



Introduction to Magellan's Adopted Clinical Practice Guidelines for the Treatment of Schizophrenia

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Purpose of This Document

This document is an introduction and update to Magellan Health Services' (Magellan) adopted clinical practice guidelines (CPG) for the treatment of persons with a schizophrenic disorder.

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

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

Introduction

Magellan has adopted the American Psychiatric Association's (APA) *Practice Guideline for the Treatment of Patients with Schizophrenia*, Second Edition (2004)¹ 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 is one of the most comprehensive and widely-used, evidence-based clinical practice guidelines (CPG) for this disorder. Therefore, adoption of this guideline and published update provides an excellent source of evidence-based information. Since the guideline is accepted by other managed behavioral health care companies, it reduces the burden on practitioners serving multiple organizations.

The APA guideline and watch incorporate rapidly evolving developments in pharmacotherapy, as well as developments in other areas of 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. 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 August 2009. Key relevant recommendations from this more recent literature review are summarized here. Magellan encourages providers to be familiar with this information, as well as the information provided in the APA publications.

Epidemiology

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, the guideline does indicate that the risk of having schizophrenia is greater in persons whose parents have the disorder where 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 an increasing risk with the corresponding number of affected relatives. A

more recent systematic review of family studies of probands with schizophrenia and bipolar disorder (BD) was conducted to determine whether these disorders coaggregate in families. Some 38 studies were used to investigate rates of BD in first degree relatives (FDRs) of probands with schizophrenia, while some 39 studies were used to examine 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 (Van Snellenerg et al. 2009).

First Episode/Early Psychosis

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 recent meta-analysis supported this premise and reported an association between duration of untreated psychosis and clinical outcome. 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 factor³. 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. 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.⁴

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.⁵ 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.⁶ Risperidone was shown to demonstrate 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.⁷

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 FGA (haloperidol) or a SGA (i.e., amisulpride, olanzapine, quetiapine, ziprasidone) drug. The study could not conclude that SGA drugs were more efficacious than haloperidol. However, the discontinuation rates for all SGAs were less than for haloperidol (Kahn et al. 2008). 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).

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 they could not be accounted for by medication dose, demographic variable or

intellectual level (Goldberg et al. 2009).

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.⁸

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 recovery⁹. Comprehensive (i.e., multi-element) treatment approaches show promise in reducing symptoms and hospital re-admissions. 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 can be drawn yet from the literature on groups and families for this population.⁹

Another area of renewed clinical interest is the measurement of Intelligence Quotient (IQ) as a measure of early neurodevelopmental abnormality in patients with schizophrenia. The research team of Woodberry et al. published a quantitative review of the literature on pre-morbid IQ in individuals with schizophrenia. (Woodbury 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 (Woodberry et al. 2008).

Violent Behavior

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 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. 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, violence was significantly increased by positive symptoms, 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 to be reviewed in any violence risk assessment where the focus needs to be on the whole person in the community environment.¹⁰

Cultural Factors

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 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).

In the APA guideline, the repeated observations of the race of the patient potentially eliciting a bias in the diagnostic process are discussed. It is noted 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 is related to treatment studies that have reported 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. In related studies, it also has been observed that two factors confer a higher risk of being diagnosed with schizophrenia: 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.¹¹ 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.¹² 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.¹³ 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.¹⁴

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 vs. Second-Generation Agents

Upon publication in 2004, our adopted practice guideline suggested an advantage to starting treatment with a second-generation antipsychotic (SGA) over a first-generation antipsychotic (FGA) 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). *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.^{15,16,17} 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.¹⁸ 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.¹⁶ 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?¹⁹

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.²⁰ 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.²¹ 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.²²

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.²³ Likewise, these same antipsychotic treatment groups made only modest improvements in psychosocial functions – with no one drug showing any distinct superiority.²⁴

Another randomized phase of the CATIE study studied patients with chronic schizophrenia who were prescribed a new second-generation antipsychotic after discontinuing the first-generation antipsychotic 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.²⁵ Similarly, an analysis was conducted on Phase 1 CATIE study findings to explore the advantages to continuing or switching baseline medications olanzapine or risperidone. For both treatments, findings showed that stayers on average fared somewhat better than patients newly switched to these two medications. 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.²⁶

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 these medications.²⁷

More recent research on the unique dopamine partial agonist properties of aripiprazole has 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 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).

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 (Clinical Pharmacology [database online], 2009). 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). Also, in August 2009 the FDA approved the atypical antipsychotic, asenapine, a broad spectrum, high potency serotonin, noradrenaline and dopamine antagonist (i.e., 5-HT₂/D₂ antagonist) for use in patients with 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 extrapyramidal side effects (EPS) and weight gain (Clinical Pharmacology [database online], 2009).

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. 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, Corves et al., 2009).

The research team of Leucht et al. also 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. 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 (Leucht, Komossa et al. 2009).

In, conclusion, researchers now seem to be stressing 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, Komossa et al. 2009/ Dixon et al. 2009).

Metabolic Disturbances

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.²⁸ 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.²⁹

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.³⁰ 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.³¹

In February 2004, panelists from four professional societies published a Consensus Statement after reviewing most of the evidence for these adverse events with SGAs.³² 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 this 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,³³ offer good tables of what needs monitoring and suggested frequencies so providers may refer to these tables.^{1, 32,33}

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.

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.³⁴ In this study, waist circumference greater than 102 cm/40" in males and 88 cm/35" 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 belly button >102 cm / 40" in males, 88 cm/35" 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.

A recent 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.³⁵ 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.

The oral biguanide antidiabetic agent, metformin, has recently 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, Zhao, Guo 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, Zhao, Jin et al. 2008).

Other Pharmacological Agents

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. 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 (Buchanan, Javitt et al. 2007). 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 (Kuldarni et al. 2009).

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 $\alpha_4\beta_2$ and α_7 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, Connelly et al. 2008).

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).

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.³⁶ 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.³⁷ 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.³⁸ 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.³⁶ 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

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, were found to be effective in promoting adherence. Successful behavioral techniques include the use of reminders, self-monitoring tools, cues and reinforcements.³⁹ 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.⁴⁰

Long-acting depot injections of fluphenazine (Prolixin) and haloperidol (Haldol) have long been one method to support 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 (EPS). 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.⁴¹ 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 (Clinical Pharmacology [database online], 2009/ Johnson and Johnson, 2009).

Schizophrenia in Children and Adolescents

There are few studies that evaluate the efficacy of SGA medications in children with schizophrenia, but recent research at the request of the FDA has indicated that use of Abilify (aripiprazole) in adult doses proved effective and well-tolerated.⁴² 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 Abilify did not cause the metabolic side effects, such as weight gain and lipid dysregulation, typical of drugs in this class. Using Abilify 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 groups 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 recent 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.⁴³

More recently, 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 benztropine) 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 symptoms 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/ Dixon et al. 2009).

Schizophrenia in the Elderly

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 healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly treated for dementia-related psychosis (FDA Alert 6/16/08).

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 dosaging 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.⁴⁴

Supported Employment

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.⁴⁵

A recent analysis published using baseline data, collected prior to randomization from the CATIE study, were used to examine the association of diverse socio-demographic, clinical and environmental factors with 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.⁴⁶

Social Skills Training

The APA guideline indicates that social skills training (SST) is well established for improving outcomes and reducing relapse rates and symptoms scores. However, a recent 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.^{47,48} 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.⁴⁹ 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.

Cognitive Remediation and Rehabilitation

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, research studies have been conducted providing an update to our understanding of this particular psychosocial intervention. 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).

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). 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. 2009).

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).

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.^{50,51,52} 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

Any algorithm for treatment-resistant illness must begin with recommendations to re-evaluate the accuracy of the diagnosis and assess for treatment compliance. A recent study of California Medicaid patients with schizophrenia found that partial compliance (e.g., intermittent taking of medications) is much more common than non-compliance (stopping of medications).⁵³ 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. A recent study suggests that both olanzapine and risperidone are also effective in such patients.⁵⁴ 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.⁵⁵ It is further emphasized that medication trials in such patients may need to last at least 12 weeks. However, another study concerning olanzapine calls this conclusion into question.⁵⁶ Further research is needed in the area of medication for treatment-resistant illness and augmentation strategies.

Other Psychotic Disorders

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®)* describes Schizophrenia and Other Psychotic Disorders (American Psychiatric Association, 2000).⁸³ According to the DSM-IV-TR, “In Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, and Brief Psychotic Disorder, the term *psychotic* refers to delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior. In Psychotic Disorder Due to a General Medical Condition and in Substance-Induced Psychotic Disorder, *psychotic* refers to delusions or only those hallucinations that are not accompanied by insight. Finally, in Delusional Disorder and Shared Psychotic Disorder, *psychotic* is equivalent to delusional.”

The DSM-IV-TR describes the following psychotic disorders:

- “**Schizophrenia** is a disorder that lasts for at least 6 months and includes at least 1 month of active-phase symptoms (i.e., two [or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms).”
- “**Schizophreniform Disorder** is characterized by a symptomatic presentation that is equivalent to Schizophrenia except for its duration (i.e., the disturbance lasts from 1 to 6 months) and the absence of a requirement that there be a decline in functioning.”
- “**Schizoaffective Disorder** is a disorder in which a mood episode and the active-phase symptoms of Schizophrenia occur together and were preceded or are followed by at least 2 weeks of delusions or hallucinations without prominent mood symptoms.”
- “**Delusional Disorder** is characterized by at least 1 month of nonbizarre delusions without other active-phase symptoms of Schizophrenia.”
- “**Brief Psychotic Disorder** is a disorder that lasts more than 1 day and remits by 1 month”.
- “**Shared Psychotic Disorder** is characterized by the presence of a delusion in an individual who is influenced by someone else who has a longer-standing delusion with similar content.”
- “In **Psychotic Disorder Due to a General Medical Condition**, the psychotic symptoms are judged to be a direct physiological consequence of a general medical condition.”
- “In **Substance-Induced Psychotic Disorder**, the psychotic symptoms are judged to be a direct physiological consequence of a drug of abuse, a medication, or toxin exposure.”
- “**Psychotic Disorder Not Otherwise Specified** is included for classifying psychotic presentations that do not meet the criteria for any of the specific Psychotic Disorders...or psychotic symptomatology about which there is inadequate or contradictory information.” (American Psychiatric Association, 2000)

It is important to determine the etiology of any psychotic disorder so that a proper diagnosis is established and proper treatment is instituted. Psychotic disorders that may be caused by underlying medical conditions, abuse of substances, medications, toxins and other psychiatric conditions that may involve psychotic symptoms (e.g., Schizoaffective Disorder, Major Depressive Disorder with Psychotic Features and Bipolar I Disorder Single Manic Episode/Most Recent Episode Manic/Most Recent Episode Mixed/Most Recent Episode Depressed and Bipolar II Disorder and Bipolar Disorder Not Otherwise Specified) all exist. 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 drugs, particularly stimulants (American Psychiatric Association, 2000; Hales et al., 2008).⁸²

DSM-IV-R also discusses other diagnoses that are to be considered in the differential diagnosis of schizophrenia: Psychotic Disorder Due to a General Medical Condition, delirium, dementia, Substance-Induced Psychotic Disorder, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Related Disorders which may produce symptoms similar to those of Schizophrenia ("e.g., sustained amphetamine or cocaine use may produce delusions or hallucinations; phencyclidine use may produce a mixture of positive and negative symptoms"), Mood Disorder with Psychotic Features, Schizoaffective Disorder, Depressive Disorder Not Otherwise Specified, Bipolar Disorder Not Otherwise Specified, Mood Disorder with Catatonic Features, Schizophreniform Disorder, Brief Psychotic Disorder, Delusional Disorder, Psychotic Disorder Not Otherwise Specified, Pervasive Developmental Disorders, childhood presentations combining disorganized speech (from a Communication Disorder) and disorganized behavior (from Attention Deficit/Hyperactivity Disorder) as well as Schizotypal, Schizoid or Paranoid Personality Disorder (American Psychiatric Association, 2000). DSM-IV-TR also notes that some individuals with Borderline Personality Disorder "...develop psychotic-like symptoms (e.g., hallucinations, body-image distortions, ideas of reference, and hypnagogic phenomena) during times of stress," (American Psychiatric Association, 2000). The reader is referred to DSM-IV-TR for more information on these conditions.

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).⁸⁴ 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 et al., 2009).⁸⁵ 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 (Memon et al., 2009). The pharmacotherapy and psychosocial interventions (e.g., supportive, family, vocational and educational) for Schizophreniform Disorder are similar to those for schizophrenia (Bhalla, 2009).⁸⁶

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 (APA 2000; 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, 2008).⁸⁷ 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 2008).

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 www.appi.org, by calling (800)368-5777, or by U.S. mail at:

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

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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References

1. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Schizophrenia, Second Edition. *Am J Psychiatry* 161:2, February 2004 Supplement.
2. Dixon L, Perkins D, Calmes C. Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients with Schizophrenia. Accessed website <http://www.psychiatryonline.com> on November 11, 2009.
3. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry*. 2005 Oct;162(10):1785-804.
4. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. *Am J Psychiatry*. 2006 Apr;163(4):743-5.
5. Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, Lieberman JA. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007 Jul;164(7):1061-71.
6. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, Sweitzer D, Olexy C, Weiden P, Strakowski SD. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007 Jul;164(7):1050-60.
7. Harvey PD, Rabinowitz J, Eerdeken M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry*. 2005 Oct;162(10):1888-95.
8. Robinson DG, Woerner MG, Napolitano B, Patel RC, Sevy SM, Gunduz-Bruce H, Soto-Perello JM, Mendelowitz A, Khadivi A, Miller R, McCormack J, Lorell BS, Lesser ML, Schooler NR, Kane JM. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *Am J Psychiatry*. 2006 Dec;163(12):2096-102.
9. Penn DL, Waldheter EJ, Perkins DO, Mueser KT, Lieberman JA. Psychosocial treatment for first-episode psychosis: a research update. *Am J Psychiatry*. 2005 Dec;162(12):2220-32.
10. Swanson JW, Swartz MS, Van Dorn RA, Elbogen EB, Wagner HR, Rosenheck RA, Stroup TS, McEvoy JP, Lieberman JA. A national study of violent behavior in persons with schizophrenia. *Arch Gen Psychiatry*. 2006 May;63(5):490-9.
11. Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry* 2005 Jan;162(1):12-24.
12. Copeland LA, Zeber JE, Valenstein M, Blow FC. Racial disparity in the use of atypical antipsychotic medications among veterans. *Am J Psychiatry* 2003 Oct;160(10):1817-22.
13. Opolka JL, Rascati KL, Brown CM, Gibson PJ. Ethnicity and prescription patterns for haloperidol, risperidone, and olanzapine. *Psychiatr Serv* 2004 Feb;55(2):1 51-6.
14. Montross LP, Barrio C, Yamada AM, Lindamer L, Golshan S, Garcia P, Fuentes D, Daly RE, Hough RL, Jeste DV. Tri-ethnic variations of co-morbid substance and alcohol use disorders in schizophrenia. *Schizophr Res* 2005 Jun 21.
15. Volavka J, Czobor P, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Cooper TB, Chakos M,

- Lieberman JA. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry* 2002 Feb;159(2):255-62.
16. Davis JM, Chen N, Glick ID. Meta-analysis of the efficacy of second generation antipsychotics. *Arch Gen Psychiatry* 2003 Jun; 60:553-564.
 17. Leucht S, Barnes TRE, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003 Jul;160:1209-1222.
 18. Rosenheck R, Perlick D, Bingham S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia. *JAMA* 2003 Nov 26;290(20):2693-2702.
 19. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing Clinical and Functional Outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial. *Schizophrenia Bulletin*, 29(1): 33-43, 2003.
 20. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. *N Engl J Med*. 2005 Sep 22;353(12):1209-23.
 21. Rosenheck RA, Leslie DL, Sindelar J, Miller EA, Lin H, Stroup TS, McEvoy J, Davis SM, Keefe RS, Swartz M, Perkins DO, Hsiao JK, Lieberman J; CATIE Study Investigators. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. *Am J Psychiatry*. 2006 Dec;163(12):2080-9.
 22. Polsky D, Doshi JA, Bauer MS, Glick HA. Clinical trial-based cost-effectiveness analyses of antipsychotic use. *Am J Psychiatry*. 2006 Dec;163(12):2047-56.
 23. Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA; CATIE Investigators; Neurocognitive Working Group. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007 Jun;64(6):633-47.
 24. Swartz MS, Perkins DO, Stroup TS, Davis SM, Capuano G, Rosenheck RA, Reimherr F, McGee MF, Keefe RS, McEvoy JP, Hsiao JK, Lieberman JA; CATIE Investigators Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *Am J Psychiatry*. 2007 Mar;164(3):428-36.
 25. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Capuano GA, Rosenheck RA, Keefe RS, Miller AL, Belz I, Hsiao JK; CATIE Investigators. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry*. 2007 Mar;164(3):415-27.
 26. Essock SM, Covell NH, Davis SM, Stroup TS, Rosenheck RA, Lieberman JA. Effectiveness of switching antipsychotic medications. *Am J Psychiatry*. 2006 Dec;163(12):2090-5.
 27. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2006 Jun;63(6):622-9.
 28. Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, Revicki D, Buchanan RW. An Assessment of the Independent Effects of Olanzapine and Risperidone Exposure on the Risk of Hyperlipidemia in Schizophrenic Patients. *Arch Gen Psychiatry*. 2002;59:1021-1026.
 29. Breier A, Berg PH, Thakore JH, Naber D, Gattaz WF, Cavazzoni P, Walker DJ, Roychowdhury SM, Kane JM. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry*. 2005 Oct;162(10):1879-87.
 30. Lindenmayer, JP, Changes in Glucose and Cholesterol Levels in Patients With Schizophrenia Treated

With Typical or Atypical Antipsychotics. *Am J Psychiatry* 2003; 160:290-296.

31. Lambert BL, Chou CH, Chang KY, Tafesse E, Carson W. Antipsychotic exposure and type 2 diabetes among patients with schizophrenia: a matched case-control study of California Medicaid claims. *Pharmacoepidemiol Drug Saf* 2005 Jun;14(6):417-25.
32. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, *Diabetes Care*, Volume 27, Number 2, February, 2004.
33. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004 Aug;161(8):1334-49.
34. Straker D, et al. Cost-effective screening for the metabolic syndrome in patients treated with second-generation antipsychotic medications. *Am J Psychiatry* 2005 Jun;162(6):1217-21.
35. Henderson DC, Copeland PM, Daley TB, et al. A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. *Am J Psychiatry* 2005 May;162(5):954-62.
36. American Psychiatric Association. Resource Document on Mandatory Outpatient Treatment. September, 1999.
37. Swartz MS, Swanson JW, Wagner HR, Hannon MJ, Burns BJ, Shumway M. Assessment of four stakeholder groups' preferences concerning outpatient commitment for persons with schizophrenia. *Am J Psychiatry* 2003 160: 1139-1146.
38. Rohland BM, Rohrer JE, Richards CC. The long-term effect of outpatient commitment on service use. *Adm Policy Ment Health* 2000 Nov; 27(6) 383-94.
39. Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. *Am J Psychiatry* 2002 Oct;159(10):1653-64.
40. Kemp R, Hayward P, Applewhaite G, et al. Compliance Therapy in Psychotic Patients: Randomised Controlled Trial. *British Medical Journal* 312:345-349 (1996).
41. Kane JM, Eerdeken M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003 160: 1125-1132.
42. Moyer P. AACAP: Atypical antipsychotic scores at adult doses for children and adolescents. MedPage Today conference report. Primary source: 52nd Annual Meeting JAACP Toronto, October 18-23, 2005. Abstract #C5.
43. Shaw P, Sporn A, Gogtay N, Overman GP, Greenstein D, Gochman P, Tossell JW, Lenane M, Rapoport JL. Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry*. 2006 Jul;63(7):721-3.
44. Sable JA, Jeste DV. Antipsychotic treatment for late-life schizophrenia. *Curr Psychiatry Rep* 2002 Aug;4(4):299-306.
45. McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A. Cognitive training for supported employment: 2-3 year outcomes of a randomized controlled trial. *Am J Psychiatry*. 2007 Mar;164(3):437-41.
46. Rosenheck R, Leslie D, Keefe R, McEvoy J, Swartz M, Perkins D, Stroup S, Hsiao JK, Lieberman J; CATIE Study Investigators Group. Barriers to employment for people with schizophrenia. *Am J Psychiatry*. 2006 Mar;163(3):411-7.
47. Philling S, Bebbington P, Kuipers E, et al. Psychological treatments in schizophrenia: II meta-analysis of randomized controlled trials of social skills training and cognitive remediation. *Psychol Med*

2002;32:783-791.

48. Dickerson FB, Lehman AF Evidence-based psychotherapy for schizophrenia. *J Nerv Ment Dis* 2006 Jan; 194(1):3-9 Review.
49. Glynn SM, Marder SR, Liberman RP, Blair K, Wirshing WC, Wirshing DA, Ross D, Mintz J. Supplementing clinic-based skills training with manual-based community support sessions: effects on social adjustment of patients with schizophrenia. *Am J Psychiatry* 2002 May;1 59(5):829-37.
50. Meltzer HY, Alphas L, Green AI, Altamura CA, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer J-P, Potkin S, for the International Suicide Prevention Trial (InterSePT) Study Group. Clozapine Treatment for Suicidality in Schizophrenia. *Arch Gen Psychiatry* Jan 2003;60:82-91.
51. Mamo DC. Managing suicidality in schizophrenia. *Can J Psychiatry*. 2007 Jun; 52(6 Suppl 1): 59S-70S.
52. Hennen J, Baldessarini RJ. Suicide risk during treatment with clozapine: a meta-analysis. *Schizophr Res*. 2005 Mar 1; 73(2-3): 139-45.
53. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv* 2004 Aug;55(8):886-91.
54. Dinakar HS, Sobel RN, Bopp JH, Daniels A, Mauro S. Efficacy of olanzapine and risperidone for treatment-refractory schizophrenia among long-stay state hospital patients. *Psychiatr Serv* 2002 Jun;53(6):755-7.
55. Honer WG, Thornton AE, Chen EY, Chan RC et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *N Engl J Med* 2006 Feb 2; 354 (5): 472-82.
56. Lindenmayer JP, Czobor P, Volavka J, Lieberman JA, Citrome L, Sheitman B, Chakos M, McEvoy JP. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. *J Clin Psychiatry* 2002 Oct;63(10):931-5.
57. Accessed website http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm on April 14, 2009.
58. Shim JC, Shin JG, Kelly DL, Jung DU, Seo YS, Liu KH, Shon JH, Conley RR. Adjunctive Treatment With a Dopamine Partial Agonist, Aripiprazole, for Antipsychotic-Induced Hyperprolactinemia: A Placebo-Controlled Trial. *Am J Psychiatry* 2007; 164: 1404-1410.
59. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeryer F, Kapur S. Differential Effects of Aripiprazole On D2, 5-HT2, and 5-HT1A Receptor Occupancy in Patients with Schizophrenia: A Triple Tracer PET Study. *Am J Psychiatry* 2007; 164:1411-1417.
60. Paliperidone. Clinical Pharmacology [database online]. Tampa FL: Gold Standard, Inc; copyright 2008. URL: <http://www.clinicalpharmacology.com>. Accessed website August 19, 2009.
61. Asenapine. Clinical Pharmacology [database online]. Tampa FL: Gold Standard, Inc; copyright 2008. URL: <http://www.clinicalpharmacology.com>. Accessed website August 19, 2009.
62. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Lobos CA, Schwarz S, Davis JM. A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia. *Am J Psychiatry* 2009; 166: 152-163.
63. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. www.thelancet.com. Vol 373, January 3, 2009.
64. Canuso CM, Dirks B, Carothers J, Kosik-Gonzalez C, Bossie CA, Zhu y, Damaraju CV, Kalali AH, Mahmoud R. Randomized, Double-Blind, Placebo-Controlled Study of Paliperidone Extended-Release and Quetiapine in Inpatients With Recently Exacerbated Schizophrenia. *Am J Psychiatry* 2009; 166: 691-701.

65. Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, Ambler D, Puglia M, Maloney AE, Michael E, DeJong S, Slifka K, Noyes N, Hlastala S, Pierson L, McNamara NK Double-Blind Comparizon of First- and Second-Generation Antipsychotics in Early-Onset Schizophrenia and Schizo-affective Disorder: Findings From the Treatment of Early-Onset Schizophrenia Sectrum Disorders (TEOSS) Study. *Am J psychiatry* 2008; 165: 1420-1431.
66. Van Snellenberg JX, Candia T. Meta-analytic Evidence for Familial Coaggregation of Schizophrenia and Biploar Disorder. *Arch Gen Psychiatry/Vol. 66 (No. 7), July 2009.*
67. Woodberry KA, Guiliano AJ, Seidman LJ. Premorbid IQ in Schizophrenia: A Meta-Analytic Review. *Am J Psychiatry* 2008; 165:579-587.
68. Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, Gheorghe MD, Rybakowski JD, Galderisi S, Libiger J, Hummer M, Dollfus S, Lopez-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors , Reicher-Rossler A, Grobbee DE for the EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomized clinical trial. *The Lancet Vol 371 March 29, 2008.*
69. Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS, Boter H, Keet IPM, Prelipceanu D, Rybakowski JK, Libiger J, Hummer M, Dollfus S, Lopez-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rossler A, Kahn RS. Cognitive Effects of Antipsychotic Drugs in First-Episode Schizophtrenia and Schizophreniform Disorder: A Randomized, Open-Label Clinical Trial (EUFEST). *Am J Psychiatry* 166:6, June 2009.
70. Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel R, Woerner MG, Schooler NR, Kane JM, Robinson DG. Cognitive Improvement After Treatment With Second-Generation Antipsychotic Medications in First-Episode Schizophrenia. Is It a Practice Effect? *Arch Gen Psychiatry/Vol 64 (No. 10), October 2007.*
71. Wu, RR, Zhao JP, Guo XF, He YQ, Faang MS, Guo WB, Chen JD, Li LH. Metformin Addition Attenuates Olanzapine-Induced Weight Gain in Drug-Naïve First-Episode Schizophrenia Patients: A Double-Blind, Placebo-Controlled Study. *Am J Psychiatry* 2008; 165:352-358.
72. Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XP, He YQ, Liu YJ, Chen JD, Li LH. Lifestyle Intervention and Metformin for Treatment of Antipsychotic-Induced Weight Gain. A Randomized Controlled Trial. *JAMA.* 2008; 299(2): 185-193.
73. Buchanan RW, Javitt DC, Marder SR, Schooler NR, Gold JM, McMahon RP, Heresco-Levy U, Carpenter WT. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): The Efficacy of Glutamatergic Agents for Negative Symptoms and Cognitive Impairments. *Am J Psychiatry* 2007; 164: 1593-1602,
74. Shekhar A, Potter WZ, Lightfoot J, Lienemann J, Dube S, Mallinckrodt C, Bymaster FP, McKinzie DL, Felder CC. Selective Muscarinic Receptor Agosist Xanomeline as a Novel Treatment Approach fro Schizophrenia. *Am J Psychiatry* 2008; 165: 1033-1039.
75. FDA Approves Invega @Sustenna™ for the Acute and Maintenance Treatment of Schizophrenia. Accessed website http://www.jnj.com/connect/news/all/20090731_153000. Accessed website on November 16, 2009.
76. Buchanan RW, Conley RR, Dickinson D, Ball MP, Feldman S, Gold JM, McMahon RP. Galantamine for the Treatment of Cognitive Impairments in People with Schizophrenia. *Am J Psychiatry* 2008; 165: 82-89.
77. Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, Marcus R, McQuade RD, Iwamoto T, Carson WH. *Am J Psychiatry* 2008; 165: 1432-1441.
78. Mohamed S, Rosenheck R, Swartz M, Stroup S, Lieberman JA, Keefe RSE. Relationship of Cognition and Psychopathology to Functional Impairment in Schizophrenia. *Am J Psychiatry* 2008; 165: 978-987.

79. McGurk SR, Twanmlwy EW, Sitzer DI, McHugo GJ, Mueser KT. A Meta-Analysis of Cognitive remediation in Schizophrenia. *Am J Psychiatry* 164: 12, December 2007.
80. Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC. Prefrontal Activation Deficits During Episodic Memory in Schizophrenia. *Am J Psychiatry* Volume 168; Issue 8, August 2008.
81. Fisher M, Holland C, Merzenich MM, Vinogradov S. Using Neuroplasticity-Based Auditory Training to Improve Verbal Memory in Schizophrenia. *Am J Psychiatry* 166: 7, July 2009.
82. Hales RE, Yudofsky SC, Gabbard GO, eds. *The American Psychiatric Publishing Textbook of Psychiatry, Fifth Edition, 2008, Chapter 10-Schizophrenia*. Accessed website on January 5, 2010 www.psychiatryonline.com.
83. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®)*, American Psychiatric Association, Washington, DC., 2000.
84. Chopra S, Khan R. Delusional Disorder. Accessed website December 14, 2009 <http://emedicine.medscape.com/article/292991-overview>.
85. Memon MA, Larson M. Brief Psychotic Disorder. Accessed website December 14, 2009 <http://emedicine.medscape.com/article/294416-print>.
86. Bhalla RN. Schizophreniform Disorder. Accessed website December 14, 2009 <http://emedicine.medscape.com/article/292885-print>.
87. Bienenfeld D. Personality Disorders. Accessed website December 14, 2009 <http://emedicine.medscape.com/article/294307-print>.

Additional Sources Reviewed But Not Cited

88. Benes FM. Schizophrenia, II: amygdalar fiber alteration as etiology? *Am J Psychiatry* 2003 160: 1053.
89. Breier A, Meehan K, Birkett M, David S, Ferchland I, Sutton V, Taylor CC, Palmer R, Dossenbach M, Kiesler G, Brook S, Wright P. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry* 2002 May;59(5):441-8.
90. Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology* 2003 Jan;28(1):1 82-92.
91. Clozapine and schizophrenia - Letters to the Editor. *Am J Psychiatry* 2002 Feb;1 59(2):31 5-26.
92. Couture SM, Roberts DL, et al. Do baseline client characteristics predict the therapeutic alliance in the treatment of schizophrenia? *J Nerv Ment Dis* 2006 Jan;194 (1): 10-4.
93. Dickey B, Normand SL, Hermann RC, Eisen SV, Cortes DE, Cleary PD, Ware N. Guideline recommendations for treatment of schizophrenia: the impact of managed care. *Arch Gen Psychiatry* 2003 Apr; 60(4) 340-8.
94. Dyck DG, Hendryx MS, Short RA, Voss WD, McFarlane WR. Service use among patients with schizophrenia in psychoeducational multiple-family group treatment. *Psychiatr Serv* 2002 Jun;53(6):749-54.
95. Faraone SV, Brown CH, Glatt SJ, Tsuang MT. Preventing schizophrenia and psychotic behavior: definitions and methodological issues. *Can J Psychiatry* 2002 Aug;47(6):527-37.
96. Fox V. First person account: schizophrenia, medication, and outpatient commitment. *Schizophr Bull* 2001 Feb; 27(1) 177-8.

97. Freedman R. Schizophrenia *N Engl J Med* 2003 Oct 30;349(18):1738-1749.
98. Grigoriadis S, Seeman MV. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. *Can J Psychiatry* 2002 Jun;47(5):437-42.
99. Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. *Am J Psychiatry*. 2006 Nov;163(11):1918-2.
100. Hauff E, Varvin S, Laake P, Melle I, Vaglum P, Friis S. Inpatient psychotherapy compared with usual care for patients who have schizophrenic psychoses. *Psychiatr Serv* 2002 Apr;53(4):471-3.
101. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005 Dec;150(6):1115-21 Review.
102. Heyrman MJ. Confusion about outpatient commitment. *Psychiatr Serv* 2001 Aug; 52(8) 1103-4.
103. Honigfeld G. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; 59: Suppl 3: 3-7.
104. Hsien-Yuan Lane, Yue-Cune Chang, Yi-Ching Liu, Chih-Chiang Chiu, Guochuan E. Tsai. Sarcosine of D-Serine Add-on Treatment for Acute Exacerbation of Schizophrenia: A Randomized, Double-blind, Placebo-Controlled Study. *Arch Gen Psychiatry*/Vol 62. Nov 2005.
105. Hunter MD, Ganesan V, Wilkinson ID, Spence SA. Impact of modafinil on prefrontal executive function in schizophrenia. *Am J Psychiatry*. 2006 Dec;163(12):2184-6.
106. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*. 2006 Oct;63(10):1079-87.
107. Kane, JM, Leucht S, Carpenter D, and Docherty, JP. The Expert Consensus Guidelines Series: Optimizing Pharmacologic Treatment of Psychotic Disorders. Editors: *Journal of Clinical Psychiatry*. Volume 64; sup 12; 2003.
108. Kemmler G, Hummer M, Widschwendter C, Fleischhacker WW. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. *Arch Gen Psychiatry*. 2005 Dec;62(12):1305-12.
109. Leucht S, McGrath J, White P, Kissling W. Carbamazepine augmentation for schizophrenia: how good is the evidence? *J Clin Psychiatry* 2002 Mar;63(3):218-24.
110. Meltzer HY. Suicidality in schizophrenia: a review of the evidence for risk factors and treatment options. *Curr Psychiatry Rep* 2002 Aug;4(4):279-83.
111. Milner KK, Valenstein M. A comparison of guidelines for the treatment of schizophrenia. *Psychiatr Serv* 2002 Jul;53(7):888-90.
112. Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry* 2002 Dec;63(12):1 121-8.
113. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry*. 2007 Jan;64(1):19-28.
114. Pickar D, Bartko JJ. Effect size of symptom status in withdrawal of typical antipsychotics and subsequent clozapine treatment in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 2003 160: 1133-1138.
115. Rector NA, Beck AT. Cognitive therapy for schizophrenia: from conceptualization to intervention. *Can*

- J Psychiatry 2002 Feb;47(1) :39-48.
- 116.Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, Trivedi MH, Suppes T, Miller AL, Biggs MM, Shores-Wilson K, Witte BP, Shon SP, Rago WV, Altshuler KZ. Texas Medication Algorithm Project, phase 3 (TMAP-3): rationale and study design. J Clin Psychiatry 2003 Apr; 64(4) 357-69.
- 117.Sernyak MJ, Desai R, Stolar M, Rosenheck R. Impact of Clozapine on completed suicide. AM J Psychiatry 2001 Jun;158:931-937.
- 118.Strous RD, Maayan R, Lapidus R, Stryjer R, Lustig M, Kotler M, Weizman A. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch Gen Psychiatry 2003 Feb;60(2):1 33-41.
- 119.Suvisaari J, Mautemps N, Haukka J, Hovi T, Lönnqvist J. Childhood central nervous system viral infections and adult schizophrenia. Am J Psychiatry 2003 160: 1183-1185.
- 120.Torres A, Mendez LP, Merino H, Moran EA. Improving social functioning in schizophrenia by playing the train game. Psychiatr Serv 2002 Jul;53(7):799-801.