti-cytokine treatment improved depressive symptoms with a small to moderate size effect. Authors recommended future randomized controlled trials of anti-cytokine treatment where depression is the primary outcome (participants with high inflammation but without other physical illnesses). They concluded that anti-cytokine drugs may be effective for some patients with depression and recommended more studies (Kappelmann et al., 2016).

Researchers investigated the feasibility, safety, and efficacy of psilocybin, a serotonin receptor agonist occurring naturally in some mushroom species, in a recent small open-label feasibility trial including patients (n=12) with treatment-resistant major depression (Carhart-Harris et al., 2016). Psilocybin was administered in two dosing sessions, with the first a low dose of 10 mg (initial safety dose) and a high dose (25 mg) one week later. Patients were assessed for depression severity with assessment tools, e.g., HAM-D, MADRS, Global Assessment of Functioning (GAF) and QUIDS, prior to treatment with the first dose. The outcome measure was patient-rated subjective intensity of the effect of psilocybin, which was well tolerated by all of the patients with no unexpected adverse events. Results showed that relative to baseline, there was marked reduction in depressive symptoms at one week and three months after the high dose treatment. Researchers concluded that strong inferences about efficacy are lacking due to the size of the study, and **suggested** further research is warranted (Carhart-Harris et al., 2016).

In a recent double-blind, randomized, placebo-controlled trial, researchers investigated the effects of single-dose modafinil (200 mg), a wake promoting agent often used for treatment of narcolepsy, on cognition and fatigue in adults patients (n=60) with remitted depression (Kaser et al., 2017). Results **suggested** that modafinil improved domains of cognition, i.e., episodic memory as measured by the Paired Associates Learning (PAL) test and working memory as measured on the Spatial Working Memory (SWM) test in remitted depressed patients. They indicated the need for further research of treatment with modafinil over a longer time and in combination with psychological treatments (Kaser et al., 2017).

In a current review, authors discussed research that "highlighted the potential role of monitoring peripheral polyunsaturated fatty acids (PUFAs) and cholesterol in the prediction, stratification and management of MDD" (Parekh et al., 2017). Noting that studies have shown that increased HDL and omega-3 PUFA could protect against depression-mediated inflammation, they **suggested** further research to determine whether the complex relationship between PUFAs and cholesterol are involved in the pathology of MDD and could lead to potential treatment of MDD (Parekh et al., 2017).

Other Somatic Treatments

Noting previous studies have shown that high-frequency left prefrontal rTMS was effective for treatment-resistant depression, Kito et al. examined changes in resting electroencephalogram (EEG) functional connectivity before and after high-frequency left prefrontal rTMS in patients (n=14) (with treatment resistant depression) in order to understand better antidepressant mechanisms of rTMS (Kito et al., 2016). Researchers found more synchronized middle beta band activity between the left DLPFC and limbic regions with "no significant changes in other frequency bands" (Kito et al., p. 4). Other studies have proposed modulation of GABA function as a possible mechanism of action for rTMS; Kito et al. "assumed that more synchronized middle beta band activity between the left DLPFC and limbic regions might be related to GABAergic circuits

modulation" (Kito et al., p. 16). Researchers indicated the need the further well designed studies that will add further insights into the antidepressant mechanism of rTMS in the treatment of major depressive disorder (Kito et al., 2016).

In a recent retrospective chart review that included patients (n=225) who received rTMS for treatment-resistant depression, authors identified patients (18) meeting criteria for reintroduction of rTMS (Kelly et al., 2016). Criteria for reintroduction included positive response to initial treatment, withholding additional treatment until relapse; and treating relapse with 3-5 treatments per week for 2 to 6 weeks. In this study, authors tested whether a favorable response to first induction course would predict response to a subsequent course. They found that 16 patients met full inclusion criteria for reintroduction, of which 10 were >50% responders to initial treatment, and 4 had 25-50% response to initial induction. Of the patients who were > 50% and 25-50% responders to initial treatment, 80% and 75%, respectively, responded to reintroduction. Patients with <25% response to induction had 0% response to reintroduction. Authors concluded that these results suggest that "therapeutic response to an initial course of rTMS for depression is a significant predictor of response to a subsequent course" (Kelly et al., p. 2). Due to the limitation of this study, i.e., small sample identified retrospectively via chart review, additional research is needed comparing long-term rTMS treatment strategies, including reintroduction or maintenance rTMS (Kelly et al., 2016).

Kellner et al. recently reported results of Phase 2 of the Prolonging Remission in Depressed Elderly (PRIDE) study, which compared the effects of continuation electroconvulsive therapy (ECT) plus medication (venlafaxine plus lithium) to medication only (venlafaxine plus lithium) in the treatment of depressed geriatric patients (over age 60) after a successful Phase 1 treatment. The patients (n=120) had remitted after a Phase 1 course of right unilateral ultrabrief pulse ECT, augmented with venlafaxine (Kellner et al., 2016). Outcome measures after 24 weeks of treatment in Phase 2 were the HMA-D and the Clinical Global Impressions Severity Scale (CGI-S). Results demonstrated that the ECT plus medication group had significantly greater improvement in maintaining low depression symptom severity for six months than the medication-only group. Authors concluded, "Additional ECT beyond the traditional endpoint of an acute course, plus rescue as needed, is valuable and feasible in maintaining the long-term antidepressant benefits of ECT in a vulnerable geriatric population" (Kellner et al., p. 1116).

Psychosocial Treatments

In a recent review, authors reported studies showing that several high-intensity psychosocial interventions are as effective and long lasting as medications in the treatment of nonpsychotic depression (Hollon and Williams, 2016). Established high-intensity interventions discussed included cognitive-behavioral therapy (CBT) "conducted according to a treatment manual and delivered by trained and competent practitioners who receive ongoing supervision" (Hollon and Williams, p. 175). Other high-intensity interventions discussed included behavioral activation therapy with focus on behavior more than on cognition; mindfulness-based cognitive therapy (MBCT) integrating meditation training with cognitive therapy; acceptance and commitment therapy, a "third wave" behavior therapy; interpersonal psychotherapy; and dynamic psychotherapy with an emphasis on brief interventions. Authors noted that each of the above interventions have a clear structure, relationship with practitioner, and a focus on problems relevant to the patient. Due to service demand, authors noted the importance of low-intensity psychosocial interventions, delivered in more focused ways with less practitioner time overall. These include CBT delivered using computers and self-help books and manuals, accompanied by practitioner support from either experts or non-experts in CBT. In conclusion, authors recognized

the established evidence base for traditionally delivered high-intensity interventions while also noting the growing evidence base suggesting effective delivery of low-intensity CBT and behavioral activation. Authors emphasized the need for an approach "consistently delivered in high-quality ways to maximize outcomes" (Hollon and Williams, p. 177).

A recent meta-analysis of 44 randomized clinical trials investigated the effectiveness of psychotherapy on global quality of life (QoL) and on the mental health and physical health components of QoL in patients (n=5264) 18 years or older with depression (Kolovos et al., 2016). The reviewed trials compared psychotherapy (including either high or low intensity interventions) with control conditions (including waiting list, care as usual, placebo or another minimal treatment). Results found larger improvements in QoL in those treated with psychotherapy than in the control conditions. The effect sizes for depressive symptoms and physical health component of QoL were unrelated, whereas authors found a positive relationship between the effect sizes for the mental health component and the depressive symptoms. Results of meta-regression analyses found, "Overall, changes in QoL were not fully explained by changes in depressive symptoms. We can thus infer that decreased depressive symptom severity at the end of the treatment is not necessarily a manifestation of improvement in QoL of the patient *or vice versa*" (Kolovos et al., p. 466). They concluded that this meta-analysis demonstrated that psychotherapy is efficacious in reducing depression symptoms and in improving additional outcomes related to depression. They emphasized that the effects of psychotherapy are different for the mental health and physical health components of QoL (Kolovos et al., 2016).

A meta-analysis of sixteen randomized clinical trials including patients (n=1700) with depression compared divergent outcomes, i.e., deterioration (symptom severity increases from beginning to end of treatment and severe symptoms of depression posttreatment) in CBT and pharmacotherapy (Vittengl et al., 2016). Researchers tested frequencies of deterioration, extreme nonresponse, and superior response between CBT and pharmacotherapy, finding that pharmacotherapy compared with CBT increased odds of superior improvement (from the HAM-D) but not from the patients' perspective (Beck Depression Inventory-BDI); pharmacotherapy also predicted more attrition than CBT. Researchers emphasized that although pretreatment symptoms levels may help forecast negative and positive outcomes, they do not determine whether CBT or pharmacotherapy is the desired treatment. Among patients with high pretreatment severity, researchers recommended assessing symptom levels frequently and making treatment changes, e.g., switching or augmenting treatment. They concluded, "Choosing pharmacotherapy versus CBT may increase patients' odds of both discontinuing treatment and clinician-rated superior response" (Vittengl et al., p.489).

In a meta-analysis update including 54 studies totaling patients (n=3946) with diagnosis of major depressive disorder or another mood disorder accompanied by elevated score on a depression measure, researchers examined the efficacy of short-term psychodynamic psychotherapy (STPP) for depression (Driessen et al., 2015). The APA does not consider STPP, a treatment rooted in psychoanalytical theories (e.g., drive psychology, ego psychology, object-relations psychology and attachment theory), a first-choice treatment in the treatment of depression (APA, 2010). Only in recent years have many studies examining the efficacy of STPP for depression been published. In this study, STPP pre- to post-treatment findings included the following: significant improvement in depression symptoms; significant improvement in anxiety symptoms in individual format STPP, but not group STPP; and significant improvement in general psychopathology in individual format STPP. STPP post-treatment to six-month follow-up findings included the following: non-significant change for interpersonal functioning and significant improvement in symptoms of anxiety and general psychopathology. At post-treatment, the other psychotherapies showed significant superiority across all studies of STPP. At six-month follow-up findings, no significant differences

between STPP and other psychotherapies or depression symptoms were evident. At post treatment, the study found no significant differences between STPP and antidepressant medication, and no significant difference was shown between combination STPP + medication and combination medication +other psychotherapy on outcomes of depression. Researchers concluded that this study "found clear indications that STPP is effective in the treatment of depression in adults" (Driessen et al., p.1). They recommended additional studies are needed to "assess the efficacy of STPP compared to control conditions at follow-up and to antidepressants" (Driessen et al., p.1).

In a review by Chakrabarty et al., authors discussed the lack of consensus on how best to monitor cognition clinically in non-elderly patients with depression, and noted that the clinical significance of treatments, i.e., antidepressant medications, psychotherapy, and neuromodulation is unclear (Chakrabarty et al., 2016). Although there are currently no approved treatments specifically for cognitive dysfunction in major depressive disorder, studies have shown evidence regarding the effects of antidepressants on cognition among adults. Authors reported two large randomized controlled trials finding strong evidence for efficacy of vortioxetine in improving cognition while noting few studies comparing different agents. They also cautioned that ongoing antidepressant treatment may adversely affect cognition. Authors reported encouraging results from small studies of the cognitive effects of augmentation agents, e.g., aripiprazole, olanzapine, lisdexamfetamine, and S-adenosylmethionine (SAMe). Studies of neuromodulation treatments, i.e., ECT and rTMS, have found an association between treatment and improved cognition. Psychotherapy may have a beneficial effect on cognition in major depressive disorder. Authors reported studies showing combined long-term psychodynamic therapy and fluoxetine improved cognitive symptoms greater than fluoxetine alone. Authors **suggested** a multifaceted approach to improve cognitive outcomes because of numerous and complex factors that mediate cognition and cognitive dysfunction (Chakrabarty et al., 2016).

A multicenter, three-group parallel, randomized control trial compared the effectiveness of internet-based cognitive-behavioral therapy (ICBT), exercise, and usual care in the treatment of patients (n=757) with mild to moderate depression (Hallgren et al., 2016). Patients (n=740) were randomized to one of the three 12-week parallel treatment with three-month post-treatment and 12-month end-point. Patients treated with ICBT worked through a self-help online manual, which included separate modules. In the first few week of treatment, patients completed modules addressing problems related to depressive symptoms, e.g., inactivity and avoidance behaviors. Later patient-specific modules targeted comorbid symptoms, e.g., worry, panic attacks, social anxiety, stress, insomnia and pain. Assigned clinicians monitored patients' responses weekly and provided needed assistance; a psychologist monitored cooperation with therapy. The exercise intervention included light, moderate, or vigorous exercise by qualified trainers in three 60-minute sessions per week during 12 weeks. Examples of light, moderate and vigorous exercise included yoga, aerobics, and body strengthening exercises, respectively. Weekly meetings with trainer or physiotherapist monitored adherence to the regimen. Treatment as usual or 'usual care' consisted of 45-60 minutes of CBT delivered face-to-face by a counselor or psychologist. Results found depression severity at 12-month follow-up reduced in all groups, with the largest treatment effect obtained at three months, and the exercise and ICBT groups showed greater reduction of severity than the usual care group. Researchers concluded, "Prescribed exercise and clinician-supported ICBT are at least equally effective long-term treatment alternatives for adults with mild to moderate depression" compared with usual care by a physician (Hallgren et al., 2016, p. 419).

Combination Psychotherapy and Pharmacotherapy for Depression

A recent clinical synthesis of evidence-based applications of combination psychotherapy and pharmacotherapy for depression reported results of meta-analyses showing that the combination produces small effect sizes, favoring it over pharmacotherapy or psychotherapy alone (Dunlop, 2016). The World Federation of Societies for Biological Psychiatry recommended the combination of psychotherapy and antidepressants in the treatment of patients with moderate to severe depression, with only partial response to antidepressant medication, and with problems adhering to antidepressant medications (Bauer et al., 2015). Acknowledging that two separate clinicians, i.e., pharmacotherapist and psychotherapist, commonly provide the two treatment components separately, Dunlop **suggested** that communication is the greatest challenge in combination treatment. Other challenges discussed included identification of the optimal timing of delivery of the two treatment components. He noted that a sequential combination strategy is most common, where the patient's initial treatment includes either pharmacotherapy or psychotherapy followed by combination treatment if initial treatment provided inadequate benefit. Dunlop reported the results of a large randomized trial evaluating the cognitive-behavioral analysis system of psychotherapy (CBASP) and nefazodone, either combined or alone, as initial treatment of adults (n=681) with chronic depressive symptoms. Results found combination treatment to be superior to either treatment alone, without significant difference in remission rates between the treatments. Results of this study were not replicated in two later studies (Dunlop, 2016). Dunlop reported a mega-analysis of studies comparing combined interpersonal therapy and medication versus psychotherapy alone in the treatment of patients with both mild and severe depression (Dunlop, 2016). Results found that time to sustained remission recovery did not differ between treatments in patients with mild depression, whereas combination treatment was faster than psychotherapy alone in generating a response in patients with more severe depression (Dunlop, 2016). The results of these studies as well as other cited in the clinical synthesis found the following:

- Strongest evidence for combining psychotherapy with medication at treatment initiation is for patients with high levels of symptoms, and inpatients;
- Where flexible application of antidepressants is available, evidence does not justify combined psychotherapy and medication for patients with non-severe depression;
- Combination treatments have shown improved symptoms of depression in patients with chronic forms of MDD, but effects are small;
- CBASP is not proven to be more efficacious in treating chronic forms of MDD than other forms of psychotherapy;
- Maintenance antidepressant medication typically is required for patients in remission with combination treatment to remain well; and
- "For patients with residual symptoms after antidepressant treatment alone, addition of an evidence-based psychotherapy can improve acute phase outcomes but not necessarily more than continued medication optimization" (Dunlop, p. 169).

Complementary and Alternative Treatments

A recent study aimed to determine the reasons why some controlled studies have found omega-3 highly unsaturated fatty acids (HUFAs) effective in the treatment of depression while others have not, and to assess implications for future trials (Hallahan et al., 2016). Authors performed a meta-analysis including 35 randomized controlled trials, with a median duration of 12 weeks, including participants (n=11038) receiving omega-3 HUFAs or placebo. They evaluated whether biological differences between docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) affected findings

of the efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. Noting that EPA has a greater anti-inflammatory effect in the brain than DHA, authors tested whether EPA predominant formulations of omega-3 HUFA compared to placebo demonstrated superior efficacy. The study found that when compared with placebo, EPA-pre-dominant formulations used alone or as augmentative agents demonstrated superior antidepressant efficacy while DHA-predominant formulations demonstrated no benefit. Further, the study demonstrated no evidence that EPA prevented depressive symptoms in patients without a diagnosis of depression. Authors stated a need for larger studies of EPA-predominant formulations in monotherapy and as an augmentation agent in populations with moderate to severe clinical depression (Hallahan et al., 2016).

A systematic review and meta-analysis including 40 trials, of which three-fourths were randomized, double blind, and controlled, compared adjunctive nutraceuticals to placebo in the treatment of patients with depression (Sarris et al., 2016). Authors discussed how standardized pharmaceutical-grade nutrients (nutraceuticals) **may** be effective in enhancing antidepressant effects when used adjunctively. Results of analyses showed positive effects in replicated studies for SAMe, methylfolate, omega-3 (EPA or ethyl-EPA specifically), and vitamin D. Authors indicated the need for further research to clarify whether other agents, i.e., zinc, vitamin C, or tryptophan, **may** be beneficial (Sarris et al., 2016).

A recent randomized clinical trial tested whether a single session of whole-body hyperthermia (WBH) is effective in reducing depressive symptoms one week after treatment compared with a sham condition in adults (n=34) with MDD (Jannsen et al., 2016). Authors also tested whether observed improvements would persist across follow-up period of six weeks. This study, believed by authors to be the first randomized, double-blind, sham-controlled study of WBH for the treatment of MDD, found that WBH substantially reduced depressive symptoms within one week of treatment compared with sham condition. Additionally, participants receiving WBH had significantly reduced HAM-D scores across the six-week post-intervention study period compared to sham. Authors cautioned, however, that the therapeutic effects of WBH should not be "oversold" since "rates of response and remission at each post-intervention assessment were lower than are typically observed in antidepressant trials in which the intervention is delivered on a daily basis throughout the study period" (Jannsen et al., p. 793). Authors also noted that these results **may** not apply to patients with treatment-resistant depression, as this trial did not specifically enroll such participants. Study results "suggest that WBH holds promise as a safe, rapid-acting antidepressant modality with a prolonged therapeutic benefit" and that more studies are needed (Jannsen et al., 2016).

Depression and Older Adults

Maust et al. discussed how recent analyses of nationally representative surveys and a private insurance claims database suggest extensive use of antidepressants without a diagnosis of MDD or significant depressive symptoms (Maust et al., 2016). In some studies, authors noted that patients, contacted by telephone after prescribed a new antidepressant, described depressive symptoms that were too mild to suggest the presence of MDD. Another analysis found that 26% of persons ages 65 or older who were prescribed an antidepressant did not meet the threshold suggesting MDD. Authors **suggested** that based on these findings, "at least one-quarter of antidepressant use occurs in the absence of significant depressive symptoms" and that these older patients are subject to side effects of the medication and adverse events (Maust et al., p. 2). Using data from the Treatment Initiation and Participation (TIP) Program study, a randomized controlled trial of an intervention to improve antidepressant adherence and depression outcomes among older adults (n=231), authors analyzed data to determine why patients had been prescribed antidepressants. Noting that

previously, race, gender and comorbidity have influenced assessment of MDD, authors analyzed the following: demographic variables, e.g., age, gender, race, living alone or with others; clinical variables, e.g., medical comorbidity, overall physical well-being, and outpatient care; and psychosocial variables, e.g., distress, beliefs and fears, and perceived needs. Results found that the majority of patients prescribed an antidepressant did not meet criteria for MDD. Those who were prescribed antidepressants without MDD were older, more likely to be white, and reported better well-being. Researchers **suggested** various forces driving the use of antidepressants for patients without MDD include the following: subsyndromal symptoms (although authors noted no evidence that antidepressants are beneficial for the symptoms); treatment of the "worried well" with concern about depression rather than the actual presence of depression; lower threshold for prescribing antidepressants; direct-to-consumer advertising; and incorrect diagnosis due to difficulties in accurately diagnosing depression in primary care settings. Researchers emphasized the importance of recognizing the potential for overtreatment of older patients with depression, stating, "Depression has a significant adverse impact on older adults and magnifies the morbidity associated with other chronic medical illness" (Maust et al., p. 5).

Discussion and Conclusions

A study compared published outcomes of trials investigating the use of antidepressants in the treatment of depression with FDA outcomes in unpublished studies (Turner et al, 2008). The study noted, "We compared the effect size derived from the published reports with the effect size derived from the entire FDA data set" (Turner et al., p. 252). Authors reported 94% of the published trials were positive, whereas only 51% of the trials in the entire FDA data set were positive. "Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall (Turner et al., p. 262). Authors clarified that although this study **suggests** bias toward publication of positive results and selective reporting of clinical trial results, **it does not indicate lack of efficacy of antidepressants in treating depression; however, they indicated the effects may be overestimated**.

A more recent systematic review and meta-analysis assessed the extent of study publication bias in trials examining the efficacy of psychological treatments for depression (Driessen et al., 2015). Researchers examined whether grants, awarded by the U.S. National Institutes of Health (NIH) and supporting randomized clinical trials that compared psychological treatments to control or other conditions in patients with MDD, led to published studies. Researchers identified 4,073 NIH grants of which only 56 met inclusion criteria, e.g., intention-to-treat analysis, blind assessment of outcome, adequate sequence generation, and independent randomization. Researchers also found one additional study meeting criteria among 38 published studies acknowledging NIH support but not included in the NIH grant database. Out of 55 grants meeting researchers' criteria, published articles were located corresponding to 42 of the studies. To better estimate the effect of psychological treatment on major depressive disorder, researchers pooled findings from the published studies (42) and the unpublished studies (13). "When the unpublished findings were added to the published findings for comparisons of psychological treatments vis-à-vis control conditions (in aggregate), the effect size point estimate was reduced 0.13 standard deviations (from g-0.52 to g=0.39). **Researchers concluded that although psychological interventions for depression are efficacious, the interventions may not be as efficacious as published studies suggest**. They further recommended that clinicians, guideline developers, and decision makers be made aware of overestimated effects in published studies (Driessen et al., 2015).

A recent study analyzed data from patients (n=28498) who accessed psychological treatment for problems, e.g., recurrent depression, mixed anxiety and depression, generalized anxiety disorder,

and depressive episodes. Data also included patient-reported long-term conditions such as asthma, hypertension, and musculoskeletal problems (Delgadillo et al., 2017). The study's goals were to predict depression and anxiety symptom severity at end of treatment using the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder scale (GAD-7), respectively, and to compare outcomes of individuals with and without long-term conditions. This study found many patients with certain long-term conditions were more likely to complete psychological treatment with greater depression and anxiety severity than those without long-term conditions, and they were more likely to have received more intensive and costly psychological interventions consistent with higher level of impairment and symptom severity. In secondary analyses, high intensity therapy and higher average post-treatment distress were associated. Integrated mental health service from a medical perspective, i.e., bringing psychological professionals into medical contexts, or from a mental health perspective, i.e., bringing medical expertise into mental health contexts, **may** improve treatment outcomes in each setting (Delgadillo et al., 2017). Authors questioned the effectiveness of routinely delivered stepped care psychological treatments for people with comorbid conditions, e.g., diabetes and chronic pain, as these conditions can easily exacerbate psychological distress. They recommended multidisciplinary care targeting multiple facets of well-being, adjustment and quality of life, and offering integrated multidisciplinary care for individuals with both psychological problems and long-term medical conditions. ***Authors concluded, "Overall, we conclude that standard stepped-care interventions are insufficient to support patients with multimorbidity, especially if delivered in isolation from other healthcare specialists***. Our observations concur with recent calls for closer integration of physical and mental healthcare" (Deflgadillo et al., p. 52). They **suggested** exploring new benchmarking models and quality indicators within primary care psychological services (Delgadillo et al., 2017).

The 2015 World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance Treatment of Major Depressive Disorder-Update 2015, emphasizes that "the ultimate judgment regarding a particular treatment procedure must be made by the responsible treating physician in light of the clinical picture presented by the patient and the diagnostic and treatment options available" (Bauer et al., 2015, p. 78). Depression poses challenges to the physician treating a patient's depression; although remission of all symptoms is the goal of therapy, many patients do not remit and suffer from residual symptoms and functional impairment (Culpepper et al., 2015). Individualized treatment, (e.g., matching therapy to specific symptom clusters; multimodal treatment targeting multiple neurotransmitters; and individualizing drug selection) have been proposed to improve outcomes of depression. The application of neurobiology principles to treatment choices provides guidance in the choice of antidepressant, switching of antidepressant, augmenting antidepressant with another pharmacologic agent or psychotherapy. Although a goal of treatment is to reduce total symptom severity, the optimal outcome for patients is symptomatic remission allowing patients to return to premorbid level of functioning (Culpepper et al., 2015). **With individualized treatment and implementation of evidence-based collaborative care in the treatment of depression, more patients with residual symptoms or treatment-resistant depression can achieve complete remission and regain functionality.**

Introduction

Disease Definition, Natural History, and Course and Epidemiology

The 2015 National Survey on Drug Use and Health (NSDUH) estimated that in 2015, 16.1 million adults aged 18 years or older (representing 6.7% of this age group) experienced at least one major depressive episode (MDE) in the past year (Substance Use and Mental Health Services [SAMHSA]), 2016). The definition of a MDE included a "period of 2 weeks or longer in the past 12 months when they experienced a depressed mood or loss of interest or pleasure in daily activities, and they had at least some additional symptoms, such as problems with sleep, eating, energy, concentration, and self-worth" (SAMHSA, 2016, p. 34). The NSDUH also estimated that in 2015, almost two thirds of adults aged 18 years or older with a past-year MDE had an MDE with severe impairment, including "severe problems with their ability to manage at home, manage well at work, have relationships with others, or have a social life (SAMHSA, 2016, p. 34). Between 2005 and 2015, the percentage of adults aged 18 years or older who had a past-year MDE, as well as the percentage of adults with a past-year MDE with severe impairment, remained stable.

The NSDUH provided additional estimates as follows (SAMHSA, 2016):
- Adults aged 18 to 25: 3.6 million young adults aged 18 to 25, representing 10.3% of this age group, had a past-year MDE; and 2.2 million young adults aged 18 to 25, representing 6.5% of this age group, had a past-year MDE with severe impairment.
- Adults aged 26 to 49: : 7.3 million adults aged 26 to 49, representing 7.5% of this age group, had a past-year MDE; and 4.8 million adults aged 26 to 49, representing 4.9% of this age group, had a past-year MDE with severe impairment.
- Adults aged 50 or older: 5.2 million adults aged 50 or older, representing 4.8% of this age group, had a past-year MDE; and 3.2 million young adults aged 50 or over, representing 3.0% of this age group, had a past-year MDE with severe impairment.

The NSDUH also provided estimates for the treatment of depression in adults aged 18 or over who had a past-year MDE as follows (SAMHSA, 2016):
- Adults 18 years or older: 10.8 million adults with a past-year MDE, representing 67.2% of this age group, received treatment in the past year for depression; and 7.5 million adults with a past-year MDE along with severe impairment, representing 72.7% of this age group, received treatment in the past year for depression.
- Adults 18 to 25: 1.7 million adults 18 to 25 with a past-year MDE, representing 46.8% of this age group, received treatment in the past year for depression; and 1.2 million young adults with a past-year MDE along with severe impairment, representing 52.0% of this age group, received treatment in the past year for depression.
- Adults 26 to 49: 4.9 million adults 26 to 49 with a past-year MDE, representing 67.4% of this age group, received treatment in the past year for depression; and 3.4 million young adults with a past-year MDE along with severe impairment, representing 72.0% of this age group, received treatment in the past year for depression.
- Adults 50 or over: 4.2 million adults 50 or older with a past-year MDE, representing 80.9% of this age group, received treatment in the past year for depression; and 2.8 million adults 50 or over with a past-year MDE along with severe impairment, representing 87.9% of this age group, received treatment in the past year for depression.

In a recent study, utilizing data from the World Health Organization (WHO) World Mental Health Surveys and including 23 community epidemiological surveys administered in 21 countries,

authors examined prevalence and treatment of MDD (Thornicroft et al., 2016). This included the following: 12-month prevalence of major depressive disorder (MDD) in adults aged 18 years or older; proportion of those with MDD who were aware of their problem and who wanted to receive care; proportion of those wanting care who received care; and proportion of treatment meeting minimal standards (Thornicroft et al, 2016). Results found an average percentage of 4.6% of respondents meeting 12-month criteria for MDD (based on DSM-IV/Composite International Diagnostic Interview [CIDI] MDD), with prevalence higher in higher income countries than in lower income countries. Among those with 12-month MDD, 56.7% recognized the need for treatment, with greater recognition in higher income than lower income countries. A large percentage (71.1%) of individuals recognizing a need for treatment visited a service provider at least once for their emotional problems. Treatment proportions were greater in high income than lower income countries. Of those receiving treatment, 41% met criteria for minimally adequate treatment. The percentage was lower (16.5%) for all individuals with 12-month MDD. **Authors concluded that there is a large "treatment gap" for individuals with MDD** (Thornicroft et al., 2016, p. 3). They also noted that a perceived need for treatment in only 56.7% of persons who had access to acceptable treatment; in low-/lower-middle-income countries, the proportion was only 34.6%. Authors **suggested** the need to both decrease the treatment gap and scale up the quality of treatment to meet criteria for evidence-based treatment (Thornicroft et al., 2016).

The 2015 National Survey on Drug Use and Health estimated that in 2015, 3.0 million adolescents aged 12 to 17 (representing 12.5% of this age group) experienced at least one major depressive episode (MDE) in the past year (SAMHSA, 2016). Persons were defined as having an MDE if they had a "period of 2 weeks or longer in the past 12 months when they experienced a depressed mood or loss of interest or pleasure in daily activities, and they had at least some additional symptoms, such as problems with sleep, eating, energy, concentration, and self-worth" (SAMHSA, 2016, p. 38). The NSDUH also estimated that in 2015, more than two thirds (70.7%) of adolescents aged 12 to 17 with a past-year MDE had severe impairment, including "severe problems with their ability to do chores at home, do well at work or school, get along with their family, or have a social life" (SAMHSA, 2016, p. 38). The NSDUH also reported that between 2005 and 2015, the percentage of adolescents aged 12 to 17 who had a past-year MDE and the percentage of adolescents with a past-year MDE along with severe impairment, **increased** (SAMHSA, 2016). A recent study examining national trends in depression treatment of adolescents and young adults found that the increase in prevalence was larger among non-Hispanic whites than minorities, and among adolescent girls than boys (Mojtabia et al., 2016).

The NSDUH also provided estimates for the treatment of depression in youth aged 12 to 17 who had a past-year MDE. In 2015, 1.2 million youths with a past year MDE (39.3% of this age group) received treatment in the past year for depression; and 945,000 youths who had a past-year MDE with severe impairment (72.7% of this age group) received treatment in the past year for depression (SAMHSA, 2016). Mojtabia et al., concerned about the growing numbers of adolescents and young adults who receive no treatment for their MDE, called for outreach effort in schools, counseling services, and pediatric practices to improve detection and management of depression in this group (Mjotabia et al., 2016).

Researchers have attempted to find genetic sequences that link to depression with the hopes that genetic markers representing the inherited sequence of DNA **may** help identify individuals that are likely to benefit from specific treatment with the least adverse events (McMahon, 2015). The author **suggested** that "more progress can be made if we can develop models that incorporate clinical, genetic, and other biomarker data that can be applied to more biologically valid clinical subtypes of depression" (McMahon, p. 698). In a recent, large, randomized, prospective trial, Schatzberg et al.

examined genetic variation of the ABCB1 gene (Schatzberg et al., 2015). Researchers noted that ABCB1 variation has been associated with efficacy and side effects in small sample studies, but there had been no tests of ABCB1 genetic effects in large trials or in patients with cognitive impairment. This study "examined ABCB1 genetic variants as predictors of remission and side effects in this clinical trial that also incorporated cognitive assessment. Researchers examined 10 ABCB1 single-nucleotide polymorphisms (SNPS) in patients (n=683) with MDD who had received treatment for at least two weeks. Of these, almost 600 individuals had completed eight weeks of treatment with escitalopram, sertraline, or extended release venlafaxine. Assessment of antidepressant efficacy utilized the Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR) and a rating scale for frequency, intensity, and burden of side effects. A battery of 13 tests assessed general and emotional cognition. Patients were from the International Study to Predict Optimized Treatment in Depression (iSPOT-D) cohort that provided DNA. Researchers found that a common variation for the ABCB1 gene (SNP rs10245483) predicted high rate of response and lower side effects to specific antidepressants. The presence of cognitive impairment did not lessen the predictive power of the SNP for either response or side effects (Schatzberg et al., 2015).

Cai et al. analyzed DNA sequences from saliva samples of Chinese women with recurrent MDD (5,303) and Chinese women without depression (n=5,337), recruited by the China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) consortium, to identify genetic sequences linked to MDD (Cai et al., 2015). This study found two genetic sequences that seemed to be linked to depression. One of the genome-wide significant loci was near the SIRT1 gene and the other "in an intron of the LHPP gene" (Cai et al., p. 588). At the SIRT1 locus, an increased genetic signal was associated with melancholia. Authors **suggested** that MDD is highly polygenic, with future discoveries of more loci likely. Others have noted, "The hope is that as more genetic links are found, they will flag up groups of proteins known to work together to affect certain cellular functions: these 'pathways' could be investigated as drug targets, and for their potential to make diagnosis of depression more definitive" (Ledford, 2015).

In a recent study, authors discussed the difficulty in identifying single candidate genes associated with MDD as "complex psychiatric illnesses are under polygenic influence and are associated with interactions between genetic variants and environmental exposures" (Kupfer et al., 2014). They discussed studies that examined a combination of genetic, molecular, and neuroimaging measures to identify relations among genes, molecules, neural systems, and behavior in major depressive disorder, noting how these studies "could increase our understanding of the underlying pathophysiological processes and prediction of treatment response" (Kupfer et al., p. 221).

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 (SAMHSA, 2012). 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 (SAMHSA, 2014).

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 9SAMHSA, 2012). 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 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 (Kendler and Gardner, 2014). 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 (Kendler and Gardner, 2014).

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 (Pies, 2013). 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 (Pies, 2013).

Individualizing Treatment

In a review of the literature for treatment of major depression, Culpepper et al. discussed how an understanding of neurobiology provides a basis for individualizing treatment (Culpepper et al., 2015). Authors noted how the effectiveness of all antidepressants is similar in first-line therapy, although only about one-third of patients improve with first-line treatment. For patients not responding to initial treatment, they **suggested** switching to a drug whose mechanism of action is different or adding another drug whose mechanism of action is based on potential molecular targets, e.g., 12-transmembrane region transporter, 7 transmembrane region G-protein linked receptors, 4 transmembrane region ligand-gated ion channel, 6-transmembrane region voltage gated ion channel, or an enzyme. Culpepper et al. discussed how individualizing drug selection in the initial treatment, as well as in treatment-refractory depression, can improve outcomes. With the knowledge that symptom domains correlate somewhat with malfunctioning brain circuits, treatment that restores neurotransmitter activity in the circuits with impaired information

processing **may** restore function (Culpepper et al., 2015). Authors **suggested** that application of neurobiology principles to treatment selection influences decisions to switch antidepressants, add another antidepressant medication, or augment with another pharmacologic agent or a nonpharmacologic treatment (Culpepper et al., 2015).

Measurement-based care is another form of individualized care, allowing treatment decisions for major depression based on changes in psychopathology and side effects. A recent randomized controlled trial investigated the effect of measurement-based care compared with standard treatment on time-to-response and remission in patients with depression (Guo et al., 2015). In this trial, outpatients (n=120), 18-65 years of age, were randomized to 24 weeks of either measurement-based care utilizing guideline and rating scale based decisions or standard treatment including decisions by clinicians. Pharmacotherapy included paroxetine (20-60 mg/day) or mirtazapine (15-40 mg/day). Measurement of depressive symptoms included the Hamilton Depression Rating Scale (HAM-D) and the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR). Results found that time-to-response and time-to-remission was significantly shorter in patients receiving measurement-based care than those in the standard treatment group. Researchers noted that dosages of antidepressants were higher from week two to week 24 in the measurement-based care group, which had more treatment adjustments, than in the standard treatment group, and **suggested** that the most critical time for fine-tuning the treatment approach is between one and three months. They concluded that measurement-based care is more effective in treating patients with moderate to severe major depression than standard treatment (Guo et al., 2015).

Depression Treatment in the Emergency Department

A recent study evaluated the test-retest reliability of the Computerized Adaptive Testing – Depression Inventory (CAT-DI) for assessment of depression at an academic emergency department (ED) (Beiser et al., 2016). The development goal of CAT-DI, based on multidimensional item response theory (IRT), was decreased patient and clinician burden while increasing measurement precision. Unlike traditional measurement fixing the number of items administered, CAT allows the number of items to vary, reducing the number of items needed to measure depression. Questions "tap every domain, subdomain, and facet of an underlying disorder" (Beiser et al., p. 1039). This study measured test-retest reliability of the CAT-DI for assessment of depression in an ED setting where an estimated 8 to 32% of patients present for depression. A random sample of adult patients (n=101) were screened twice with the CAT-DI, using tablet computers, during their ED visit; the second test was administered 1-3 minutes after the end of the first testing. Questions inquired about how they were feeling during the initial and repeated administration of the test, with questions on the second test based on previous responses on the first test and a given patient's severity level. Researchers assessed test-retest reliability and found **consistent results between the two testing sessions**. Based on test scores, 79% of patients were free of depression, while 14% had mild depression; 4% had moderate depression, and 3% had severe depression. Researchers concluded that the CAT-DI "provided reliable screening results among ED patients. Concerns about whether changes in item presentation during repeat testing would affect test-retest reliability were not supported" (Beiser et al., p. 1039). Researchers found no evidence of bias, and scores were highly correlated between the two tests. They reported that test-retest reliability exceeded the reported reliability for the fixed-length PHQ-9. Recognizing that items providing good discrimination of high and low levels of depression in psychiatric settings and in a general ED **may** not be the same, they stated the need for examining differential item

functioning between the two settings to determine items that **may** be less useful in the ED for the assessment of depression (Beiser et al., 2016).

Depression Treatment in Primary Care

A recent randomized controlled trial evaluated practice nurse-led proactive care for chronic depression in primary care (Buszewicz et al., 2016). Although chronic depression is associated with high use of primary care services, high mortality, and increased psychological morbidity, investigation of these patients as a distinct group is rare. Trial participants (n=558) aged 18 or over, with evidence of recurrent and/or chronic depression and a baseline Beck Depression Inventory (BDI-II) of 14 or above, were randomized by telephone to general practitioner (GP) treatment as usual or to proactive care involving regular scheduled follow-up appointments with trained nurses over a 24 month period. Proactive care included 10 appointments, most of which were face to face. Although there was no significant improvement in depression score (BDI-II) or quality of life (EuroQuol EEQ-5D) in the intervention group at 24 months, there was a significant improvement in functional impairment in the group, measured by the Work and Social Activity Schedule (WSAS). Researchers concluded that "although overall improvements in depressive symptoms were small and non-significant for patients receiving the intervention, there were significant improvements in work and social functioning" (Buszewicz et al., p. 379). They also **suggested** that the improved levels of functioning were a result of the nurses' focus and approach on practical goals and problem-solving (Buszewicz et al., 2016).

A recent study investigated the relationship between primary care mental health integration (PCMHI) staffing characteristics in the Department of Veterans Affairs (VA) health system and the quality-of-care processes among VA patients who had received a diagnosis of depression by primary care physicians (PCPs) or PCMHI providers (Levine et al., 2016). Implementation of VA policies that require primary care mental health integration (PRMHI) began in 2007 and require all VA medical centers and large community-based outpatient clinics to have services including "care management and collocated collaborative care components" (Levine et al., p. 1). The requirements include "routine monitoring of medication effectiveness, adherence, and treatment needs, provided by a care manager in coordination with PCPs"...and "mental health practitioners working in the primary care clinic setting, with shared responsibility for evaluation and treatment of mental health conditions " (Levine et al., p. 1). Using data obtained from the VA Corporate Data Warehouse (CDW), this study examined whether PCMHI provider staffing affected performance on indicators of depression care quality at the facility level. Depression treatment measures across the facilities for patients (n=279,199) with a new episode of depression and at a primary care or PCMHI clinic encounter were calculated. Results found that higher facility staffing ratios resulted in a greater percentage of patients receiving psychotherapy treatment, but not with higher rates of medication use. Authors noted that primary care providers often prescribe antidepressant medications without specialty prescriber input and psychiatrists often have a supervisory/consultative role in collaborative care models. Higher proportions of PCMHI social worker staffing were "positively correlated with the percentage of patients with adequate antidepressant treatment continuation" (Levine et al., p. 1).

Another randomized controlled trial, Patients, Providers, and Clinics Together (PACT), examining the effectiveness of collaborative care for depression in three public-sector primary care clinics serving Latinos, found culturally relevant collaborative care that accommodates patient treatment preferences for depression significantly improves depression, quality of life, and satisfaction outcomes (Lagomasino et al, 2016). Improved quality of care indicators included the proportion of

patients receiving either psychotherapy or antidepressant medication. Systematic random sampling in waiting rooms and referrals of clinic patients by primary care providers resulted in participants (n=400) who completed a baseline assessment and were randomly assigned to collaborative care group or to an enhanced usual care control group. The collaborative care group received education about depression and its treatments from social workers, functioning as depression care specialists. They were allowed to choose to receive psychotherapy, antidepressant medication or both. If psychotherapy was the choice, the depression care specialists provided the 12-week CBT intervention. The depression care specialists also communicated with primary care providers about adherence to medication, side effects and treatment response. The control group received an educational pamphlet about depression and its treatment as well as a list of mental health resources. A letter stating that they screened positive for depression was available for sharing with their primary care providers. Participants receiving collaborative care for depression "had reduced depressive symptomatology, increased satisfaction with overall and emotional health care, and a much higher likelihood of receiving a minimum level of adequate depression care, compared with patients in enhanced usual care" (Lagomasino et al, p. 5). The greatest effect on quality of care was an increase in psychotherapy visits, provided in Spanish.

A sample of adults from the 2008-2012 NSDUH included 17,700 respondents meeting the criteria for a major depressive episode in the past 12 months, of whom 8,900 (61.5%) received treatment for depression from general providers, specialty mental health providers only, or from both types of providers (Kuramoto-Crawford et al., 2016). The breakdown was 21% from general providers, 19% from specialty mental health providers only, and 19% from both. This study compared individuals receiving care from both primary care and specialty mental health providers with those receiving care from only one of the provider types to provide "characterization of persons who receive treatment from both general medical providers (GMPs and specialty mental health providers (SMHPs)" (Kuramoto-Crawford et al., p. 758). This study found that adults receiving care from both types of provider were younger and more highly educated, had more suicidal ideation and functional impairment, and had more access to psychiatrists providing patient care than those who received care from general GMPs only. This highlights the need for continuing education and training for the prevention of suicide in primary care (Kuramoto-Crawford et al., 2016). Of those receiving care from both types of provider, more were females, had higher education, more general medical comorbidities, and more functional impairment than those who received care only from a SMHP. Authors concluded that efforts to "understand differences in depression care in specialty mental health and general medical settings **may** help improve the provision of mental health services as health care reform continues" (Kuramoto et al., p. 758). Collaborative care for depression in primary care settings along with the increased role of mental health care in patient-centered medical home projects is a part of the move towards coordination and integration of behavioral health care and primary health care (Kuramoto et al., 2016).

Antidepressant Medications

The APA guideline recommends an antidepressant medication for the initial treatment of patients with mild to moderate major depression and those with severe major depressive disorder unless electroconvulsive therapy (ECT) is planned (APA, 2010). Selection of an antidepressant should consider tolerability, safety, cost, patient preference and history of prior medication treatment. First line pharmacotherapeutic options for treatment include second-generation antidepressants: **selective serotonin reuptake inhibitors (SSRIs)**, i.e., citalopram, escitalopram fluoxetine, fluvoxamine, paroxetine, sertraline; **serotonin norepinephrine reuptake inhibitors (SNRIs)**, i.e., duloxetine, desvenlafaxine, levomilnacipran and venlafaxine; **norepinephrine-dopamine**

reuptake inhibitors (NDRIs)), i.e., bupropion; and **atypical antidepressants**, i.e., trazodone, mirtazapine, nefazonde, vortioxetine, and vilazodone. First-generation antidepressants include the older and less commonly prescribed classes including the **tricyclic antidepressants (TCAs)**, e.g., amitriptyline, imipramine, and nortriptyline; and **monoamine oxidase inhibitors (MAOIs)**, e.g., phenelzine and tranyleypromine. The use of these drugs is limited although they **may** be beneficial when patients do not respond to first line pharmacotherapies. Caution **may** be required in prescribing and treatment due to harmful side effects.

Noting that it takes several weeks before an antidepressant is fully effective and that a significant percentage of people may not respond to a prescribed antidepressant, the FDA advises continuation of the medication for several weeks before switching to a different antidepressant or adding another medication. Common side effects of antidepressants may include nausea and vomiting, weight gain, diarrhea, sleep disturbances and sexual problems, and some antidepressants can have serious risks, e.g., suicidal thinking or suicidal behavior, birth defects, and high blood pressure leading to a stroke or other complications (FDA, 2016).

A recent observational, retrospective analysis evaluated antidepressant prescription claims of insured patients (n=54,107) with MDD, who had a prescription for an antidepressant filled during 2013, to determine the most commonly prescribed antidepressant medications along with their most common dosages (Treviño et al., 2016). From most prescribed to least prescribed, the most commonly prescribed medications were SSRIs, SNRIs, serotonin antagonist and reuptake inhibitors (SARIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Doses of the most frequently prescribed drugs generally were within established guidelines, e.g., APA guidelines and Centers for Medicare and Medicaid Services (CMS). Authors reported "an incidental finding from the study sample derivation was that approximately 80% of patients who were diagnosed as having MDD filled an

antidepressant medication within the study period" (Treviño et al., p.3). This finding correlated with findings of past studies reporting that 73.8 and 75.3 % of patients with MDD received antidepressant medication in 1998 and 2007, respectively. Authors concluded that encouraging findings showed that "most physicians followed treatment guidelines" while also indicating a need for further research to investigate cases where guidelines are not being met for some drug prescribing (Treviño et al., 2016).

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 (U.S. Food and Drug Administration, 2011). 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 (Montgomery et al., 2013). 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 (Montgomery et al., 2013).

On September 30, 2013, the FDA approved vortioxetine, a so-called "serotonin modulator and stimulator" for the treatment of major depressive disorder (U.S. Food and Drug Administration, 2013). 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 (Mahablershwarkar et al., 2015). 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 Mahablershwarkar et al., 2015).

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 (De Silva and Hanwella, 2012). 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 (Gartlehner et al, 2011). 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 (FDA, 2008).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 MAOs. 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 (FDA, 2009). 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 (Wimbuscus, 2010).

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 (Pigott et al, 2010).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

Patients with MDD who do not achieve adequate response to first-line antidepressant treatment (approximately 50% of patients with MDD) **may** benefit from switching antidepressants, adding another antidepressant, or adding adjunctive therapy with an atypical antipsychotic (Sussman et al., 2017). Even among those responding to initial treatment, only 50-65% of patients achieve remission (Singh et al., 2017). A recent study discussed the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial which found that "bupropion, sertraline, and venlafaxine are comparable in terms of therapeutic effectiveness following unsuccessful treatment with citalopram" (Singh et al., p. 81). Authors, in this current study, tried to determine whether

treatment with one of the drugs was more cost-effective relative to others. They found that although costs of the medications differed significantly, there were no significant differences in the pairwise comparisons of total costs and cost effectiveness of the three medications. They emphasized the importance of other factors considered in choosing an antidepressant over another: preference of the clinician, family history, or treatment of most evident cardinal symptoms (Singh et al., p. 81).

For treatment-resistant depression, the STAR*D study found a small decrease in remission rates from first-line initial treatment, e.g., SSRI or SNRI, to the next course of treatment including a dissimilar antidepressant or a combination of antidepressants (Thase, 2016). Author noted, "Chances for recovering from an episode of major depressive disorder become progressively smaller as the number of fail treatment trials mount" (Thase, p. 181). Thase reported that the trials in STAR*D suggest, "patients who received adjunctive therapies were more likely to remit than those who were switched to another course of antidepressant monotherapy" (Thase, p. 181). The author noted that the most widely used form of adjunctive treatment for MDD appears to be treatment with second-generation antipsychotics, e.g., aripiprazole, olanzapine, and quetiapine. The efficacy of aripiprazole, olanzapine, and quetiapine in treatment of depression is "observed at doses that are only one-fourth to one-half those used to treat acute schizophrenia or mania" (Thase, p. 181) which **suggests** the effects **may** not be "directly tied to their antipsychotic effects" (Thase, p. 181). Author noted the need for answers to the following concerns: how long the second-generation antipsychotic should be continued; the relative efficacy compared with older standards, e.g., lithium; and whether this treatment is cost effective. Thase stated, "At present, there is no better proven strategy for treatment-resistant depression, given that multiple positive, placebo-controlled studies have been conducted for adjunctive therapy with five second-generation antipsychotics: aripiprazole, brexpiprazole, olanzapine, risperidone, and quetiapine" (Thase p. 183). He further stated that second-generation antipsychotics "should indeed by thought of as one of the gold standards for treating antidepressant nonresponders" although potential benefits must be carefully balanced against both the higher cost of these medications and the several manageable but real risks" (Thase p. 183). Consideration of the risks of adverse events, e.g., weight gain and extrapyramidal symptoms, when augmenting antidepressants with antipsychotic treatment in patients is advised.

A recent randomized prospective open-label multi-center study compared the efficacy and safety of aripiprazole versus bupropion augmentation for the treatment of patients (n=103) with major depressive disorder unresponsive to SSRIs (Cheon et al., 2017). Over a 6-week treatment period, patients were randomized to receive an SSRI plus aripiprazole (2.5-20 mg/day) or an SSRI plus bupropion (150-300 mg/day) augmentation. Results found reductions in MADRS scores at 6 weeks were not significantly different in the two groups, and the scores were much improved compared to baseline scores in both groups. Researchers **suggested** that aripiprazole augmentation therapy and bupropion combination therapy with SSRI have comparative efficacy and tolerability in the treatment of MDD (Cheon et al., 2017).

On July 13, 2015, the U.S. Food and Drug Administration (FDA) approved an atypical antipsychotic, brexpiprazole, to treat schizophrenia and as add on to an antidepressant medication to treat patients with major depressive disorder (FDA, 2015). The FDA News Release reported the results of two six-week trials comparing brexpiprazole combined with an antidepressant to placebo plus an antidepressant for patients (n=1046) for whom an antidepressant alone was not adequate in treating their symptoms. These trials found adjunctive oral brexpiprazole (2 or 3 mg once per day) plus antidepressant was more effective than placebo plus antidepressant in improving depressive symptoms. Brexpiprazole has a Boxed Warning about an increased risk of death associated with off-

label use in treating older people with dementia-related psychosis. The Boxed Warning also includes an alert about an increased risk of suicidal thinking and behavior in children, adolescents, and youth who are taking antidepressants (FDA, 2015).

A recent trial randomized patients (n=379) with MDD and inadequate response to antidepressants to treatment with an antidepressant plus brexpiprazole 2 mg/d or to an antidepressant plus placebo for six weeks to determine efficacy, tolerability, and safety of adjunctive brexpiprazole (Thase et al., 2015). Results of this randomized, placebo-controlled study found adjunctive brexpiprazole reduced the mean score on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Sheehan Disability Scale (SDS) greater from baseline to week six compared with placebo. The study found adjunctive brexpiprazole well tolerated, with weight gain and akathisia the most frequently reported treatment emergent adverse effects (Thase et al., 2015). Another randomized, double-blind placebo-controlled trial randomized patients (n=677) with MDD and inadequate response to antidepressants to brexpiprazole 1 mg, brexpiprazole 3 mg, or placebo for six weeks adjunctive to antidepressant to determine efficacy, tolerability, and safety of adjunctive brexpiprazole (Thase et al., 2015). Results found that adjunctive brexpiprazole 3 mg reduced mean score on the MADRS compared with placebo, while adjunctive brexpiprazole 1 mg did not reduce the score significantly. Both brexpiprazole 1 mg and 3 mg showed greater reductions from baseline to week six than placebo in SDS mean scores. This study found adjunctive brexpiprazole at both 1 mg and 3 mg dosage well tolerated (Thase et al., 2015).

Another randomized, double-blind, placebo-controlled trial compared the efficacy of ziprasidone as an adjunct to escitalopram with adjunctive placebo in adult patients (n=139) with MDD who had not responded to eight weeks of flexible dosing of escitalopram (Papakostas et al., 2015). Results found that adjunctive ziprasidone had greater antidepressant efficacy than adjunctive placebo based on response rates of the HAM-D. Although more patients discontinued adjunctive ziprasidone than placebo (due principally to sedation, anxiety, agitation, and insomnia), more serious adverse events were equal with ziprasidone and placebo (Papakostas et al., 2015). Among patients treated with adjunctive ziprasidone, two serious events occurred, i.e., hospitalization due to suicidal ideation and hospitalization due to a fall. Serious adverse events in the group treated with adjunctive placebo also had two serious adverse events, i.e., hospitalization for treatment-emergent viral meningitis and hospitalization for pneumonia. Another atypical antipsychotic under investigation as an adjunctive treatment for patients who inadequately respond to standard antidepressant therapy is cariprazine (Durgam et al., 2016). In another recent randomized, double-blind, placebo-controlled study including patients (n=810) with MDD and inadequate antidepressant response, patients were randomized to adjunctive cariprazine 1-2 mg/d, adjunctive cariprazine 2-4.5 mg/d, or adjunctive placebo for eight weeks (Durgam et al., 2016). Stable doses of antidepressant treatment, i.e., sertraline, citalopram and escitalopram, continued during the eight-week treatment period. Results found that treatment with cariprazine 2-4.5 mg/d resulted in greater reduction in MADRS total score at week eight than placebo or the lower dose of cariprazine. Adverse events in both dosage groups of those treated with cariprazine were akathisia, insomnia, and nausea; however, in all three groups, changes in metabolic parameters, vital signs and ECG parameters were significantly similar (Durgam et al., 2016).

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) (Rocha et al, 2012). 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 (Tohen, 2010). 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 (PsychCentral, 2009). 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 (Bauer et al., 2010). 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 antipsychotic 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) (Nelson et al, 2012). 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 (Kalsekar et al, 2012). 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 (Clayton et al., 2014).   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 (Clayton et al., 2014).

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 (Bauer et al., 2010). 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 eight-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 (Lyoo et al., 2012). 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 (Lyoo et al., 2012).

Treatment Strategies for Depression with Psychotic Features

The APA practice guideline recommends Electroconvulsive Therapy (ECT) or pharmacology as first-line treatment for psychotic depression (APA, 2010). Many patients prefer pharmacologic treatment instead of ECT. The guideline recommends combination of an antipsychotic and an antidepressant, rather than either component alone, to provide better response in the treatment of psychotic depression. Although clinical trials indicate greater efficacy of the combination treatment based on HAM-D scales, Østergaard et al. noted in a new study that the HAM-D scales were not

subjected to validation, clinical and psychometric, in relation to psychotic depression and covered only a fraction of the psychotic symptoms in psychotic depression (Østergaard et al., 2014). Acknowledging no established psychometric instrument dedicated to measurement of severity in psychotic depression, authors investigated a new rating scale covering both the psychotic and the depressive domains of psychotic depression, i.e., the Psychotic Depression Assessment Scale (PDAS), to determine whether it "could detect differences in effect between two psychopharmacological treatment regimens" (Østergaard et al., p. 69). They compared its performance to that of the HAM-D, using data from the Study of Pharmacotherapy of Psychotic Depression (STOP-PD). They addressed the following: whether measured responses to treatment regimens were similar across the PDAS and the HAM-D; whether the PDAS and HAM-D were sensitive to differences in the effects of different drug combination on severity of psychotic depression; and the proportion of patients still psychotic at end of participation in the STOP-PD. The investigation found that the PDAS and HAM-D distinguished between the effect of different combinations of treatment in psychotic depression, and effect sizes of the rating scales were similar, although slightly lower for the PDAS than for the HAM-D. Of the patients included in the STOP-PD, 45% continued to experience at least probable psychotic symptoms at the end of the trial, underscoring "the importance of including items that assess psychotic symptoms in rating scales for psychotic depression" (Østergaard et al., p. 74). Authors indicated the need for further study of the PDAS while noting, "measurement of severity and treatment response in *psychotic depression* should take both *psychotic and depressive* symptoms into account (Østergaard et al., p. 74).

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 (Farahani and Correll, 2012). 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 (Gaudiano et al., 2013). 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 (Gaudiano et al., 2013).

Antidepressants and Suicidal Ideation and Behaviors

Barbui and Patten reported the results of a propensity score-matched cohort study by Miller et al., (Miller et al., 2014) based on data from a large clinical population of patients (n=162,625) with depression who received initial treatment of citalopram, sertraline or fluoxetine (Barbui and Patten, 2014). Patients were divided into two age groups: 10-24 or 25-64, with patients in each group assigned to either modal or higher-than-modal doses of the drugs. Results showed that patients receiving higher doses of drugs in the 10-24 age groups had a rate of deliberate self-harm (DSH) almost twice as high as the patients in the modal dose group. In the age 25-64 group, this effect was not detected. Authors considered the fact that most individuals who engage in DSH do not commit suicide and that if the study was replicated employing completed suicide instead of deliberate self-harm, the findings **may** be different. Authors argued that this study "**may** have at least partially captured DSH as a consequence of impulsivity linked to borderline personality traits, rather than suicidality as a consequence of adverse effects of antidepressant exposure" (Barbui and Patten, p. 330). They also noted that in the study population, nearly 20% of individuals began treatment with high-dose antidepressants that could have been related to the severity of depression or previous suicide ideas, identifying patients at greater risk for DSH for reasons other than higher dose of antidepressant. Authors noted that the findings of the Miller et al. study have implications for clinical practice, and suggest that antidepressant treatment "should not be started with greater than modal doses" (Barbui and Patten, p. 331). Dose change or dose escalation was not a focus of the Miller study. In another review of the Miller study, Petersen and Nazareth **suggested** "the jury is still out on whether antidepressants are indeed likely to enhance suicidation in younger people receiving high doses of selective serotonin reuptake inhibitors. In any circumstances, the study by Miller et al. highlights close clinical monitoring of young people with severe and potential acute psychiatric problems" (Petersen and Nazareth, 2015).

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 (Gibbons et al, 2012). 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 (Cheung et al., 2015). 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 (Cheung et al., 2015).

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

Past studies have shown that in addition to the monoaminergic system, the glutamatergic system is targeted for treating major depressive disorder (Schoevers et al., 2016). Schoevers et al. noted that those studies found short-term success within hours of rapid intravenous infusion, but at seven days post-infusion, effects were not significantly different between ketamine and placebo. A recent review of literature including 88 small, uncontrolled studies obtained information including number of individuals receiving ketamine, study types and sizes, dosing regimens, and effects of treatment for depression. Studies included intravenous ketamine, oral ketamine, intranasal ketamine, sublingual ketamine and intramuscular ketamine. In one study, patients (n=4) receiving up to 1.25 mg/kg oral ketamine for two weeks showed depression relief. Another study found that patients (n=2) showed significant improvements after one oral dose of 0.5 mg/kg, with the improvement lasting 1-2 weeks. In another study, patients (n=14) were administered daily oral ketamine (0/5 me/kg over 28 days), with eight patients completing the trial and showing significant improvement in depression with few side effects. Two patients with chronic suicidal ideation and two prior suicide attempts, both of whom received 3 mg/kg, sustained remission from suicidal ideation. In another study, 10 mg sublingual ketamine was administered once, or every 2, 3, or 7 days for a total of 20 doses in 26 patients of whom 20 showed improved mood. Authors concluded that results of these small, uncontrolled studies suggest that oral ketamine **may** be well tolerated; however, long-term consequences have not been systematically studied. They discussed potential misuse of ketamine warranting monitoring and cautioned that although side effects of oral ketamine appear milder than that reported in intravenous studies, a hospital setting is necessary for ketamine administration. Authors further cautioned that more studies are needed examining long-term effects of repeated use of ketamine (Schoevers et al., 2016). Magellan continues to consider the use of ketamine in the treatment of depression highly investigational (Magellan Health, 2013).

The results of a systematic review and meta-analysis of ketamine and other N-methyl-D-aspartate (NMDA) receptor antagonists found that "the antidepressant efficacy of ketamine, and perhaps D-cycloserine and rapastinel, holds promise for future glutamate-modulating strategies" (Newport et al., 2015). They also tempered enthusiasm about ketamine's use due to limited clinical trial data demonstrating only a "transient benefit" (Newport et al., p. 950). Authors also noted that high-dose D-cycloserine and rapastinel "behave as classic partial agonists within a low (weak agonist activity) to moderate (relative antagonist activity) dose range but at especially high doses exhibit full agonist activity via GluN2C glycine binding sites activation. These agents are certainly worthy of further scrutiny" (Newport et al., p. 961). Authors **suggested** other ionotropic receptors within the glutamatergic system, e.g., AMPA and kainate receptors, metabotropic glutamate receptors, and glutamate transporters (Newport et al, 2015).

A systematic review and meta-analysis of 20 studies examined the potential role of cytokines in the treatment of depression in participants (n=5063) using trials of chronic inflammatory conditions where secondary outcome measure was depressive symptoms (Kappelmann et al., 2016). Authors noted, "cytokine-mediated communication between the immune system and the brain has been implicated in the pathogenesis of depression" and that "major depression is common (one in four) in individuals after interferon treatment, a potent inducer of cytokines, in patients affected by hepatitis C virus" (Kappelmann et al., p. 1). Studies included randomized controlled trials of anti-

cytokine drugs vs. placebo, as well as non-randomized and non-placebo trials in patients with several conditions, e.g., psoriasis, Crohn's disease, atopic dermatitis, and rheumatoid arthritis. Results of the studies showed that anti-cytokine treatment improved depressive symptoms with a small to moderate size effect. Authors recommended future randomized controlled trials of anti-cytokine treatment where depression is the primary outcome (participants with high inflammation but without other physical illnesses). They concluded that anti-cytokine drugs **may** be effective for some patients with depression and recommended more studies (Kappelmann et al., 2016).

Researchers investigated the feasibility, safety, and efficacy of psilocybin, a serotonin receptor agonist occurring naturally in some mushroom species, in a recent small open-label feasibility trial including patients (n=12) with treatment-resistant major depression (Carhart-Harris et al., 2016). Psilocybin was administered in two dosing sessions, with the first a low dose of 10 mg (initial safety dose) and a high dose (25 mg) one week later. Patients were assessed for depression severity with assessment tools, e.g., HAM-D, MADRS, Global Assessment of Functioning (GAF) and QUIDS, prior to treatment with the first dose. The outcome measure was patient-rated subjective intensity of the effect of psilocybin, which was well tolerated by all of the patients with no unexpected adverse events. Results showed that relative to baseline, there was marked reduction in depressive symptoms at one week and three months after the high dose treatment. Researchers concluded that strong inferences about efficacy are lacking due to the size of the study, and **suggested** further research is warranted (Carhart-Harris et al., 2016).

In a recent double-blind, randomized, placebo-controlled trial researchers investigated the effects of single-dose modafinil (200 mg), a wake promoting agent often used for treatment of narcolepsy, on cognition and fatigue in adults patients (n=60) with remitted depression (Kaser et al., 2017). Results **suggested** that modafinil improved domains of cognition, i.e., episodic memory as measured by the Paired Associates Learning (PAL) test and working memory as measured on the Spatial Working Memory (SWM) test in remitted depressed patients. They indicated the need for further research of treatment with modafinil over a longer time and in combination with psychological treatments (Kaser et al., 2017).

In a current review, authors discussed research that "highlighted the potential role of monitoring peripheral polyunsaturated fatty acids (PUFAs) and cholesterol in the prediction, stratification and management of MDD" (Parekh et al., 2017). Noting that studies have shown that increased HDL and omega-3 PUFA could protect against depression-mediated inflammation, they **suggested** further research to determine whether the complex relationship between PUFAs and cholesterol are involved in the pathology of MDD and could lead to potential treatment of MDD (Parekh et al., 2017).

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 under investigation 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 (Marks et al, 2008). Triple-reuptake inhibitors (TRIs) inhibit the serotonin transporter, the norepinephrine transporter and the dopamine transporter. Murrough and Charney 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 (Murrough and Charney, 2012). 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 (Murrough and Charney, 2012).

Magellan has reviewed the literature and evaluated published research studies on the use of ketamine in the treatment of treatment-resistant depression (Magellan Health, 2013). 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 (Magellan Health, 2013). Future studies should test ketamine's antidepressant effect beyond a single administration, and characterize its longer-term safety profile (Murrough et al., 2013).

A later study tested the antidepressant effects of nitrous oxide, an agent with a similar mechanism of action as ketamine (Nagele et al., 2015). 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 (Nagele et al., 2015). The FSA has not approved the use of nitrous oxide in the treatment of depression.

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 (Taylor et al., 2014). 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 (Taylor et al., 2014). 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 (Thase et al., 2014).

Other Somatic Treatments

Noting previous studies have shown that high-frequency left prefrontal rTMS was effective for treatment-resistant depression, Kito et al. examined changes in resting electroencephalogram (EEG) functional connectivity before and after high-frequency left prefrontal rTMS in patients (n=14) (with treatment-resistant depression) in order to understand better antidepressant mechanisms of rTMS (Kito et al., 2016). Researchers found more synchronized middle beta band activity between the left DLPFC and limbic regions with "no significant changes in other frequency bands" (Kito et al., p. 4). Other studies have proposed modulation of GABA function as a possible mechanism of action for rTMS; Kito et al. "assumed that more synchronized middle beta band activity between the left DLPFC and limbic regions might be related to GABAergic circuits modulation" (Kito et al., p. 16). Researchers indicated the need the further well designed studies that will add further insights into the antidepressant mechanism of rTMS in the treatment of major depressive disorder (Kito et al., 2016).

In a recent retrospective chart review that included patients (n=225) who received rTMS for treatment-resistant depression, authors identified patients (18) meeting criteria for reintroduction of rTMS (Kelly et al., 2016). Criteria for reintroduction included positive response to initial treatment, withholding additional treatment until relapse; and treating relapse with 3-5 treatments per week for two to six weeks. In this study, authors tested whether a favorable response to first induction course would predict response to a subsequent course. They found that 16 patients met full inclusion criteria for reintroduction, of which 10 were >50% responders to initial treatment, and 4 had 25-50% response to initial induction. Of the patients who were > 50% and 25-50% responders to initial treatment, 80% and 75%, respectively, responded to reintroduction. Patients with <25% response to induction had 0% response to reintroduction. Authors concluded that these results suggest that "therapeutic response to an initial course of rTMS for depression is a significant predictor of response to a subsequent course" (Kelly et al., p. 2). Due to the limitation of this study,

i.e., small sample identified retrospectively via chart review, additional research is needed comparing long-term rTMS treatment strategies, including reintroduction or maintenance rTMS (Kelly et al., 2016).

Kellner et al. recently reported results of Phase 2 of the Prolonging Remission in Depressed Elderly (PRIDE) study, which compared the effects of continuation electroconvulsive therapy (ECT) plus medication (venlafaxine plus lithium) to medication only (venlafaxine plus lithium) in the treatment of depressed geriatric patients (over age 60) after a successful Phase 1 treatment. The patients (n=120) had remitted after a Phase 1 course of right unilateral ultrabrief pulse ECT, augmented with venlafaxine (Kellner et al., 2016). Outcome measures after 24 weeks of treatment in Phase 2 were the HMA-D and the Clinical Global Impressions Severity Scale (CGI-S). Results demonstrated that the ECT plus medication group had significantly greater improvement in maintaining low depression symptom severity for six months than the medication only group. Authors concluded, "Additional ECT beyond the traditional endpoint of an acute course, plus rescue as needed, is valuable and feasible in maintaining the long-term antidepressant benefits of ECT in a vulnerable geriatric population" (Kellner et al., p. 1116).

Electroconvulsive therapy is considered the gold standard for treatment of depression that has not responded to two or more adequate pharmacologic trials (Cusin et al., 2012).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 (Petrides et al., 2011). 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 (Petrides et al., 2011).

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 (Nordenskjöld et al., 2013). 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 (Nordenskjöld et al., 2013).

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 (Cusin et al., 2012). 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 (Loo et al., 2014). 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 (Loo et al., 2014).

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 **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 <u>not</u> 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 (Magellan Health, 2010). 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 (Trojak et al, 2012; Bersani et al., 2013; Downar, 2012).

Further study is still necessary in order to confirm the durability of rTMS compared to ECT (Magellan Health, 2010). 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 (Trojak et al., 2012; Bersani et al, 2013; Downar, 2012; Herbsman et al., 2009; Berlim et al., 2012). 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 (Magellan Health, 2010). 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 (FDA, 2013; FDA, 2012).

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 (Berlim et al., 2014). 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 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 (Berlim et al., 2014).

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 (Shafi and Stern, 2014). 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 (Shafi and Stern, 2014).

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 (Magellan Health, 2012). 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 (Magellan Health, 2012).

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 (Magellan Health, 2012). 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 (Magellan Health, 2012).

Psychosocial Treatments

In a recent review, authors reported studies showing that several high-intensity psychosocial interventions are as effective and long lasting as medications in the treatment of nonpsychotic depression (Hollon and Williams, 2016). Established high-intensity interventions discussed included cognitive-behavioral therapy (CBT) "conducted according to a treatment manual and delivered by trained and competent practitioners who receive ongoing supervision" (Hollon and Williams, p. 175). Other high-intensity interventions discussed included behavioral activation therapy with focus on behavior more than on cognition; mindfulness-based cognitive therapy (MBCT) integrating meditation training with cognitive therapy; acceptance and commitment therapy, a "third wave" behavior therapy; interpersonal psychotherapy; and dynamic psychotherapy with an emphasis on brief interventions. Authors noted that each of the above interventions have a clear structure, relationship with practitioner, and a focus on problems relevant to the patient. Due to service demand, authors noted the importance of low-intensity psychosocial interventions, delivered in more focused ways with less practitioner time overall. These include CBT delivered using computers and self-help books and manuals, accompanied by practitioner support from either experts or non-experts in CBT. In conclusion, authors recognized the established evidence base for traditionally delivered high-intensity interventions while also noting the growing evidence base suggesting effective delivery of low-intensity CBT and behavioral activation. Authors emphasized the need for an approach "consistently delivered in high-quality ways to maximize outcomes" (Hollon and Williams, p. 177).

A recent meta-analysis of 44 randomized clinical trials investigated the effectiveness of psychotherapy on global quality of life (QoL) and on the mental health and physical health components of QoL in patients (n=5264) 18 years or older with depression (Kolovos et al., 2016). The reviewed trials compared psychotherapy (including either high or low intensity interventions) with control conditions (including waiting list, care as usual, placebo or another minimal treatment). Results found larger improvements in QoL in those treated with psychotherapy than in the control conditions. The effect sizes for depressive symptoms and physical health component of QoL were unrelated, whereas authors found a positive relationship between the effect sizes for the mental health component and the depressive symptoms. Results of meta-regression analyses found, "Overall, changes in QoL were not fully explained by changes in depressive symptoms. We can thus infer that decreased depressive symptom severity at the end of the treatment is not necessarily a manifestation of improvement in QoL of the patient *or vice versa*" (Kolovos et al., p. 466). They concluded that this meta-analysis demonstrated that psychotherapy is efficacious in reducing depression symptoms and in improving additional outcomes related to depression. They emphasized that the effects of psychotherapy are different for the mental health and physical health components of QoL (Kolovos et al., 2016).

A meta-analysis of sixteen randomized clinical trials including patients (n=1700) with depression compared divergent outcomes, i.e., deterioration (symptom severity increases from beginning to end of treatment) and severe symptoms of depression posttreatment) in CBT and pharmacotherapy (Vittengl et al., 2016). Researchers tested frequencies of deterioration, extreme nonresponse, and superior response between CBT and pharmacotherapy, finding that pharmacotherapy compared with CBT increased odds of superior improvement (from the HAM-D) but not from the patients' perspective (Beck Depression Inventory-BDI); pharmacotherapy also predicted more attrition than CBT. Researchers emphasized that although pretreatment symptoms levels **may** help forecast negative and positive outcomes, they do not determine whether CBT or pharmacotherapy is the desired treatment. Among patients with high pretreatment severity, researchers recommended

assessing symptom levels frequently and making treatment changes, e.g., switching or augmenting treatment. They concluded, "Choosing pharmacotherapy versus CBT **may** increase patients' odds of both discontinuing treatment and clinician-rated superior response" (Vittengl et al., p.489).

In a meta-analysis update including 54 studies totaling patients (n=3946) with diagnosis of major depressive disorder or another mood disorder accompanied by elevated score on a depression measure, researchers examined the efficacy of short-term psychodynamic psychotherapy (STPP) for depression (Driessen et al., 2015). The APA does not consider STPP, a treatment rooted in psychoanalytical theories (e.g., drive psychology, ego psychology, object relations psychology and attachment theory), a first-choice treatment in the treatment of depression (APA, 2010). Only in recent years have many studies examining the efficacy of STPP for depression been published. In this study, STPP pre- to post-treatment findings included the following: significant improvement in depression symptoms; significant improvement in anxiety symptoms in individual format STPP, but not group STPP; and significant improvement in general psychopathology in individual format STPP. STPP post-treatment to six-month follow-up findings included the following: non-significant change for interpersonal functioning and significant improvement in symptoms of anxiety and general psychopathology. At post-treatment, the other psychotherapies showed significant superiority across all studies of STPP. At six-month follow-up findings, no significant differences between STPP and other psychotherapies or depression symptoms were evident. At post-treatment, the study found no significant differences between STPP and antidepressant medication, and no significant difference were shown between combination STPP + medication and combination medication +other psychotherapy on outcomes of depression. Researchers concluded that this study "found clear indications that STPP is effective in the treatment of depression in adults" (Driessen et al., p.1). They recommended additional studies are needed to "assess the efficacy of STPP compared to control conditions at follow-up and to antidepressants" (Driessen et al., p.1).

In a review by Chakrabarty et al., authors discussed the lack of consensus on how best to monitor cognition clinically in non-elderly patients with depression, and noted that the clinical significance of treatments, i.e., antidepressant medications, psychotherapy, and neuromodulation is unclear (Chakrabarty et al., 2016). Although there are currently no approved treatments specifically for cognitive dysfunction in major depressive disorder, studies have shown evidence regarding the effects of antidepressants on cognition among adults. Authors reported two large randomized controlled trials finding strong evidence for efficacy of vortioxetine in improving cognition while noting few studies comparing different agents. They also cautioned that ongoing antidepressant treatment **may** adversely affect cognition. Authors reported encouraging results from small studies of the cognitive effects of augmentation agents, e.g., aripiprazole, olanzapine, lisdexamfetamine, and S-adenosylmethionine (SAMe). Studies of neuromodulation treatments, i.e., ECT and rTMS, have found an association between treatment and improved cognition. Psychotherapy **may** have a beneficial effect on cognition in major depressive disorder. Authors reported studies showing combined long-term psychodynamic therapy and fluoxetine improved cognitive symptoms greater than fluoxetine alone. Authors **suggested** a multifaceted approach to improve cognitive outcomes because of numerous and complex factors that mediate cognition and cognitive dysfunction (Chakrabarty et al., 2016).

A multicenter, three-group parallel, randomized control trial compared the effectiveness of internet-based cognitive-behavioral therapy (ICBT), exercise, and usual care in the treatment of patients (n=757) with mild to moderate depression (Hallgren et al., 2016). Patients (n=740) were randomized to one of the three 12-week parallel treatment with three-month post-treatment and 12-month end-point. Patients treated with ICBT worked through a self-help online manual, which

included separate modules. In the first few week of treatment, patients completed modules addressing problems related to depressive symptoms, e.g., inactivity and avoidance behaviors. Later patient-specific modules targeted comorbid symptoms, e.g., worry, panic attacks, social anxiety, stress, insomnia and pain. Assigned clinicians monitored patients' responses weekly and provided needed assistance; a psychologist monitored cooperation with therapy. The exercise intervention included light, moderate, or vigorous exercise by qualified trainers in three 60-minute sessions per week during 12 weeks. Examples of light, moderate and vigorous exercise included yoga, aerobics, body strengthening exercises, respectively. Weekly meetings with a trainer or physiotherapist monitored adherence to the regimen. Treatment as usual or 'usual care' consisted of 45-60 minutes of CBT delivered face-to-face by counselor or psychologist. Results found depression severity at 12-month follow-up reduced in all groups, with the largest treatment effect obtained at three months, and the exercise and ICBT groups showed greater reduction of severity than the usual care group. Researchers concluded, "Prescribed exercise and clinician-supported ICBT are at least equally effective long-term treatment alternatives for adults with mild to moderate depression" compared with usual care by a physician (Hallgren et al., 2016, p. 419).

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 (MCBT) for prevention of relapse or recurrence among patients (n=593) with recurrent major depressive disorder in remission (Piet and Hougaard, 2011). MCBT 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 MCBT to controls, including treatment as usual (TAU), placebo plus clinical management (PLA), and maintenance antidepressant medication (MADM). Results showed that the relapse rate of MCBT 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 (Piet and Hougaard, 2011).

A later study compared MCBT 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 (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 (Williams et al., 2014).

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 (Hopko et al, 2011). 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 (Cuijpers et al, 2011). 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 (Cuijpers et al, 2011).

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 (Van Hees et al., 2013). 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 (Van Hees et al., 2013).

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 (Jacobsen et al., 2012). 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 (Jacobsen et al., 2012).

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 (Driessen et al., 2013). 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 (Driessen et al., 2013).

Studies cited in the APA guideline **suggested** that problem-solving therapy **may** have advantages over usual care for homebound 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 (Alexopoulos et al, 2011). 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 (Alexopoulos et al, 2011).

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. (Mulcahy et al., 2010). 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 (Neuwsma et al., 2012). 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 (Neuwsma et al., 2012).

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 (Richards and Richardson, 2012). 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 (Richards and Richardson, 2012).

Combination Pharmacology and Psychotherapy Treatments

A recent clinical synthesis of evidence-based applications of combination psychotherapy and pharmacotherapy for depression reported results of meta-analyses showing that the combination produces small effect sizes favoring it over pharmacotherapy or psychotherapy alone (Dunlop, 2016). The World Federation of Societies for Biological Psychiatry recommended the combination of psychotherapy and antidepressants in the treatment of patients with moderate to severe depression, with only partial response to antidepressant medication, and with problems adhering to antidepressant medications (Bauer et al., 2015). Acknowledging that two separate clinicians, i.e., pharmacotherapist and psychotherapist, commonly provide the two treatment components separately, Dunlop **suggested** that communication is the greatest challenge in combination treatment. Other challenges discussed included identification of the optimal timing of delivery of the two treatment components. He noted that a sequential combination strategy is most common, where the patient's initial treatment includes either pharmacotherapy or psychotherapy followed by combination treatment if initial treatment provided inadequate benefit. Dunlop reported the results of a large randomized trial evaluating the cognitive-behavioral analysis system of psychotherapy (CBASP) and nefazodone, either combined or alone, as initial treatment of adults (n=681) with chronic depressive symptoms. Results found combination treatment to be superior to either treatment alone, without significant difference in remission rates between the treatments. Results of this study were not replicated in two later studies (Dunlop, 2016). Dunlop reported a mega-analysis of studies comparing combined interpersonal therapy and medication versus

psychotherapy alone in the treatment of patients with both mild and severe depression (Dunlop, 2016). Results found that time to sustained remission recovery did not differ between treatments in patients with mild depression, whereas combination treatment was faster than psychotherapy alone in generating a response in patients with more severe depression (Dunlop, 2016). The results of these studies as well as other cited in the clinical synthesis found the following:

- Strongest evidence for combining psychotherapy with medication at treatment initiation is for patients with high levels of symptoms, and inpatients;
- Where flexible application of antidepressants is available, evidence does not justify combined psychotherapy and medication for patients with non-severe depression;
- Combination treatments have shown improved symptoms of depression in patients with chronic forms of MDD, but effects are small;
- CBASP is not proven to be more efficacious in treating chronic forms of MDD than other forms of psychotherapy;
- Maintenance antidepressant medication typically is required for patients in remission with combination treatment to remain well; and
- "For patients with residual symptoms after antidepressant treatment alone, addition of an evidence-based psychotherapy can improve acute phase outcomes but not necessarily more than continued medication optimization" (Dunlop, p. 169).

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 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 (Cuijpers et al., 2009). 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** the need for more research to examine further the effectiveness of psychotherapy in dysthymic disorder (Cuijpers et al., 2009).

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 (Moran, 2013). The FDA has not indicated any medications for the treatment of chronic depression (Hellerstein et al, 2012), but a current clinical trial is investigating desvenlafaxine for the treatment of people with chronic depression (National Institutes of Health,2013). 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 (Hellerstein et al., 2012). 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 (Hellerstein et al., 2012).

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 (Hollon et al., 2014). 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 (Hollon et al., 2014).

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 (Cuijpers et al., 2014). 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 (Cuijpers et al., 2014).

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, McClintock et al. investigated the efficacy of augmenting ECT with psychotherapy to prolong remission (McClintock et al., 2011). 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 (McClintock et al., 2011).

Complementary and Alternative Treatment

A recent study aimed to determine the reasons why some controlled studies have found omega-3 highly unsaturated fatty acids (HUFAs) effective in the treatment of depression while others have not, and to assess implications for future trials (Hallahan et al., 2016). Authors performed a meta-analysis including 35 randomized controlled trials, with a median duration of 12 weeks, including participants (n=11038) receiving omega-3 HUFAS or placebo. They evaluated whether biological differences between docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) affected findings of the efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. Noting that EPA has a greater anti-inflammatory effect in the brain than DHA, authors tested whether EPA predominant formulations of omega-3 HUFA compared to placebo demonstrated superior efficacy. The study found that when compared with placebo, EPA-pre-dominant formulations used alone or as augmentative agents, demonstrated superior antidepressant efficacy, while DHA-predominant formulations demonstrated no benefit. Further, the study demonstrated no evidence that EPA prevented depressive symptoms in patients without a diagnosis of depression. Authors stated a need for larger studies of EPA-predominant formulations in monotherapy and as an augmentation agent in populations with moderate to severe clinical depression (Hallahan et al., 2016).

A systematic review and meta-analysis including 40 trials, of which three-fourths were randomized, double blind, and controlled, compared adjunctive nutraceuticals to placebo in the treatment of patients with depression (Sarris et al., 2016). Authors discussed how standardized pharmaceutical-grade nutrients (nutraceuticals) **may** be effective in enhancing antidepressant effects when used adjunctively. Results of analyses showed positive effects in replicated studies for SAMe, methylfolate, omega-3 (EPA or ethyl-EPA specifically), and vitamin D. Authors indicated the need for further research to clarify whether other agents, i.e., zinc, vitamin C, or tryptophan, **may** be beneficial (Sarris et al., 2016).

A recent randomized clinical trial tested whether a single session of whole-body hyperthermia (WBH) is effective in reducing depressive symptoms one week after treatment compared with a sham condition in adults (n=34) with MDD (Jannsen et al., 2016). Authors also tested whether observed improvements would persist across follow-up period of six weeks. This study, believed by authors to be the first randomized, double-blind, sham-controlled study of WBH for the treatment of MDD, found that WBH substantially reduced depressive symptoms within one week of treatment compared with sham condition. Additionally, participants receiving WBH had significantly reduced HAM-D scores across the six-week post-intervention study period compared to sham. Authors cautioned, however, that the therapeutic effects of WBH should not be "oversold" since "rates of response and remission at each post-intervention assessment were lower than are typically observed in antidepressant trials in which the intervention is delivered on a daily basis throughout the study period" (Jannsen et al., p. 793). Authors also noted that these results **may** not apply to patients with treatment-resistant depression, as this trial did not specifically enroll such participants. Study results "suggest that WBH holds promise as a safe, rapid-acting, antidepressant

modality with a prolonged therapeutic benefit" and that more studies are needed (Jannsen et al., 2016).

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 (Chen et al., 2011). 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 (Chen et al., 2011). 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 (Olomon et al., 2011).

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 (Papakostas et al., 2010). 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 (Papakostas et al., 2010). 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 (Mischoulon et al., 2012). Researchers noted limitations of their findings, e.g., relatively small patient sample and short-term (six-week) trial, concluding that further investigation is necessary to better understand the role of s-adenosyl homocysteine in the treatment of depression and its relationship with SAMe.

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 (Subleete et al., 2011). 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** 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 (Subleete et al., 2011).

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 (Papakostas et al., 2012). 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 (Papakostas et al., 2012).

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 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 (Roecklein et al., 2012). 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 (Roecklein et al., 2012).

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 (Wu et al., 2012). 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 (Wu et al., 2012).

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 (Chan et al., 2015). 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 (Chan et al., 2015).

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 (Chaudron, 2013). 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 (Yonkers et al., 2012).

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 (Chaudron, 2013). Some studies show associations between antidepressant use and outcomes, while other studies do not. 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/SNRI 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 (FDA, 2005). 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) (FDA, 2006). 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 (FDA, 2011).

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 (Cohen et al., 2006; Yonkers et al., 2011). 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 (Guille and Epperson, 2013). 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 (Guille and Epperson, 2013).

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" (Pies, 2013). 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

Maust et al. discussed how recent analyses of nationally representative surveys and a private insurance claims database suggest extensive use of antidepressants without a diagnosis of MDD or significant depressive symptoms (Maust et al., 2016). In some studies, authors noted that patients, contacted by telephone after prescribed a new antidepressant, described depressive symptoms that were too mild to suggest the presence of MDD. Another analysis found that 26% of persons ages 65 or older who were prescribed an antidepressant did not meet the threshold suggesting MDD. Authors **suggested** that based on these findings, "at least one-quarter of antidepressant use occurs in the absence of significant depressive symptoms" and that these older patients are subject to side effects of the medication and adverse events (Maust et al., p2). Using data from the Treatment Initiation and Participation (TIP) Program study, a randomized controlled trial of an intervention to improve antidepressant adherence and depression outcomes among older adults (n=231), authors analyzed data to determine why patients had been prescribed antidepressants. Noting that previously, race, gender and comorbidity have influenced assessment of MDD, authors analyzed the following: demographic variables, e.g., age, gender, race, living alone or with others; clinical variables, e.g., medical comorbidity, overall physical well-being, and outpatient care; and psychosocial variables, e.g., distress, beliefs and fears, and perceived needs. Results found that the majority of patients prescribed an antidepressant did not meet criteria for MDD. Those who were prescribed antidepressants without MDD were older, more likely to be white, and reported better well-being. Researchers **suggested** various forces driving the use of antidepressants for patients without MDD include the following: subsyndromal symptoms (although authors noted no evidence that antidepressants are beneficial for the symptoms); treatment of the "worried well" with concern about depression rather than the actual presence of depression; lower threshold for prescribing antidepressants; direct-to-consumer advertising; and incorrect diagnosis due to difficulties in accurately diagnosing depression in primary care settings. Researchers emphasized the importance of recognizing the potential for overtreatment of older patients with depression, stating, "Depression has a significant adverse impact on older adults and magnifies the morbidity associated with other chronic medical illness" (Maust et al., p. 5).

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 untreatable. 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 (Tedeschini et al., 2011). 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 (Tedeschini et al., 2011).

A recent study evaluated whether adding methylphenidate to treatment with citalopram improves antidepressant response in older outpatients with major depression (Lavretsky et al., 2015). 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 (Lavretsky et al., 2015). Yager commented that these findings suggest that carefully selected depressed seniors **may** benefit from combining a selective serotonin reuptake inhibitor with methylphenidate (Yager, 2015).

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 (Gartlehner et al., 2010).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).

Discussion and Conclusions

A study compared published outcomes of trials investigating the use of antidepressants in the treatment of depression with FDA outcomes in unpublished studies (Turner et al, 2008). The study

noted, "We compared the effect size derived from the published reports with the effect size derived from the entire FDA data set" (Turner et al., p. 252). Authors reported 94% of the published trials were positive, whereas only 51% of the trials in the entire FDA data set were positive. "Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall (Turner et al., p. 262). Authors clarified that although this study **suggests** bias toward publication of positive results and selective reporting of clinical trial results, **it does not indicate lack of efficacy of antidepressants in treating depression; however, they indicated the effects may be overestimated**.

A more recent systematic review and meta-analysis assessed the extent of study publication bias in trials examining the efficacy of psychological treatments for depression (Driessen et al., 2015). Researchers examined whether grants, awarded by the U.S. National Institutes of Health (NIH) and supporting randomized clinical trials that compared psychological treatments to control or other conditions in patients with MDD, led to published studies. Researchers identified 4,073 NIH grants, of which only 56 met inclusion criteria, e.g., intention-to-treat analysis, blind assessment of outcome, adequate sequence generation, and independent randomization. Researchers also found one additional study meeting criteria among 38 published studies acknowledging NIH support but not included in the NIH grant database. Out of 55 grants meeting researchers' criteria, published articles were located corresponding to 42 of the studies. To better estimate the effect of psychological treatment on major depressive disorder, researchers pooled findings from the published studies (42) and the unpublished studies (13). "When the unpublished findings were added to the published findings for comparisons of psychological treatments vis-à-vis control conditions (in aggregate), the effect size point estimate was reduced 0.13 standard deviations (from g-0.52 to g=0.39). **Researchers concluded that although psychological interventions for depression are efficacious, the interventions may not be as efficacious as published studies suggest.** They further recommended that clinicians, guideline developers, and decision makers be made aware of overestimated effects in published studies (Driessen et al., 2015).

A recent study analyzed data from patients (n=28,498) who accessed psychological treatment for problems, e.g., recurrent depression, mixed anxiety and depression, generalized anxiety disorder, and depressive episodes. Data also included patient-reported long-term conditions such as asthma, hypertension, and musculoskeletal problems (Delgadillo et al., 2017). The study's goals were to predict depression and anxiety symptom severity at end of treatment using the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder scale (GAD-7), respectively, and to compare outcomes of individuals with and without long-term conditions. This study found many patients with certain long-term conditions were more likely to complete psychological treatment with greater depression and anxiety severity than those without long-term conditions, and they were more likely to have received more intensive and costly psychological interventions consistent with higher level of impairment and symptom severity. In secondary analyses, high intensity therapy and higher average post-treatment distress were associated. Integrated mental health service from a medical perspective, i.e., bringing psychological professionals into medical contexts, or from a mental health perspective, i.e., bringing medical expertise into mental health contexts, **may** improve treatment outcomes in each setting (Delgadillo et al., 2017). Authors questioned the effectiveness of routinely delivered stepped care psychological treatments for people with comorbid conditions, e.g., diabetes and chronic pain, as these conditions can easily exacerbate psychological distress. They recommended multidisciplinary care targeting multiple facets of well-being, adjustment and quality of life, and offering integrated multidisciplinary care for individuals with both psychological problems and long-term medical conditions. ***Authors concluded, "Overall, we conclude that standard stepped-care interventions are insufficient to support patients with multimorbidity, especially if delivered in isolation from other healthcare specialists***. Our

observations concur with recent calls for closer integration of physical and mental healthcare" (Deflgadillo et al., p. 52). They **suggested** exploring new benchmarking models and quality indicators within primary care psychological services (Delgadillo et al., 2017).

The 2015 World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 2: Maintenance Treatment of Major Depressive Disorder-Update 2015 emphasizes that "the ultimate judgment regarding a particular treatment procedure must be made by the responsible treating physician in light of the clinical picture presented by the patient and the diagnostic and treatment options available" (Bauer et al., 2015, p. 78). Depression poses challenges to the physician treating a patient's depression; although remission of all symptoms is the goal of therapy, many patients do not remit and suffer from residual symptoms and functional impairment (Culpepper et al., 2015). Individualized treatment, (e.g., matching therapy to specific symptom clusters; multimodal treatment targeting multiple neurotransmitters; and individualizing drug selection) have been proposed to improve outcomes of depression. The application of neurobiology principles to treatment choices provides guidance in the choice of antidepressant, switching of antidepressant, augmenting antidepressant with another pharmacologic agent, or psychotherapy. Although a goal of treatment is to reduce total symptom severity, the optimal outcome for patients is symptomatic remission allowing patients to return to premorbid level of functioning (Culpepper et al., 2015). **With individualized treatment and implementation of evidence-based collaborative care in the treatment of depression, more patients with residual symptoms or treatment-resistant depression can achieve complete remission and regain functionality.**

Obtaining Copies of the Guideline

Copies of the *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* are available at http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx.

Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. We take all suggestions and recommendations into consideration in our ongoing review of guidelines. Submit comments to:

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