GUIDELINE WATCH (SEPTEMBER 2009): PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH SCHIZOPHRENIA

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APA's *Practice Guideline for the Treatment of Patients With Schizophrenia, Second Edition*, was published in April 2004 (1). This watch highlights key research studies published since that date. The studies were identified by a MEDLINE literature search for meta-analyses and randomized, controlled trials published between 2002 and 2008, using the same key words used for the literature search performed for the 2004 guideline.

With regard to pharmacotherapy, there have been several important randomized trials of antipsychotics. For chronic schizophrenia, trials include the National Institute of Mental Health (NIMH) Clinical Antipsychotic Trial for Intervention Effectiveness (CATIE) and the United Kingdom–funded Cost Utility of the Latest Antipsychotics in Schizophrenia (CUtLASS). For first-episode schizophrenia, there are two industry-funded trials, the European First Episode Schizophrenia Trial (EUFEST)—funded by AstraZeneca, Pfizer, and Sanofi-Aventis—and the Comparison of Atypicals for First Episode Schizophrenia (CAFE)—funded by AstraZeneca. For early-onset schizophrenia, there is one trial, the NIMH-funded Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS). These trials point to a reconsideration of treatment with the antipsychotics perphenazine and molindone and by extension other first-generation antipsychotics, with the possible exception of haloperidol, for which some trials have shown greater rates of extrapyramidal side effects or less favorable clinical response (2). In addition, a recent population-based cohort study (3) that encompassed 11 years of follow-up showed decreased rates of mortality with perphenazine as compared with other first- and second-generation antipsychotic agents; only clozapine use was associated with lower rates of overall mortality.

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The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available. Guideline watches summarize significant developments in practice since publication of an APA practice guideline. Watches may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent opinion of the authors and approval of the Executive Committee but not policy of the APA. This guideline watch was published in September 2009.

In addition, randomized controlled trials have demonstrated the safety and efficacy of a new antipsychotic, paliperidone, leading to its approval by the U.S. Food and Drug Administration (FDA). Several controlled clinical trials have investigated treatments to prevent or treat antipsychotic-related weight gain and metabolic changes. Additionally, there have been promising clinical trials of bupropion and behavioral interventions to reduce smoking in schizophrenia patients.

With regard to psychosocial treatments, new studies lend some additional support to the treatments recommended in the 2004 guideline. In addition, combinations of treatments have begun to be tested to enhance supported employment and social skills training. An evidence base has developed for interventions for obesity and for smoking cessation. There also has been continued study of cognitive remediation and peer support and peer-delivered services, which have the potential to play a useful role in recovery.

PHARMACOTHERAPY

COMPARATIVE EFFECTIVENESS OF ANTIPSYCHOTICS

The 2004 guideline recommends that selection of an antipsychotic agent be guided by the patient's past medication history, current symptoms and co-occurring conditions, other concurrent treatments, and preferences. The guideline states that second-generation agents should be considered first-line options for patients in the acute phase, mainly because of the decreased risk of extrapyramidal side effects and tardive dyskinesia, but acknowledges debate over the relative advantages, disadvantages, and cost-effectiveness of first- and second-generation agents. The guideline also states that for some patients, a first-generation agent may be an appropriate first-line option. This latter recommendation has been strengthened by the results of several recently published effectiveness studies that suggest that the first-generation antipsychotics perphenazine and molindone may be equally effective as second-generation agents. In fact, the distinction between first- and second-generation antipsychotics appears to have limited clinical utility.

Phase I of the double-blind CATIE clinical trial randomized 1,490 patients to available FDA-approved second-generation antipsychotics—risperidone, olanzapine, quetiapine, and ziprasidone—and to the first-generation antipsychotic perphenazine (4). There were few exclusion criteria, and patients were recruited from diverse programs in order to include "real-world" patients with potential co-occurring psychiatric or general medical conditions. The primary outcome measure was discontinuation from the randomized treatment, and by the end of the 18-month trial 74% of patients had switched to another antipsychotic or discontinued treatment. Olanzapine was the most effective medication, with 64% discontinuing, compared with the discontinuation rates for risperidone (74%) and quetiapine (82%). Perphenazine discontinuation rates (75%) were comparable to the other second-generation antipsychotics, including ziprasidone (79%). A similar pattern of results was found when symptom outcomes or hospitalization rates were examined. Extrapyramidal side effects were uncommon and similar across drugs, but olanzapine carried the greatest burden of metabolic side effects.

In the CUtLASS trial (5), 227 patients with schizophrenia who were judged by their treating clinician to potentially benefit from a new antipsychotic medication trial "because of inadequate response or adverse effects" were randomized to receive either a first- or a second-generation (excluding clozapine) antipsychotic. The specific antipsychotic was chosen by the treating clinician. The primary outcome measure, assessed by blind raters at 12, 26, and 56 weeks, was "quality of life," reflecting social and vocational function. Symptom changes were secondary outcomes. There was no difference in any outcome measures between groups.

In the EUFEST trial (6), 498 patients experiencing their first episode of schizophrenia were randomized to receive haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone. The study was conducted at 50 sites in 13 European countries and Israel, and treatment was not blinded. The primary outcome measure was discontinuation from treatment. At 1-year follow-up, all-cause discontinuation was higher for haloperidol (72%) than that for amisulpride (40%), olanzapine (33%), quetiapine (53%), or ziprasidone (45%). Global ratings of symptoms were least improved by treatment with quetiapine or haloperidol and most improved by treatment with amisulpride; however, there were no differences in symptom improvement as measured by the Positive and Negative Syndrome Scale or in rates of hospital admission. Extrapyramidal side effects were most severe in patients treated with haloperidol, and weight gain was most severe in patients treated with olanzapine.

In the CAFE trial (7), 400 patients early in the course of psychotic illness were randomly assigned in a double-

blind manner to receive olanzapine, quetiapine, or risperidone. At 1-year follow-up, all-cause discontinuation rates were similar for all groups (68.4%–71.4%), and there was no difference in symptom severity measures. Side effects were common and in line with the known side-effect profile of these antipsychotics.

The TEOSS study (8) was a double-blind, randomized trial comparing olanzapine, risperidone, and molindone in 119 pediatric patients with early-onset schizophrenia and schizoaffective disorder. "Response" was defined as improvement on the Clinical Global Impression scale of "very much" or "much" improved, at least a 20% reduction in symptom severity as measured by the Positive and Negative Syndrome Scale, and tolerating treatment for at least 8 weeks. A significant difference in response likelihood was not found between groups (molindone 50%, olanzapine 34%, risperidone 46%). Treatment with risperidone and olanzapine was associated with significant weight gain and metabolic side effects, and patients treated with molindone were more likely to report akathisia.

PALIPERIDONE

Paliperidone, marketed in an extended-release (ER) formulation, is the major active metabolite (9-hydroxyrisperidone) of risperidone. It is mainly cleared by the kidneys, with negligible hepatic metabolism. Five randomized, double-blind trials, sponsored by the manufacturer, Janssen Pharmaceuticals, involving 1,647 acutely ill patients with schizophrenia, demonstrated paliperidone ER to have greater efficacy than placebo at a fixed dose over 6 weeks (9) and led to the medication receiving FDA approval in 2006. Side effects included marked prolactin elevation in men and women, a greater incidence of extrapyramidal side effects at higher doses (>6 mg/day), dose-related weight gain, and tachycardia. Comparisons with fixed-dose (10 mg/day) olanzapine (N=1,332) showed similar efficacy and less liability for weight gain but greater liability for extrapyramidal side effects. Paliperidone ER thus appears to have a similar side-effect profile to its parent compound, risperidone. The relative advantages or disadvantages of paliperidone compared with risperidone are unknown.

MANAGING SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS

As described in the 2004 guideline, weight gain and metabolic side effects are common or frequent adverse effects of the second-generation antipsychotics clozapine, olanzapine, risperidone, and quetiapine. The guideline recommends regular monitoring of weight, body mass index, serum lipids, and fasting glucose levels of all patients. When patients gain weight, it is recommended that clinicians discuss treatment options, which may include switching medications, to prevent further weight gain and encourage weight loss.

Several clinical trials have investigated pharmacological and cognitive-behavioral treatments that may attenuate or reverse antipsychotic-related weight gain and lipid, glucose, and insulin changes (10). The nonpharmacological weight management interventions are described in greater detail in the subsection "Psychosocial Interventions for Weight Management," later in this watch. There have been several pharmacological clinical trials investigating metformin (a peripheral insulin-sensitizing agent), topiramate (an anticonvulsant), reboxetine (a selective norepinephrine reuptake inhibitor), and amantadine (a dopamine agonist). Metformin has been investigated in five randomized controlled studies, with four showing some indication of benefits (11–14), and one negative trial (15). The most promising results were reported in a randomized, double-blind trial in which 128 olanzapine-treated first-episode patients received adjunctive metformin 750 mg/day, metformin 750 mg/day plus lifestyle changes, lifestyle changes plus placebo, or placebo (11). The patients who received adjunctive metformin plus lifestyle changes had the most robust weight loss, body mass index (BMI) reduction, waist circumference reduction, and fasting insulin and insulin-resistance level reduction; these outcomes were significantly better than lifestyle changes plus placebo or placebo alone. For example, BMI significantly decreased by 1.8 units on average in the metformin plus lifestyle changes group, by 1.2 units in the metformin alone group, and by 0.5 units in the lifestyle changes plus placebo group. In the placebo group, in contrast, BMI increased by an average of 0.7 units. No increase in adverse events, including nausea, occurred in the patients treated with metformin.

Two randomized, placebo-controlled trials of adjunctive topiramate have reported weight loss in overweight patients who were already receiving treatment with olanzapine (16) or with risperidone, olanzapine, quetiapine, or clozapine (17). In patients who had gained weight during olanzapine treatment, two randomized, placebo-controlled trials reported that further weight gain was less pronounced with adjunctive amantadine treatment (18, 19). Two randomized, placebo-controlled trials also reported significant attenuation of weight gain when adjunctive reboxetine was initiated concomitantly with olanzapine in patients with a first episode of schizophrenia (20, 21). However, the clinical utility of these adjunctive treatments is unclear, given their relatively small impact on weight as well as their cost, potential side effects, and potential interactions with other medications.

PSYCHOSOCIAL TREATMENTS

As described in the 2004 guideline, psychosocial treatments such as family intervention, supported employment, assertive community treatment, skills training, and cognitive-behavioral therapy (CBT) can prevent relapse and enable recovery during the stable phase of treatment. Some interventions, such as family psychoeducation, may also be initiated during the acute phase. "Recovery," a construct that overlaps with but differs from treatment goals of cure or remission of symptoms, is defined by the President's New Freedom Commission on Mental Health as the "process in which people are able to live, work, learn, and participate fully in their communities" (22). The Substance Abuse and Mental Health Services Administration (23) has identified 10 components of recovery: "self-direction; individualized and person-centered; empowerment; holistic; non-linear; strengths-based; peer support; respect; responsibility; and hope." These components refer to the nature of treatment and the individual experience of the recovery process.

FAMILY PSYCHOEDUCATION

The 2004 guideline recommends engaging and collaborating with family members during an acute episode, whether first episode or relapse. Studies cited in the guideline and more recent studies have shown that family psychoeducation, delivered for 6–9 months following recent illness exacerbation or hospitalization, including family support, education, access to providers during crises, and some type of problem-solving skills, can reduce relapse rates among persons with schizophrenia as well as reduce family burden (24). Other studies that have focused on individuals who have not had an illness exacerbation have found that family psychoeducation contributed to improved social and vocational outcomes for individuals with schizophrenia and lower levels of distress and increased perceptions of professional and social support among family members (25, 26). Family psychoeducation programs lasting less than 6 months have been shown to contribute to positive outcomes for patients, including increased treatment adherence (27), and for family members, including increased knowledge about schizophrenia and improved family relationships (28–30).

ASSERTIVE COMMUNITY TREATMENT

Studies have continued to demonstrate that assertive community treatment (ACT) results in reduced hospitalization rates and reduced homelessness (31–34), particularly among individuals with high rates of hospitalization (35). Interventions that show higher fidelity to the ACT model show stronger outcomes (35).

SUPPORTED EMPLOYMENT

Recent studies of supported employment offer further evidence for its role in helping individuals with schizophrenia obtain competitive employment, earn more wages, and work more hours (36–38). Employment outcomes are better when there is greater fidelity to the supported employment model (39–41). Recent studies of supported employment have focused on improving long-term job retention and economic independence by augmenting supported employment with cognitive remediation (42, 43), social skills training (44, 45), and CBT (46, 47).

COGNITIVE-BEHAVIORAL THERAPY

Recent studies continue to offer support for the role of CBT in reducing both positive and negative symptoms (48–51) and improving social functioning (52). However, there is not consistent evidence that CBT improves outcomes among individuals who are experiencing acute psychotic symptoms (52–54). A recent meta-analysis suggests that CBT can be delivered in both individual and group formats with similar benefits, improving overall outcome in patients with schizophrenia who have residual symptoms (55).

SOCIAL SKILLS TRAINING

Similar to supported employment, social skills training assumes that recovery requires a multifaceted approach. Recent studies suggest that skills training contributes to improvements in broader functional outcomes (24, 56) and has been shown to lead to improved skills in refusing drugs of abuse (57), as well as improved communication in the workplace (44, 45) and with health care professionals (58). More recently, social skills training has been combined with family interventions (59, 60), case management (58), and CBT (61). There have been attempts to facilitate generalization of skills training to real world settings through application of skills training outside of the therapeutic context (58, 62). Skills training has evolved into so-called illness management and recovery programs (63).

COGNITIVE REMEDIATION

The 2004 guideline characterizes cognitive remediation as a variety of experimental treatments addressing the cognitive deficits associated with schizophrenia. A large number of studies on these approaches have been conducted over the last 5 years. This emerging literature continues to be limited by the wide variation in cognitive targets, small sample sizes, and a tendency for outcomes to be performance on neuropsychological tests rather than functional status or even symptoms. Studies using cognitive remediation in combination with vocational rehabilitation to enhance work functioning (42, 47, 64–66) have yielded positive findings, but more research is needed.

PEER SUPPORT AND PEER-DELIVERED SERVICES

A critical part of the emerging focus on recovery has been recognition of the importance of enhancing the role of individuals who have mental illness in the delivery of services and in roles in which the value of this experience is appreciated as therapeutic. Programs have been developed in which individuals with serious mental illness deliver traditional services, either as paid staff or as volunteers, as well as provide support to other individuals with serious mental illness. Peer-to-peer services include in-person self-help groups, Internet support groups, peer-delivered services, peer-run or peer-operated services, peer partnerships, and peer employees (67). Davidson et al. (68) outline three types of peer programs: mutual support, participation in peer-run programs, and the use of individuals with severe mental illness as a source of support and services for other individuals with severe mental illness.

When the evidence base for peer-delivered services is being considered, it is important to note a critical disconnect between these types of programs and traditional diagnostic-driven treatment systems. Peer-based programs and services tend to discount or deemphasize formal psychiatric diagnoses. Therefore, the formal psychiatric diagnoses of persons served in these studies may be unknown. A majority of randomized trials that compare peer-delivered with non–peer-delivered services do not show differences on most outcome measures (69–72). It is notable that despite the lack of significant group differences in these randomized, controlled trials, participants improved over the course of their participation in peer-delivered services (70, 71). Studies have shown that the delivery of peer-based services is feasible despite the fact that the precise benefits of peer-delivered services are as yet uncertain because of poorly defined comparison groups, small samples sizes, and the heterogeneity of outcomes. Future work needs to focus on either documenting advantages to consumer-delivered services or identifying the positive effect on standard clinical outcomes (e.g., symptoms, hospitalization) or other dimensions, such as increased self-esteem, social support, and progress toward recovery.

PSYCHOSOCIAL INTERVENTIONS FOR WEIGHT MANAGEMENT

Several clinical trials have investigated pharmacological and cognitive-behavioral treatments that may attenuate or reverse antipsychotic-related weight gain and lipid, glucose, and insulin changes (10). Several recently published randomized, controlled trials investigating psychoeducation and behavioral interventions for weight loss for individuals with schizophrenia found support for modest weight loss (mean weight loss across seven studies was 5.8 lbs) (11, 73–81). Moreover, recent reviews and meta-analyses further support the use of a psychoeducation or cognitive-behavioral intervention to promote weight loss among individuals with schizophrenia who are overweight or have experienced antipsychotic-related weight gain (82–85). Two studies also found support for psychoeducation and behavioral interventions in the prevention of weight gain among individuals with schizophrenia who had recently begun taking antipsychotic medications (86, 87). Despite these positive findings, it should be noted that retention of weight loss was either not measured or problematic in many of the aforementioned investigations. Moreover, there is marked variability across studies in terms of treatment modality and length and format of treatment. It appears that individuals with schizophrenia can successfully participate in weight loss interventions. Future investigations should target weight loss retention strategies and weight prevention interventions.

SUBSTANCE USE DISORDERS

APA's 2007 *Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition* (88) reviews newer literature available on the treatment of substance use disorders, including among individuals with schizophrenia. Important developments in this area are highlighted in the following subsections.

SMOKING

As noted in the 2004 guideline, smoking cessation is a critical health challenge for individuals with schizophrenia. Smoking treatments include nicotine replacement therapies (NRTs), bupropion, and psychosocial approaches (88).

Recent studies have examined combined pharmacological and psychosocial approaches in individuals with schizophrenia. For example, Baker et al. (89) found higher abstinence rates among smokers with psychotic disorders who were enrolled in an 8-session behavioral/motivational enhancement intervention combined with NRT relative to those in routine care over a 12-month period. Several randomized, placebo-controlled trials suggest that bupropion (90), bupropion plus NRT (91, 92), and bupropion plus a cognitive-behavioral intervention (93) significantly improve the likelihood of smoking reduction or smoking cessation among individuals with schizophrenia. However, the fact that these studies found significant rates of relapse following study termination suggests that smokers with schizophrenia may require more extended pharmacological treatment in combination with continuous and active support for smoking cessation. Bupropion is FDA approved for the treatment of smoking cessation and thus can be recommended as an intervention for smoking cessation for individuals with schizophrenia. Varenicline is also FDA approved for the treatment of smoking cessation but has not been studied in a randomized fashion among individuals with schizophrenia. With bupropion and varenicline treatment, a recent FDA boxed warning has highlighted a potential for serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide (94).

Research on psychosocial interventions suggests that smokers with schizophrenia will attend psychosocial smoking cessation programs, that interventions can have some benefit in terms of smoking reduction, and that, for those who attend, quitting is possible (89). Programs designed for individuals with schizophrenia may need to include extended outreach to improve treatment engagement and retention, training in coping skills that can be used to manage negative affect in place of smoking, and other strategies that can overcome some of the common barriers to smoking cessation found among this group of smokers.

OTHER SUBSTANCE USE DISORDERS

Recent studies suggest that a motivational intervention designed for individuals with schizophrenia and substance use disorders may improve substance use and psychiatric outcomes for individuals with a dual diagnosis. Two recent studies found that brief interventions incorporating motivational and behavioral techniques to treat substance use disorders contributed to reductions in substance use among individuals with schizophrenia spectrum diagnoses (95, 96). Specifically, Graeber et al. (95) found higher abstinence rates among individuals with schizophrenia and alcohol use disorders who were involved in a three-session motivational enhancement program relative to those involved in an educational intervention. Similarly, James et al. (96) found that individuals involved in a six-session, manualized group intervention with motivational enhancement and relapse prevention showed greater improvements in drug-related consequences and reductions in marijuana, alcohol, and polydrug use at follow-up relative to individuals who attended a one-session drug education class. Sigmon and Higgins (97) used a within-subjects reversal design to test the impact of a voucher-based contingent reinforcement intervention to reduce marijuana use in seven participants (86% having a schizophrenia diagnosis). Participants completed 4 weeks of baseline monitoring, during which they received $10 vouchers per urine specimen independent of result, followed by 12 weeks of intervention, during which they received $10 per urine specimen that was negative for marijuana, followed by another 4 weeks of baseline monitoring. The percentage of negative tests was significantly greater during the intervention weeks. However, two studies did not find that involvement in a substance use intervention contributed to lower rates of substance use (98, 99). Although there is variability in research methodology and findings, motivational and behavioral interventions targeting substance use for individuals with dual diagnoses appear to be feasible and beneficial.

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