Introduction to Magellan’s Adopted Clinical Practice Guidelines
For the Treatment of Schizophrenia
Magellan Clinical Practice Guideline Task Force Membership

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Purpose of This Document

This document is an introduction and update to Magellan Healthcare’s (Magellan’s) adopted clinical practice guideline (CPG) for the treatment of persons with a schizophrenic disorder.

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

This guideline presents the results of published, peer-reviewed studies including clinical trials, systematic reviews and meta-analyses. Many are early studies, not yet reproduced, and some are very small, or may include a narrow population of participants. Clinicians should exercise caution when interpreting results of these studies, especially when the author(s) describe study results as insignificant, or where suggestions, rather than conclusions, are based on the results of the studies. Clinicians should also note that some are international studies including the use of medications that are not available in the United States or are “off label” for a particular condition.

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

Introduction

Magellan has adopted the American Psychiatric Association’s (APA) Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition (2004) (American Psychiatric Association, 2004) and Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients with Schizophrenia (Dixon et al. 2009). Both documents serve as a framework for practitioners’ clinical decision-making with patients who have schizophrenia. The APA guideline, one of the most comprehensive, widely used, evidence-based clinical practice guidelines for this disorder, provides an excellent source of evidence-based information. Accepted by other managed behavioral healthcare companies, it reduces the burden on practitioners serving multiple organizations.

The APA guideline and guideline watch incorporate rapidly evolving developments in pharmacotherapy, as well as developments in other areas of the psychiatric management of individuals with schizophrenia. Additionally, they provide information covering all areas of psychiatric management of patients with this disorder, from understanding the clinical features and epidemiology, to treatment approaches and planning.

Additional Recommendations Based on Recent Literature Review

The APA guideline is based on a literature review through 2002, while the APA guideline watch reviewed the clinical literature between 2002 and 2008. Magellan conducted a further review of the
clinical literature on assessment and treatment of schizophrenia published through October 2015. A summary of key relevant recommendations from this more recent literature review is included in the document. Magellan encourages providers to be familiar with this information, as well as the information provided in the APA publications.

**Executive Summary**

*(Discussion of changes/new information in this updated CPG, based on a literature review through October 2015)*

**Epidemiology**

According to the National Institute of Mental Health (NIMH), the 12-month prevalence of schizophrenia is 1.1% of the U.S. population (NIMH, 2015). Lifetime prevalence is approximately 0.3% - 0.7%, with variation by race/ethnicity and country (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5], 2013). The general incidence of schizophrenia is lower in females, and negative symptoms and poorer outcomes show higher incidence for males than for females. The first psychotic episode usually occurs in the early-to-mid 20s for males and in the late 20s for females, with the majority of individuals manifesting a gradual development of clinical signs and symptoms (DSM-5). In the United States, approximately 100,000 adolescents and young adults experience a first psychotic episode each year.

Environmental as well as genetic and physiological factors link to the incidence of schizophrenia. Incidence is higher for children who grow up in an urban environment, and although most individuals diagnosed with schizophrenia have no family history of psychosis, genetic factors are involved in the causes of schizophrenia. Higher risk also occurs with pregnancy and birth complications as well as other prenatal and perinatal adversities, e.g., stress, infection and malnutrition. Approximately 20% of individuals with schizophrenia attempt suicide at least once, and 5-6% die by suicide (DSM-5, 2013).

Results of recent studies are **suggestive** that “immune and inflammatory cascades in conjunction with infection may play a role in the pathology of schizophrenia” (Hayes et al., 2014, p. 963). Researchers investigated molecular changes in cerebrospinal fluid from patients (n=46) with schizophrenia, compared with a control group, to determine how the stressors affect the pathology of the disease. An evaluation of levels of 90 different molecules, including some with primarily immune-system functions, found differences between the schizophrenia group and the control group on levels of 15 of the molecules. Based on this study, researchers **suggested** that nine molecules, i.e., α2M, fibrinogen, IL-6R, SCF, TGFα, TRFR2, IL-8, MCP-2, CCL8, and testosterone **might help** in predicting markers for early stage psychosis (Hayes et al., 2014, p. 963).

In a recent study, authors sought to uncover the hidden risks of schizophrenia to demonstrate that schizophrenia is a heterogeneous group of heritable disorders (Arnedo et al., 2015). They identified sets of interacting single-nucleotide polymorphisms (SNP sets) in a large genome-wide association study, Molecular Genetics of Schizophrenia (MGS), of cases with schizophrenia and controls. All subjects had consistent and detailed genotypic and phenotypic assessment. After examining the risk of schizophrenia for each SNP set, researchers tested replicability in two independent samples: the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) and the Portuguese Island studies from the Psychiatric Genomics Consortium (PGC). Their analysis showed that the heritability of schizophrenia is “encoded in a complex distribution of genotypic-phenotypic relationships” (Arnedo et al, p. 147). Further, they found that 42 interactive SNP sets had more than 70% risk of
schizophrenia. Authors suggested their approach "is a pioneering effort to specify complex but manageable patterns of gene-gene interaction underlying the polygenic risk of schizophrenia" and that these results hold promise for the emergence of a new era in clinical psychiatry in which person-centered treatment of complex disorders can be guided by reliable assessments of well-validated clinical syndromes and their specific causes (Arnedo et al., p 151).

**Impact of DSM-5 Changes on Diagnosis of Schizophrenia**

A recent study examined the effect of the following major changes in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) criteria:

1. Requirement that at least two of the Criterion A symptoms must be present for a month and that at least one of the Criterion A symptoms must be either delusions, hallucinations or disorganized speech;
2. Omission of schizophrenia “subtypes”; and

Authors examined data from 22 double-blind, randomized, placebo-controlled pre-DSM-5 trials of second generation antipsychotics for the treatment of acute psychotic episodes in patients with schizophrenia (n=5233), finding that more than 99% of patients met DSM-5 diagnostic criteria for schizophrenia with no differences in effect size between schizophrenia subtypes. Authors also found that the symptoms responding best to treatment with second-generation antipsychotics were hallucinations, delusions, disorganized speech, and mania. They concluded that the classic “subtypes” are not predictive of treatment response and their omission is justified (Matilla et al., 2015).

**First Episode/Early Psychosis**

In a recent study, researchers examined psychotropic medication prescription patterns, including factors associated with choice of medication strategy, for people with first-episode schizophrenia spectrum disorders in 34 U.S. community mental health settings (Robinson et al., 2015). They examined data for a sample of patients (n=404) obtained from the Recovery after an Initial Schizophrenia Episode Project’s Early Treatment Program (RAISE-ETP), a nationwide effectiveness study for patients with first-episode schizophrenia spectrum disorders. Researchers sought to determine the medication treatments prescribed currently in community settings. The mean age of participants was 23.6 years; the majority was male; and participants were of diverse racial backgrounds (Robinson et al., 2015).

Researchers in the above study noted that practice guidelines support the following first-episode treatment: “1) the need for antipsychotic treatment, 2) the use of low antipsychotic dosing, and 3) the need to minimize side effects, especially metabolic ones” (Robinson et al., p. 244). Although antipsychotic prescriptions were mostly in accordance with recommendations, 17% of antipsychotics prescribed were for olanzapine, although guidelines recommend against its use due to frequent adverse metabolic side effects. Further, treatment with olanzapine was often at higher-than-recommended dosages. Demographics showed that younger patients were more likely to receive prescriptions for risperidone; women were more likely to receive lower dosages of antipsychotics, and women were more likely to receive more prescriptions for long-acting injectable (LAI) antipsychotics and antidepressants. Prescription practices were also affected by regional differences as well as insurance status. Private insurance was associated with a higher
likelihood of receiving a prescription of an antipsychotic as well as a lower likelihood of receiving more than one antipsychotic or receiving a first-generation antipsychotic (FGA). African Americans were also more likely to receive prescriptions for first-generation antipsychotics. Researchers noted that about one-third of patients received prescriptions for antidepressants although only about half of those patients had clear symptoms indicating the need for antidepressants. They suggested that cumulatively 39.4% of patients could have benefitted from changes in their psychotropic prescriptions, e.g., not prescribing two or more antipsychotics and not prescribing olanzapine, especially at high dosages. They concluded that training is warranted to improve clinicians’ ability to diagnose schizophrenia disorders as distinct from mood or anxiety disorder to avoid antidepressant medication prescription where there are no symptom indications supporting the medication (Robinson et al., p. 244).

A recent study described data from a large double-masked randomized trial comparing aripiprazole and risperidone for the acute treatment of first-episode schizophrenia and related conditions (Robinson et al., 2015). Patients aged 15-40, with schizophrenia, schizoaffective disorder, schizoaffective disorder, or psychotic disorder not otherwise specified (n=198) who had received treatment with antipsychotics for two weeks or less were randomly assigned to double-masked treatment with aripiprazole (5-30 mg/day) or risperidone (1-6 mg/day) over a period of 12 weeks. Analysis comparing the cumulative 12-week response rates between treatments included symptom analyses, metabolic effects, and motor effects. Results showed that time to response and positive symptom response rates were equivalent, whereas patients receiving aripiprazole had somewhat better negative symptom outcomes, e.g., improvement of avolition-apathy, compared with patients receiving risperidone. However, those treated with aripiprazole experienced more akathisia. On outcomes for fasting glucose, and total and LDL (low density lipoprotein) cholesterol and prolactin, aripiprazole was associated with better outcomes than risperidone. Researchers concluded that, based on data from this large trial, aripiprazole is preferred over risperidone for the treatment of first-episode schizophrenia in most situations, due to its preferred metabolic outcomes and symptom advantages. They also advised that risperidone is preferable if the potential for akathisia is a concern (Robinson et al., 2015).

The NAVIGATE program for first-episode psychosis was developed by the RAISE Early Treatment Project with its focus on psychosocial interventions to help individuals with a first episode of psychosis improve their psychological and functional health (Mueser et al., 2015). Core services include family education program (FEP), individual resiliency training (IRT) and supported employment and education (SEE). In NAVIGATE, engagement of family members is important in providing social support and as “allies in treatment” (Mueser, p. 685). The four stages of FEP help develop a working relationship between family and clinician; provide families with information about psychosis and how to reduce stress, prevent relapses and work with the NAVIGATE team; and help families address specific problems while preparing for the patient’s transition to less intensive services. IRT, provided by a clinician in sessions focusing on helping patients achieve personal goals, teaches patients how to manage their illnesses to improve functioning. Modules use individualized, structured format with a cognitive-behavioral therapy approach, combined with psychoeducation and motivational enhancement. IRT’s emphasis is on encouraging the patient to create a story, which helps in processing aspects of the psychotic episode, while using cognitive restructuring to challenge self-stigmatizing beliefs. Patients learn how to refocus their attention and memory on positive aspects of life, and record positive things that have happened. SEE helps patients who are recovering from a first episode return to work or school. The stages of SEE services include development of career and educational profile; job search or educational enrollment; and follow-along supports to help the patient succeed at job or school. In the NAVIGATE model, recovery is facilitated by small teams of providers who help patients build skills
for individual resiliency and provide tailored pharmacological treatment (Mueser et al., 2015).

**Violent Behavior in Persons with Schizophrenia Spectrum Disorders**

Victoroff et al. undertook a recent systematic review of literature to determine the efficacy of neuropharmacological agents for the management of violence among persons with schizophrenia spectrum disorders (SSD) (Victoroff et al., 2014). Authors discussed conclusions from other studies finding that SSDs are a risk factor for violence, resulting in problematic consequences, e.g., threatened lives and well-being of both patients and others; non-compliance with treatment; disruption of families; increased need for institutionalization; and contribution to the stigma bias against all mental illness. They noted that although SSDs are associated with only about 5% of total societal violence, SSD accounts for between 6% - 28% of homicides. From their study including a review of 86 peer-reviewed articles reporting clinical effects of pharmacological agents on aggression or hostility, authors suggested that evidence supports the following:

- In the management of hostility among inpatients with SSDs (not preselected for aggression), paliperidone ER is **probably** effective (strongest evidence of efficacy);
- For the management of overt aggression among inpatients with SSDs (not preselected for aggression), clozapine is **possibly** more effective than haloperidol;
- For the management of hostility among inpatients with SSDs (not preselected for aggression), clozapine is **possibly** more effective than chlorpromazine;
- For reducing aggression among physically assaultive inpatients with SSDs, clozapine is **possibly** more effective than olanzapine or haloperidol; and
- For reducing aspects of hostility or aggressions among inpatients with SSDs, adjunctive propranolol, valproic acid, and famotidine is **possibly** effective.

Authors cautioned that the majority of research on the efficacy of interventions fails to differentiate results between patients with and without comorbid substance abuse. They **suggest the need for a “state-of-the art study” of neuropharmacological management of aggressive and violent behavior among persons with SSDs** which includes accounting for dual diagnosis (Victoroff et al., 2014).

**Cultural Factors**

A recent study, part of the Connecticut Department of Mental Health and Addiction Service, Health Disparities Initiative, investigated disparities in access, diagnosis, and mental health treatment outcomes in a state inpatient mental health service, while controlling for demographic variables and symptom severity (Delphin-Rittmon et al, 2015). Authors hypothesized that African and Hispanic Americans would be less likely to self-refer for inpatient services due in part to stigmatizing views about seeking mental health services. They also hypothesized that African Americans receive more diagnoses of schizophrenia and less with affective disorders than white Americans, even with demographic variables controlled. A third hypothesis was that African Americans as well as Hispanic Americans display lower treatment completion rates and poorer symptom severity ratings at discharge.

Results of the above study showed that Hispanic Americans were significantly more likely to enter inpatient services through crisis/emergency sources than African Americans and white Americans. Authors suggested their delay in seeking help was due to cultural and systemic barriers related to language, culture, and immigration. Hispanic Americans were more likely to receive diagnoses of “other psychotic disorders” than white Americans and they “displayed treatment completion and
symptom severity rates at discharge comparable to White Americans” (Delphin-Rittmon et al., p. 164). African Americans were more likely to be diagnosed with schizophrenia, drug-related than other groups. They were more likely than other groups to come to inpatient units from self-referral and family or outpatient services, and were more likely to terminate treatment against medical advice. Although they received ratings of greater symptom severity at discharge, they displayed shorter length of stay. Authors suggested the need for cultural competence education and training for all staff, focusing on translation of cultural competence principles, with modules addressing racial and ethnic behavioral health disparities and how to eliminate them (Delphin-Rittmon et al., 2015).

**First-Generation vs. Second-Generation Antipsychotics**

A recent meta-analysis of randomized controlled trials (n=212 studies) compared 15 antipsychotic drugs and placebo in the acute treatment of patients with schizophrenia (n=43049) (Leucht et al., 2014). Researchers compared the two prototypal first-generation antipsychotics (haloperidol and chlorpromazine) and 13 second-generation antipsychotic drugs. This multiple-treatments meta-analysis, using both direct and indirect comparisons, provided evidence-based hierarchies of comparative efficacy, risk of all-cause discontinuation, and major side effects. Researchers excluded trials in patients with predominant negative symptoms, concomitant medical illness, or treatment resistance, and those conducted in stable patients in order to have a reasonably homogeneous sample. The mean age of patients was 38.4 years and the mean duration of illness was 12.4 years. The mean overall change in symptoms was the primary outcome, assessed by change in Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Secondary outcomes included all-cause discontinuation, weight gain, and antiparkinson drug use as measures of extrapyramidal side effects, prolactin increase, QTc prolongation, and sedation. Statistical analysis used data from acute treatment during a 6-week period (Leucht et al., 2014).

Results from the above study showed that differences between drugs were small and gradual, and all drugs were superior to placebo (Leucht et al., 2014). The efficacy hierarchy generated by the analysis showed that clozapine was significantly more effective than all the other drugs compared with placebo, but in direct pairwise comparisons was no more effective than any other second-generation antipsychotic. The most effective drugs when compared with placebo were second-generation antipsychotics (SGAs), i.e., clozapine, amisulpride, clonazapine, and risperidone. Researchers noted that differences in efficacy between drugs were smaller overall than the differences in side effects. They found that the most effective drugs also had the lowest discontinuation rates with the exception that haloperidol, the worst drug with respect to lowest discontinuation, had a middle rank for efficacy when compared with placebo. Clozapine, olanzapine, quetiapine and aripiprazole, iloperidone, amisulpride, and asenapine did not cause significantly more extrapyramidal side effects than placebo, while haloperidol and chlorpromazine caused the most extrapyramidal side effects. Some of the least well tolerated drugs, chlorpromazine, lurasidone, risperidone, and paliperidone, produced significantly more extrapyramidal side effects than did several others in the analysis. Researchers noted that the dichotomy between first- and second-generation antipsychotics based on extrapyramidal side effects is an oversimplification. They recognized that weight gain and associated metabolic problems are major issues linked to new antipsychotic drugs, and in this study olanzapine, zotepine, and clozapine were the worst. However, ziprasidone and lurasidone (as well as haloperidol) were without significantly more weight gain than placebo, and chlorpromazine was among the worst. Researchers noted that the dichotomy between first-generation and second-generation antipsychotics based on weight gain is another oversimplification (Leucht et al., 2014).
In the study discussed above, Leuchet et al. discussed how the antipsychotic drugs assessed differed with respect to QTc prolongation, which can lead to life-threatening torsades de pointes. Researchers found that amisulpride, regarded as benign in some guidelines, was associated with QTc prolongation, consistent with reported amisulpride overdoses. Findings showed large differences between drugs with respect to prolactin increase. Compared with placebo, paliperdione and risperidone increased prolactin by more than one standard deviation. Researchers concluded that because antipsychotic drugs differ in many properties, clinicians should adapt choice of antipsychotic drugs to the needs of individual patients (Leuchet et al., 2014).

A recent systematic review and meta-analysis compared relapse/hospitalization risks of stabilized patients with schizophrenia under active versus placebo or intermittent treatment conditions (De Hert et al., 2015). This review included two groups of randomized controlled studies (n=46 studies) investigating relapse/hospitalization rates and/or time to relapse in stabilized patients with schizophrenia:

1) Studies comparing treatment with placebo (i.e., replacement of oral or long-acting first- or second-generation antipsychotics with placebo) versus continuous treatment with antipsychotics; and

2) Studies comparing intermittent dosing, a stepwise discontinuation and use of antipsychotic drugs only when needed, e.g., reemergence of prodromal symptoms or psychotic symptoms, versus continuous treatment.

In background information, researchers noted that the 2003 World Health Organization's statement reported, "Increasing the effectiveness of adherence interventions may have a greater effect on the health of the population than any improvement in specific medical treatments" (World Health Organization, 2003). Researchers noted that side effects associated with continuous treatment with antipsychotics often lead to medication discontinuation in patients. Further, antipsychotics only control symptoms, but do not reverse the underlying etiology. Clinicians have questioned whether continuous antipsychotics are necessary for every patient after a first-episode psychosis (De Hert et al., 2015).

Results of the above review and meta-analysis found odds of relapse for patients treated with placebo for at least six months were five times higher than for those in the continuous treatment condition (De Hert et al., 2015). These results were based on 36 studies with stabilized patients (n=4657) with a psychotic disorder. Other results based on 10 studies with stabilized patients (n=1230) showed that patients in the intermittent dosing condition were three times more likely to relapse compared with patients in the continuous treatment condition. Patients treated with intermittent techniques versus continuous treatment showed higher relapse rates regardless of whether they were first-episode or multi-episode psychotic patients. Further, compared with placebo or intermittent treatment, continuous treatment resulted in not only a lower risk of relapse, but also delayed time to (impending) relapse. Researchers concluded that the evidence from this systematic review, along with existing guidelines and algorithms for antipsychotic treatment of the maintenance phase of schizophrenia, supports continuous treatment. They suggested that continuous antipsychotic treatment remains the cornerstone of treatment of patients with schizophrenia, and that patients may benefit from the addition of psychotherapy (i.e., cognitive-behavioral therapy) added to pharmacotherapy (De Hert et al., 2015).

In a U.S. Food and Drug Administration (FDA) drug safety communication on September 15, 2015, FDA modified requirements for monitoring, prescribing, and dispensing clozapine to address safety concerns and current knowledge about severe neutropenia associated with clozapine. The Clozapine REMS Program, a new, shared risk evaluation and mitigation strategy (REMS) for all
clozapine medicines was approved (FDA, 2015).

On December 11, 2014, the FDA added a warning to the label for ziprasidone (Geodon®) (FDA, 2014). The label warns that ziprasidone is associated with a rare but serious skin reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can affect several parts of the body.

**New FDA Approved Drugs for the Treatment of Schizophrenia**

On July 10, 2015, the U.S. Food and Drug Administration approved Rexulti® (brexpiprazole), a serotonin-dopamine activity modulator, to treat adults with schizophrenia (FDA, 2015). An FDA news release discussed the results of two 6-week clinical trials, evaluating the effectiveness of Rexulti in treating schizophrenia, finding Rexulti reduced the occurrence of symptoms of schizophrenia compared to placebo. Weight gain and a sense of restlessness, e.g., feeling the need to move, was the most common side effect. A 6-week multicenter, randomized, double blind, placebo-controlled study by Correll et al. compared the efficacy, safety, and tolerability of brexpiprazole and placebo in adults (n=636) with schizophrenia experiencing an acute exacerbation (Correll et al., 2015). In this acute, short-term regulatory approval study, patients were assigned to 0.25, 2, or 4 mg of oral brexpiprazole or placebo once daily. Beginning dosage at 1 mg/day was titrated to 2 mg/day on day 5, and 4 mg/day on day 8 in patients receiving 2 or 4 mg/day of brexpiprazole. Outcome measures included change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score and other efficacy and tolerability measures. Results of this study found brexpiprazole at a dosage of either 2 or 4 mg/day resulted in greater improvement in outcome measures than placebo within 1-2 weeks of initiating treatment as well as throughout the treatment period. It demonstrated efficacy in the treatment of both positive and negative symptoms of schizophrenia. Brexpiprazole was well tolerated, with minimal changes in extrapyramidal symptom scales, low incidence of akathisia, only a moderate increase in body weight, and no evidence of significant adverse effects on metabolic measures and prolactin when compared with those for placebo (Correll et al., 2015).

On Sept. 17, 2015, FDA approved Vraylar® (cariprazine) capsules to treat schizophrenia and bipolar disorder in adults (FDA, 2015). The FDA news release reported the results of three six-week clinical trials including 1754 participants. Compared to placebo, Vraylar reduced the symptoms of schizophrenia while associated with extrapyramidal symptoms, i.e., tremor, slurred speech, and involuntary muscle movements. An international, phase III clinical trial evaluated the efficacy and safety of this dopamine D3 and D2 receptor partial agonist, in patients with an acute exacerbation of schizophrenia (Kane et al, 2015). Researchers hypothesized that cariprazine’s high affinity for the D3 receptor may provide a potential benefit in negative symptoms and cognitive impairment. Results of this study found greater improvement in the PANSS score and Clinical Global Impressions-Severity (CGI-S) efficacy parameters in cariprazine 3-6 mg/day or 6-9 mg/day than in placebo. Additionally, cariprazine was generally well tolerated, with some mild or moderate treatment emergent adverse events (TEAEs), of which akathisia was the most common (Kane et al., 2015).

The FDA approved a new three-month, long-acting injectable (LAI) antipsychotic, Invega Trinza® (paliperidone palmitate), in May 2015. This quarterly intramuscular injection form of paliperidone provides the longest dosing interval available for patients with schizophrenia and was approved by the FDA "under its priority review process, a fast track for drugs thought to represent a significant advance in medical care" (Medscape, 2015). Patients receiving this drug must first receive Invega Sustenna®, the monthly injection version, for at least four months. A recent double-blind, placebo-
controlled study evaluated the efficacy and safety of the quarterly injection form of paliperidone versus placebo in delaying time to relapse of schizophrenia symptoms in patients (n=305) previously treated with once-monthly paliperidone for at least four months (Berwaerts et al., 2015). The four phases of this two-year maintenance trial included: transition phase where patients received once-monthly doses of the 1-month formulation of paliperidone palmitate; maintenance phase where patients received a single dose of the 3-month formulation; and the open-ended double-blind phase where patients received a fixed dose of 3-month paliperidone palmitate or placebo once every 3 months. The primary outcome variable was time from randomization to the first relapse event in the double-blind phase. Study results showed significantly delayed time to relapse of schizophrenia symptoms for patients receiving the 3-month paliperidone palmitate compared with those receiving placebo. A relapse event during the double-blind phase occurred in 9% of the group receiving 3-month paliperidone palmitate compared with 29% in the placebo group.

The most recently FDA-approved drug to treat schizophrenia is Aristada® (aripiprazole lauroxil). On October 5, 2015, the FDA approved this long-acting injectable, administered every four to six weeks (FDA, 2015). The director of the Division of Psychiatry Products in the FDA’s Center for Drug Evaluation and Research emphasized the long-acting medications can improve the lives of patients with schizophrenia. In a 12-week randomized, double-blind, placebo-controlled trial including participants (n=622) with acute schizophrenia who had been stabilized with oral aripiprazole, Aristada demonstrated improvement in schizophrenia symptoms and a safety and tolerability profile not unlike that of oral aripiprazole. The most common side effect reported was akathisia (Meltzer et al., 2015).

**Polypharmacy**

A recent retrospective claims-based analysis of patients with schizophrenia (n=4156) characterized patterns of treatment, e.g., medication switching and discontinuation in those treated with antipsychotic monotherapy versus those treated with polypharmacy (Fisher et al, 2014). The study included patients between the ages of 13 and 64, studying treatment patterns for patients at the earliest stages of their diagnosis as well as patients with chronic schizophrenia. In this study, 23% of patients with schizophrenia received treatment with two or more antipsychotic agents simultaneously. Combinations of SGAs were the most frequently used combination, while a quarter of patients receiving polypharmacy received a combination that included a first-generation antipsychotic. In the oldest patients, combinations of FGAs were more frequent, whereas the youngest patients more frequently received combinations of SGAs. Data from this study showed that when transitioned off a single antipsychotic, patients more often received a second antipsychotic rather than beginning treatment with two antipsychotics. This practice is consistent with the APA's guideline recommending polypharmacy only after the patient has not benefitted by monotherapy (APA, 2004). In addition to finding polypharmacy in almost one fourth of patients with schizophrenia, researchers noted higher discontinuation rates, i.e., a 90-day gap in at least one of the antipsychotic medications prior to the end of the one-year follow-up period, in those receiving polypharmacy compared with those receiving monotherapy (Fisher et al., 2014).

**Concurrent General Medical Conditions**

To evaluate the association between antipsychotic drug use in pregnancy and maternal and perinatal outcomes, researchers conducted a large matched cohort study, including singleton live births or stillbirths to women, including antipsychotic users (n=1021) who were matched with women not exposed to any antipsychotic drug during pregnancy (Vigod et al., 2015). Researchers
used a high-dimensional propensity scores (HDPS) matching algorithm, including data dimensions, e.g., prescription drug claims and hospitalization/emergency department diagnoses and procedures less than 365 days before cohort entry, to address treatment selection bias. Antipsychotic medication users were 1:1 matched with non-users based on the HDPS score and on maternal age at delivery. Researchers restricted the analysis to the atypical antipsychotics, i.e., quetiapine, olanzapine, and risperidone. Results found that event rates were not significantly different among antipsychotic users and non-users for gestational diabetes and hypertensive disorders in the matched group. Additionally, event rates were also not significantly different for preterm birth and birth weight. Only labor induction and operative vaginal delivery were associated with antipsychotic drug use in the matched cohort. Researchers concluded, “Antipsychotic medications themselves do not seem to have an extensive negative impact on important measures of maternal medical and short term perinatal wellbeing” although “women requiring antipsychotic medications are at higher absolute risk for certain adverse maternal and perinatal outcomes compared with the general population.” They advise closely monitoring the medical health of women requiring antipsychotic medications, with attention to diabetes, hypertension, preterm birth, and fetal growth (Vigod et al., 2015).

A large cross sectional study of 314 primary care practices in Scotland examined the range and number of the most common physical-health comorbidities in a sample of patients (n=9677) with schizophrenia or a related psychosis (Smith et al., 2013). Results found that persons with schizophrenia had significantly more primary care records of physical-health comorbidities, e.g., viral hepatitis, constipation, and Parkinson’s disease, than those without schizophrenia, even after controlling for age, gender and social deprivation. Recorded primary care rates for cardiovascular disorders, e.g., atrial fibrillation, hypertension, coronary heart disease and peripheral vascular disease, were lower in persons with schizophrenia than controls, although the most commonly diagnosed condition for patients with schizophrenia was hypertension. Authors noted that this result was somewhat unexpected, especially since another study showed that “people with incident schizophrenia were more likely to die prematurely than the general population (15 years earlier for men and 12 years earlier for women) and the leading causes of death were cardiovascular disease and cancer” (Smith et al, p. 4). Authors suggested, “GPs may not be assessing and/or recording cardiac problems as often as they might with patients who do not have schizophrenia.” They suggested the need for “a more systematic use of such screening in both primary and secondary care may improve early detection and treatment of hypertension, hypercholesterolaemia, diabetes and smoking” (Smith et al., p 6).

**Metabolic Disturbances**

A recent study reviewed clinical and molecular evidence on metabolic alterations induced by SGAs (Rojo et al., 2015). Authors noted that metabolic alterations, e.g., weight gain, insulin resistance, diabetes, dyslipidemia and increased cardiovascular risk, often develop in a short period of time (six months after initiation of treatment with SGAs). They discussed studies showing that activation of SREBP1c, D1/D2 dopamine, GABA2, and 5HT neurotransmitters are associated with cardiovascular toxicity, and that polypharmacological interventions are not significantly effective in maintaining low cardiovascular risk in patients treated with SGAs. Authors noted the effect of environmental and/or epigenetic factors on the propensity to develop metabolic syndrome in patients receiving treatment with SGAs. They reviewed results of studies assessing the efficacy of pharmacological interventions, i.e., metformin, nizatidine, orlistat, ranitidine, topiramate, etc. in treatment of metabolic side effects. Although metformin reduced body weight in clozapine-treated patients, these effects did not continue upon discontinuation of the drug. Orlistat was associated with a mild decrease in weight gain in men, but had no effect in women, and atomoxetine was not
effective in preventing obesity in patients who received olanzapine and clozapine. Authors indicated the difficulty with a single-drug therapy to treat a multifactorial problem, as current literature suggests that “mechanisms of SGAs-induced metabolic syndrome involve at least two separate systems: the peripheral lipid and glucose metabolism, controlled by SREBP1 transcriptional factor, and the alteration of appetite control in the hypothalamus through neurons of the arcuate nucleus” (Rojo et al., p. 9). They suggested future studies including the antidiabetic effect of specific polyphenols, e.g., anthocyanins, shown to be effective in ameliorating obesity.

Other Pharmacological Agents

A recent dual-site, thirteen-week, randomized, double-blind, placebo-controlled, crossover study explored the influence of adjuvant raloxifene on cognition in young to middle age men and women (n=98) with schizophrenia (Weickert et al., 2015). Researchers discussed how the “estrogen receptor is altered in the brains of people with schizophrenia, involving both lower messenger ribonucleic acid (mRNA) levels and/or failure to express the fully functional wild-type form of the estrogen receptor” (Weickert et al., p. 686). Based on several studies of estrogen therapy in schizophrenia demonstrating significant reduction of symptoms in women with schizophrenia, researchers suggested that stimulation of the estrogen signaling pathway in the brain may improve cognitive function in both men and women with schizophrenia. However, they pointed out that treatment with estrogen is not risk-free and that another agent that stimulates estrogen action in brain cells is needed that is relatively free of adverse events. Researchers cited studies reporting that adjunctive raloxifene, a second-generation selective estrogen receptor modulator approved for use in treating osteoporosis, also has beneficial effects on brain function. In this randomized, crossover study, they predicted that cognitive deficits, e.g., verbal memory, would improve with treatment of adjunctive raloxifene at 120 mg/day. Patients alternated between receiving raloxifene HCl orally and a placebo during the first six weeks of the trial, followed by a one-week “washout,” after which they all received the alternate treatment (placebo or raloxifene) for the trial’s last six weeks. Monitoring for adverse events occurred throughout the trial. Treatment outcomes at the end of the first six-week period showed that 40% of patients receiving raloxifene had significant improvement on measures of cognition, e.g., memory and processing speed, compared with improvement in only 15% of patients in the placebo condition. The difference in improvement of these measures in the second six-week period between the raloxifene and placebo were less than during the first six-week period, suggesting persistence of the improvement in the raloxifene group even after changing to placebo in the second period. No significant difference in adverse events occurred in 93% of patients between the raloxifene and placebo condition. Researchers concluded that this trial was the first demonstration that adjunctive administration of raloxifene at 120 mg/day can improve outcomes, e.g., verbal memory and attention, in both men and women with schizophrenia, suggesting a potential novel treatment for these defects in patients with schizophrenia (Weickert et al., 2015).

A recent proof-of-concept study investigated the effectiveness of low-dose sodium nitroprusside administered intravenously to 20 patients with schizophrenia, 19-40 years of age, currently receiving treatment with available antipsychotics (i.e., risperidone, olanzapine, chlorpromazine, quetiapine, ziprasidone, haloperidol, aripiprazole) (Hallak et al., 2013). Output measures included changes in positive, negative, anxiety, and depressive symptoms during four weeks following the treatment. Patients randomly assigned to receive sodium nitroprusside (0.5 ug/kg/minute for 4 hours), or placebo (5% glucose solution infused over same time period) were interviewed by a psychiatrist using the Brief Psychiatric Rating Scale (BPRS-18) to measure efficacy and the Positive and Negative Syndrome Scale (PANNS-negative subscale) to detect and rate symptoms. During the seven-day follow-up period, no changes in antipsychotic medications were allowed. Results showed
the sodium nitroprusside group improved from the second hour of infusion and persisted for the four-week observation period, with the BPRS-18 revealing reduced scores in participants receiving sodium nitroprusside versus placebo. Additionally the sodium nitroprusside group improved rapidly after infusion in contrast to the placebo group in the PANSS-negative subscale scores. Findings did not show significant differences in physical parameters, e.g., systolic blood pressure, diastolic blood pressure, heart rate and blood oxygen saturation level, between the two groups. Researchers noted that although this study showed that “sodium nitroprusside administration significantly and rapidly improved the positive, negative, anxiety, and depressive symptoms of schizophrenia,” there is a need for larger confirmatory studies with longer follow-up periods (Hallak, p. 675).

The National Institute of Mental Health-sponsored initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), is an assessment battery for patients with schizophrenia, while the associated Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) project deploys the MATRICS battery in treatment trials (Koola et al., 2014). These projects were designed to facilitate development of drugs to treat cognitive impairment in patients with schizophrenia. Authors noted that no approved medications for impairment of this core feature of schizophrenia have been FDA approved, and the MATRICS project identified dopaminergic, cholinergic, and glutamatergic drug mechanisms of particular interest. Citing studies showing that the combination of an acetylcholinesterase inhibitor (AChEI) and memantine is more effective than either medication alone to treat cognitive impairment in Alzheimer’s dementia, authors suggested a potential role of this combination to improve cognitive impairments in schizophrenia. They suggested future research is needed “to shed light on the association of biomarkers and cognitive enhancement with treatment interventions” (Koola et al., p. 88).

**Promoting Treatment Adherence**

A new cross sectional survey conducted in Germany with hospital psychiatrists and their inpatients with schizophrenia or schizoaffective disorder examined the association between clinicians’ underestimation of treatment nonadherence and low implementation rates of structured adherence-enhancing interventions (Hamann et al., 2014). Researchers interviewed psychiatrists (n=121) and their inpatients (n=213) within the week before hospital discharge. They asked psychiatrists open-ended questions about the main reasons for their patient’s hospitalization, followed by how they intervened to improve treatment adherence. They also asked patients about the reasons for their hospital admission and about their communication with physicians. Physicians reported that one-to-one discussions with patients concerning the need for regular drug intake was the measure most often used to improve future adherence, while depot medications were rarely cited as interventions. Although patients and physicians reported approximately the same rates of depot medication prescriptions (32%), rates reported for the other measures differed. Physicians reported that 40% and 9% of patients and relatives, respectively, received psychoeducation, whereas patients reported only 36% and 5%, respectively. Additionally, physicians reported arranged follow-up visits for 18% of patients, whereas patients reported only 16%. Researchers suggested the main barriers to an intensive response to patient nonadherence: underestimation by physician of treatment nonadherence; lack of proper discharge planning; and limited resources. They also questioned “whether or not psychiatrists address the issue of adherence properly when talking to their patients in order to avoid patients’ refusal of adherence interventions” (Hamann, p. 886).

Researchers sought to identify the prevalence and management strategies of nine categories of
antipsychotic adverse effects: extrapyramidal symptoms; sedation; weight gain; type 2 diabetes; hyperprolactinaemia; metabolic syndrome, dyslipidaemia; sexual dysfunction; and cardiovascular effects in a recent systematic review (Young et al., 2015). Authors noted both while antipsychotic medications are the cornerstone treatment for schizophrenia, adverse effects of the medications also influence nonadherence with treatment. This review of 53 studies found that sexual dysfunction and weight gain are the most commonly occurring antipsychotic adverse effects with significant implications for medication adherence. Other findings included: scarcity of scientific studies of antipsychotic adverse effects; exacerbation of adverse effects with antipsychotic polypharmacy, a common clinical practice; occurrence of adverse effects of the newer antipsychotics as much of a problem as with older equivalents for patients long-term physical health; low rates of documented baseline monitoring; low compliance with management strategies for follow-up; and lack of adequate recognition and treatment of the physical health of patients with schizophrenia. Authors stressed the importance of prevention and management of adverse effects, and suggested that clinicians adhere to and improve monitoring guidelines, using validated antipsychotic side effect scales, e.g., Glasgow Antipsychotic Side-effect Scale (GASS).

Poor or nonadherence to oral antipsychotics surfaced as a critical issue soon after their introduction in the 1950s, leading to the development of the first long-acting injectable antipsychotic, (LAI) fluphenazine decanoate (Brissos et al., 2015). Its development was followed over the years by haloperidol decanoate, aripiprazole (Abilify Maintena), risperidone (Risperdal Consta), paliperidone (Invega Sustenna), paliperidone palmitate (Invega Trinza), and the latest, aripiprazole lauroxil (Aristade). Injectable antipsychotics may help to maintain adherence, while assuring stable blood levels, and reducing the risk of relapse. However, negative attitudes of both clinicians who think that patients will not accept LAI antipsychotics and patients who perceive them as coercive (with attached stigmas) may negatively affect their use (Brissos et al., 2015).

A recent randomized clinical trial compared the efficacy of the oral formulation of risperidone with the LAI formulation (Risperdal) in the early course of schizophrenia (Subotnik et al., 2015). In this 12-month trial, patients (n=86) with recent onset of schizophrenia were randomized to receive either the oral medication or the LAI formulation while half of each group were at the same time randomized to receive either cognitive remediation or healthy-behaviors training. Dosage of oral risperidone ranged from 1.0 to 7.5 mg/day and for the LAI formulation the range was from 12.5 to 37.5 mg every two weeks. Results showed a relapse rate of only 5% in the LAI group compared with 33% in the oral group, with hallucinations and delusions throughout follow-up better controlled with the long-acting risperidone group. Psychotic relapse, psychotic symptom control, or hospitalization did not differ significantly between the two psychosocial groups and there was a lack of significant interactions between medications and psychosocial treatments. Researchers found that discontinuation due to inadequate clinical response occurred more often in the oral group than the LAI group. They concluded that LAI formulations have significant advantages for clinical outcomes due to their more consistent administration, and suggested that LAs become a first-line treatment soon after the first episode of schizophrenia (Subotnik et al., 2015).

A recent multi-site, double-blind randomized clinical trial compared the effectiveness of two LAIs, i.e., paliperidone palmitate and haloperidol decanoate. Researchers found no statistically significant differences with respect to “prevention of efficacy failure” in the newer second-generation antipsychotic and the older LAI antipsychotic medication in patients (n=311) with schizophrenia or schizoaffective disorder, although the possibility of a clinically meaningful difference was not ruled out (McEvoy et al., 2014, p. 1984). Haloperidol decanoate 25-200 mg or paliperidone palmitate 39-234 mg was administered every month for as long as 24 months. Researchers noted “no statistically significant advantage for paliperidone palmitate when compared with haloperidol decanoate in
ratings of the severity of abnormal involuntary movements and parkinsonism, or in the incidence of
tardive dyskinesia“ (McEvoy et al., p. 1984). They found, however, that with haloperidol decanoate,
.akathisia increased more than with paliperidone palmitate and that the propensity to cause
extrapyramidal symptoms is lower in paliperidone palmitate than in haloperidol decanoate.
Although this study did not include a comparison with oral medications, researchers noted that
systematic reviews and expert panels support the use of long-acting injectable antipsychotic
medications to reduce medication nonadherence for outpatients at increased risk of relapse
(McEvoy et al., 2014).

In a randomized head-to-head study, researchers compared aripiprazole once-monthly (Abilify
Maintena®) 400 mg and paliperidone palmitate once-monthly to assess non-inferiority and
superiority on clinician-rated, health-related quality of life in adult patients (n=295) with
schizophrenia (Naber et al., 2015). Treatment occurred over a 28-week period. Results, supported
by Clinical Global Impression – Severity Scale (CGI-S) and Investigator’s Assessment Questionnaire
(IAQ) scores, showed superior results for patients receiving long-acting injectable aripiprazole over
paliperidone palmitate. Patients treated with the long-acting injectable aripiprazole had superior
improvement in functioning, including emotional interactions, empathy, sense of purpose, and
motivation than those treated with paliperidone palmitate. Additionally, there were lower
incidences of adverse events and a lower all-cause discontinuation rate suggesting greater overall
effectiveness for long-acting injectable aripiprazole (Naber et al., 2015).

**Schizophrenia in Children and Adolescents**

A recent article discussed the clinical connections between schizophrenia and autism spectrum
disorder (ASD), noting the marked similarities in clinical presentation (Hommer and Swedo, 2015).
They cited epidemiologic and retrospective clinical studies suggesting an association between ASD
diagnosis or childhood autistic traits and later psychotic experiences. Social cueing deficits as well
as impairments in emotion processing have occurred in both groups. Authors reported that meta-
analyses of schizophrenia suggested a correlation between negative symptoms and
disorganization, and an association of neurodevelopmental disorders with known genetic defects
associated with high rates of both ASD and schizophrenia. They suggested that examining
commonalities as well as differences between the two disorders provides insights into treatment
and prevention.

A recent study investigated the degree to which sensory dysfunction, well documented in
schizophrenia, leads to secondary impairment in reading ability (Revheim et al., 2014). Researchers
assessed reading ability including fluency of reading, comprehension and sensory function in
patients (n=45) with schizophrenia or schizoaffective disorder; patients (n=19) ages 12-30 with
high clinical risk for schizophrenia (based on Structured Interview for Prodromal Syndromes/Scale
of Prodromal Symptoms); and in healthy age-matched individuals (n=65). The Gray Oral Reading
Test and the Comprehensive Test of Phonological Processing assessed reading. Results found that
73% of schizophrenia patients met criteria for dyslexia although their reading ability was intact
prior to onset of schizophrenia. Across all test batteries, patients with schizophrenia or
schizoaffective disorder displayed highly significant impairments in reading compared with the
control group, and individuals at high clinical risk for schizophrenia showed deficits in visual
reading scores. Authors concluded, “The decline in reading ability from premorbid levels, which
appears to occur during early stages of the illness, correlates highly with the failure to meet
socioeconomic expectations, and may thus represent a remediable cause of persistent occupational
disability in schizophrenia“ (Revheim et al., 2014).
The Centers for Medicare & Medicaid Services (CMS) has prepared a chart of FDA-approved pediatric age ranges and indications for atypical antipsychotics, i.e., aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone in the treatment of children and adolescents with schizophrenia (CMS, 2013). It indicated a warning that risperidone should not be used by patients older than age 16 if diagnosed with irritability with autistic spectrum disorder.

**Schizophrenia in Later Life**

In a pilot feasibility study adapting a cognitive remediation (CR) protocol involving restorative and strategy-based methods, researchers targeted cognitive deficits associated with aging and schizophrenia in older community-dwelling individuals (Golas et al., 2015). In addition to accessing the feasibility of CR and its effects on cognitive performance, researchers assessed its effect on functional competence. Four cohorts of older outpatients (n=22) aged 60 or over with a current diagnosis of schizophrenia or schizoaffective disorder received CR in eight, 2-hour/week therapist-guided group sessions. CR included didactic teaching, computerized drill and practice, in-class strategic monitoring, and discussion of applying cognitive skills to daily life. No significant improvement on the cognitive or functional measures resulted although there was a positive correlation between time spent on homework and improvement in verbal memory. Researchers noted that verbal feedback from patients indicated they found the intervention helpful and even showed interest in participating in more sessions. They concluded that patients tolerated CR well, but it did not show improvement in global cognition or function in this study. They further suggested that it *holds promise* for its future implementation in clinical settings” although it may “also be necessary to combine CR with a psychosocial intervention to result in improvement” (Golas et al., 2015).

**Supported Employment**

A recent systematic literature review examined existing evidence from small studies (n=18) investigating relationships between employment and outcomes, e.g., symptom remission, neurocognitive functioning, social cognitive functioning, and quality of life, in patients with schizophrenia (Charzyńska et al., 2014). Studies showed increased levels of social functioning and improvement in symptoms and quality of life in participants with supported employment. However, authors noted the need for larger, high quality, long term follow-up, randomized studies further exploring the relationships between employment and non-vocational outcomes.

A more recent study evaluated cognitive enhancement interventions for improving cognitive and work functioning for individuals with schizophrenia and other mental illness (McGurk et al., 2015). In this randomized controlled trial, participants (n=107) with severe mental illness (46% with schizophrenia or schizoaffective disorder) who had failed to respond to supported employment and who expressed a desire to work were randomly assigned to enhanced supported employment only or enhanced supported employment plus the Thinking Skills for Work program. This additional intervention included cognitive exercise practice, strategy coaching, and teaching coping/compensatory strategies taught by a cognitive specialist. Results found that improvement in cognitive and vocational functioning improved significantly more in the Thinking Skills for Work group than in the group receiving only the supported employment intervention. Over a two-year period, 60% of participants in the Thinking Skills for Work group obtained competitive work compared with 36% of those in the enhanced supported employment only group. The Thinking Skills for Work participants worked an average of 6.0 weeks per six-month period compared with only 2.3 weeks in the supported employment group. Improvement on cognitive functioning was greater in the Thinking Skills for Work group than in the supported employment group.
Researchers concluded that the Thinking Skills for Work program helps individuals who have not responded to supported employment enjoy financial, social, and clinical benefits of competitive work.

**Social Skills Training (compared with other psychological interventions)**

A recent meta-analysis of psychological interventions for psychosis identified outcome trials (n=48) comparing psychological treatments for participants (n=3295) with psychosis (Turner et al., 2014). The goal of this study was a better understanding of which therapy is more effective for particular symptoms. Researchers grouped interventions into six common types for treatment comparison: befriending, cognitive-behavioral therapy, cognitive remediation, psychoeducation, social skills training, and supportive counseling. They grouped psychosis symptoms into separate meta-analyses. Results from the series of meta-analyses found small but significant differences in efficacy between pooled psychological interventions for the reduction of psychotic symptoms. Cognitive-behavioral therapy was more effective for all symptom outcome measures pooled when compared to other interventions pooled and “showed a small but robust superiority in reducing positive symptoms” (Turner, p. 532). Social skills training was more effective for negative symptoms compared with other interventions pooled. Compared with other interventions pooled, befriending was less effective for all symptoms outcome measures pooled. After sensitivity analyses for risk of bias, benefits of cognitive behavioral therapy, social skills training, and cognitive remediation for all symptom measures pooled were not significant. In sensitivity analyses, the effect of CBT on positive symptoms lost significance, but the same was not true for the effect of social skills on negative symptoms. Researchers concluded that although observed differences between interventions for psychosis were small, the nature and pattern of the differences have implications for improving psychosocial therapies for psychosis (Turner et al., 2014).

**Cognitive Remediation and Rehabilitation**

Studies have shown that most approaches to cognitive remediation for schizophrenia have positive impact on cognition, but have little impact on functional outcomes and improvement in community functioning. In this current literature review, authors focused on studies reporting psychosocial outcomes, e.g., quality of life, academic functioning, social functioning, and employment outcomes. They acknowledged their goal to identify strategies and methods associated with enhanced cognition as well as improved community functioning. Authors noted an emerging trend of examining personal goal attainment as a route to vocational, educational, social, or independent living, thus transferring cognitive gains to everyday life. They cited studies that employed cognitive remediation as an integrative skill intervention, teaching compensatory strategies and linking cognitive gains to functional skills rather than repeated drill and practice of targeted cognitive skills. Studies found that incorporating such strategies demonstrated a positive impact on psychosocial outcome. The studies suggest that cognitive remediation, combined with psychosocial interventions including sufficient opportunities to practice and utilize newly acquire skills, leads to the transfer of cognitive gains to everyday life. Generalization of cognitive to functional gains occurred in studies where participants with schizophrenia received cognitive remediation (including computer-based training, strategic monitoring, and verbal discussion groups) combined with Functional Adaptation Skills Training (FAST) (including skills training for social functioning, transportation, medication management, and community activities planning). Authors concluded that, based on recently published studies, cognitive remediation that goes beyond methods to improve cognitive function and that includes “systematic application of cognitive skills to real-world behaviors” can positively impact psychosocial outcomes and enhance functioning in patients with schizophrenia (Medalia and Saperstein, 2013).
Peer Support and Peer-Delivered Service

In a recent review of the literature in the fields of peer support and peer-led family psychoeducation to support individuals with schizophrenia and their families, authors looked at evidence from various programs. These programs are Wellness Recovery Action Plan (WRAP), an evidence-based practice by the National Registry of Evidence-Based Practices; Building Recovery of Individual Dreams & Goals through Education & Support (BRIDGES); and Family to Family (FTF), a family psychoeducation course. Authors emphasized that both peer support and peer-led psychoeducation are psychosocial interventions that focus on recovery, i.e., “living well with an illness process as opposed to from an illness process” (Duckworth and Halpern, 2014). Studies examining the impact of peer-led self-management education in the WRAP program found that those who received WRAP training were more likely to engage in self-advocacy behaviors. Randomized controlled trials have found that BRIDGES led to higher levels of self-perceived recovery and empowerment. Authors suggested that peer-run programs help reduce overcrowding in psychiatric emergency rooms while improving the experience of people with schizophrenia. They noted the emergence of peer-run crisis respite (PRCRs), a form of acute residential crisis service for persons with schizophrenia and other psychiatric disorders. The Whole Health Action Management (WHAM) program, developed by the Substance Abuse and Mental Health Services Administration/Health Resources Administration (SAMHSA-HRSA) utilizes and strengthens peer support in healthcare delivery (Duckworth and Halpern, 2014).

FTF, promulgated by the National Alliance on Mental Illness (NAMI), is well studied (Duckworth and Halpern, 2014). In a randomized controlled trial studying family members of individuals with schizophrenia (n=318), those assigned to active FTF group had greater improvements in problem-focused and emotion-focused coping than the control group. Studies have shown that family psychoeducation be delivered as early as possible with families for the best benefits. Authors suggested that peer support and peer-led family support, both of which have randomized control trial evidence, seem to have sustained benefits and no material risks (Duckworth and Halpern, 2014).

Suicide Prevention

Individuals with schizophrenia are four times more likely to die of suicide than the general United States population (McManus et al., 2015). The identification and effective treatment of individuals with schizophrenia may lessen the likelihood of suicide in this population. A recent study discovered microblogging tendencies distinguishing individuals with schizophrenia from the general population. Researchers’ analysis including a cohort of Twitter (social media) users who self-identified as having schizophrenia (n=96) and age-matched controls who did not self-identify as having any mental disorder (n=200) to discover patterns of Twitter usage. After discovering microblogging tendencies distinguishing the individuals with schizophrenia from those without schizophrenia, researchers mined Twitter data to identify individuals who met the tendencies of those who self-identified as having schizophrenia. They concluded that this technique with large-scale Twitter data accurately classified Twitter users with schizophrenia and suggested that clinicians may be able to “incorporate Twitter posts into a diagnostic tool for diagnosing schizophrenia on an individual level” that “will lead to an increase in the number of individuals with schizophrenia receiving treatment” (McManus, p. 125). The identification and treatment of persons with schizophrenia may also be associated with suicide prevention.
Treatment Resistant Illness

Strassnig and Harvey analyzed three large databases including schizophrenia patients (n=600) from various settings, e.g., state hospital-based and community based (Strassnig and Harvey, 2014). Very few of the patients were receiving first generation antipsychotics, depot antipsychotics, or clozapine. However, authors found frequent use of polypharmacy with prescription of two or even three atypical antipsychotics, and the addition of mood stabilizers. Only 8 of the 600 patients were receiving clozapine, which has been confirmed by the CATIE and CUTLASS trials to be more effective than other antipsychotics in the treatment of partial and nonresponders. Authors discussed the need for “therapeutic approaches beyond antipsychotics, e.g., cognitive remediation combined with functional skills training, pharmacological cognitive enhancement, treatment of residual depression, and physical exercise interventions” as well as more frequent use of clozapine along with less reliance on polypharmacy (Strassnig and Harvey, p. 16).

Neurostimulation

A recent meta-analysis of prospective studies on the therapeutic application of Repetitive Transcranial Magnetic Stimulation (rTMS) in schizophrenia assessed the effects of both low-frequency and high-frequency rTMS on the negative symptoms of schizophrenia (Shi et al., 2014). Authors reviewed past meta-analyses examining the efficacy of rTMS on negative symptoms in schizophrenia that found small effect size supporting its efficacy. In this meta-analysis including 16 studies and 348 participants, authors sought to clarify the effects of rTMS and review possible moderators of rTMS efficacy on negative symptoms in schizophrenia. Only five of the studies used the Scale for the Assessment of Negative Symptoms (SANS) to assess negative symptoms. Authors found that patients with the most prominent negative symptoms at baseline were more responsive to rTMS and that patients with a longer duration of illness were less responsive. Additionally, rTMS treatment for less than 15 sessions did not result in improvement of negative symptoms. In this meta-analysis, 15 of the studies applied rTMS at the prefrontal cortex associated with negative symptoms. Where the stimulation was applied at the left dorsolateral prefrontal cortex (DLPFC), the mean effect size was moderate and significant compared to other locations, demonstrating that dopamine release in brain regions related to negative symptoms was modulated. Authors also found that type of antipsychotics had no impact on the efficacy of rTMS on negative symptoms when rTMS was an add-on treatment. Authors concluded that although the studies had limitations including the relatively small number of studies, participants, and use of the SANS as outcome measure, there was evidence to “support that rTMS is an efficacious add-on treatment for negative symptoms in schizophrenia, especially for individuals with early stage schizophrenia” (Shi et al, p. 10). They suggested the need for further studies. At this time, schizophrenia is not an approved indication for rTMS.

A recent study investigated the neurobiological effect of transcranial direct-current stimulation (tDCS) in patients (n=23) with schizophrenia and treatment-resistant auditory verbal hallucinations (AVH) (Mondino et al., 2015). Patients, all of whom exhibited daily AVH while receiving antipsychotic medications, were randomly assigned to receive active tDCS or sham tDCS. Before the first tDCS session and following the final tDCS session, global symptoms of schizophrenia and AVH were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Auditory Hallucinations Rating Scale (AHRS). Researchers investigated the effect of tDCS on the resting-state functional connectivity (rs-FC) of the left temporo-parietal junction. Results showed that relative to sham tDCS, active tDCS significantly reduced both negative symptoms and AVH. Further, the findings suggested, “that the reduction of AVH induced by tDCS is associated with a modulation of the rs-FC within an AVH-related brain network, including brain areas involved in inner speech.
production and monitoring” (Mondino et al, p 1).

In a randomized single-blind eight-week study, authors examined the use of electroconvulsive therapy (ECT) as an augmentation to clozapine for treating patients with refractory schizophrenia (Petrides et al., 2015). Patients (n=39) with antipsychotic and clozapine-resistant schizophrenia were randomly assigned to treatment as usual (clozapine) or bilateral ECT plus clozapine during eight weeks. For the first four weeks, ECT was administered three times per week followed by twice weekly for the next four weeks. If patients assigned to treatment as usual did not respond after eight weeks of treatments, they then received another eight-week trial of ECT (cross-over trial) with the same schedule of treatments and ratings as the ECT plus clozapine group. The primary outcome measure was response as a 40% reduction in symptoms based on the psychotic symptom subscale of the Brief Psychiatric Rating Scale (BPRS). None of the patients in the treatment-as-usual group met the response criterion of 40% reduction in symptoms, whereas 50% of those in the ECT augmentation group were responders at 40% or greater. The ECT augmentation group had significantly greater reduction in ratings on both the BPRS and the Clinical Global Impressions (CGI) -severity scale compared with the clozapine only group. These differences persisted throughout the eight-week trial. In the crossover trial, 47.4% of patients were responders at 40% or greater. Of all 39 patients receiving ECT in the randomized and in the crossover arms, 48.7% showed reductions in ratings on the psychotic symptom subscale. Limitations of the study included the lack of a placebo arm, a relatively low number of patients, and the lack of a diverse set of patients (only inpatients were included). Based on this study, authors concluded that the augmentation of clozapine with ECT is a safe and effective treatment option for the treatment of refractory schizophrenia, while suggesting the need for further research (Petrides et al., 2015).

Magellan’s Adopted Clinical Practice Guidelines for the Treatment of Schizophrenia

Epidemiology

According to the National Institute of Mental Health (NIMH), the 12-month prevalence of schizophrenia is 1.1% of U.S. population (NIMH, 2015). Lifetime prevalence is approximately 0.3% - 0.7%, with variation by race/ethnicity and country (DSM-5, 2013). The general incidence of schizophrenia is lower in females, and negative symptoms and poorer outcomes show higher incidence for males than for females. The first psychotic episode usually occurs in the early-to-mid 20s for males and in the late 20s for females, with the majority of individuals manifesting a gradual development of clinical signs and symptoms (DSM-5). In the United States, approximately 100,000 adolescents and young adults experience a first psychotic episode each year.

Environmental as well as genetic and physiological factors link to the incidence of schizophrenia. Incidence is higher for children who grow up in an urban environment and although most individuals diagnosed with schizophrenia have no family history of psychosis, genetic factors are involved in the causes of schizophrenia. Higher risk also occurs with pregnancy and birth complications as well as other prenatal and perinatal adversities, e.g., stress, infection and malnutrition. Approximately 20% of individuals with schizophrenia attempt suicide at least once, and 5–6% die by suicide (DSM-5, 2013).

Results of recent studies are suggestive that “immune and inflammatory cascades in conjunction with infection may play a role in the pathology of schizophrenia” (Hayes et al., 2014, p. 963). Researchers investigated molecular changes in cerebrospinal fluid from patients (n=46) with schizophrenia, compared with a control group, to determine how the stressors affect the pathology
of the disease. An evaluation of levels of 90 different molecules, including some with primarily immune-system functions, found differences between the schizophrenia group and the control group on levels of 15 of the molecules. Based on this study, researchers suggested that nine molecules, i.e., α2M, fibrinogen, IL-6R, SCF, TGFα, TRFR2, IL-8, MCP-2/CCL8, and testosterone might help in predicting markers for early stage psychosis (Hayes et al., 2014, p. 963).

In a recent study, authors sought to uncover the hidden risk architecture of the schizophrenias to demonstrate that schizophrenia is a heterogeneous group of heritable disorders (Arnedo et al., 2015). They identified sets of interacting single-nucleotide polymorphisms (SNP sets) in a large genome-wide association study, Molecular Genetics of Schizophrenia (MGS), of cases with schizophrenia and controls. All subjects had consistent and detailed genotypic and phenotypic assessment. After examining the risk of schizophrenia for each SNP set, researchers tested replicability in two independent samples: the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) and the Portuguese Island studies from the Psychiatric Genomics Consortium (PGC). Their analysis showed that the heritability of schizophrenia is “encoded in a complex distribution of genotypic-phenotypic relationships” (Arnedo et al, p. 147). Further, they found that 42 interactive SNP sets had more than 70% risk of schizophrenia. Authors suggested their approach “is a pioneering effort to specify complex but manageable patterns of gene-gene interaction underlying the polygenic risk of schizophrenia” and that these results hold promise for the emergence of a new era in clinical psychiatry in which person-centered treatment of complex disorders can be guided by reliable assessments of well-validated clinical syndromes and their specific causes” (Arnedo et al., p 151).

The APA guideline reports that the lifetime morbidity risk for schizophrenia is 1.0 percent and that 80 percent of patients with schizophrenia have parents who do not have the disorder. However, it also indicates that the risk of having schizophrenia is greater in persons whose parents have the disorder. The lifetime risk is 13 percent for a child who has one parent with schizophrenia, 35 to 40 percent for a child with two affected parents, and the risk increases with the corresponding number of affected relatives. The guideline indicates that advanced paternal age is a risk factor associated with schizophrenia. This was corroborated with more recent findings from both the Collaborative Perinatal Project and meta-analysis conducted by the research team of Torrey et al. where increased paternal age was found to be a risk factor of schizophrenia primarily among offspring of fathers aged 55 and older (Torrey et al., 2009). A later study using a large sample (Swedish Multi-Generation and Hospital Discharge Registers) compared paternal and grandpaternal ages at offspring birth to the risk of schizophrenia in a grandchild (Frans et al., 2011). Among patients with schizophrenia (n=2,511) and non-affected patients (n=15,619), ages of grandparents at the birth of the parents were compared and analyzed finding that older maternal, but not paternal, grandfather age was associated with an increased risk of schizophrenia in a grandchild. Researchers acknowledged the difficulty in explaining the selective effect for maternal but not paternal grandpaternal age, suggesting this result may provide clues to biological mechanisms; e.g., inheritance of the maternal grandfather’s X chromosome by his daughter and to half of her sons and half of her daughters.

A systematic review of family studies of probands with schizophrenia and bipolar disorder (BD) was conducted to determine whether these disorders coaggregate in families (Van Snellenberg and Candia, 2009). Some 38 studies investigated rates of BD in first-degree relatives (FDRs) of probands with schizophrenia, while some 39 studies examined rates of schizophrenia in FDRs of BD probands. The FDRs of probands with schizophrenia showed significantly increased rates of BD relative to control FDRs. The FDRs of probands with BD showed a marginally increased rate of schizophrenia relative to control FDRs. Researchers argued that this meta-analysis provided direct
evidence for familial coaggregation of schizophrenia and BD. They also purported that these findings argue against the view that these disorders are entirely discrete diagnostic entities and support a continuum model. Similarly, Danish researchers have shown evidence supporting BRD1 single nucleotide polymorphism (SNP) locus involvement in susceptibility to both schizophrenia and bipolar disorder (Nyegaard et al., 1010).

A later large-scale nationwide family study, comparing persons (n=61,187) with attention-deficit hyperactivity disorder (ADHD) and their first- and second-degree relatives with a control group of people without ADHD and their corresponding relatives, investigated the risks of BD and schizophrenia in the relatives of each group (Larsson et al., 2013). First-degree relatives of probands with ADHD were found to have more risk of schizophrenia than relatives of the control group. Findings also showed that first-degree relatives of the ADHD proband group had increased risk of both BD and schizophrenia; among second-degree relatives, the risks of BD and schizophrenia were substantially lower than among full siblings. Researchers suggested that shared genetic factors may explain these results.

Another study investigated movement disorders typically seen in patients with schizophrenia in order to determine whether they may be an inherent part of the disease (Koning et al., 2010). Investigators identified studies that assessed dyskinesia and Parkinsonism in antipsychotic-naïve patients with schizophrenia (n=213) and controls (n=242) and non-ill FDRs (n=395) and controls (n=379). Study findings showed that antipsychotic-naïve schizophrenia was found to be strongly associated with dyskinesia and Parkinsonism compared with controls. Dyskinesia and Parkinsonism were also significantly more prevalent in healthy FDRs of patients with schizophrenia as compared with healthy controls. Investigators postulated from these findings that movement disorders and abnormalities in the nigrostriatal pathway may be related to the genetic risk of developing the disease just as they are associated with the disease itself. Researchers also acknowledged these results were consistent with reports of motor symptoms in schizophrenia described in the literature prior to the use of neuroleptic drugs along with more recent published observations on neuroleptic-naïve patients and their relatives (Koning et al., 2010).

Novel findings of a recent study showed that elevated plasma levels of the inflammatory biomarker C-reactive protein (CRP) were associated with increased risk of late- and very-late-onset of schizophrenia in the general population (Wium-Andersen et al., 2014). Researchers performed prospective and cross-sectional analyses of data from men and women (n=78,810) aged 20 to 100 from two population studies in Denmark with up to 20-years of follow-up. This study found that mean CRP levels for men and women with schizophrenia were 63 percent higher compared to those without schizophrenia, even when adjusting for age, gender or multifactorially. Another recent study, using linear regression analysis, measured levels of CRP in three groups of individuals (n=715): 295 with schizophrenia, 192 with bipolar disorder and 228 controls with no psychiatric conditions (Dickerson et al., 2013). Results showed significantly higher levels of CRP in individuals with schizophrenia than in controls, even when adjusted for factors, e.g., age, gender, race, smoking status, body mass index. Using the same analysis, individuals with bipolar disorder did not have significantly elevated CRP levels when compared with controls. Researchers acknowledged that the association between elevated CRP and schizophrenia may be linked to genetic and environmental factors, noting no linkage between CRP levels and treatment with antipsychotic medications. They recommended future studies to determine the relationship between genetic susceptibility, environmental exposure and the increased CRP levels in schizophrenia.
Impact of DSM-5 Changes on the Diagnosis of Schizophrenia

A recent study examined the effect of the following major changes in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria:

1. Requirement that at least two of the Criterion A symptoms must be present for a month, and that at least one of the Criterion A symptoms must be either delusions, hallucinations or disorganized speech;
2. Omission of schizophrenia “subtypes”; and

Authors examined data from 22 double-blind, randomized, placebo-controlled pre-DSM-5 trials of second generation antipsychotics for the treatment of acute psychotic episodes in patients with schizophrenia (n=5,233), finding that more than 99% of patients met DSM-5 diagnostic criteria for schizophrenia with no differences in effect size between schizophrenia subtypes. Authors also found that the symptoms responding best to treatment with second-generation antipsychotics were hallucinations, delusions, disorganized speech, and mania. They concluded that the classic “subtypes” are not predictive of treatment response and their omission is justified (Matilla et al., 2015).

First Episode/Early Psychosis

In a recent study, researchers examined psychotropic medication prescription patterns, including factors associated with choice of medication strategy, for people with first-episode schizophrenia spectrum disorders in 34 U.S. community mental health settings (Robinson et al., 2015). They examined data for a sample of patients (n=404) obtained from the Recovery after an Initial Schizophrenia Episode Project’s Early Treatment Program (RAISE-ETP), a nationwide effectiveness study for patients with first-episode schizophrenia spectrum disorders. Researchers sought to determine the medication treatments prescribed currently in community settings. The mean age of participants was 23.6 years; the majority was male; and participants were of diverse racial backgrounds (Robinson et al., 2015).

Researchers in the above study noted that practice guidelines support the following first-episode treatment: “1) the need for antipsychotic treatment, 2) the use of low antipsychotic dosing, and 3) the need to minimize side effects, especially metabolic ones” (Robinson et al., p. 244). Although antipsychotic prescriptions were mostly concordant with recommendations, 17% of antipsychotics prescribed were for olanzapine, although guidelines recommend against its use due to frequent adverse metabolic side effects. Further, treatment with olanzapine was often at higher-than-recommended dosages. Demographics showed that younger patients were more likely to receive prescriptions for risperidone; women were more likely to receive lower dosages of antipsychotics, and women were more likely to receive more prescriptions for long-acting injectable antipsychotics and antidepressants. Prescription practices were also affected by regional differences as well as insurance status. Private insurance was associated with a higher likelihood of receiving a prescription of an antipsychotic as well as a lower likelihood of receiving more than one antipsychotic or receiving a first-generation antipsychotic. African Americans were also more likely to receive prescriptions for first-generation antipsychotics. Researchers noted that about one-third of patients received prescriptions for antidepressants, although only about half of those patients had clear symptoms indicating the need for antidepressants. They suggested that cumulatively, 39.4% of patients could have benefitted from changes in their psychototropic prescriptions, e.g., not prescribing two or more antipsychotics and not prescribing olanzapine, especially at high dosages.
They concluded that training is warranted to improve clinicians’ ability to diagnose schizophrenia disorders as distinct from mood or anxiety disorders to avoid antidepressant medication prescription where there are no symptom indications supporting the medication (Robinson et al., p. 244).

A recent study described data from a large double-masked randomized trial comparing aripiprazole and risperidone for the acute treatment of first-episode schizophrenia and related conditions (Robinson et al., 2015). Patients aged 15-40 with schizophrenia, schizoaffective disorder, schizoaffective disorder, or psychotic disorder not otherwise specified (n=198) who had received treatment with antipsychotics for two weeks or less were randomly assigned to double-masked treatment with aripiprazole (5-30 mg/day) or risperidone (1-6 mg/day) over a period of 12 weeks. Analysis comparing the cumulative 12-week response rates between treatments included symptom analyses, metabolic effects, and motor effects. Results showed that time to response and positive symptom response rates were equivalent, whereas patients receiving aripiprazole had somewhat better negative symptom outcomes, e.g., improvement of avolition-apathy, compared with patients receiving risperidone. However, those treated with aripiprazole experienced more akathisia. On outcomes for fasting glucose, and total and LDL cholesterol and prolactin, aripiprazole was associated with better outcomes than risperidone. Researchers concluded that, based on data from this large trial, aripiprazole is preferred over risperidone for the treatment of first-episode schizophrenia in most situations, due to its preferred metabolic outcomes and symptom advantages. They also advised that risperidone is preferable if the potential for akathisia is a concern (Robinson et al., 2015).

The NAVIGATE program for first-episode psychosis was developed by the RAISE Early Treatment Project with its focus on psychosocial interventions to guide individuals with a first episode of psychosis toward psychological and functional health (Mueser et al., 2015). Core services include family education program (FEP), individual resiliency training (IRT) and supported employment and education (SEE). In NAVIGATE, engagement of family members is important in providing social support and as “allies in treatment” (Mueser, p. 685). The four stages of FEP help develop a working relationship between family and clinician; provide families with information about psychosis and how to reduce stress, prevent relapses and work with the NAVIGATE team; and help families address specific problems while preparing for the patient’s transition to less intensive services. IRT, provided by a clinician in sessions focusing on helping patients achieve personal goals, teaches patients how to manage their illnesses to improve functioning. Modules use an individualized, structured format with a cognitive-behavioral therapy approach, combined with psychoeducation and motivational enhancement. IRT’s emphasis is on encouraging the patient to create a story, which helps in processing aspects of the psychotic episode, while using cognitive restructuring to challenge self-stigmatizing beliefs. Patients learn how to refocus their attention and memory on positive aspects of life, and record positive things that have happened. SEE helps patients who are recovering from a first episode return to work or school. The stages of SEE services include development of career and educational profile; job search or educational enrollment; and follow-along supports to help the patient succeed at job or school. In the NAVIGATE model, recovery is facilitated by small teams of providers who help patients build skills for individual resiliency and also provide tailored pharmacological treatment (Mueser et al., 2015).

Included in the APA guideline section titled “Clinical Features Influencing the Treatment Plan,” is an important discussion on the psychiatric features of schizophrenia and specifically, the first episode of the illness. This section stresses the importance of treating the condition immediately after psychosis is evident in order to ensure patient safety and to prevent the negative affect of delay on prognosis. A meta-analysis by Perkins et al. supported this premise and reported an association
between duration of untreated psychosis and clinical outcome (Perkins et al., 2005). Results of this review offer hope that early intervention programs are effective in reducing the length of the initial psychotic episode, and may enhance the likelihood of recovery and reduction in cumulative morbidity. Thus, duration of untreated psychosis may be a potentially modifiable prognostic factor. There have been a number of other studies since the publication of the APA guideline on various treatment factors influencing the outcome of first episodes or early schizophrenia, such as choice of medications and the efficacy of psychosocial treatments.

One study measuring treatment response in first-episode schizophrenia to either risperidone or haloperidol revealed that the time to antipsychotic response varied widely (Rabinowitz and Medori, 2006). These findings suggested that in first-episode schizophrenia, longer treatment trials may be necessary and that treatment trial periods of one month or even six weeks may not be adequate.

Studies comparing olanzapine, quetiapine and risperidone in early psychosis patients showed that all of these agents produced modest but significant improvements in neurocognition and its demonstrated clinical relevance to occupational and social functioning (Keefe et al., 2007). Similarly, the all-cause discontinuation rates were comparable for all three of these drugs when used to treat patients early in the course of psychotic illness (McEvoy et al., 2007). Risperidone demonstrated superiority over haloperidol for first-episode patients with schizophrenia in one recent study and was associated with wide ranging improvements in cognitive functioning that were not influenced by changes in symptoms, as was evident in the haloperidol-treated patients (Harvey et al., 2005).

A more recent large, randomized, open-label clinical trial conducted in Europe and Israel (European First Episode Schizophrenia Trial [EUFEST]) compared symptom reductions and drug discontinuation rates of patients with schizophreniform disorder or first-episode schizophrenia who were treated with either a first-generation antipsychotic (FGA), or a second-generation antipsychotic (SGA) drug (Kahn et al., 2008). The study could not conclude that SGA drugs, i.e., amisulpride, olanzapine, quetiapine, ziprasidone, were more efficacious than the FGA, haloperidol. However, the discontinuation rates for all SGAs were less than for haloperidol. Additionally, the EUFEST findings showed that while antipsychotic medication is associated with moderate improvement in cognitive test performance, the magnitude of improvement does not differ between treatment with haloperidol and treatment with the SGA antipsychotics (Davidson et al., 2009). The most recent updated National Institute for Health and Clinical Excellence (NICE) guideline from the British National Health Service recommends considering the relative adverse event profiles when selecting either an FGA or SGA (National Institute for Health and Clinical Excellence, 2009).

Another pertinent study revealed that no differential drug effects were observed among two groups of patients with first-episode schizophrenia treated with drugs (olanzapine or risperidone) and healthy control subjects on measured cognitive improvements. In this study, researchers attributed improvements in cognition to practice effects (such as exposure, familiarity and/or procedural learning) and suggested medication dose, demographic variable or intellectual level did not account for the results (Goldberg et al., 2007).

While the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study found efficacy advantages for olanzapine in multi-episode patients, this was not found in a study that showed clinical outcomes with risperidone were as good as or better than olanzapine for patients with first-episode schizophrenia. While olanzapine treatment has an advantage for motor side effects, the weight gain differences favoring risperidone may be more important in the long term with most
patients and particularly those in their first episode (Robinson et al., 2006).

More recently, a meta-analysis of 15 randomized controlled trials that recruited a total of 2,522 patients compared the treatment effects of both SGAs and FGAs in the management of first-episode schizophrenia (Crossley and Constante, 2010). In this British study, risperidone was used in nine studies, olanzapine was used in seven trials and two studies each used quetiapine and clozapine. Amisulpride and ziprasidone were used in one study. Twelve of the fifteen studies used haloperidol as the FGA and the other three studies used chlorpromazine, oral zuclopenthixol and sulpiride. The investigators reported that although there were no significant differences between SGAs and FGAs in discontinuation rates or symptom control, there were differences in their side-effect profile. Specifically, participants prescribed an SGA would, on average, gain 2 kg more than those on a FGA; whereas those prescribed a FGA would rate 0.4 standard deviations higher in the extrapyramidal scales (Crossley and Constante, 2010).

A later prospective, randomized, flexible-dose, open-label study compared the effectiveness of three SGAs, i.e., aripiprazole, ziprasidone, and quetiapine, in the short-term treatment of first episode psychosis in patients (n=200) randomly assigned to one of the three antipsychotics and followed up for six weeks (Crespo-Facorro et al., 2013). Researchers found that patients on quetiapine showed a higher rate of treatment discontinuation than those on aripiprazole and ziprasidone, and quetiapine was less efficacious in reducing positive symptoms than aripiprazole and ziprasidone. Clozapine is an established treatment for schizophrenia only after incomplete response to two adequate antipsychotic trials or as a treatment of “last resort” due to its risk of agranulocytosis (Kane et al., 1988). The APA guideline indicates that it be considered to treat the acute phase of schizophrenia accompanied by persistent suicidal ideation or behavior, persistent hostility/aggressive behavior, and tardive dyskinesia. The guideline recommends SGA agents, excluding clozapine, as first line of treatment options for first-episode schizophrenia while acknowledging that FGA agents may be the first choice for some patients. In a later study, Remington et al. reviewed published studies comparing clozapine and FGAs as first line treatment (Remington et al., 2013). In one randomized controlled trial, patients (n=160) with first episode schizophrenia were randomized to treatment with clozapine or chlorpromazine. Results reported at one year showed patients treated with clozapine demonstrated greater symptom improvement and earlier remission than those treated with chlorpromazine. However, at 12 months, the difference was not evident, suggesting that choice of antipsychotic used as first-line treatment does not determine longer-term outcome. Other studies reviewed by authors found that response rates are almost 90 percent in first-episode schizophrenia, minimizing the distinction between different agents used in treatment. Authors noted that study results do not establish clozapine as a first-line treatment due to the practical demands of routine hematological monitoring required, but suggested the need for further research examining the clinical and functional outcomes with clozapine as a second-line treatment of first-episode schizophrenia. Findings supporting this suggestion include: 1) high response rate to first antipsychotic decreases markedly among patients requiring a second trial and continues to drop off with subsequent trials, except with clozapine, 2) higher response rate is reinstated with clozapine, even as a third-line treatment. 3) likelihood of remission diminishes with longer duration of untreated psychosis and 4) earlier and longer remission intervals result from treatment with clozapine. Authors acknowledged that there may be no added benefits to the use of clozapine as a second-line treatment, but they suggested the need for its consideration. Clozapine as a second-line treatment is not mainstream; its usage may depend on factors such as the patient’s level of illness and ability to comply with lab evaluations.

Psychopharmacology alone is not sufficient to prevent relapses or assure functional recovery from acute psychosis. Thus, there is a growing interest in psychosocial interventions as a means of
facilitating recovery from an initial episode of psychosis and reducing long-term disability associated with schizophrenia. A recent review of the published research on psychosocial treatment for first-episode psychosis supports the premise that adjunctive psychosocial interventions early in psychosis may be beneficial across a variety of domains, and can assist with symptomatic and functional recovery (Penn et al., 2005). Comprehensive approaches, i.e., multi-element and treatment-focused, show promise in reducing the rate of treatment discontinuation, symptoms, and hospital readmissions and in showing some improvements in insight and overall quality of life (Guo et al., 2010). Individual cognitive behavior therapy has shown modest efficacy in reducing symptoms, assisting individuals in adjusting to their illness, and improving subjective quality but has shown minimal efficacy in reducing relapse. However, no firm conclusions result from the literature on groups and families for this population (Penn et al., 2005). Another area of renewed clinical interest is the measurement of Intelligence Quotient (IQ) as a signal of early neurodevelopmental abnormality in patients with schizophrenia. The research team of Woodberry et al. published a quantitative review of the literature on premorbid IQ in individuals with schizophrenia (Woodberry et al., 2008). Their new meta-analysis revealed a reliable, medium-sized impairment in premorbid IQ such that years before onset of the psychotic symptoms, individuals with schizophrenia, as a group, demonstrated mean IQ scores approximately one-half of a standard deviation below that of healthy comparison subjects. Researchers also suggested that there was additional significant decline in the IQ of individuals with schizophrenia that was associated with the onset of frank psychosis.

A recent study tested the efficacy of integrated psychological intervention (IPI) compared with supporting counseling in delaying the progression to first-episode psychosis over a 24-month time period in persons (n=128) with early initial prodromal states (EIPS), experiencing thought and perception deficits (Bechdolf et al., 2012). Participants (n=63) were randomized to treatment with IPI, i.e., individual cognitive behavioral therapy (CBT), cognitive remediation, psychoeducation of family members and group skills training, while other participants (n=65) were randomized to supportive counseling; i.e., basic assessment, psychoeducation about the risk of psychosis and warm counseling on a one-to-one basis. Researchers found that during the 12-month treatment period, the incidence of and time to conversion to subthreshold psychotic symptoms, psychosis and schizophrenia/schizotypal disorder was lower in patients treated with IPI than with those who received supportive counseling, with the difference maintained during the 24-month follow-up. Although researchers acknowledged that the results may have been affected by the omission of a “no treatment” condition, they concluded that IPI has the potential to improve the prognosis of patients in EIPS, reducing the consequences of schizophrenia for patients, families and society.

Violent Behavior

Victoroff et al. undertook a recent systematic review of literature to determine the efficacy of neuropharmacological agents for the management of violence among persons with schizophrenia spectrum disorders (SSD) (Victoroff et al., 2014). Authors discussed conclusions from other studies finding that SSDs are a risk factor for violence, resulting in problematic consequences, e.g., threatened lives and well-being of both patients and others; non-compliance with treatment; disruption of families; increased need for institutionalization; and contribution to the stigma biasing laypersons against all mental illness. They noted that although SSDs are associated with only about 5% of total societal violence, SSD accounts for between 6% - 28% of homicides. From their study including a review of 86 peer-reviewed articles reporting clinical effects of pharmacological agents on aggression or hostility, authors concluded that evidence supports the following:

- In the management of hostility among inpatients with SSDs (not preselected for aggression),
paliperidone ER is probably effective (strongest evidence of efficacy);
- For the management of overt aggression among inpatients with SSDs (not preselected for aggression), clozapine is possibly more effective than haloperidol;
- For the management of hostility among inpatients with SSDs (not preselected for aggression), clozapine is possibly more effective than chlorpromazine;
- For reducing aggression among physically assaultive inpatients with SSDs, clozapine is possibly more effective than olanzapine or haloperidol; and
- For reducing aspects of hostility or aggressions among inpatients with DDS, adjunctive propranolol, valproic acid, and famotidine are possibly effective.

Authors cautioned that the majority of research on the efficacy of interventions fails to differentiate results between patients with and without comorbid substance abuse. They suggest the need for a “state-of-the art study of neuropharmacological management of aggressive and violent behavior among persons with SSDs” which includes accounting for dual diagnosis (Victoroff et al., 2014).

Also included in the APA guideline section titled “Clinical Features Influencing the Treatment Plan” is an important discussion on the psychiatric features of schizophrenia and, specifically, aggressive behavior. The guideline indicates that a while a small portion of patients with schizophrenia are violent, evidences suggest that schizophrenia is associated with an increase in the risk of aggressive behavior. More recent epidemiological meta-analyses have examined this relationship in depth and have corroborated the risk of violence was increased in people with schizophrenia and other psychoses (Fazel et al., 2009; Large et al., 2009). In addition, findings revealed the number of homicides per capita committed by those diagnosed with schizophrenia was strongly associated with the rates of all homicides. Investigators thereby suggested a relationship with social factors associated with the level of violence in the community rather than epidemiology of mental illness.

Two other large meta-analyses focused on violence and rates of homicide specifically during the first episode of psychosis. These studies provided further evidence that the rate of violence and homicide was higher than previously recognized in first episode psychosis and occurred most often before the initiation of psychiatric treatment (Nielssen et al, 2010; Large and Nielssen, 2011).

The discussion in the guideline provides information on socio-demographic risk factors for violent behavior in the schizophrenic population – male gender; being poor, unskilled, uneducated or unmarried; and having a history of prior arrests or a prior history of violence. The APA guideline notes that the risk for aggressive behavior increases with co-morbid alcohol abuse, substance abuse, antisocial personality or neurological impairment. The APA guideline also stresses that violent patients with schizophrenia have more positive symptoms and bizarre behaviors, and may act on their delusions, especially if the delusions are distressing and the patient can find evidence to support them. Also noted, patients who experience command hallucinations to harm others are more likely to be violent.

The baseline assessments for all patients included in the CATIE study included clinical assessments and interviews about violent behaviors. A recent analysis published from this particular data set from the CATIE study confirmed that positive psychotic symptoms, such as persecutory delusions, increased the risk of minor and serious violence, while negative psychotic symptoms, such as social withdrawal, lowered the risk of serious violence (Swanson et al., 2006). Minor violence was associated with co-occurring substance abuse and interpersonal and social factors. Serious violence was associated with psychotic and depressive symptoms, childhood conduct problems and victimization. The CATIE study baseline findings on violence, taken as a whole, provide some new evidence – specifically, patients living alone were significantly less likely to engage in any violence
than their counterparts who were living with family, controlling for other risk factors. This analysis showed that high negative psychotic symptoms were significantly associated with reduced risk of serious violence, and that they moderated the effect of the positive symptoms. Thus, positive symptoms significantly increased violence, but only when negative symptoms were low. Researchers noted that these findings may have intuitive clinical plausibility because a certain level of initiative, organization, psychomotor activation and social contact may be necessary to carry out violent acts – conditions that tend to be absent in persons with high negative symptoms of schizophrenia. Also, non-clinical variables such as family co-residence may affect violence risk in complex ways by either preventing or provoking violent behaviors, depending on whether the family environment serves as a protective matrix or an opportunity for aggressive interactions. Other factors, such as social interaction and lack of vocation or leisure activity, need review in any violence risk assessment where the focus needs to be on the whole person in the community environment.

A recent systematic review and meta-analysis of 110 studies investigated the direction and association of risk and protective factors for violent outcomes in individuals (n=45,553) with schizophrenia or other psychosis (Witt et al, 2013). The meta-epidemiological approach of this study grouped potential risk factors into ten domains: negative symptoms, neuropsychological, demographic, premorbid, suicidality, treatment related, substance misuse, positive symptoms, psychopathology and criminal history. Authors found that in the four domains most significantly associated with risk of violence, criminal history, e.g., previous violent behavior and prior arrests, was more strongly related to violence than substance misuse, suicidality and demographic factors. There was a significant association between the risk of victimization and the risk of violence perpetration in individuals with schizophrenia. Authors indicated that a “prior victimization may lead to a cycle of violence.” Suicidal ideation was not significantly associated with violence risk whereas previous suicide attempts were moderately associated. Although violence was not significantly associated with the neuropsychological domain, authors suggested violence risk may be related to lack of insight, attitudinal cognitions and theory of mind deficits. Another relevant finding was that non-adherence with medication increases violence risk. Studies conducted in predominately inpatient settings showed stronger associations between violence and both positive symptoms and psychopathology domains than in predominately community settings. Authors suggested that the potential risk factors for violence in patients with schizophrenia or other psychosis be examined in larger observational studies and large clinical trials.

**Cultural Factors**

A recent study, part of the Connecticut Department of Mental Health and Addiction Service, Health Disparities Initiative, investigated disparities in access, diagnosis, and mental health treatment outcomes in a state inpatient mental health service, while controlling for demographic variables and symptom severity (Delphin-Rittmon et al., 2015). Authors hypothesized that African and Hispanic Americans would be less likely to self-refer for inpatient services due in part to stigmatizing views about seeking mental health services. They also hypothesized that African Americans receive more diagnoses of schizophrenia and less with affective disorders than white Americans, even with demographic variables controlled. A third hypothesis was that African Americans as well as Hispanic Americans display lower treatment completion rates and poorer symptom severity ratings at discharge.

Results of the above study showed that Hispanic Americans were significantly more likely to enter inpatient services through crisis/emergency sources than African Americans and white Americans. Authors suggested their delay in seeking help was due to cultural and systemic barriers related to language, culture, and immigration. Hispanic Americans were more likely to receive diagnoses of
“other psychotic disorders” than white Americans and they “displayed treatment completion and symptom severity rates at discharge comparable to White Americans” (Delphin-Rittmon et al., p. 164). African Americans were more likely to be diagnosed with schizophrenia, drug-related, than other groups. They were more likely than other groups to come to inpatient units from self-referral and family or outpatient services, and were more likely to terminate treatment against medical advice. Although they received ratings of greater symptom severity at discharge, they displayed shorter length of stay. Authors suggested the need for cultural competence education and training for all staff, focusing on translation of cultural competence principles, with modules addressing racial and ethnic behavioral health disparities and how to eliminate them (Delphin-Rittmon et al., 2015).

The APA guideline includes a section titled “Clinical Features Influencing the Treatment Plan.” Within this section is an important discussion on cultural factors. Many studies have observed differences in diagnostic patterns and treatment patterns associated with cultural or racial factors. The critical component when one analyzes these different findings is to determine which ones may reflect:

- Actual racial differences in biology, e.g., metabolism of medications
- Direct influence of culture on psychology, e.g., cultural belief system influencing a response to alternative treatments, different interpretation of symptoms
- Lack of awareness on the part of the clinician (mostly Caucasian) of the effects that ethnicity and race are having on their diagnostic and treatment decisions, e.g., clinician making different diagnoses influenced by ethnic differences rather than different clinical presentations.

The APA guideline discusses that the repeated observations of the patient's race potentially elicits a bias in the diagnostic process. It notes that African Americans, particularly men, are more likely to be diagnosed with schizophrenia than with a mood disorder when compared to Caucasians. Similarly, African American men diagnosed with schizophrenia are less likely to be diagnosed with a co-morbid anxiety or mood disorder than their Caucasian counterparts.

Another observation noted in the APA guideline relates to treatment studies reporting that African Americans and other minorities are more likely to receive higher than recommended dosages of psychotropics when compared with Caucasians. Whether this is due to biological differences or cultural biases is the important question to resolve. Related studies have observed that two factors confer a higher risk of receiving a schizophrenia diagnosis: 1) if one is a migrant with darker skin than the background population of the country moved to, and 2) if the migrant is from an underdeveloped country (Cantor-Graae and Selten, 2005). As we learn more about these different patterns and their causes, it is important for clinicians to be culturally sensitive and aware of this potential issue, as the APA guideline cautions.

Other studies have looked for such cultural/racial differences in diagnosis and treatment, and have found less positive or even negative findings. For example, a review of the use of second-generation versus first-generation antipsychotics in the Veterans Administration showed only minor differences in the prescribing rates for whites, African American and Hispanic patients (Copeland et al., 2003). Another related study in a Texas Medicaid population showed some tendency of lower prescribing of second-generation antipsychotics in several populations, one of which was African Americans (Opolka et al., 2004). However, the authors noted multiple other factors that could have contributed to these results, as well as several limitations of the study. Another study in a San Diego County mental health population showed that the prevalence of co-morbid substance use disorders in schizophrenic patients was much more highly determined by
homelessness or living alone than by racial category (Montross et al., 2005).

After publication of both the APA guideline and the guideline watch, a study investigated outpatient visits to psychiatrists and primary care physicians by patients with schizophrenia to determine whether antipsychotic medication management and subsequent hospitalization differed by patients’ age, gender, race-ethnicity, insurance, rurality and region (Rost et al., 2011). Data from 3,359 office visits by individuals with schizophrenia included information from office visit forms collected in the 1999-2007 National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). Researchers tested the relationship of sociodemographic variables to antipsychotic medication management during the office visit and to subsequent hospitalization finding that non-Hispanic black patients were significantly more likely to receive antipsychotic medication management than non-Hispanic white patients and they had significantly greater odds of subsequent hospitalization. In addition, visits by patients who lacked insurance were significantly less likely to result in hospitalization than those with private insurance. Researchers concluded that these results were consistent over the nine-year period and were unexplained by clinical severity or specialty care treatment. They suggested further studies to understand the causes and consequences of the disparities.

A later study investigated racial disparities among African American inpatients (n=215) and white inpatients (n=537) diagnosed as having schizophrenia or schizoaffective, major depressive or bipolar disorder enrolled in the multisite MacArthur Violence Risk Assessment Study (Eack et al., 2012). Data for the study included assessments by research interviewers of their interactions with participants as well as diagnostic data from participants’ charts. After conducting each interview, interviewers completed a questionnaire including ratings of the perceived honesty of the participant during the interview. Analysis of the data investigated disparities in rates of diagnosis of schizophrenia among African Americans and whites, with a threefold increase in the rates of schizophrenia spectrum disorders among African Americans compared with whites. Researchers examined systematic differences in the demographic and clinical characteristics and in interviewers’ perceptions of honesty of participants of different races. Results showed significant racial differences in both sociodemographic and clinical characteristics, e.g., African Americans had lower socioeconomic status, greater rates of hallucinations, delusions and substance use problems and greater levels of thought disturbance. Additionally, African Americans were consistently perceived (by interviewers) to be less honest than whites during diagnostic interview. Logistic regression models, examining the degree to which disparities in sociodemographic and clinical characteristics affected the increased rates of schizophrenia among African Americans compared with whites, found that clinical and demographic characteristics alone could not account for the increased diagnosis of schizophrenia among African Americans. Results showed that individuals were nearly one-and-a-half times as likely to be diagnosed with schizophrenia if they were perceived to be dishonest by the interviewer during the diagnostic assessments. Researchers concluded that these findings indicate the importance of developing a trusting, open and collaborative relationship in the assessment of African Americans.

In conclusion, in the face of these mixed findings, the APA guideline cautions clinicians to be aware of the issues of race, culture and social class, and not allow such factors to inappropriately affect diagnostic and treatment decisions.

**First-Generation Versus Second-Generation Agents**

A recent meta-analysis of randomized controlled trials (n=212 studies) compared 15 antipsychotic drugs and placebo in the acute treatment of patients with schizophrenia (n=43049) (Leucht et al., 2014). Researchers compared the two prototypical first-generation (haloperidol and
chlorpromazine) and 13 second-generation anti-psychotic drugs. This multiple-treatments meta-
alysis, using both direct and indirect comparisons, provided evidence-based hierarchies of
comparative efficacy, risk of all-cause discontinuation, and major side effects. Researchers excluded
trials in patients with predominant negative symptoms, concomitant medical illness, or treatment
resistance, and those conducted in stable patients in order to have a reasonably homogeneous
sample. The mean age of patients was 38.4 years and the mean duration of illness was 12.4 years.
The mean overall change in symptoms was the primary outcome, assessed by change in Positive
and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Secondary
outcomes included all-cause discontinuation, weight gain, and antiparkinson drug use as measures
of extrapyramidal side effects, prolactin increase, QTc prolongation, and sedation. Statistical
analysis used data from acute treatment during a six-week period (Leucht et al., 2014).

Results from the above study showed that differences between drugs were small and gradual, and
all drugs were superior to placebo (Leucht et al., 2014). The efficacy hierarchy generated by the
analysis showed that clozapine was significantly more effective than all the other drugs compared
with placebo, but in direct pairwise comparisons was no more effective than any other second-
generation antipsychotic. The most effective drugs when compared with placebo were second-
generation antipsychotics, i.e., clozapine, amisulpride, clonazapine, and risperidone. Researchers
noted that differences in efficacy between drugs were smaller overall than the differences in side
effects. They found that the most effective drugs also had the lowest discontinuation rates with the
exception that haloperidol, the worst drug with respect to lowest discontinuation, had a middle
rank for efficacy when compared with placebo. Clozapine, olanzapine, quetiapine and aripiprazole,
iloperidone, amisulpride, and asenapine did not cause significantly more extrapyramidal side
effects than placebo, while haloperidol and chlorpromazine caused the most extrapyramidal side
effects. Some of the least well tolerated drugs, chlorpromazine, lurasidone, risperidone, and
paliperidone, produced significantly more extrapyramidal side effects than did several others in the
analysis. Researchers noted that the dichotomy between first- and second-generation
antipsychotics based on extrapyramidal side effects is an oversimplification. They recognized that
weight gain and associated metabolic problems are major issues linked to new antipsychotic drugs,
and in this study olanzapine, zotepine, and clozapine were the worst. However, ziprasidone and
lurasidone (as well as haloperidol) were without significantly more weight gain than placebo, and
chlorpromazine was among the worst. Researchers noted that the dichotomy between first-
generation and second-generation antipsychotics based on weight gain is another
oversimplification (Leucht et al., 2014).

In the study discussed above, Leucht et al. discussed how the assessed antipsychotic drugs differed
with respect to QTc prolongation, which can lead to life-threatening torsades de pointes.
Researchers found that amisulpride, regarded as benign in some guidelines, was associated with
QTc prolongation, consistent with reported amisulpride overdoses. Findings showed large
differences between drugs with respect to prolactin increase. Compared with placebo, paliperidone
and risperidone increased prolactin by more than one standard deviation. Researchers concluded
that because antipsychotic drugs differ in many properties, clinicians should adapt choice of
antipsychotic drugs to the needs of individual patients (Leucht et al., 2014).

A recent systematic review and meta-analysis compared relapse/hospitalization risks of stabilized
patients with schizophrenia under active versus placebo or intermittent treatment conditions (De
Hert et al., 2015). This review included two groups of randomized controlled studies (n=46 studies)
investigating relapse/hospitalization rates and/or time to relapse in stabilized patients with
schizophrenia:

1) Studies comparing treatment with placebo (i.e., replacement of oral or long-acting
first- or second-generation antipsychotics with placebo) vs. continuous treatment with antipsychotics; and
2) Studies comparing intermittent dosing, a stepwise discontinuation and use of antipsychotic drugs only when needed, e.g., reemergence of prodromal symptoms or psychotic symptoms, versus continuous treatment.

In background information, researchers noted that the 2003 World Health Organization’s statement reported, "Increasing the effectiveness of adherence interventions may have a greater effect on the health of the population than any improvement in specific medical treatments" (World Health Organization, 2003). Researchers noted that side effects associated with continuous treatment with antipsychotics often lead to medication discontinuation in patients. Further, antipsychotics only control symptoms, but do not reverse the underlying etiology. Clinicians have questioned whether continuous antipsychotics are necessary for every patient after a first-episode psychosis (De Hert et al, 2015).

Results of the above review and meta-analysis found that the odds of relapse for patients treated with placebo for at least six months were five times higher than for those in the continuous treatment condition (De Hert et al., 2015). These results were based on 36 studies with stabilized patients (n=4657) with a psychotic disorder. Other results based on 10 studies with stabilized patients (n=1230) showed that patients with the intermittent dosing condition were three times more likely to relapse compared with patients in the continuous treatment condition. Patients treated with intermittent techniques versus continuous treatment showed higher relapse rates regardless of whether they were first-episode or multi-episode psychotic patients. Further, compared with placebo or intermittent treatment, continuous treatment resulted in not only a lower risk of relapse, but also delayed time to (impending) relapse. Researchers concluded that the evidence from this systematic review along with existing guidelines and algorithms for antipsychotic treatment of the maintenance phase of schizophrenia supports continuous treatment. They suggested that continuous antipsychotic treatment remains the cornerstone of treatment of patients with schizophrenia, and that patients may benefit from the addition of psychotherapy (i.e., cognitive-behavioral therapy) added to pharmacotherapy (De Hert et al., 2015).

In a FDA drug safety communication on September 15, 2015, FDA modified requirements for monitoring, prescribing, and dispensing clozapine to address safety concerns and current knowledge about severe neutropenia associated with clozapine. The Clozapine REMS Program, a new, shared risk evaluation and mitigation strategy (REMS) for all clozapine medicines, was approved (FDA, 2015).

On December 11, 2014, the FDA added a warning to the label for ziprasidone (Geodon®) (FDA, 2014). The label warns that ziprasidone is associated with a rare but serious skin reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can affect several parts of the body.

Upon publication in 2004, our adopted practice guideline suggested an advantage to starting treatment with a second-generation over a first-generation antipsychotic agent in the acute phase of the illness. The main demonstrated advantage of SGAs is their relative lack of extrapyramidal side effects at usual therapeutic dosages and perhaps some better efficacy at improving cognitive symptoms. The SGAs probably owe their differences to the different pharmacodynamic profile, with a lower affinity for dopamine D2 receptors (main effect of the FGAs) and a higher affinity for other neurotransmitters like 5-HT and NE. Following their introduction, the SGAs soon became recommended as first-line treatments in schizophrenia since it was felt that their unique
pharmacodynamic profile made them more efficacious for the negative symptoms of schizophrenia, while also less apt to cause tardive dyskinesia and other extrapyramidal movement disorders. However, given more recent findings of cumulative research on their comparative clinical effectiveness, the APA Guideline Watch (2009) indicated that the distinction between FGA and SGA agents appears now to have limited clinical value. Additionally, the guideline watch authors noted that the published positive research findings for perphenazine and molindone lead to a “reconsideration of their usage...and by extension other FGAs with the exception of haloperidol” (Dixon et al., 2009; Kane and Correll, 2010). Note: See findings from the European First Episode Schizophrenia Trial (EUFEST) in the First Episode/Early Psychosis section, the CATIE study described below in this section, and the Treatment of Early-onset Schizophrenia Spectrum Disorders study (TEOSS) in the Schizophrenia in Children and Adolescents section for detailed information on these seminal studies. This purported advantage of the SGAs was put to the test in many studies (Volavka et al., 2002; Davis et al., 2003; Leucht et al., 2003). These studies led to a relative consensus that SGAs as a class had advantages over the FGAs in terms of efficacy, effects on negative and cognitive symptoms, better side effect profiles, and more cost-effectiveness when overall medical costs were considered. Despite this relative consensus, some experts and studies questioned the validity of this purported better efficacy and safety of the SGAs. One such study found that in a two-year comparison study, haloperidol actually proved to yield significantly higher quality of life scores compared to olanzapine (Rosenheck et al, 2003). This was accomplished at lower total costs due mainly to the lower medication cost. One drawback of this study was that the subjects averaged 20 years of schizophrenic illness, a duration that makes it very difficult to reliably ascertain an improvement in functioning.

In a meta-analysis that sought to test this perceived superiority by reviewing studies from 1953-2002, clozapine, risperidone, and olanzapine emerged as superior to the FGAs, showing greater effect sizes, with the effect for clozapine most pronounced (Davis et al., 2003). Additionally, whereas olanzapine and risperidone were only *slightly* superior to FGAs on positive symptoms, they were *moderately* superior to the FGAs on negative symptoms, as well as thought disorder, mood and impulse control/excitement. The conclusion of this analysis was that this superiority was true for certain SGAs but did not hold up across the entire class of SGAs.

The primary questions addressed by the CATIE Schizophrenia Trial were:

1. How do the second-generation antipsychotics compare with a representative first-generation antipsychotic?
2. What is the comparative effectiveness of the second-generation antipsychotic drugs?
3. Are the second-generation drugs cost-effective? (Swartz et al., 2003)

The completed first phase of the CATIE study was specifically undertaken to test the hypothesis that the SGAs were not only safer but also more effective than the FGAs. However, the first phase revealed that the one FGA studied (perphenazine) was as efficacious as all of the studied SGAs, with the exception of olanzapine, which had slightly greater efficacy than all of the other studied medications (Lieberman et al., 2005). However, this efficacy was countered by olanzapine’s greater propensity to cause hyperglycemia, hyperlipidemia, and weight gain. This study also pointed out the great limitations of all of these medications since only 26 percent of subjects remained on their initial medication for the full 18 months of the study, the primary outcome measure. In addition, further analysis of CATIE study data showed that perphenazine was less costly than each of the four SGAs studied where average total monthly health care costs were 20 percent to 30 percent lower because of lower drug costs (Rosenheck et al., 2006). Similarly, a recent review of cost-effectiveness studies revealed no clear evidence that atypical antipsychotics generate cost savings or are cost-effective, i.e., measuring health benefits achieved, in general use among schizophrenic patients.
Further analysis of CATIE study findings have demonstrated that after both two and six months of treatment with olanzapine, quetiapine, risperidone, ziprasidone or perphenazine, all treatment groups had small but significant improvement in neurocognition (Keefe et al., 2007). Likewise, these same antipsychotic treatment groups made only modest improvements in psychosocial functions – with no one drug showing any distinct superiority (Swartz et al., 2007).

Another randomized phase of the CATIE study studied patients with chronic schizophrenia who were prescribed a new SGA after discontinuing the FGA, perphenazine. Results showed that quetiapine and olanzapine were more effective than risperidone in this group of patients. The findings from this phase of the CATIE study can be viewed in the context of recommendations about selection of sequential treatments based on efficacy rather than solely on side effect profile (Stroup et al., 2007). Similarly, an analysis conducted on Phase 1 CATIE study explored the advantages of continuing or switching baseline medications olanzapine or risperidone. For both treatments, findings showed that continuing on average fared somewhat better than switching. These findings suggest that unless the clinical situation requires a medication change, prescribers should take steps to optimize current medication regimens, e.g., via dosage changes, behavioral or psychosocial interventions, adjunctive medications, before switching medications (Essock et al., 2006).

Using data accrued from the large, naturalistic three-year Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO) study, a post hoc analysis examined the clinical status and tolerability outcomes of switching from olanzapine to risperidone and vice versa in patients with schizophrenia (Hong et al., 2012). This study focused on a subsample of patients (n=298) who made the first switch to risperidone monotherapy from olanzapine monotherapy at baseline and vice versa. Clinical improvement as assessed by the Clinical Global Impressions Severity Scale – Schizophrenia version (CGI-SCH) was experienced by patients who started treatment with either olanzapine or risperidone for clinical reasons and further improvement was experienced after the medication switch. The percentage of patients switching to olanzapine (48 percent) remaining on the medication without further switches was greater than that of the patients switching to risperidone (39 percent). Those switching to olanzapine experienced significant improvement in tolerability outcomes, e.g., extrapyramidal symptoms (EPS), amenorrhea/galactorrhea; patients who switched to risperidone from olanzapine did not experience improvement in tolerability outcomes. Multivariate analyses ruled out patient characteristics before switching as the explanation for the differential effect between the two groups. Researchers concluded that these results do not suggest that one drug is more effective in symptom control, but that olanzapine seems to be superior to risperidone in EPS, relapse prevention and reproductive adverse events, i.e., amenorrhea/galactorrhea.

An additional study compared the efficacy of two atypical antipsychotic agents, clozapine and olanzapine, with one another and with haloperidol in the treatment of physical assaults and other aggressive behaviors in physically assaultive patients with schizophrenia and schizoaffective disorder. The results showed that clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of physical assaults, and in reducing overall aggressions. Further, this anti-aggressive effect appears to be separate from the antipsychotic and sedative action of the medications (Krakowski et al., 2006).

Since publication of the CATIE study, Leucht et al. conducted a very large meta-analysis (150 double-blind trials with 21,533 participants) comparing first- and second-generation antipsychotics used in the United States and Europe (Leucht et al., 2009). These findings were
somewhat different with regard to previously reported comparisons of these two classes of antipsychotics. This analysis reported that amisulpride (not available in the U.S.), clozapine, olanzapine and risperidone were more efficacious than first-generation drugs in the main domains, i.e., overall change in symptoms and positive and negative symptoms. Additionally, their findings showed that the remaining drugs in the SGA class were only as efficacious as FGA drugs, even in terms of negative symptoms, and stressed that “efficacy on negative symptoms cannot be considered a core component of atypicality (Leucht et al., 2009).

A more recent systematic review and meta-analysis compared the benefits and harms associated with commercially available FDA-approved antipsychotics in the treatment of adults, aged 18 to 64, with schizophrenia and related psychosis (Hartling et al., 2012). Researchers assessed 1,216 full-text articles for eligibility, selecting 114 for inclusion in quantitative or qualitative synthesis. Studies selected included randomized controlled trials (RCTs), nonrandomized, controlled RCTs, and retrospective cohort studies with at least two years follow-up. In comparisons of haloperidol with five SGAs, i.e., olanzapine, aripiprazole, risperidone, clozapine and quetiapine, low strength evidence showed benefit for risperidone compared with haloperidol in positive symptom alleviation, whereas moderate strength evidence showed benefit of haloperidol compared with olanzapine. All remaining comparisons showed no favored drug. Moderate evidence showed SGAs, i.e., olanzapine, aripiprazole and risperidone, were more beneficial in treating negative symptoms when compared with haloperidol. Comparisons of other SGAs, clozapine, quetiapine and ziprasidone, with haloperidol showed low strength of evidence with no favored drug. Authors indicated that since only two retrospective cohort studies provided follow-up data for at least two years in duration, data on long-term safety was limited. Authors pointed out that the strength of evidence, in most of these studies, was insufficient or low; they highlighted the need for future research and a stronger evidence base. They also noted that the APA guidelines provide specific recommendations on medication timing, but provide only broad variables for medication options, reflecting the current state of evidence for FGAs and SGAs.

Recent research on the unique dopamine partial agonist properties of aripiprazole have been conducted as the need continues to more fully understand differences among each of the SGA drugs. One early published study has reported that high resolution positron emission tomography (PET) brain scans in patients receiving clinically effective doses of aripiprazole showed very high striatal D₂ occupancies of >80 percent and an increased risk of extrapyramidal side effects at >90 percent occupancy. Researchers suggested that this is a shift in occupancy threshold for both clinical effect and extrapyramidal side effects compared with other antipsychotic drugs (Mamo et al., 2007).

Another more recent post hoc analysis of pooled data from both short- and long-term aripiprazole comparison trials against haloperidol (a D₂ antagonist) or olanzapine (a D₂/5HT₃ antagonist) have found incidence rates of akathisia in patients as follows: akathisia in 9 percent of aripiprazole versus 6 percent of placebo-treated patients; 12.5 percent of aripiprazole vs. 24 percent of haloperidol-treated patients and 11 percent of aripiprazole versus 6 percent of olanzapine-treated patients. Additionally, the study indicated that mild/moderate treatment-emergent akathisias was not associated with a poorer clinical response (Kane et al., 2010). Another study demonstrated that adjunctive aripiprazole treatment successfully alleviated hyperprolactinemia and menstrual disturbances in patients with schizophrenia currently taking haloperidol. Researchers suggested that the likely cause of this observation was due to aripiprazole having a higher affinity to D₂ receptors than haloperidol (Shim et al., 2007).

One meta-analysis examined (n=3,479) the relationship between the use of psychoactive substances (PAS) in patients with schizophrenia treated with antipsychotic agents and their impact
on extrapyramidal symptoms (EPS). Investigators found that PAS negatively impacted EPS in schizophrenia where an overall moderate and positive effect size (g=0.401) was found and where cocaine was associated with the largest effect size estimate (g=0.613) suggesting increased EPS in substance abusing patients (Potvin et al., 2009).

A new atypical antipsychotic, iloperidone, with dual-acting dopamine and serotonin receptor antagonist properties was approved for the treatment of acute schizophrenia in elderly people in May 2009. Initial study findings showed low potential for weight gain, i.e., comparable to risperidone, induction of diabetes and low incidences of extrapyramidal side effects including akathisia, sleepiness and effects on cognition. Additionally, long-term maintenance studies demonstrated iloperidone’s non-inferiority to haloperidol for relapse prevention (Citrome, 2009). The atypical antipsychotic, paliperidone extended-release (major active metabolite of risperidone), was approved in July 2009 by the FDA as an osmotically released oral formulation that minimizes peak-to-trough fluctuation and allows initiation at a once-daily therapeutic dose (Paliperidone, 2008). A clinical trial compared paliperidone with quetiapine in patients with recently exacerbated schizophrenia requiring hospitalization. This study reported favorable findings of improved symptoms earlier and to a greater degree in the group treated with paliperidone (Canuso et al., 2009). Another more recent analysis of pooled data from three paliperidone ER multicenter pivotal Phase III clinical trials showed that the drug had a meaningful treatment benefit in improving personal and social functioning in patients with acute schizophrenia where 46.9 percent to 63.6 percent of patients treated with the drug achieved at least a 10-point category improvement in the Personal and Performance Scale (Patrick et al., 2010).

In August 2009, the FDA approved the atypical antipsychotic, asenapine, a broad spectrum, high potency serotonin, noradrenaline and dopamine antagonist for use in patients with acute schizophrenia and bipolar disorder. Unlike other atypical antipsychotics, asenapine may not exhibit some of the more troublesome side effects, e.g., QT prolongation, of other agents in the class and may cause less risk of EPS and weight gain (Asenapine, 2008). It is the only antipsychotic agent available exclusively in a rapidly dissolvable sublingual form providing a number of advantages, e.g., preference of patients with impaired swallowing mechanisms and easier monitoring due to difficulty to cheek (Bobo, 2013). In October 2010, lurasidone, a novel atypical antipsychotic agent, was approved by the FDA for the treatment of acute schizophrenia in adults. Lurasidone belongs to the chemical class of benzoisothiazol derivatives with high affinities to dopamine D2, serotonin 5-HT2A, 5-HT2A receptors and α2C adrenoreceptor. The drug’s unique chemical properties are purported to enhance cognitive functions. In addition, lurasidone is under investigation for the treatment of bipolar disorder (FDA News Release, 2010; Lurasidone, 2010).

A recent study, reviewing the role of iloperidone, asenapine and lurasidone in the treatment of schizophrenia, reviewed published clinical efficacy and tolerability/safety of these drugs (Bobo, 2013). Based on indirect comparisons of available outcome data, authors concluded while there is no evidence of superior clinical effectiveness for any one of these agents over other available antipsychotic drugs, these new drugs may have advantages over other available antipsychotics in terms of metabolic safety, e.g., low propensity for clinically significant weight gain. Based on their review of the three drugs, lurasidone seemed to have the lowest impact on body weight and metabolic indices. Iloperidone appeared to be associated with the lowest EPS and asenapine was associated with a minimal effect on prolactin concentration. Authors suggested the need for comparative effectiveness studies with older and more established antipsychotics and long-term trials to assess the effectiveness of the newer antipsychotics.

The research team of Leucht et al. conducted the first large meta-analysis (78 studies with 13,558
participants) comparing the efficacy of all SGAs in randomized trials that compared two or more of these agents head-to-head (Leucht et al., 2009). Their analysis suggested that certain SGAs may be somewhat more efficacious than others. Specifically, olanzapine proved superior to aripiprazole, quetiapine, risperidone and ziprasidone. Also, risperidone was more efficacious than quetiapine and ziprasidone. Clozapine proved superior to zotepine (not available in the U.S.) and, in doses > 400mg/day, to risperidone. Researchers also noted these differences were due to improvement in positive symptoms rather than negative symptoms. A more recent combined analysis of two double-blind and one open label trial (total n=129) performed by researchers in Germany, compared the effects of four different atypical antipsychotics (aripiprazole, olanzapine, quetiapine and risperidone) on neurocognition (Reedel et al., 2010). Findings after regression analysis revealed that all cognitive domains showed significant improvement from baseline to week eight with quetiapine showing the most favorable cognitive improvement.

Another new noteworthy area of inquiry was identification of early changes in specific symptoms that may predict longer-term response to atypical antipsychotics in the treatment of schizophrenia. Pooling data from moderately to severely ill patients (n=1494) from six randomized controlled trials, the team of Ruberg et al. identified decision rules from selected Positive and Negative Syndrome Scale (PANSS) items to construct a simple decision tree in the development of an evaluation tool to guide treatment decisions (Ruberg et al., 2011). The investigators noted their exploratory analyses consistently showed that the key predictors of response (“likely responders”) were whether a patient had at least a two-point drop in any of the following items from the PANSS Positive subscore: delusion, conceptual disorganization, hallucinatory behavior, suspiciousness and unusual thought content. A “likely non-responder” also showed no improvement of at least two points on the excitement item at week two, but improvement in these same items were classified as “not predictable”. In addition, investigators indicated that response to treatment could be predicted in most patients (92 percent) with high positive predictive value (79 percent) and high negative predictive value (75 percent) (Ruberg et al, 2011).

In conclusion, researchers suggest that large differences in side effects may be more important than small efficacy superiorities for individual patients. Therefore, practitioners need to select medications based on individual factors with each patient such as previous response, side effect susceptibilities, family history, medical vulnerabilities, tolerances and patient preference (Leucht et al, 2009; Dixon et al., 2009, Kane et al., 2010).

New FDA Approved Drugs for the Treatment of Schizophrenia

On July 10, 2015, the U.S. Food and Drug Administration approved Rexulti® (brexpiprazole), a serotonin-dopamine activity modulator, to treat adults with schizophrenia (FDA, 2015). An FDA news release discussed the results of two six-week clinical trials, evaluating the effectiveness of Rexulti in treating schizophrenia, finding Rexulti reduced the occurrence of symptoms of schizophrenia compared to placebo. Weight gain and a sense of restlessness, e.g., feeling the need to move, was the most common side effect. A six-week multicenter, randomized, double-blind, placebo-controlled study by Correll et al. compared the efficacy, safety, and tolerability of brexpiprazole and placebo in adults (n=636) with schizophrenia experiencing an acute exacerbation (Correll et al., 2015). In this acute, short-term regulatory approval study, patients were assigned to 0.25, 2, or 4 mg of oral brexpiprazole or placebo once daily. Beginning dosage at 1 mg/day was titrated to 2 mg/day on day 5, and 4 mg/day on day 8 in patients receiving 2 or 4 mg/day of brexpiprazole. Outcome measures included change from baseline to week six in Positive and Negative Syndrome Scale (PANSS) total score and other efficacy and tolerability measures. Results of this study found brexpiprazole at a dosage of either 2 or 4 mg/day resulted in greater improvement in outcome measures than placebo within 1-2 weeks of initiating treatment as well as
throughout the treatment period. It demonstrated efficacy in the treatment of both positive and negative symptoms of schizophrenia. Brexpiprazole was well tolerated, with minimal changes in extrapyramidal symptom scales, low incidence of akathisia, only a moderate increase in body weight, and no evidence of significant adverse effects on metabolic measures and prolactin when compared with those for placebo (Correll et al., 2015).

On September 17, 2015, FDA approved Vraylar® (cariprazine) capsules to treat schizophrenia and bipolar disorder in adults (FDA, 2015). The FDA news release reported the results of three six-week clinical trials including 1,754 participants. Compared to placebo, Vraylar reduced the symptoms of schizophrenia while associated with extrapyramidal symptoms, i.e., tremor, slurred speech, and involuntary muscle movements. An international, phase III clinical trial evaluated the efficacy and safety of this dopamine D3 and D2 receptor partial agonist in patients with an acute exacerbation of schizophrenia (Kane et al., 2015). Researchers hypothesized that cariprazine’s high affinity for the D3 receptor may provide a potential benefit in negative symptoms and cognitive impairment. Results of this study found greater improvement in the Positive and Negative Syndrome Scale (PANSS) score and Clinical Global Impressions-Severity (CGI-S) efficacy parameters in cariprazine 3-6 mg/day or 6-9 mg/day than in placebo. Additionally, cariprazine was generally well tolerated, with some mild or moderate treatment-emergent adverse events (TEAEs), of which akathisia was the most common (Kane et al., 2015).

The FDA approved a new three-month, long-acting antipsychotic, Invega Trinza® (paliperidone palmitate), in May 2015. This quarterly intramuscular injection form of paliperidone provides the longest dosing interval available for patients with schizophrenia and was approved by the FDA “under its priority review process, a fast track for drugs thought to represent a significant advance in medical care” (Medscape, 2015). Patients receiving this drug must first receive Invega Sustenna®, the monthly injection version, for at least four months. A recent double-blind, placebo-controlled study evaluated the efficacy and safety of the quarterly injection form of paliperidone versus placebo in delaying time to relapse of schizophrenia symptoms in patients (n=305) previously treated with once-monthly paliperidone for at least four months (Berwaerts et al., 2015). The four phases of this two-year maintenance trial included: transition phase where patients received once-monthly doses of the 1-month formulation of paliperidone palmitate; maintenance phase where patients received a single dose of the 3-month formulation; and the open-ended double-blind phase where patients received a fixed dose of 3-month paliperidone palmitate or placebo once every three months. The primary outcome variable was time from randomization to the first relapse event in the double-blind phase. Study results showed significantly delayed time to relapse of schizophrenia symptoms for patients receiving the 3-month paliperidone palmitate compared with those receiving placebo. A relapse event during the double-blind phase occurred in 9% of the group receiving 3-month paliperidone palmitate compared with 29% in the placebo group.

The most recently FDA-approved drug to treat schizophrenia is Aristada® (aripiprazole lauroxil). On October 5, 2015, the FDA approved this long-acting injectable, which is administered every four to six weeks (FDA, 2015). The director of the Division of Psychiatry Products in the FDA’s Center for Drug Evaluation and Research emphasized that the long-acting medications can improve the lives of patients with schizophrenia. In a 12-week randomized, double-blind, placebo-controlled trial including participants (n=622) with acute schizophrenia who had been stabilized with oral aripiprazole, Aristada demonstrated improvement in schizophrenia symptoms, and a safety and tolerability profile that is not unlike that of oral aripiprazole. The most common side effect that was reported was akathisia (Meltzer et al., 2015).

In addition to the antipsychotics, i.e., iloperidone, asenapine and lurasidone, discussed above and
approved by the FDA after publication of the guideline watch, the FDA on December 21, 2012 approved adasuve (loxapine) inhalation powder for the acute treatment of agitation in adults with schizophrenia and bipolar disorder (Adasuve, 2012). In clinical trials, this drug showed potential for bronchospasm and increased mortality in certain asthma and chronic obstructive pulmonary disease patients; therefore, it is available only through a Risk Evaluation and Mitigation Strategy program (Adasuve REMS). On February 28, 2013, the FDA approved Abilify Maintena (aripiprazole) for extended-release injectable suspension for the treatment of schizophrenia. This intramuscular (IM) depot formulation provides a new once-monthly treatment option, helping reduce risk of relapse (FDA, 2013). The FDA approval does not include treatment of patients with dementia-related psychosis and aripiprazole is contraindicated in patients with reactions, e.g., pruritus/urticaria to anaphylaxis. On October 24, 2011, the FDA approved the first generic olanzapine (tablets and orally disintegrating tablets) to treat schizophrenia and bipolar disorder, offering greater access to a widely used treatment for schizophrenia (FDA, 2011).

### Polypharmacy

A recent retrospective claims-based analysis of patients with schizophrenia (n=4156) characterized patterns of treatment, e.g., medication switching and discontinuation in those treated with antipsychotic monotherapy versus those treated with polypharmacy (Fisher et al, 2014). The study included patients between the ages of 13 and 64, studying treatment patterns for patients at the earliest stages of their diagnosis as well as patients with chronic schizophrenia. In this study, 23% of patients with schizophrenia received treatment with two or more antipsychotic agents simultaneously. Combinations of SGAs were the most frequently used combination, while a quarter of patients receiving polypharmacy received a combination that included a first-generation antipsychotic. In the oldest patients, combinations of FGAs were more frequent, whereas the youngest patients more frequently received combinations of SGAs. Data from this study showed that when transitioned off a single antipsychotic, patients more often received a second antipsychotic rather than beginning treatment with two antipsychotics. This practice is consistent with the APA’s guideline recommending polypharmacy only after the patient has not benefitted from monotherapy (APA, 2004). In addition to finding polypharmacy in almost one-fourth of patients with schizophrenia, researchers noted higher discontinuation rates, i.e., a 90-day gap in at least one of the antipsychotic medications prior to the end of the one-year follow-up period, in those receiving polypharmacy compared with those receiving monotherapy (Fisher et al., 2014).

A recent study examined the effectiveness of switching individuals with schizophrenia from antipsychotic polypharmacy to monotherapy (Essock et al., 2011). Researchers noted that although antipsychotic polypharmacy is a prevalent practice and one that appears to be increasing through time, there is a lack of supporting evidence for it and treatment guidelines discourage the practice. This randomized trial assigned participants (n=127) to stay on both antipsychotic medications (Stay) or to switch to monotherapy (Switch). Participants in the Switch group discontinued one medication within 30 days and were to continue the treatment regimen for a six-month study period unless clinically contraindicated. Primary outcome measure was the amount of time to all-cause treatment discontinuation and the secondary outcome measures included psychiatric symptomatology, side effects of medications and hospitalization. Polypharmacy combinations included quetiapine+risperidone, quetiapine+FGA, risperidone+FGA, olanzapine+FGA, ziprasidon+FGA, aripiprazole+quetiapine, olanzapine+risperidone, other combinations. Results of this study showed that the time to all cause treatment discontinuation was shorter for the Switch than the Stay group and treatment discontinuation occurred significantly more often in the Switch group. However, the study also showed that switches to monotherapy from polypharmacy are successful for most patients as 69 percent of those switched to monotherapy remained on monotherapy for six months. The two groups did not differ significantly on psychopathology over
time or in hospitalization. The Switch group had a significant decrease in body mass of 0.5 BMI units compared with a gain of 0.3 BMI units at six months in the Stay group. Researchers concluded that individuals on polypharmacy may benefit from discontinuing one of the medicines.

**Concurrent General Medical Conditions**

To evaluate the association between antipsychotic drug use in pregnancy and maternal and perinatal outcomes, researchers conducted a large matched cohort study, including singleton live births or stillbirths to women, including antipsychotic users (n=1021) who were matched with women not exposed to any antipsychotic drug during pregnancy (Vigod et al., 2015). Researchers used a high-dimensional propensity scores (HDPS) matching algorithm, including data dimensions, e.g., prescription drug claims and hospitalization/emergency department diagnoses and procedures less than 365 days before cohort entry, to address treatment selection bias. Antipsychotic medication users were 1:1 matched with non-users based on the HDPS score and on maternal age at delivery. Researchers restricted the analysis to the atypical antipsychotics, i.e., quetiapine, olanzapine, and risperidone. Results found that event rates were not significantly different among antipsychotic users and non-users for gestational diabetes and hypertensive disorders in the matched group. Additionally, event rates were also not significantly different for preterm birth and birth weight. Only labor induction and operative vaginal delivery were associated with antipsychotic drug use in the matched cohort. Researchers concluded, “Antipsychotic medications themselves do not seem to have an extensive negative impact on important measures of maternal medical and short term perinatal well-being” although “women requiring antipsychotic medications are at higher absolute risk for certain adverse maternal and perinatal outcomes compared with the general population.” They advise closely monitoring the medical health of women requiring antipsychotic medications, with attention to diabetes, hypertension, preterm birth, and fetal growth (Vigod et al., 2015).

A large cross sectional study of 314 primary care practices in Scotland examined the range and number of the most common physical health comorbidities in a sample of patients (n=9677) with schizophrenia or a related psychosis (Smith et al., 2013). Results found that persons with schizophrenia had significantly more primary care records of physical health comorbidites, e.g., viral hepatitis, constipation, and Parkinson’s disease, than those without schizophrenia, even after controlling for age, gender and social deprivation. Recorded primary care rates for cardiovascular disorders, e.g., atrial fibrillation, hypertension, coronary heart disease and peripheral vascular disease, were lower in persons with schizophrenia than controls, although the most commonly diagnosed condition for patients with schizophrenia was hypertension. Authors noted that this result was somewhat unexpected, especially since another study showed that “people with incident schizophrenia were more likely to die prematurely than the general population (15 years earlier for men and 12 years earlier for women), and the leading causes of death were cardiovascular disease and cancer” (Smith et al, p. 4). Authors suggested, “GPs may not be assessing and/or recording cardiac problems as often as they might with patients who do not have schizophrenia.” They suggested the need for “a more systematic use of such screening in both primary and secondary care may improve early detection and treatment of hypertension, hypercholesterolaemia, diabetes and smoking” (Smith et al, p 6).

Included in the APA guideline section titled “Clinical Features Influencing the Treatment Plan” is a valuable discussion on concurrent general medical conditions which acknowledges that patients with schizophrenia suffer disproportionately from a variety of comorbidities. The guideline specifically identifies cardiovascular disease, respiratory disease, diabetes, infectious diseases and substance use disorders (SUD) as most the prevalent conditions leading to an increased non-suicidal mortality rate in this patient population where lifestyle, environment, psychotropic
medications are contributing factors. Since publication of the guideline, researchers conducted a systematic review of 17 studies investigating whether disparities in medical treatment of cardiovascular conditions, i.e., medical procedures and receipt of prescribed medication, were associated with elevated rates of mortality in people with schizophrenia and severe mental illness (Mitchell and Lord, 2010). These studies analyzed care delivered in the United States, Canada, United Kingdom or Australia. Findings showed that in six of eight studies, the adequacy of cardiac procedures was lower than the average provision of medical care. Meta-analytic pooling of nine medication studies showed lower than average rates of prescribing for angiotensin converting enzyme inhibitors, beta-blockers and statins, higher than expected prescribing for older non-statin cholesterol-lowering agents and no inequality for aspirin. Additionally, investigators reported that ten studies linked poor quality of care and possible effects on mortality in specialist setting and half of the studies showed a significantly higher mortality in patients suffering from mental illness compared with controls. While authors cautioned that a causal role was not determined, the findings revealed strong evidence of inequalities in cardiac treatment posing disadvantages to those with schizophrenia (Mitchell and Lord, 2010).

Researchers conducted a recent retrospective cross-sectional study analyzing medical and surgical hospitalizations (n=15,275,337) in the United States to evaluate the association between schizophrenia and ambulatory care sensitive (ACS) hospitalizations, i.e., hospitalizations potentially preventable by timely primary care (Cahoon et al., 2013). They reviewed past studies showing that although persons with schizophrenia have higher rates of medical comorbidity, e.g., cardiovascular disease, diabetes, HIV infection, respiratory illness, obesity, compared to the overall population; they experience inadequate access to timely primary care or poor quality of care. Findings from this study showed that schizophrenia was consistently associated positively with increased odds of acute ACS hospitalization and increased odds of chronic ACS hospitalization for conditions such as chronic obstructive pulmonary disease (CPOD), uncontrolled diabetes, asthma and short-term complications of diabetes mellitus. Researchers reported studies suggesting that primary care physicians sometimes perceive physical symptoms as psychosomatic rather than recognizing the associated specific medical condition, thus delaying treatment that could prevent hospitalization. They suggested additional research to determine factors associated with the increased odds of acute ACS hospitalization and to examine potentially modifiable barriers to coordination between primary care and mental health care providers.

The adopted guideline discusses the clinical challenges of managing pregnancy in patients with schizophrenia due the risks of various psychotropic medications to the fetus, newborn and breast-fed infant and other problems encountered from the relatively poor prenatal care they receive. In a later review of studies or articles addressing the safety and efficacy of antipsychotic medication use in pregnancy and in breastfeeding, authors found that over a follow-up period of up to two years, relapse of schizophrenia occurred in about 50 percent of patients who had withdrawn from antipsychotics compared with 15 percent of patients who continued on medication. Further, the risk of relapse was greater with abrupt compared to gradual withdrawal (Robinson, 2012). Due to the relative paucity of comparative studies, the efficacy, tolerability and outcome of FGAs vs. SGAs in pregnant patients remain inconclusive. A wide range of literature examines the known effects, e.g., mechanisms of action, side effect profiles and efficacy, of FGAs in the treatment of pregnancy, but there are few studies on the use of SGAs in this population. FGAs remain the first line treatment. Pregnancy characteristics and outcomes were elucidated in a meta-study of 63 quasi-randomized, case-control linkage studies of 216 pregnant and puerperal women with schizophrenia compared to the 487 births of unaffected women (Matevosyan, 2011). Older age, smoking and less antenatal vitamin intake related to perinatal risk in schizophrenia along with higher rates of cumulative obstetrical complication, i.e., miscarriages and preterm labor. Other findings showed that neonates
to mothers with schizophrenia manifested lower five-minute Apgar scores, intrauterine growth retardation and congenital defects, i.e., holoprosencephaly, microcephaly, spina bifida and chromosomal syndromes. Conversely, women with schizophrenia had lower rates of preeclampsia, fetal malposition and placenta previa. The postpartum period in this patient population was marked with high rates of psychotic relapse and parenting difficulties (Matevosyan, 2011).

**Metabolic Disturbances**

A recent study reviewed clinical and molecular evidence on metabolic alterations induced by SGAs (Rojo et al., 2015). Authors noted that metabolic alterations, e.g., weight gain, insulin resistance, diabetes, dyslipidemia and increased cardiovascular risk, often develop in a short period of time (six months after initiation of treatment with SGAs). They discussed studies showing that activation of SREBP1c, D1/D2 dopamine, GABA2, and 5HT neurotransmitters, are associated with cardiovascular toxicity, and that polypharmacological interventions are not significantly effective in maintaining low cardiovascular risk in patients treated with SGAs. Authors noted the effect of environmental and/or epigenetic factors on the propensity to develop metabolic syndrome in patients receiving treatment with SGAs. They reviewed results of studies assessing the efficacy of pharmacological interventions, i.e., metformin, nizatadine, orlistat, ranitidine, topiramate, etc. in treatment of metabolic side effects. Although metformin reduced body weight in clozapine-treated patients, these effects did not continue upon discontinuation of the drug. Orlistat was associated with a mild decrease in weight gain in men, but had no effect in women, and atomoxetine was not effective in preventing obesity in patients who received olanzapine and clozapine. Authors indicated the difficulty with a single-drug therapy to treat a multifactorial problem, as current literature suggests that "mechanisms of SGAs-induced metabolic syndrome involve at least two separate systems: the peripheral lipid and glucose metabolism, controlled by SREBP1 transcriptional factor, and the alteration of appetite control in the hypothalamus through neurons of the arcuate nucleus" (Rojo et al., p. 9). They suggested studies including the antidiabetic effect of specific polyphenols, e.g., anthocyanins, shown to be effective in ameliorating obesity.

Metabolic disturbances, particularly weight gain, hyperlipidemia and hyperglycemia, have been reported as adverse events for the SGAs. Multiple case reports have suggested that clozapine and olanzapine in particular may induce weight gain and hyperlipidemia. A recent study of a large patient population indicated a significantly increased risk of developing hyperlipidemia if taking olanzapine. Specifically, a three-fold risk compared with patients taking FGAs, and a five-fold risk compared to those on no antipsychotic medication was found (Koro et al., 2002). This same increased risk did not appear to occur with risperidone in this study. Another recent study comparing olanzapine treatment with ziprasidone treatment resulted in significantly greater psychopathology improvement with olanzapine but ziprasidone was found to be superior for weight change and lipid profile. There was no significant difference in fasting glucose levels between treatment groups for both agents (Breier et al., 2005). A more recent pooled analysis of six randomized, double-blind trials in the treatment of schizophrenia, schizoaffective disorder or schizotypal disorder compared white (n=605) and black (n=375) patients treated with olanzapine (5 to 20 mg/day) for 24 to 28 weeks. These findings did not show any substantive differences in efficacy, safety or metabolic parameters, i.e., fasting and random lipids and glucose, between races. However, a significantly greater percentage of black patients (36.1 percent) experienced clinically significant weight gain compared to white patients (30.4 percent) (Stauffer et al., 2010).

Multiple case reports also have associated clozapine and olanzapine with the adverse event of hyperglycemia, although it has been reported with other SGAs, such as risperidone. One recent study confirmed this association for olanzapine and clozapine, or at least an association with
increased blood glucose levels, and also observed an association with haloperidol and increased blood glucose levels (Lindenmayer, 2003). These authors recommended baseline and six-month monitoring of glucose, glycated hemoglobin and lipid profiles on all patients receiving antipsychotic medications. A more recent study confirmed the higher risk of inducing new onset type 2 diabetes from olanzapine and clozapine, finding 34 percent to 41 percent increased odds, as compared to typical antipsychotics (Lambert et al., 2005).

In February 2004, panelists from four professional societies published a Consensus Statement after reviewing most of the evidence for these adverse events with SGAs (American Diabetes Association, 2004). The Consensus Panel determined that the evidence supports the conclusions that olanzapine and clozapine were the most likely to induce these side effects while ziprasidone and aripiprazole were the least likely. They also concluded that the risks with risperidone and quetiapine were somewhere in the middle. The panel also recommended a schedule of monitoring physical signs and lab tests for the early emergence of warning signs. The provider should note that the APA guideline shares the view that physical findings and laboratory tests should be monitored, but differs in that it concludes that there is no one correct monitoring schedule. These documents, as well as a more recent article by Marder (Marder et al., 2004) offer good tables of what needs monitoring and suggested frequencies so providers may refer to these tables.

Because of the serious morbidity and mortality that could arise from these adverse events, the prudent prescriber needs to be aware of the potential for weight gain, hyperglycemia and dyslipidemia, and should monitor for emergence of these side effects as the clinical situation warrants. In a more recent historical and clinical review of the pharmacologic treatment of schizophrenia, Kane and Correll argued that the cumulative evidence now suggests that “neither second- nor first-generation antipsychotics are homogenous classes regarding adverse effect risk” (Kane and Correll, 2010). Further, the authors noted that “although clozapine and olanzapine are among the most weight gain-producing and metabolically problematic antipsychotics, the low-potency FGA, chlorpromazine, is also associated with considerable adverse cardiometabolic effects.” In addition, the authors indicated that high-and mid-potency FGAs most likely have a similar cardiometabolic risk as low-risk SGAs and that all antipsychotics are associated with considerable weight gain for the treatment-naïve and first episode patients.

An intention-to-treat, secondary analysis of data from a randomized, controlled trial, Cost Utility of the Latest Antipsychotics in Schizophrenia Study Band 1 (CUtLASS-1), examined non-neurological and metabolic side effects of FGAs and SGAs in patients (n=227) treated for schizophrenia (Peluso et al., 2013). Although the results of this analysis found that patients on SGAs at both 12- and 52-week follow-up showed a clinically significant increase in cardiovascular problems compared with patients on FGAs, the expected corresponding increase in weight gain in patients on SGAs did not occur. Instead, the data from CUtLASS-1 showed no difference in weight gain between patients on SGAs and FGAs at 12 and 26 weeks. At 52 weeks, patients on SGAs showed a decreased risk of weight gain compared with the FGA group. Authors suggested that these findings demonstrate the heterogeneity and complexity of the traditional classes of antipsychotic drugs in terms of side effects and that each class has advantages and disadvantages in terms of non-neurological sexual, and metabolic effects. They concluded that SGAs and FGAs should not be considered two distinct classes; instead, all antipsychotics drugs have a place on a spectrum of beneficial and adverse effects. They further suggested, “Antipsychotic prescription in this patient population is as much an art in matching therapeutic color to a person, as it is a science generalizing from group data to an individual’s characteristics (Peluso et al, 2013).

According to suggestive findings from a study with a small sample of inpatients treated with SGAs, a
practical, cost-effective, and simple method of assessing and monitoring for metabolic syndrome is the combination of measurement of waist circumference and fasting blood glucose (Straker et al., 2005). In this study, waist circumference greater than 102 cm/40 inches in males and 88 cm/35 inches in females, with fasting blood glucose of 110mg/dl or a history of diabetes mellitus, predicted with 100 percent accuracy patients that had metabolic syndrome with elevated risk of future cardiovascular morbidity. If fasting blood glucose was not available, the combination of waist circumference and blood pressure greater than 130/85 mm HG predicted with 96 percent accuracy those patients with metabolic syndrome. In the study, metabolic syndrome was defined as presence of three of the following: 1) blood pressure > 130/85 mm HG; abdominal obesity at navel >102 cm /40 inches in males, 88 cm/35 inches in females; fasting blood glucose > 110mg/dl or history of diabetes mellitus; fasting HDL cholesterol <40mg/dl in males and <50mg/dl in females; fasting triglycerides > 150mg/dl.

An article with an n of 37 subjects indicated that sibutramine was an effective and well-tolerated adjunct to behavior modification for weight loss in patients with schizophrenia and schizoaffective disorder being treated with olanzapine (Henderson et al., 2005). In addition, sibutramine treatment improved several health status markers that are predictive of cardiovascular disease, e.g., reduced weight, reduced BMI, improved A1c hemoglobin, decreased overeating and decreased “empty calorie” food intake. However, long-term use of sibutramine was not evaluated and use with other antipsychotic medications was not studied. In 2010, the manufacturer voluntarily recalled sibutramine from the U.S. market and this drug is no longer available due to increased risk of heart attack and stroke (Stokowski, 2010).

The oral biguanide antidiabetic agent, metformin, has been studied in China in two clinical trials for the treatment of antipsychotic-induced weight gain. In the first study, the research team of Wu et al. found that when patients on olanzapine 15 mg per day were treated with metformin 750 mg per day, metformin was effective and safe in attenuating olanzapine-induced weight gain and insulin resistance in drug-naive first-episode schizophrenia patients (Wu et al., 2008). Their other clinical trial involved some 128 adult patients with schizophrenia who were allowed to continue their antipsychotic medication (i.e., clozapine, olanzapine, risperidone and sulpiride) while being randomized into four treatment study arms. These patients received either 12 weeks of placebo, 750 mg per day of metformin alone, 750 mg per day of metformin and lifestyle intervention, i.e., psychoeducational, dietary and exercise programs, or lifestyle intervention only. Researchers found statistically significant decreases in mean weight, BMI, waist circumference, insulin and insulin resistance index (IRI) in all groups except the placebo group. Additionally, lifestyle intervention and metformin alone and in combination demonstrated efficacy for antipsychotic-induced weight gain. Lifestyle intervention plus metformin showed the best effect on weight loss. Metformin alone was more effective in weight loss and improving insulin sensitivity than lifestyle intervention alone (Wu et al., 2008).

Two meta-analyses on the efficacy of metformin for the treatment of olanzapine induced weight gain and glucose parameters were published with positive results. One analysis using four studies (n=105) demonstrated that the weighted mean difference for body weight was 5.02 kg lower and for Body Mass Index (BMI) was 1.42 cm. lower with metformin than with placebo at 12 weeks (Prahraj et al., 2011). A larger meta-analysis using some nine randomized controlled studies and two open cohort studies (n=495) showed that in ten studies, the addition of metformin to antipsychotic treatment was associated with either significantly attenuated weight gain or weight loss compared with control groups (Bushe et al., 2009). Four of nine studies showed that metformin significantly improved glucose parameters against controls. In addition, patients with first-episode schizophrenia demonstrated the largest improvement in weight and glucose parameters in two
studies. With these promising findings, investigator noted that longer term studies still need to be conducted with metformin against drugs other than olanzapine and with Caucasian patients who were not represented in their patient group (Bushe et al., 2009).

An analysis of published studies examined the use of topiramate for use as an adjunctive strategy in antipsychotic-induced metabolic disturbances (Hahn et al., 2013). Authors acknowledged clozapine’s superiority in treatment resistant schizophrenia, while also noting its link to increased liability of weight gain and metabolic disturbance. They suggested that switching treatment-refractory patients to another antipsychotic with less weight gain liability was not always feasible, and analyzed studies evaluating topiramate as an augmentation strategy in treatment resistant schizophrenia. Studies examining improvement in psychopathology during adjunctive treatment with topiramate showed small to moderate benefit, with improvements in general psychopathology rather than positive symptoms. Authors cited two randomized, double-blind controlled trials examining topiramate use as augmentation strategy in patients (n=138) treated with atypical antipsychotics, each of which showed greater weight loss in patients treated with adjunctive topiramate than in the control group treated with only antipsychotics. Authors concluded that topiramate as adjunctive strategy in refractory schizophrenia is unlikely to result in dramatic clinical benefits, but may lower cardiovascular risk factors. They cautioned that its use must be considered exploratory until further studies provide additional data.

Researchers conducted a systematic review and meta-analysis of pharmacological interventions for the management of antipsychotic or mood stabilizer-induced weight gain, indicating that clozapine and olanzapine have been associated with the greatest weight gain, while quetiapine and risperidone have been associated with significant weight gain (Fiedorowicz et al., 2012). Pharmacological agents in this review of randomized, double-blind placebo-controlled trials (n=32) included metformin, H2 antagonists, topiramate and norepinephrine reuptake inhibitors.

Metformin, the most studied agent for antipsychotic related weight gain, showed a difference from placebo by a mean of about 6.6 pounds, or a reduction in body mass index of 1 kg/m² in trials ranging from 12-16 weeks. In these studies, metformin also demonstrated decreased glucose/hemoglobin, insulin resistance and triglyceride/high density lipoprotein cholesterol ratio. Studies also demonstrated positive results for topiramate as adjunctive treatment for both weight gain and psychotic symptoms. In studies, it differed from placebo by a mean of 8.8 pounds and demonstrated decreased total cholesterol, low density-lipoprotein cholesterol, blood pressure and glucose. Researchers concluded that evidence supports the use of metformin or topiramate to attenuate the potential of antipsychotics or mood stabilizers to increase weight, but potential risks, e.g., adverse effects, drug interactions, must be considered. They also stressed the importance of non-pharmacological strategies, i.e., lifestyle interventions for weight gain maintenance in schizophrenia.

The efficacy of a lifestyle intervention, i.e., Lifestyle Wellness Program (LWP), for weight gain management in schizophrenia was tested in a six-month multicentric, randomized, controlled trial (Attux et al., 2013). LWP is a 12-week weight management intervention including a one-hour weekly session led by mental health professionals to discuss certain topics, e.g., lifestyle, physical activity, dietary choices, self-esteem, with patients and their relatives. It also included behavioral techniques, e.g., use of diaries and role-play, and psychoeducation components combined. Patients (n=160) with schizophrenia and schizoaffective disorders who had used any antipsychotic in the past three months and who were motivated to lose weight were randomized to LWP or to the standard care (SC) group which included regular visits to the psychiatrist and regular sessions of other psychosocial interventions. Results showed that after six months, patients in the intervention group had lost weight whereas those in the SC group had gained weight. The magnitude of the
difference was statistically, but not clinically, significant. Researchers acknowledged the risk of pharmacological interventions for weight loss in schizophrenia, pointing out the safety and efficacy of lifestyle interventions delivered at low cost.

Other Pharmacological Agents

A recent dual-site, thirteen-week, randomized, double-blind, placebo-controlled, crossover study explored the influence of adjuvant raloxifene on cognition in young to middle age men and women (n=98) with schizophrenia (Weickert et al, 2015). Researchers discussed how the “estrogen receptor is altered in the brains of people with schizophrenia, involving both lower mRNA levels and/or failure to express the fully functional wild-type form of the estrogen receptor” (Weickert et al, p 686). Based on several studies of estrogen therapy in schizophrenia demonstrating significant reduction of symptoms in women with schizophrenia, researchers suggested that stimulation of the estrogen signaling pathway in the brain may improve cognitive function in both men and women with schizophrenia. However, they pointed out that treatment with estrogen is not risk-free and that another agent that stimulates estrogen action in brain cells is needed that is relatively free of adverse events. Researchers cited studies reporting that adjunctive raloxifene, a second-generation selective estrogen receptor modulator approved for use in treating osteoporosis, also has beneficial effects on brain function. In this randomized crossover study, they predicted that cognitive deficits, e.g., verbal memory, would improve with treatment of adjunctive raloxifene at 120 mg/day. Patients alternated between receiving raloxifene HCL orally and a placebo during the first six weeks of the trial, followed by a one-week “washout,” after which they all received the alternate treatment (placebo or raloxifene) for the trial’s last six weeks. Monitoring for adverse events occurred throughout the trial. Treatment outcomes at the end of the first six-week period showed that 40% of patients receiving raloxifene had significant improvement on measures of cognition, e.g., memory and processing speed, compared with improvement in only 15% of patients in the placebo condition. The difference in improvement of these measures in the second six-week period between the raloxifene and placebo were less than during the first six-week period, suggesting persistence of the improvement in the raloxifene group even after changing to placebo in the second period. No significant difference in adverse events occurred in 93% of patients between the raloxifene and placebo condition. Researchers concluded that this trial was the first demonstration that adjunctive administration of raloxifene at 120 mg/day can improve outcomes, e.g., verbal memory and attention, in both men and women with schizophrenia, suggesting a potential novel treatment for these defects in patients with schizophrenia (Weickert et al., 2015).

A recent proof-of-concept study investigated the effectiveness of low-dose sodium nitroprusside administered intravenously to 20 patients with schizophrenia, 19-40 years of age, currently receiving treatment with available antipsychotics (i.e., risperidone, olanzapine, chlorpromazine, quetiapine, ziprasidone, haloperidol, aripiprazole) (Hallak et al., 2013). Output measures included changes in positive, negative, anxiety, and depressive symptoms during four weeks following the treatment. Patients randomly assigned to receive sodium nitroprusside (0.5 µg/kg/minute for 4 hours), or placebo (5% glucose solution infused over same time period) were interviewed by a psychiatrist using the Brief Psychiatric Rating Scale (BPRS-18) to measure efficacy, and the Positive and Negative Syndrome Scale (PANNS-negative subscale) to detect and rate symptoms. During the seven-day follow-up period, no changes in antipsychotic medications were allowed. Results showed the sodium nitroprusside group improved from the second hour of infusion and persisted for the four-week observation period, with the BPRS-18 revealing reduced scores in participants receiving sodium nitroprusside versus placebo. Additionally, the sodium nitroprusside group improved rapidly after infusion in contrast to the placebo group in the PANSS-negative subscale scores. Findings did not show significant differences in physical parameters, e.g., systolic blood pressure, diastolic blood pressure, heart rate, blood oxygen saturation level, between the two groups.
Researchers noted that although this study showed that "sodium nitroprusside administration significantly and rapidly improved the positive, negative, anxiety, and depressive symptoms of schizophrenia," there is a need for larger confirmatory studies with longer follow-up periods (Hallak, p. 675).

The National Institute of Mental Health-sponsored initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), is an assessment battery for patients with schizophrenia, while the associated Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) project deploys the MATRICS battery in treatment trials (Koola et al., 2014). These projects were designed to facilitate development of drugs to treat cognitive impairment in patients with schizophrenia. Authors noted that no approved medications for impairment of this core feature of schizophrenia have been FDA approved, and the MATRICS project identified dopaminergic, cholinergic, and glutamatergic drug mechanisms of particular interest. Citing studies showing that the combination of an acetylcholinesterase inhibitor (AChEI) and memantine is more effective than either medication alone to treat cognitive impairment in Alzheimer’s dementia, authors suggested a potential role of this combination to improve cognitive impairments in schizophrenia. They conclude the need for future research “to shed light on the association of biomarkers and cognitive enhancement with treatment interventions” (Koola et al., p. 88).

The APA guideline reported promising early evidence on the use of glutamatergic agents, i.e., glycine and D-cycloserine, as additions to both first- and second-generation antipsychotics and concluded that more research was required on both agents to further determine and compare their efficacy. Since then, the Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) was conducted at four sites in the United States and one site in Israel (Buchanan et al., 2007). In this study, all 157 inpatients were allowed to remain on any of their currently prescribed antipsychotic medications (except clozapine) and other concomitant medication regimens, i.e., anticholinergic, beta-blocker, mood stabilizer, antidepressant, antianxiety or anticonvulsant drugs. Researchers found that neither glycine nor D-cycloserine was an effective therapeutic option for treating negative symptoms or cognitive impairments. Another more recent clinical trial of new adjunctive agents involved the use of transdermal estradiol in women with schizophrenia. In this preliminary clinical trial of 102 women of childbearing age, those who received an addition of 100 µg of transdermal estradiol, in addition to their usual medication FGA or SGA regime, experienced a significant reduction in both positive and general psychopathological symptoms (Kulkarnki et al., 2008).

The APA guideline also discussed the interest in using the acetylcholinesterase inhibitors ("cognitive enhancers"), developed for use in dementia, to treat the cognitive deficits in patients with schizophrenia. In this regard, the guideline indicated that there was an insufficient evidence base to support their usage. More recently, researchers evaluated the efficacy of galantamine (an acetylcholinesterase inhibitor that acts as an allosteric modulator at the α4β2 and α7 nicotinic receptors) on various cognitive skills such as attention, motor speed, processing speed, verbal and visual memory, and working memory. Researchers concluded that galantamine did not exhibit a significant global benefit for cognitive impairments but did have selective benefits for aspects of processing speed and verbal memory (Buchanan et al., 2008). These findings are somewhat similar to more recent meta-analytic findings published by a Brazilian team of investigators. Findings from their analysis of 13 double-blind studies (four with rivastigmine, six with donepezil and three with galantamine; total n=564) showed that use of these drugs as adjunctive therapy improves specific cognitive deficits, i.e., memory, and the motor speed and attention part of executive function, in both patients with schizophrenia and schizoaffective disorder (Ribeiz et al. 2010).
In addition, since publication of the APA guideline, a new agent has been identified and studied. A randomized, double-blind clinical pilot study demonstrated that the selective muscarinic receptor agonist, xanomeline, may provide a potentially new mechanism to treat multiple symptom domains in schizophrenia. Researchers argued that these results support the need for further investigation of xanomeline as a novel approach to treat schizophrenia (Shekhar et al., 2008).

The APA guideline also discussed the efficacy of antidepressants in treating the negative symptoms of schizophrenia. The guideline specifically commented on the overlap between depressive and negative symptoms which complicates study design and interpretation while also noting that research findings to date were modest. Since publication of the guideline, however, a large meta-analysis (23 randomized controlled trials, n=819) examined the efficacy of add on antidepressant therapy. The overall conclusions supported the treatment efficacy for the negative symptoms of chronic schizophrenia using ritanserin, trazodone and fluoxetine with a modest effect size (SMD=-0.48), but not for mirtazapine, reboxetine, mianserin, fluvoxamine, sertraline, paroxetine and citalopram. The investigators acknowledged the need for further inquiry regarding side-effects, adherence, cost-effectiveness and effect on quality of life for this particular combination of psychotherapeutic agents as well as focused study of different subdomains of negative symptoms (Singh et al., 2010).

An investigational pharmacological approach to schizophrenia, based on the expanding field evidence of N-methyl-D-aspartate (NMDA), was the focus of a recent small randomized, double-blind, placebo-controlled trial investigating the effectiveness and safety of a single low-dose intravenous administration of sodium nitroprusside (0.5 µg/kg/min for four hours) in patients (n=20) with acute schizophrenia (Hallak et al., 2013). Outcome measures, i.e., positive, negative, anxiety and depressive symptoms, were measured by psychiatrists using the Brief Psychiatric Rating Scale-18 (BPRS-18) and the negative subscale of the Positive and Negative Syndrome Scale (PANSS). Patients, relatively early in their disease course, were interviewed by the same psychiatrist every hour for the four hours during infusion. Compared with placebo (5 percent glucose solution), a rapid and long lasting, significant effect of sodium nitroprusside on BPRS-18 was evident from the second hour and through the four-week observation period, showing improvement of positive, negative, anxiety and depressive symptoms. At the tested low dose, sodium nitroprusside produced no adverse reactions.

Researchers conducted a recent 16-week, multi-site, randomized, double-blind, placebo-controlled clinical trial to determine whether folic acid plus vitamin B₁₂ supplementation reduces negative symptoms of schizophrenia and whether treatment response is influenced by genetic variation in folate absorption (Roffman et al., 2013). Patients (n=140) with chronic schizophrenia and receiving antipsychotic treatment were randomized to receive daily 2 mg of folate and 400 µg of vitamin B₁₂ or placebo over a period of 16 weeks. The study showed significant improvement in negative symptoms compared with placebo, but only when genotype was taken into account. Folic acid plus vitamin B₁₂ demonstrated greater effect only in patients homozygous for the 484T allele of FOLH1. Researchers concluded that this treatment response supports a personalized medicine approach for the treatment of negative symptoms of schizophrenia.

**Outpatient Commitment**

Outpatient commitment or “mandatory outpatient treatment” has been defined by the APA as court-ordered outpatient treatment for patients who are otherwise unlikely to be compliant with such treatment and who do not currently meet inpatient commitment criteria, but would meet such criteria if it were not for this outpatient treatment (American Psychiatric Association, 1999).
Studies reviewing outpatient commitment demonstrate a promising role for this option in certain patients. One study assessing clinician, consumer and general public opinion found an acceptance of this option if it was in the service of reducing the risk of re-hospitalization (Swartz et al., 2003). Another study of outpatient commitment in a seriously ill population found a significant reduction in readmissions, hospital days, and emergency room visits along with increased outpatient visits (Rohland et al., 2000). Based on these and other studies, it does appear that outpatient commitment is a viable option to consider, particularly with recidivistic patients.

Debate exists, however, on the degree of perceived coercion patients experience from outpatient commitment and the clinical and ethical ramifications of such. Another difficulty in this area is the great variability between states in entrance criteria for outpatient commitment and the definition of outpatient commitment. The APA’s Council on Psychiatry and the Law addressed these issues in a 1999 resource document on Mandatory Outpatient Commitment (American Psychiatric Association, 1999). The APA’s conclusion is that outpatient commitment is potentially beneficial for recidivistic patients who are non-compliant with medication and/or outpatient follow-up. Since state law varies on outpatient commitment, providers need to educate themselves on the laws in the states in which they practice.

**Promoting Treatment Adherence**

A new cross sectional survey conducted in Germany with hospital psychiatrists and their inpatients with schizophrenia or schizoaffective disorder examined the association between clinicians’ underestimation of treatment nonadherence and low implementation rates of structured adherence-enhancing interventions (Hamann et al., 2014). Researchers interviewed psychiatrists (n=121) and their inpatients (n=213) within the week before hospital discharge. They asked psychiatrists open-ended questions about the main reasons for their patient’s hospitalization, followed by how they intervened to improve treatment adherence. They also asked patients about the reasons for their hospital admission and about their communication with physicians. Physicians reported that one-to-one discussions with patients concerning the need for regular drug intake was the measure most often used to improve future adherence, while depot medications were rarely cited as interventions. Although patients and physicians reported approximately the same rates of depot medication prescriptions (32%), rates reported differed for the other measures. Physicians reported that 40% and 9% of patients and relatives, respectively, received psychoeducation, whereas patients reported receiving only 36% and 5%, respectively. Additionally, physicians reported arranged follow-up visits for 18% of patients, whereas patients reported only 16%. Researchers suggested the main barriers to an intensive response to patient nonadherence: underestimation by physician of treatment nonadherence; lack of proper discharge planning; and limited resources. They also questioned, “whether or not psychiatrists address the issue of adherence properly when talking to their patients in order to avoid patients’ refusal of adherence interventions” (Hamann, p. 886).

Researchers sought to identify the prevalence and management strategies of nine categories of antipsychotic adverse effect: extrapyramidal symptoms; sedation; weight gain; type 2 diabetes; hyperprolactinaemia; metabolic syndrome, dyslipidaemia; sexual dysfunction; and cardiovascular effects in a recent systematic review (Young et al., 2015). Authors noted both while antipsychotic medications are the cornerstone treatment for schizophrenia, adverse effects of the medications also influence nonadherence with treatment. This review of 53 studies found that sexual dysfunction and weight gain are the most commonly occurring antipsychotic adverse effects with significant implications for medication adherence. Other findings included: scarcity of scientific studies of antipsychotic adverse effects; exacerbation of adverse effects with antipsychotic polypharmacy, a common clinical practice; occurrence of adverse effects of the newer
antipsychotics as much of a problem as with older equivalents for patients' long-term physical health; low rates of documented baseline monitoring; low compliance with management strategies for follow-up; and lack of adequate recognition and treatment of the physical health of patients with schizophrenia. Authors stressed the importance of prevention and management of adverse effects, and suggested that clinicians adhere to and improve monitoring guidelines, using validated antipsychotic side effect scales, e.g., Glasgow Antipsychotic Side-effect Scales (GASS).

Poor or nonadherence to oral antipsychotics surfaced as a critical issue soon after their introduction in the 1950s, leading to the development of the first long-acting injectable antipsychotic, (LAI) fluphenazine decanoate (Brissos et al., 2015). Its development was followed over the years by haloperidol decanoate, aripiprazole (Abilify Maintena), risperidone (Risperdal Consta), paliperidone (Invega Sustenna), paliperidone palmitate (Invega Trinza), and the latest, aripiprazole lauroxil (Aristade). Injectable antipsychotics may help to maintain adherence, while assuring stable blood levels, and reducing the risk of relapse. However, negative attitudes of both clinicians who think that patients will not accept LAI antipsychotics and patients who perceive them as coercive (with attached stigmas) may negatively affect their use (Brissos et al., 2015).

A recent randomized clinical trial compared the efficacy of the oral formulation of risperidone with the LAI formulation (Risperdal) in the early course of schizophrenia (Subotnik et al., 2015). In this 12-month trial, patients (n=86) with recent onset of schizophrenia were randomized to receive either the oral medication or the LAI formulation while half of each group were at the same time randomized to receive either cognitive remediation or healthy-behaviors training. Dosage of oral risperidone ranged from 1.0 to 7.5 mg/day, and for the LAI formulation the range was from 12.5 to 37.5 mg every two weeks. Results showed a relapse rate of only 5% in the LAI group compared with 33% in the oral group, with hallucinations and delusions throughout follow-up better controlled with the long-acting risperidone group. Psychotic relapse, psychotic symptom control or hospitalization did not differ significantly between the two psychosocial groups, and there was a lack of significant interactions between medications and psychosocial treatments. Researchers found that discontinuation due to inadequate clinical response occurred more often in the oral group than the LAI group. Researchers concluded that LAI formulations have significant advantages for clinical outcomes due to their more consistent administration, and suggested that LAIs become a first-line treatment soon after the first episode of schizophrenia (Subotnik et al., 2015).

A recent multi-site, double-blind randomized clinical trial compared the effectiveness of two LAIs, i.e., paliperidone palmitate and haloperidol decanoate. Researchers found no statistically significant differences with respect to “prevention of efficacy failure” in the newer second-generation antipsychotic and the older LAI antipsychotic medication in patients (n=311) with schizophrenia or schizoaffective disorder, although the possibility of a clinically meaningful difference was not ruled out (McEvoy et al., 2014, p. 1984). Haloperidol decanoate 25-200 mg or paliperidone palmitate 39-234 mg was administered every month for as long as 24 months. Researchers discussed that contrary to expectations, “there was no statistically significant advantage for paliperidone palmitate when compared with haloperidol decanoate in ratings of the severity of abnormal involuntary movements and parkinsonism, or in the incidence of tardive dyskinesia” (McEvoy et al., p. 1984). They found, however, that with haloperidol decanoate, akathisia increased more than with paliperidone palmitate and that the propensity to cause extrapyramidal symptoms is lower in paliperidone palmitate than in haloperidol decanoate. Although this study did not include a comparison with oral medications, researchers noted that systematic reviews and expert panels support the use of long-acting injectable antipsychotic medications to reduce medication nonadherence for outpatients at increased risk of relapse (McEvoy et al., 2014).
In a randomized head-to-head study, researchers compared aripiprazole once-monthly (Abilify Maintena®) 400 mg and paliperidone palmitate once-monthly to assess non-inferiority and superiority on clinician-rated health-related quality of life in adult patients (n=295) with schizophrenia (Naber et al., 2015). Treatment occurred over a 28-week period. Results, supported by Clinical Global Impression – Severity Scale (CGI-S) and Investigator’s Assessment Questionnaire (IAQ) scores, showed superior results for patients receiving long-acting injectable aripiprazole over paliperidone palmitate. Patients treated with the long-acting injectable aripiprazole had superior improvement in functioning, including emotional interactions, empathy, sense of purpose, and motivation than those treated with paliperidone palmitate. Additionally, there were lower incidences of adverse events and a lower all-cause discontinuation rate suggesting greater overall effectiveness for long-acting injectable aripiprazole (Naber et al., 2015).

Various psycho-educational approaches have been developed for promoting patient adherence to treatment. However, a more recent systematic review of the literature found no effect for broadly based psycho-educational approaches. Rather, psycho-educational approaches with a behavioral, cognitive or motivational focus, or tied to supportive or rehabilitative services, are effective in promoting adherence. Successful behavioral techniques include the use of reminders, self-monitoring tools, cues and reinforcements (Zygmunt et al., 2002). Effective cognitive and motivational approaches include reviewing the benefits and drawbacks of drug treatment, exploring sources of ambivalence, confronting stigma, pointing out discrepancies between the patient’s beliefs and actions, and focusing on adaptive behaviors (Kemp et al., 1996). Similarly, the APA guideline discusses the use of case management services as a means to ensure that patients “do not fall through the cracks” of the health care system and to deliver care in a coordinated, continuous and comprehensive fashion. The adopted guideline acknowledges that studies of routine case management services have produced inconsistent findings but that enhanced or intensive case management (ICM) services, i.e., diminished staff caseloads or use of a team approach, with clinical experts have yielded more promising results. These early findings were more recently substantiated by the results of a very large meta-analysis of 38 clinical trials (n=7,328) where compared to routine case management, ICM was found effective in ameliorating many outcomes relevant to people with severe mental illness, i.e., reducing hospitalization, increasing retention in care and improvement in social functioning, but not conclusively shown to effect mental state and quality of life (Dietrich et al., 2010).

Researchers conducted a pilot trial of a novel interactive mobile phone text message assessment and intervention, Mobile Assessment and Treatment for Schizophrenia (MATS), to assess and improve outcomes in patients with schizophrenia (Granholm et al., 2011). Over a 12-week intervention period, patients (n=55) with schizophrenia or schizoaffective disorder received up to 840 text messages, sent from a remote preprogrammed server to their mobile phones, to administer cognitive-behavioral interventions in support of medication adherence, social functioning and coping with auditory hallucinations. Researchers reported that participants living independently were less likely to report medication adherence at baseline than those in assisted living facilities, but over the 12-week intervention period, the number of patients reporting that they had forgotten to take medications diminished. Researchers suggested that mobile interventions that incorporate routines and natural prompts in daily life, e.g., reminding patients to take medications, improve adherence. Over the 12-week period, patients were less likely to report that medications did not help them “stay healthy;” researchers suggested that the text message intervention was associated with a reduction in negative beliefs about medications and improved adherence. Additionally, MATS was associated with improvement in socialization as well as reduction in severity of auditory hallucinations. Researchers concluded that mobile technologies may facilitate more naturalistic interventions outside of clinical settings.
Long-acting depot injections of fluphenazine (Prolixin) and haloperidol (Haldol) have long been one method supporting treatment adherence in select patients who are having difficulty reliably taking daily oral medication. One drawback of these medications has been the significant problem with extrapyramidal side effects. In 2003, the FDA approved depot IM risperidone (Risperdal Consta). Dosages of 25-50 mgs administered every two weeks were well-tolerated and efficacious, with steady state blood levels achieved in four to six weeks (Kane et al, 2003). Until this steady state is achieved, one should probably use oral medication as a supplement. The efficacy appears equivalent to IM Haldol Decanoate, but the distinct advantage is a very low EPS profile. In 2009, the FDA approved paliperidone palmitate extended-release (Invega Sustenna) injectable suspension for the acute and maintenance treatment of schizophrenia in adults. FDA approval followed positive findings from a long-term efficacy trial where relapse prevention was noted in 77.9 percent of patients receiving the drug versus 48.5 percent of those receiving placebo in the maintenance treatment of schizophrenia. It is the first once-monthly, long-acting, injectable, atypical antipsychotic approved in the United States for this use and is available in pre-filled syringes requiring no reconstitution or refrigeration (FDA, 2009).

In a later narrative review, authors discussed the utility of long-acting depot antipsychotic formulations for increasing medication adherence (Morissette and Stahl, 2012). Authors cited studies finding that both FGA and SGA depot formulations are associated with reduced relapse rates, but they suggested that the primary advantage of depot antipsychotics over oral formulations is due to their more dependable method of delivery allowing for continued antipsychotic treatment. They suggested further that oral antipsychotics may be as effective as depot formulations if only patients would diligently take their medications. Authors cited studies indicating improved tolerability and patient satisfaction with depot antipsychotics whose side effects may occur less often than with oral antipsychotics. They reported clinical trials showing that a depot version of aripiprazole intramuscular depot has shown good efficacy with excellent tolerability.

**Schizophrenia in Children and Adolescents**

A recent article discussed the clinical connections between schizophrenia and autism spectrum disorder (ASD), noting the marked similarities in clinical presentation (Hommer and Swedo, 2015). They cited epidemiologic and retrospective clinical studies suggesting an association between ASD diagnosis or childhood autistic traits and later psychotic experiences. Social cueing deficits as well as impairments in emotion processing have occurred in both groups. Authors reported that meta-analyses of schizophrenia suggested a correlation between negative symptoms and disorganization, and an association of neurodevelopmental disorders with known genetic defects associated with high rates of both ASD and schizophrenia. They suggested that examining commonalities as well as differences between the two disorders provides insights into treatment and prevention.

A recent study investigated the degree to which sensory dysfunction, well documented in schizophrenia, leads to secondary impairment in reading ability (Revheim et al, 2014). Researchers assessed reading ability including fluency of reading, comprehension and sensory function in patients (n=45) with schizophrenia or schizoaffective disorder; patients (n=19) ages 12-30 with high clinical risk for schizophrenia (based on Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms); and in healthy age-matched individuals. The Gray Oral Reading Test and the Comprehensive Test of Phonological Processing assessed reading. Results found that 73% of schizophrenia patients met criteria for dyslexia although their reading ability was intact prior to onset of schizophrenia. Across all test batteries, patients with schizophrenia or schizoaffective
disorder displayed highly significant impairments in reading compared with the control group, and individuals at high clinical risk for schizophrenia showed deficits in visual reading scores. Authors concluded, “The decline in reading ability from premorbid levels, which appears to occur during early stages of the illness, correlates highly with the failure to meet socioeconomic expectations, and may thus represent a remediable cause of persistent occupational disability in schizophrenia” (Rehveim et al., 2014).

The Centers for Medicare & Medicaid Services (CMS) has prepared a chart of FDA-approved pediatric age ranges and indications for atypical antipsychotics, i.e., aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone in the treatment of children and adolescents with schizophrenia (CMS, 2013). It indicated a warning that risperidone should not be used by patients older than age 16 if diagnosed with irritability with autistic spectrum disorder.

There are few studies that evaluate the efficacy of SGA medications in children with schizophrenia, but research at the request of the FDA has indicated that use of aripiprazole in adult doses proved effective and well-tolerated (Moyer, 2005). The patients were started at doses of 2 mg daily, followed by an increase to 5 mg daily. After that, over a period of 10 to 15 days, doses increased in increments of 5 mg until reaching 20 mg, 25 mg or 30 mg. In children and adolescents, this regimen of aripiprazole did not cause the metabolic side effects, such as weight gain and lipid dysregulation, typical of drugs in this class. Using aripiprazole to treat severe mental illnesses in children and adolescents represents one of the latest developments in the quest for a more benign antipsychotic medication.

Similar positive findings on the use of aripiprazole in the younger population were demonstrated in a more recently published, large study of some 302 adolescents with schizophrenia. The results of this double-blind, randomized, placebo-controlled trial showed that both a 10 mg and 30 mg/day dosage of aripiprazole were superior to placebo in the acute treatment of adolescents with schizophrenia, and was generally well tolerated. Neither active treatment group exhibited substantial weight gain in this study. However, change in weight differed across groups because of weight loss in the placebo group, but not in the active groups. Therefore, researchers did issue a cautionary note to clinicians treating adolescents with aripiprazole that they should remain concerned about the potential for adverse long-term changes in weight with the drug (Findling et al., 2008).

Another trial compared the efficacy and safety of olanzapine and clozapine in treating children with treatment refractory schizophrenia. These results showed clozapine to have a more even profile of clinical improvement and a unique, predicted superiority in ameliorating negative symptoms. A two-year follow-up of patients on clozapine demonstrated sustained clinical improvement balanced by a profile of serious metabolic and neurological adverse effects. Despite its limitations, the study provides controlled data supporting clozapine’s use in treatment-resistance childhood-onset schizophrenia (Shaw et al., 2006).

The publicly funded study, Treatment of Early-Onset Schizophrenia Spectrum Disorder (TEOSS), was designed to compare the efficacy and safety of a FGA, molindone, with two SGAs, olanzapine and risperidone, in the treatment of early-onset schizophrenia and schizoaffective disorder. This study was deemed necessary given some of the questions raised about the superiority of SGAs over FGAs in recent large clinical trials such as the CATIE study, the EUFEST and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CutLASS 1). The double-blind, multi-site TEOSS trial randomly assigned 116 pediatric patients with early onset schizophrenia and schizoaffective disorder to treatment with either olanzapine (2.5-20 mg/day), risperidone (0.5-6
mg/day), or molindone (10-140 mg/day, plus 1 mg of benztrapine) for eight weeks. No significant differences were found among treatment groups in response rates (molindone: 50 percent; olanzapine: 34 percent; risperidone: 46 percent) or magnitude of symptom reduction. Other important study results found that molindone led to more self-reports of akathisia and that olanzapine and risperidone were associated with significantly greater weight gain. Additionally, olanzapine showed the greatest risk of weight gain and significant increases in fasting cholesterol, low density lipoprotein, insulin and liver transaminase levels. These findings led researchers to question the nearly exclusive use of SGAs to treat patients with early-onset schizophrenia and schizo-affective disorder and its widespread use in other non-psychotic mood and behavioral disorders in youth (Sikich et al., 2008).

Magellan's 2013 monograph, *Appropriate Use of Psychotropic Drugs in Children and Adolescents: A Clinical Monograph*, reviewed clinical pharmacological studies on the treatment of childhood schizophrenia (Magellan Health, Inc., 2013). It reported published findings from head-to-head trials comparing antipsychotics in youth with schizophrenia or psychosis revealing no significant differences in efficacy among non-clozapine antipsychotics, i.e., olanzapine vs. risperidone; olanzapine vs. risperidone and haldol; olanzapine vs. molindone; olanzapine vs. quetiapine. The monograph cited findings from an international trial demonstrating that aripiprazole, olanzapine, quetiapine, risperidone and paliperidone were all superior to placebo in adolescents with schizophrenia. It also cited studies reviewing both FGAs and SGAs used in treatment of childhood schizophrenia, concluding that clinical improvements were greater for patients receiving SGAs than FGAs with no differences in patient adherence to medication. The monograph discussed the broadened use of psychotropic medications in children and adolescents today, and cautioned that enough is not known about the efficacy, tolerability and long-term safety of these drugs in young people. It referred to the AACAP Practice Parameter for the Use of Atypical Antipsychotic Medication in Children and Adolescents that provides specific recommendations for baseline assessment and routine ongoing medical monitoring of the following significant safety issues/concerns associated with SGA side effects: weight gain, diabetes and hyperlipidemia; cardiovascular problems; neutropenia and potential agranulocytosis; hepatic dysfunction; elevation of prolactin levels; electroencephalogram abnormalities and possible seizure activity; extrapyramidal symptoms, tardive dyskinesia and withdrawal dyskinesia potential; neuroleptic malignant syndrome; and cataract formation.

Extended release (ER) oral paliperidone was approved by the FDA in April 2011 for the treatment of schizophrenia in adolescent patients aged 12 to 17 years based upon the findings of a randomized, double-blind, parallel-group, placebo-controlled, multisite six-week trial (Younis et al., 2013). Adolescents with schizophrenia (n=201) were randomly assigned to receive placebo or one of three weight-based, fixed, once-daily doses of paliperidone ER. Change from baseline in the PANSS total score to the final assessment at end of trial was the primary efficacy variable. This trial found significant improvements in mean PANSS total scores for the medium-dose (3-6mg) treatment group compared with placebo, while there were no significant differences in the total scores for the patients receiving either the weight-based low-dose or high-dose versus placebo. Results found that paliperidone well tolerated, with common side effects, i.e., somnolence, insomnia, tremor, headache and akathisia (Maloney et al., 2012).

**Schizophrenia in Later Life**

In a pilot feasibility study adapting a cognitive remediation (CR) protocol involving restorative and strategy-based methods, researchers targeted cognitive deficits associated with aging and schizophrenia in older community-dwelling individuals (Golas et al., 2015). In addition to accessing the feasibility of CR and its effects on cognitive performance, researchers assessed its effect on
functional competence. Four cohorts of older outpatients (n=22) aged 60 or over with a current diagnosis of schizophrenia or schizoaffective disorder, received CR in eight, 2-hour/week therapist-guided group sessions. CR included didactic teaching, computerized drill and practice, in-class strategic monitoring, and discussion of applying cognitive skills to daily life. No significant improvement on the cognitive or functional measures resulted, although there was a positive correlation between time spent on homework and improvement in verbal memory. Researchers noted that verbal feedback from patients indicated they found the intervention helpful and even showed interest in participating in more sessions. They concluded that patients tolerated CR well, but it did not show improvement in global cognition or function in this study. They further suggested that it “holds promise for its future implementation in clinical settings” although it may “also be necessary to combine CR with a psychosocial intervention to result in improvement” (Golas et al., 2015).

The elderly patient with schizophrenia presents unique concerns, which will become more visible to providers since the population is aging. Similar to the younger patient with schizophrenia, there is increasing data supporting use of SGAs as first line agents in the elderly patient because of their favorable side effect profiles. Clozapine, however, is not recommended as first line in the elderly patient because of its adverse side effect profile, specifically significant anticholinergic and hematologic adverse effects. In addition to these drug selection considerations, antipsychotic drug dosages should be halved for elderly patients, with particular caution when the patient is on multiple medications and/or has co-morbid medical conditions. Also relevant to the discussion on use of psychotropic medications, is a FDA Alert that clinicians should consider when treating elderly patients. Specifically, this FDA Alert was issued notifying health care professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly treated for dementia-related psychosis (FDA Alert, 2009).

As part of an appropriate initial assessment of an elderly patient with schizophrenia, it is relevant to distinguish whether or not schizophrenia had its onset before or after the age of 40. Onset prior to age 40 can be called Early Onset Schizophrenia (EOS), and onset after 40 can be called Late Onset Schizophrenia (LOS). Evidence is accumulating that this differentiation may be relevant in dosing considerations. Studies suggest that the recommended daily dosages for risperidone and olanzapine in elderly EOS patients be approximately 2 mg and 10 mg, respectively, while in elderly LOS patients, even lower doses of these medications may be effective (Sable and Jeste, 2002). A recent study assessed the safety and effectiveness of four commonly prescribed atypical antipsychotics, i.e., aripiprazole, olanzapine, quetiapine and risperidone, in patients (n=332) over age 40 with psychotic symptoms associated with schizophrenia and other psychiatric disorders over a two year period (Jin et al., 2013). The study used hybrid randomization allowing patients or their psychiatrists to exclude one or more of the atypical antipsychotics due to anticipated risk or past experience, and there was no placebo group due to ethical considerations. With each of the drugs, researchers found a lack of effectiveness and a high incidence of side effects, with few differences among the drugs on outcome measures, e.g., metabolic markers, psychopathology, development of metabolic syndrome and serious adverse events. However, quetiapine was discontinued from the trial before the study was completed because of a high incidence of serious adverse events. Researchers suggested caution in the use of these drugs is warranted in both middle-aged and older patients, referring to the high discontinuation rate, lack of significant improvement in psychopathology, high cumulative incidence of metabolic syndrome and adverse events for all of the four antipsychotics in the study.

In a review of literature on the use of the most recently available antipsychotic medications, i.e., paliperidone, iloperidone, asenapine and lurasidone, in patients greater than 65 years of age with
schizophrenia, authors found one randomized controlled study of paliperidone in patients (n=114) (Rado and Janicak, 2012). Although tachycardia was more prevalent in the paliperidone group than in the control group, the study found that paliperidone was well tolerated in older patients. Authors noted that although these newer drugs may have comparatively less risk of metabolic or electrocardiographic alterations than other FGAs and SGAs, they caution that all of them have the class-level boxed warning of increased mortality in elderly patients with dementia-related psychosis. They also noted the need for future adequately designed and powered studies addressing the role of these recent antipsychotics in older patients with schizophrenia.

Supported Employment

A recent systematic literature review examined existing evidence from small studies (n=18) investigating relationships between employment and outcomes, e.g., symptom remission, neurocognitive functioning, social cognitive functioning, and quality of life, in patients with schizophrenia (Charzyńska et al., 2014). Studies showed increased levels of social functioning and improvement in symptoms and quality of life in participants with supported employment. However, authors noted the need for larger, high-quality, long-term follow-up, randomized studies further exploring the relationships between employment and non-vocational outcomes.

A more recent study evaluated cognitive enhancement interventions for improving cognitive and work functioning for individuals with schizophrenia and other mental illness (McGurk et al., 2015). In this randomized controlled trial, participants (n=107) with severe mental illness (46% with schizophrenia or schizoaffective disorder) who had failed to respond to supported employment and who expressed a desire to work were randomly assigned to enhanced supported employment only or enhanced supported employment plus the Thinking Skills for Work program. This additional intervention included cognitive exercise practice, strategy coaching, and teaching coping/compensatory strategies taught by a cognitive specialist. Results found that improvement in cognitive and vocational functioning improved significantly more in the Thinking Skills for Work group than in the group receiving only the supported employment intervention. Over a two-year period, 60% of participants in the Thinking Skills for Work group obtained competitive work compared with 36% of those in the enhanced supported employment only group. The Thinking Skills for Work participants worked an average of 6.0 weeks per six-month period compared with only 2.3 weeks in the supported employment group. Improvement on cognitive functioning was greater in the Thinking Skills for Work group than in the supported employment group. Researchers concluded that the Thinking Skills for Work program helps individuals who have not responded to supported employment enjoy financial, social, and clinical benefits of competitive work.

The APA guideline indicates that supported employment should be offered to any person with schizophrenia who expresses an interest in work. The APA guidelines also notes that current evidence shows that engagement in supported employment does not lead to stress, increased symptoms or negative outcome. One recent study examined the effectiveness of a cognitive training program that was integrated into a supported employment program. Findings showed that patients in the supported employment with cognitive training program demonstrated significant greater improvements in cognitive functioning, depression and autistic preoccupation. Over two to three years, patients in supported employment with cognitive training were more likely to work, hold more jobs, worked more weeks, worked more hours and earned more wages than patients in the program offering supported employment alone (McGurk et al., 2007).

A published analysis using baseline data collected prior to randomization from the CATIE study, examined the association of diverse socio-demographic, clinical and environmental factors with

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participation in competitive employment, other employment (e.g., volunteer, workshop, prevocational) activities and reported monthly earnings. Results showed that overall employment of persons with schizophrenia seems to be impeded by clinical problems, including symptoms of schizophrenia and poorer neurocognitive and intrapsychic functioning. However, participation in employment may be specifically impeded by potentially adverse incentives of disability payments and by race. Specifically, competitively employed patients tended to be younger, less likely to be African-American, and received lower public support payments on average, e.g., DDS and SSI payments. The study showed that depression, substance abuse, tardive dyskinesia, extrapyramidal symptoms and waist-to-hip ratio did not impact employment (Rosenheck et al., 2006).

**Social Skills Training**

A recent meta-analysis of psychological interventions for psychosis identifies outcome trials (n=48) comparing psychological treatments for participants (n=3295) with psychosis (Turner et al., 2014). The goal of this study was a better understanding of which therapy is more effective for particular symptoms. Researchers grouped interventions into six common types for treatment comparison: befriending, cognitive-behavioral therapy, cognitive remediation, psychoeducation, social skills training, and supportive counseling; researchers grouped psychosis symptoms into separate meta-analyses. Results from the series of meta-analyses found small but significant differences in efficacy between pooled psychological interventions for the reduction of psychotic symptoms. Cognitive-behavioral therapy was more effective for all symptom outcome measures pooled when compared with other interventions pooled and “showed a small but robust superiority in reducing positive symptoms” (Turner, p. 532). Social skills training was more effective for negative symptoms compared with other interventions pooled. Compared with other interventions pooled, befriending was less effective for all symptoms outcome measures pooled. After sensitivity analyses for risk of bias, benefits of cognitive behavioral therapy, social skills training, and cognitive remediation for all symptom measures pooled were not significant. In sensitivity analyses, the effect of CBT on positive symptoms lost significance, but the same was not true for the effect of social skills on negative symptoms. Researchers concluded that although observed differences between interventions for psychosis were small, the nature and pattern of the differences have implications for improving psychosocial therapies for psychosis (Turner et al., 2014).

The APA guideline indicates that social skills training (SST) is well established for improving outcomes and reducing relapse rates and symptoms scores. However, a meta-analysis based on a review of the randomized controlled trial literature from 1966 through 1999, in which inclusion criteria were strictly defined, yielded a result that brings this broad conclusion into question (Philling et al., 2002; Dickerson and Lehman, 2006). In this review of nine trials that met the inclusion criteria, none supported the conclusion that relapse rates or symptom scores were diminished as a result of social skills training. However, one study did demonstrate a significant improvement in the outcome measure of quality of life and another study supported a similar trend without offering a statistically significant finding.

Another study indicated that manual-based community support in addition to traditional skills-based training in the clinic led to greater improvements than traditional SST in the clinic alone. The improvements were noted in instrumental role functioning and close family relationships, as well as overall adjustment as measured on the Quality of Life Scale instrument (Glynn et al., 2002). Also, patients in the manual-based, community support group often made gains more quickly and gained higher levels of scores than those in traditional clinic-based SST alone. The variety of findings does not diminish the potential value of SST, but does indicate the need for further research on the most effective methods.
In a more recent clinical trial, patients (n=36) with schizophrenia or schizoaffective disorder were randomly assigned to treatment as usual (TAU) or to a very brief, 16-session SST interventions which focused on both social cognition and social competence (Rus-Calafell et al., 2013). Patients in the control group received individual psychotherapy, medication management and family support, but no socio-cognitively oriented treatment during the study. The SST intervention consisted of seven blocks of training: social perception; social information processing; responding and sending skills; affiliative skills; instrumental role skills; interactional skills; and behavior governed by social norms. At the beginning of the eight-week program, participants received a user manual including slides and activities between sessions. Structured SST sessions consisted of a review of the last session’s material, a discussion about the between-session activity, a theoretical/didactic presentation of the session material, and group practice and individual exercises. Assessment of participants in clinical symptomatology, social cognition, cognitive performance and psychosocial functioning occurred at baseline, across post-treatment and at the end of the six-month follow-up appointment. Results showed that participants in the SST group showed significant improvements in positive self-statements from pre-to post-treatment, but this improvement was not evident at six-month follow-up. Negative self-statements of the SST group also improved after the intervention and this improvement was evident at follow-up. No improvement in these variables was evident in the TAU group at post treatment or at follow-up. The SST group showed significant improvement in social activities from pre to six months follow-up whereas the TAU group did not show any changes. Researchers pointed out the positive correlation between the increase of positive self-statements during social interaction and the improvement of self-reported mental health after the SST intervention.

**Cognitive Remediation and Rehabilitation**

Studies have shown that most approaches to cognitive remediation for schizophrenia have positive impact on cognition, but have little impact on functional outcomes and improvement in community functioning. In this current literature review, authors focused on studies reporting psychosocial outcomes, e.g., quality of life, academic functioning, social functioning, and employment outcomes. They acknowledged their goal to identify strategies and methods associated with enhanced cognition as well as improved community functioning. Authors noted an emerging trend of examining personal goal attainment as a route to vocational, educational, social, or independent living, thus transferring cognitive gains to everyday life. They cited studies that employed cognitive remediation as an integrative skill intervention, teaching compensatory strategies and linking cognitive gains to functional skills rather than repeated drill and practice of targeted cognitive skills. Studies found that incorporating such strategies demonstrated a positive impact on psychosocial outcome. The studies suggest that cognitive remediation, combined with psychosocial interventions including sufficient opportunities to practice and utilize newly acquire skills, leads to the transfer of cognitive gains to everyday life. Generalization of cognitive to functional gains occurred in studies where participants with schizophrenia received cognitive remediation (including computer-based training, strategic monitoring, and verbal discussion groups) combined with Functional Adaptation Skills Training (FAST) (including skills training for social functioning, transportation, medication management, and community activities planning). Authors concluded that, based on recently published studies, cognitive remediation that goes beyond methods to improve cognitive function and that includes “systematic application of cognitive skills to real-world behaviors” can positively impact psychosocial outcomes and enhance functioning in patients with schizophrenia (Medalia and Saperstein, 2013).

The APA guideline acknowledges that cognitive deficits associated with schizophrenia have assumed an increasingly central role in explaining the disability associated with the disorder. The
guideline cites the cognitive impairments that are most pervasive include distractibility, memory problems, lack of vigilance, attentional deficits, and limitations in planning and decision making. In their discussion, the APA indicates that while cognitive remediation strategies have attempted to address these problems using restorative, compensatory and environmental approaches, the body of evidence is not strong enough to recommend its use in practice. In particular, the guideline specifies that the studies reviewed, did not demonstrate durability and generalizability of the intervention, nor did they adequately control for medication use.

Since publication of the APA guideline, additional research studies have been conducted providing an update to our understanding of the specific cognitive deficits of schizophrenia and the efficacy of cognitive remediation/rehabilitation interventions. The CATIE study protocol gathered data from the 1,386 patients with schizophrenia on symptoms, neurocognitive functioning and social/vocational function at baseline, six-month and 18-month follow-ups. Researchers examined the relationship of both neurocognition and schizophrenia symptoms to social and vocational functioning at the macrosocial level, using the Heinrichs-Carpenter Quality of Life Scale, reported days of employment and a modification of the Positive and Negative Syndrome Scale (PANSS) negative syndrome scale. Study findings revealed that both psychotic symptoms and neurocognitive deficits appear to contribute independently to decreased quality of life in schizophrenia (Mohamed et al., 2008). More recent meta-analytic findings by Ventura et al. have also shown that the relationship of negative symptoms to community based functioning was relatively strong and linked to impairment. However, this study found that the relationship of non-disorganizing positive symptoms, e.g., hallucinations and delusions, to impairment was relatively weak and did not consistently interfere with a person’s ability to socialize or perform at work perhaps due to patient ability to compensate for positive symptom deficits in such settings (Ventura et al., 2009).

More recently, a meta-analysis conducted by Knowles et al. confirmed that processing speed impairment was the single largest cognitive impairment in schizophrenia. Investigators argued that while anti-psychotic medication may contribute to this impairment, the underlying deficit in schizophrenia remained substantial (Knowles et al., 2010). Findings from another meta-analysis by Rajji et al. revealed that while individuals with youth-onset and first-episode schizophrenia demonstrated large deficits on almost all cognitive measures, the former group had even larger deficits in arithmetic, executive function, IQ, psychomotor speed of processing and verbal memory. Conversely, patients with late-onset schizophrenia demonstrated some relatively preserved cognitive functions (Rajji et al., 2009).

There was renewed scientific inquiry in the area of facial emotion perception in schizophrenia with results of two meta-analyses confirming large deficits in emotion identification and differentiation in this population (Chan et al., 2010; Kohler et al., 2010). Investigators discussed the tendency of persons with schizophrenia to visually scan features of the face that are not important in the expression of a particular emotion. Greater impairment was associated with increased age but not with race or level of education. Other findings showed that paranoid patients were highly accurate in recognition of genuine rather than posed emotions and showed less impairment than other patient subtypes of schizophrenia. Contrary to what is generally seen with cognitive function, researchers reported unexpected finding where later age at onset was associated with greater emotional impairment (Kohler et al., 2010). Another related meta-analysis compared laboratory emotion induction procedures in patients with schizophrenia against healthy controls. These findings suggested that patients with schizophrenia experienced hedonic emotions but showed relatively strong and simultaneously occurring aversive emotion when processing stimuli considered by others to be pleasant or neutral Cohen and Minor, 2010). Similarly, misperception of
both threatening and non-threatening (positive) social cues was found to be a general cognitive performance deficit in patients with schizophrenia. The conclusions from this meta-analysis by Huang et al. also indicated that these deficits became larger with increasing delusions (Huang et al., 2011).

Regarding treatment efficacy, a meta-analytic review of 26 randomized controlled trials of cognitive remediation in schizophrenia found that this treatment produced moderate improvement in cognitive performance. When combined with psychiatric rehabilitation, it also improved functional outcomes (McGurk et al., 2007). Findings supporting such combined treatment were consistent with another large and comprehensive meta-analysis conducted in 2011 by Wykes et al. which reviewed 40 studies of some 2,104 participants (Wykes et al., 2011). Their results also showed that there was a small to moderate durable effect on cognition and functioning that was not affected by the study methodology. Additionally, the investigators found strategic approaches to cognitive remediation rather than “drill and practice” achieved better outcomes and may support transfer of training. Another meta-analysis examined functional imaging studies that contrasted patients with schizophrenia and healthy subjects during episodic encoding and retrieval. Findings provided strong support for the conclusion that episodic memory impairments in schizophrenia during encoding and retrieval are related to a reduction in memory control mechanisms implemented by the anterior, ventrolateral, and dorsolateral prefrontal cortex. Researchers suggested that behavioral interventions and pharmacotherapy approaches developed for remediating memory deficits in patients with frontal lobe damage may be applicable to schizophrenia (Ragland et al., 2008).

Additionally, an innovative approach using neuroplasticity-based auditory training to improve verbal memory in schizophrenia has been investigated. While cognitive remediation trials demonstrate some efficacy, the research team of Fisher et al., have noted that current evidence “reveal a ‘glass ceiling’ of low to medium effect sizes across a large variety of methods” (Fisher et al., 2009). These researchers studied a new auditory training program consisting of a set of computerized exercises designed to improve the speed and accuracy of auditory information processing while engaging neuromodulatory systems involved in attention and reward. Their study findings showed initial promising results in that the 55 clinically stable patients with schizophrenia who were randomly assigned to 50 hours of computerized auditory training showed significant gains in global cognition, verbal working memory, and verbal learning and memory (Fisher et al., 2009).

Newer methods of cognitive remediation have been studied with results supporting its clinical efficacy but continuing to demonstrate low to medium effect sizes as discussed above (Grynszpan et al., 2008; Hodge et al., 2010). The Neuropsychological Educational Approach to Remediation (NEAR) used drill and practice techniques to improve cognitive functioning. This multi-site study examined the effects of the technique on patients with schizophrenia (n=40), who remained on stable doses of antipsychotic medications throughout the 15 week trial, and compared their outcomes to waitlist controls. Investigators reported that patients participating in NEAR showed significant improvement from baseline to post-treatment in outcome measures, i.e., verbal and visual memory, sustained attention, executive functioning and social/occupational functioning, that persisted for four months post treatment. Average treatment effect sizes in these domains were mild to moderate (Hodge et al., 2010). A meta-analysis conducted by French researchers consisted of 16 randomized control trials evaluating computer-assisted cognitive remediation (CACR) against control conditions, i.e., treatment as usual or additional psychotherapeutic programs unavailable to active condition group. These investigators cited the strengths of prolonged multimedia stimulation via computer activities as favoring neuroplasticity, acquiring new compensatory strategies,
providing numerous forms of reinforcements and unlimited training possibilities. The overall results showed that CACR enhanced general cognition and social cognition with mean effect sizes of 1.38 and 0.64 respectively. While improvements were also significant in verbal/working memory, attention/vigilance and speed of processing, these effect sizes were small (Grynszpan et al., 2011).

In a recent randomized study, researchers examined the effects, in individuals with schizophrenia living in community settings, of cognitive remediation on functional competence and real world functioning delivered as a standalone treatment and when combined with a functional skills treatment (Bowie et al., 2012). Outpatients (n=107) with schizophrenia were randomly assigned to one of three treatment conditions: cognitive remediation therapy for 12 weeks followed by treatment as usual (TAU) for 12 weeks; cognitive remediation for 12 weeks followed by functional skills training for 12 weeks; or functional adaptation skills training for 12 weeks followed by TAU for 12 weeks. TAU included case management services without cognitive-enhancing or functional-adaptive strategies. Cognitive remediation, based on the Thinking Skills for Work Program, used computer-based exercises, Scientific Brain Training PRO, the Neuropsychological Education Approach to Remediation programs, and therapist involvement to stimulate the forming and testing of alternative strategies to help transfer cognitive skills to everyday activities. Functional adaptation skills training used props and role-playing to increase competence in social skills and aspects of independent living. Findings from study showed the following:

- Neurocognition improved after cognitive remediation, but not after functional skills training.
- Social competence improved with functional skills training and with combined treatment, but not with standalone cognitive remediation.
- Greater and more durable improvements in functional competence occurred with combined treatment than with either standalone treatment.

Researchers concluded that although cognitive remediation produced robust improvements in neurocognition, it has limited transfer to functional competence and real world behavior as a standalone treatment. Functional competence improvements were greater and more durable with combined cognitive remediation and functional skills training for schizophrenia.

**Peer Support and Peer-Delivered Services**

In a recent review of the literature in the fields of peer support and peer-led family psychoeducation to support individuals with schizophrenia and their families, authors looked at evidence from various programs. These programs are Wellness Recovery Action Plan (WRAP), an evidence-based practice by the National Registry of Evidence-Based Practices; Building Recovery of Individual Dreams & Goals through Education & Support (BRIDGES); and Family to Family (PTF), a family psychoeducation course. Authors emphasized that both peer support and peer-led psychoeducation are psychosocial interventions that focus on recovery, “living well with an illness process as opposed to from an illness process” (Duckworth and Halpern, 2014). Studies examining the impact of peer-led self-management education in the WRAP program found that those who received WRAP training had greater propensity to engage in self-advocacy behaviors. Randomized controlled trials have found that BRIDGES led to higher levels of self-perceived recovery and empowerment. Authors suggested that peer-run programs help reduce overcrowding in psychiatric emergency rooms while improving the experience of people with schizophrenia. They noted the emergence of peer-run crisis respite (PRCRs), a form of acute residential crisis service for persons with schizophrenia and other psychiatric disorders. The Whole Health Action Management (WHAM) program, developed by the Substance Abuse and Mental Health Services Administration/Health Resources Administration (SAMHSA-HRSA) is intended to utilize and
strengthen peer support in healthcare delivery (Duckworth and Halpern, 2014).

FTF, promulgated by the National Alliance on Mental Illness (NAMI), is well studied (Duckworth and Halpern, 2014). In a randomized controlled trial studying family members of individuals with schizophrenia (n=318), those assigned to active FTF group had greater improvements in problem-focused and emotion-focused coping than the control group. Studies have shown that family psychoeducation should be delivered as early as possible for families in order to obtain the best benefits. Authors suggested that peer support and peer-led family support, both of which have randomized control trial evidence, seem to have sustained benefits and no material risks (Duckworth and Halpern, 2014).

The growth of peer support service models in the treatment of schizophrenia are discussed in the “Specific Psychosocial Interventions” section of APA guideline where they are defined as “social, emotional and sometimes instrumental support that is mutually offered or provided by persons having a mental health condition, e.g., consumers of mental health services, to bring about a desired social or personal change” (p. 112). The APA guideline indicates that self-help groups are the oldest and most common type of peer-support programs and may be offered in a traditional face-to-face venue or more recently, via the internet as online support. The guideline indicates that research findings of peer support/consumer provided services have revealed positive but tentative results with patients who have severe mental illness and therefore, are categorized as psychosocial treatments with very limited evidence bases.

Since publication of the guideline, researchers at Yale University reviewed four comparative group clinical studies of differing models of peer-delivered services: 1) intensive case management teams staffed by peers vs. non-peers, 2) standard case management versus client-focused case management with and without a peer advocate, 3) standard case management versus peer-based case management and 4) monetary allowance for recreational activities with social support by peer volunteer or non-peer volunteer versus recreational monetary allowance alone (Davidson et al., 2006). While these studies demonstrated few differences between outcomes of conventional care when provided by peer versus non-peers, the investigators cautioned interpretation until it becomes very clear how best to characterize “peer support” – i.e., are they unique treatment modalities or are they conventional services that happen to be delivered by people in recovery (Davidson et al., 2006).

These findings were further corroborated by The 2009 Schizophrenia Patient Outcomes Research Team (PORT) Psychosocial Treatment Recommendations and Summary Statements, where peer support and peer-delivered services were classified as not yet having enough evidence to merit a treatment recommendation, but remaining an emerging area of interest. The PORT team further noted that the research literature to date is small, with weak experimental designs and minimal specifications in how consumers were selected and trained. However, the PORT recommendations stressed that peer support services should continue to be developed and explored because consumers can play a unique role in treatment by sharing experiences, serving as role models for one another, reducing stigma and removing inappropriate hiring barriers for people with severe mental illness (Dixon et al., 2009).

**Suicide Prevention**

Individuals with schizophrenia are four times more likely to die of suicide than the general United States population (McManus et al., 2015). The identification and effective treatment of individuals with schizophrenia may lessen the likelihood of suicide in this population. A recent study discovered microblogging tendencies distinguishing individuals with schizophrenia from the
general population. Researchers analyzed a cohort of Twitter (social media) users who self-identified as having schizophrenia (n=96) and age-matched controls who did not self-identify as having any mental disorder (n=200) to discover patterns of Twitter usage. After discovering microblogging tendencies distinguishing the individuals with schizophrenia from those without schizophrenia, researchers mined Twitter data to identify individuals who met the tendencies of those who self-identified as having schizophrenia. They concluded that this technique with large-scale Twitter data accurately classified Twitter users with schizophrenia and suggested that clinicians may be able to “incorporate Twitter posts into a diagnostic tool for diagnosing schizophrenia on an individual level” that “will lead to an increase in the number of individuals with schizophrenia receiving treatment” (McManus, p. 125). The identification and treatment of persons with schizophrenia may also be associated with suicide prevention.

Clozapine therapy demonstrated superiority to the other atypical antipsychotic drugs in reducing suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide (Meltzer et al., 2003; Mamo, 2007; Hennen and Baldessarini, 2005). Magellan recommends considering clozapine as an option in the treatment of patients with schizophrenia who have a high degree of suicide risk. Magellan's Clinical Practice Guideline for Assessing and Managing the Suicidal Patient contains additional guidance on the treatment of patients at risk for self-harm.

**Treatment-Resistant Illness**

Strassnig and Harvey analyzed three large databases including schizophrenia patients (n=600) from various settings, e.g., state hospital-based and community-based (Strassnig and Harvey, 2014). Very few of the patients were receiving first generation antipsychotics, depot antipsychotics, or clozapine. However, authors found frequent use of polypharmacy with prescription of two or even three atypical antipsychotics, and the addition of mood stabilizers. Only 8 of the 600 patients were receiving clozapine which has been confirmed by the CATIE and CUtLASS trials to be more effective than other antipsychotics in the treatment of partial and nonresponders. Authors discussed the need for “therapeutic approaches beyond antipsychotics, e.g., cognitive remediation combined with functional skills training, pharmacological cognitive enhancement, treatment of residual depression, and physical exercise interventions” as well as more frequent use of clozapine along with less reliance on polypharmacy (Strassnig and Harvey, p. 16).

Any algorithm for treatment-resistant illness must begin with recommendations to re-evaluate the accuracy of the diagnosis and assess for treatment compliance. A study of California Medicaid patients with schizophrenia found that partial compliance, i.e., intermittent taking of medications, is much more common than non-compliance (stopping of medications) (Weiden et al., 2004). Gaps in medication taking as short as 10 days double the annualized risk of re-hospitalization. Gaps of 30 days or longer quadruple the risk of re-hospitalization. The authors suggest that partial compliance should be thoroughly considered before concluding that a particular medication or dosage is ineffective.

It has been demonstrated that clozapine is effective in a significant percentage of patients with schizophrenic symptomatology who have not responded to initial adequate medication trials. One study suggests that both olanzapine and risperidone are also effective in such patients (Dinakar et al., 2002). However, another medication trial in refractory patients with schizophrenia showed that the addition of risperidone to clozapine did not improve symptoms in these patients with severe symptoms (Honert et al., 2006). It is further emphasized that medication trials in such patients may need to last at least 12 weeks. However, another study concerning olanzapine questions this conclusion (Lindenmayer et al., 2002). Further research is needed in the area of medication for treatment-resistant illness and augmentation strategies.
Researchers performed a recent literature review of published studies including randomized trials, prospective open-label trials, and retrospective studies that evaluated the efficacy of alternative antipsychotic medication in patients with schizophrenia who had discontinued clozapine (Mustafa, 2013). Based on the researcher’s review of fifteen papers, including two randomized trials, nine prospective open-label trials, and four retrospective studies, he concluded that solid evidence is lacking with regard to the treatment of patients with schizophrenia who discontinue clozapine treatment. Most of the studies reviewed included small sample size (more than half had 20 or fewer participants). Studies, following subjects for twelve months or longer, showed that alternative antipsychotics changed often and subjects were often reinstated on clozapine. The review suggested that olanzapine was the most tested clozapine alternative and it had a generally favorable outcome in most of the studies. However, researcher pointed out that studies reporting positive outcome with olanzapine lacked active comparators, thus not showing that olanzapine was more efficacious than other antipsychotics for the treatment of refractory schizophrenia. The researcher suggested modest evidence that a trial of olanzapine would be worthwhile in patients who discontinue clozapine.

Neurostimulation

A recent meta-analysis of prospective studies on the therapeutic application of Repetitive Transcranial Magnetic Stimulation (rTMS) in schizophrenia assessed the effects of both low-frequency and high-frequency rTMS on the negative symptoms of schizophrenia (Shi et al., 2014). Authors reviewed past meta-analyses examining the efficacy of rTMS on negative symptoms in schizophrenia that found small effect size supporting its efficacy. In this meta-analysis including 16 studies and 348 participants, authors sought to clarify the effects of rTMS and review possible moderators of rTMS efficacy on negative symptoms in schizophrenia. Only five of the studies used the Scale for the Assessment of Negative Symptoms (SANS) to assess negative symptoms. Authors found that patients with the most prominent negative symptoms at baseline were more responsive to rTMS, and that patients with a longer duration of illness were less responsive. Additionally, rTMS treatment for less than 15 sessions did not result in improvement of negative symptoms. In this meta-analysis, 15 of the studies applied rTMS at the prefrontal cortex associated with negative symptoms. Where the stimulation was applied at the left dorsolateral prefrontal cortex (DLPFC), the mean effect size was moderate and significant compared to other locations, demonstrating that dopamine release in brain regions related to negative symptoms was modulated. Authors also found that the type of antipsychotic had no impact on the efficacy of rTMS on negative symptoms when rTMS was an add-on treatment. Authors concluded that although the studies had limitations including the relatively small number of studies, participants, and use of the SANS as outcome measure, there was evidence to "support that rTMS is an efficacious add-on treatment for negative symptoms in schizophrenia, especially for individuals with early stage schizophrenia. The optimal parameters appear to be a frequency of 10 hz, stimulation at the left DLPFC, a 110% MT and at least 3 consecutive weeks of treatment" (Shi et al, p. 10). They suggested the need for further studies. At this time, schizophrenia is not an approved indication for rTMS.

A recent study investigated the neurobiological effect of transcranial direct current stimulation (tDCS) in patients (n=23) with schizophrenia and treatment-resistant auditory verbal hallucinations (AVH) (Mondino et al., 2015). Patients, all of whom exhibited daily AVH while receiving antipsychotic medications, were randomly assigned to receive active tDCS or sham tDCS. Before the first tDCS session and following the final tDCS session, global symptoms of schizophrenia and AVH were assessed using the Positive and Negative Syndrome Scale (PANSS) and the Auditory Hallucinations Rating Scale (AHRS). Researchers investigated the effect of tDCS on the resting-state functional connectivity (rs-FC) of the left temporo-parietal junction. Results showed that relative to
sham tDCS, active tDCS significantly reduced both negative symptoms and AVH. Further, the findings suggested that “The reduction of AVH induced by tDCS is associated with a modulation of the rs-FC within an AVH-related brain network, including brain areas involved in inner speech production and monitoring” (Mondino et al, p 1).

In a randomized single-blind eight-week study, authors examined the use of electroconvulsive therapy (ECT) as an augmentation to clozapine for treating patients with refractory schizophrenia (Petrides et al., 2015). Patients (n=39) with antipsychotic and clozapine-resistant schizophrenia were randomly assigned to treatment as usual (clozapine) or bilateral ECT plus clozapine during eight weeks. For the first four weeks, ECT was administered three times per week followed by twice weekly for the next four weeks. If patients assigned to treatment as usual did not respond after eight weeks of treatments, they then received another eight-week trial of ECT (cross-over trial) with the same schedule of treatments and ratings as the ECT plus clozapine group. The primary outcome measure was response as a 40% reduction in symptoms based on the psychotic symptom subscale of the Brief Psychiatric Rating Scale (BPRS). None of the patients in the treatment as usual group met the response criterion of 40% reduction in symptoms, whereas 50% of those in the ECT augmentation group were responders at 40% or greater. The ECT augmentation group had significantly greater reduction in ratings on both the BPRS and the Clinical Global Impressions (CGI) -severity scale compared with the clozapine only group. These differences persisted throughout the eight-week trial. In the crossover trial, 47.4% of patients were responders at 40% or greater. Of all 39 patients receiving ECT in the randomized and in the crossover arms, 48.7% showed reductions in ratings on the psychotic symptom subscale. Limitations of the study included the lack of a placebo arm, a relatively low number of patients, and the lack of a diverse set of patients (only inpatients were included). Based on this study, authors concluded that the augmentation of clozapine with ECT is a safe and effective treatment option for the treatment of refractory schizophrenia, while suggesting the need for further research (Petrides et al, 2015).

The APA guideline indicates that various augmentation pharmacological strategies are often used in patients with schizophrenia demonstrating treatment resistance that have little or no supporting evidence supporting their efficacy. The guideline specifies that their selection should be based on residual symptoms, e.g., positive, negative, cognitive, mood symptoms or aggressive behavior, exhibited by the patient. Additionally, the guideline supports the use of ECT and acknowledges its demonstrated benefits in patients with treatment-resistant symptoms. Since publication of the APA guideline, there has been interest and research into the use of Repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment of schizophrenia, particularly focusing on the effects on either auditory verbal hallucinations (AVH) or negative symptoms. One meta-analyses reviewing nine studies (n=213) recently found that prefrontal rTMS might be beneficial for the treatment of negative symptoms of schizophrenia at a frequency of stimulation of 10 Hz and for at least three weeks duration (Dlabac-de-Lange et al., 2010). This team of investigators also found that the overall mean weighted effect size for rTMS versus sham was in the small-to-medium range and statistically significant (d=0.43; 95 percent CI, 0.05-0.80) but decreased to 0.34 when including only studies with patients on a stable drug regimen. The meta-analysis conducted by Slotema et al. reviewed the efficacy of rTMS in psychiatric disorders, i.e., depression, obsessive-compulsive disorder and schizophrenia, which included seven studies (n=189) on the treatment AVH symptoms and another seven studies (n=148) on the treatment of negative symptoms using rTMS compared to sham treatment (Slotema et al., 2010). These investigators found a moderate effect size of 0.53 (p<.001) for rTMS applied to the left temporoparietal cortex in the treatment of AVH including those resistant to antipsychotic medication and 0.39 (P=.11) for negative symptoms when rTMS was applied to the left dorso-lateral prefrontal cortex (DLPF). Both research teams noted that further study was needed to
confirm these findings (Dlabac-de-Lange et al., 2010; Slotema et al., 2010).

After publishing their meta-analysis on the efficacy of rTMS in a variety of psychiatric conditions, Slotema et al. conducted a randomized controlled trial (n=62) focusing solely on the effects of rTMS on medication-resistant AVH comparing: 1) rTMS targeted at the area of maximal hallucinatory activation calculated from individual functional magnetic resonance imaging (fMRI) scans during AVH, 2) rTMS directed at the left temporoparietal area (TP) and 3) sham treatment (Slotema et al., 2011). These findings however, did not prove to be as encouraging as those in earlier studies. Investigators reported results which showed that the effects of either fMRI-guided rTMS or left TP rTMS on the severity of AVH are comparable to those of sham treatment (Slotema et al., 2011).

A randomized double-blind study in France investigated the efficacy of transcranial direct-current stimulation (tDCS) in reducing the severity of auditory verbal hallucinations as well as negative symptoms in patients with schizophrenia (Bruelin et al., 2012). Patients (n=30) were randomly assigned either to tDCS which acts on two distinct brain areas involved in the pathophysiology of schizophrenia (left temporoparietal junction and left dorsolateral prefrontal cortex) or to sham treatment. Patients experienced persistent daily auditory verbal hallucinations without remission while receiving adequate-dose antipsychotic medication. After 10 days of active tDCS over five days, results showed a mean improvement of 31 percent in the severity of auditory verbal hallucinations compared with a mean improvement of 8 percent after 10 days of sham sessions. These effects were maintained for up to three months, also improving negative symptoms as measured by PANSS total score. Research suggests that tDCS constitutes an investigational tool in the treatment of auditory verbal hallucinations that are unresponsive to antipsychotic medication and the need for further studies.

**Other Psychotic Disorders**

In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5™)*, Schizophrenia Spectrum and Other Psychotic Disorders are “defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms” (American Psychiatric Association, 2013). Schizophrenia spectrum and other psychotic disorders include the following:

- **Schizophrenia** lasts for at least six months and includes at least one month of active-phase symptoms.” It “is characterized by two (or more) of the following which must be present for a significant portion of time during a 1-month period (or less if successfully treated) and at least one of these must be (1), (2) or (3): (1) delusions, (2) hallucinations, (3) disorganized speech, e.g., frequent derailment or incoherence, (4) grossly disorganized or catatonic behavior, (5) negative symptoms, i.e., diminished emotional expression or avolition.”

- **Schizotypal personality disorder**, a personality disorder considered within the schizophrenia spectrum, is a “pervasive pattern of social and interpersonal deficits, including reduced capacity for close relationships; cognitive or perceptual distortions; and eccentricities of behavior, usually beginning by early adulthood but in some cases first becoming apparent in childhood and adolescence.”

- **Delusional disorder** is characterized by at least one month of delusions but no other psychotic symptoms. Criterion A for schizophrenia has never been met.”
• **Brief psychotic disorder** “is characterized by a symptomatic presentation equivalent to that of schizophrenia except for its duration (less than six months) and the absence of a requirement for a decline in functioning.”

• **Schizoprophreniform disorder** “is characterized by a symptomatic presentation equivalent to that of schizophrenia except for its duration (less than six months) and the absence of a requirement for a decline in functioning.”

• “In **Schizoaffective disorder**, a mood episode and the active-phase symptoms of schizophrenia occur together and were preceded or are followed by at least two weeks of delusions or hallucinations without prominent mood symptoms.”

• “In **Substance/medication-induced psychotic disorder**, the psychotic symptoms are judged to be a physiological consequence of a drug of abuse, a medication, or toxin exposure and cease after removal of the agent.”

• “In **Psychotic disorder due to another medical condition**, the psychotic symptoms are judged to be a direct physiological consequence of another medical condition.”

• **Catatonia associated with another mental disorder (catatonia specifier)** is characterized by a “marked psychomotor disturbance that **may** involve decreased motor activity, decreased engagement during interview or physical examination, or excessive and peculiar motor activity.” Further, “the criteria are met for catatonia during the course of a neurodevelopmental, psychotic, bipolar, depressive or other mental disorder.”

• **Catatonia disorder due to another medical condition** is characterized by “marked psychomotor disturbance that **may** involve decreased motor activity, decreased engagement during interview or physical examination, or excessive and peculiar motor activity.” Further, “the catatonia is judged to be attributed to the physiological effects of another medical condition.”

• “**Unspecified catatonia** applies to presentations in which symptoms characteristic of catatonia cause clinically significant distress or impairment in social, occupational or other important areas of functioning but either the nature of the underlying mental disorder or other medical condition is unclear, full criteria for catatonia are not met, or there is insufficient information to make a more specific diagnosis. e.g., in emergency room settings.”

• **Other specified and unspecified schizophrenia spectrum and other psychotic disorders** “applies to presentations in which symptoms characteristic of a schizophrenia spectrum and other psychotic disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the schizophrenia spectrum and other psychotic disorders diagnostic class.” When the reason that the presentation does not meet the criteria is communicated by recording “other specified schizophrenia spectrum and other psychotic disorder,” the specific reason is given, e.g., persistent auditory hallucinations. When the reason that the presentation does not meet the criteria is not communicated, “unspecified schizophrenia spectrum and other psychotic disorder” is recorded.

It is important to determine the etiology of any psychotic disorder so that a proper diagnosis is established and proper treatment is instituted. Medical causes of psychotic illness are varied and include intracranial processes such as infections, as well as neoplastic, epileptic, hypoxic, ischemic, metabolic or endocrinologic disorders. Additionally, dementias, delirium, Parkinson’s disease, Pick’s disease and Huntington’s disease can have psychotic features. Symptoms of psychosis **may** occur with acute intoxication caused by substance use, including the intermittent or chronic use of
While empirical evidence for the treatment of delusional disorder is scant, treatment for this disorder has proceeded on the basis of established efficacy for delusions in schizophrenia (Hales et al., 2008). A combination of first- or second-generation antipsychotics and antidepressant medication may be used while being complemented by other interventions, e.g., cognitive behavioral therapy. Somatic delusions may be more responsive to medications than other types of delusions (Chopra et al., 2009). High potency antipsychotic agents that provide rapid, predictable and effective sedation may be used in the management of patients who are acutely psychotic in brief psychotic disorder. In these cases, protecting the patient from self-injury or harm to others is imperative. Or, if the symptoms are minimally impairing, removing the specific stress should suffice (Memon and Larson, 2013). After the acute episode is resolved, individual, family and group therapy may be considered to help the patient cope with stressors, resolve conflict and improve self-esteem. The pharmacotherapy and psychosocial interventions, e.g., supportive, family, vocational and educational, for schizophreniform disorder are similar to those for schizophrenia (Bhalla. 2013).

Cluster A personality disorders (schizotypal, paranoid and schizoid) manifest positive and/or negative subpsychotic symptoms with mild to moderate cognitive and social impairment and less functional decline than in schizophrenia. Cluster B borderline personality disorder exhibits instability in mood, impulse control and interpersonal relationships where there is less functional decline than in schizophrenia. In this condition, the symptoms are more sensitive to interpersonal factors and are more unstable over time with psychosis emerging only with significant stress (Hales et al., 2008). Psychotherapy is the core component of care for personality disorders and medications are usually seen as an adjunct to psychotherapy so that the patient may engage in psychotherapy in a productive way (Hales et al., 2008; Bienenfeld, 2013). It is generally believed that the focus of psychopharmacological therapy in the treatment of personality disorders should be on the treatment of symptom clusters – i.e., cognitive-perceptual symptoms, e.g., transient psychosis, idiosyncratic ideation, affective dysregulation symptoms, e.g., anxiety, hostility, sensitivity to rejection, and impulsive-behavioral dyscontrol symptoms, e.g., aggressive behavior. Careful use of antidepressant, anticonvulsant and antipsychotic drugs may be used in the treatment of personality disorders while symptoms are active, along with vigilant and ongoing monitoring (Hales et al., 2008; Bienenfeld, 2013).

For more information on the assessment and treatment-planning process for schizoaffective disorder, mood disorders with psychosis and drug-related psychoses, the reader is directed to review the following documents: 1) Introduction to Magellan’s Adopted Clinical Practice Guidelines for the Treatment of Schizophrenia; 2) Introduction to the Magellan’s Clinical Practice Guidelines for the Treatment of Bipolar Disorder; 3) Introduction to Magellan’s Clinical Practice Guidelines for the Assessment and Treatment of Patients with Depressive Disorders and 4) Introduction to Magellan’s Clinical Practice Guidelines for the Assessment and Treatment of Patients with Substance Use Disorders.
Obtaining Copies of the APA Guidelines

Copies of the Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition and Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients with Schizophrenia may be obtained through the APA at http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf or by calling 1-800-368-5777, or by U.S. mail at:

1000 Wilson Blvd., Suite 1825
Arlington, VA 22209-3901

Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. All suggestions and recommendations are taken into consideration in our ongoing review of the guidelines. Comments may be submitted to:

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Columbia, Maryland 21046
CPG@MagellanHealth.com
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