

Strategies for the Long-Term Treatment of Schizophrenia: Real-World Lessons From the CATIE Trial

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Patients with schizophrenia have a chronic illness necessitating a biopsychosocial model of care that addresses the multiple dimensions of the disease, including coordinated primary care. Current research, including the lessons learned from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, shows that in addition to education, adherence, and minimizing adverse effects of psychopharmacologic agents, multimodal long-term treatment strategies are needed to address medical comorbidities, substance abuse, and both cognitive and social deficits. Health care professionals have the responsibility to monitor and help prevent adverse medical outcomes related to treatment with antipsychotics, in light of evidence that patients with schizophrenia are at risk for metabolic disorders and are undertreated for highly prevalent cardiovascular risk factors. These medical problems are particularly challenging in this population due to the chronicity of symptoms, cognitive limitations, social and financial challenges, and compliance issues with recommended medication treatment and therapeutic lifestyle changes. Mental health providers in the United States are now studying models that support the integration of psychiatric and nonpsychiatric medical treatment to address the complexity of multimodal schizophrenia care.

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Schizophrenia is a multidimensional mental illness characterized by a complex set of symptoms that are usually debilitating and chronic. While schizophrenia is commonly identified by the presence of positive symptoms that include delusions, hallucinations, and disorganized speech, long-term functioning is predominantly influenced by negative symptoms—such as avolition, flattening of affect, impoverishment of speech and language, and social withdrawal—and cognitive deficits. These cognitive deficits involve impaired executive functioning that affects planning, abstract thinking, and rule flexibility; processing deficits, such as an inability to inhibit inappropriate actions and irrelevant sensory information; attention impairments; and short- and long-term memory difficulties. Severe neg-

ative and cognitive symptoms make treatment difficult, in part, because they are also associated with adaptive deficits such as problems with self-care.¹ In addition to psychiatric symptoms, patients with schizophrenia often lack basic medical care and thus suffer from greater severity of comorbid medical disorders that can have a negative impact on both psychiatric and physical health outcomes.² The net result is a 20% reduced life expectancy compared with the general population.³ Current pharmacologic treatments, social support, family interactions, work or daily life conditions, and sociocultural factors influence the effectiveness of therapeutic strategies designed to treat the whole patient. The broad range of symptoms, medical and psychiatric risk factors, and comorbidities found in patients with schizophrenia must be addressed in treatment to optimize long-term outcomes.

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SCHIZOPHRENIA REQUIRES A MULTIFACETED BIOPSYCHOSOCIAL APPROACH TO TREATMENT

Recognizing and Treating Comorbid Disorders

Substance abuse is an important comorbidity in patients with schizophrenia and produces both physical and psychiatric impairments. At least 40% of schizophrenia patients in the United States and Australia meet criteria for substance abuse or dependence (excluding nicotine), a rate 4.6 times greater than that for the general U.S. population.^{4,5} Commonly used substances include nicotine, alcohol, cannabis, amphetamines, and cocaine, and these are often abused in combination. Earlier literature suggested

that users with schizophrenia preferred substances that target negative symptoms—dysphoria, sleep problems, or adverse effects of antipsychotic medications⁶—but the fact that individuals use substances with opposing behavioral effects indicates that agents may be used mostly for their ability to stimulate dopaminergic neurons in reward pathways.⁷ Although smoking has numerous physical health consequences, nicotine has been shown to transiently improve selective attention and habituation to repeated stimuli and to counter medication-induced deficits in memory and reaction time.^{8–10} Social and recreational reasons for drug use include refusal of beneficial medication, poor social problem-solving skills, and being in a group that is more accepting of odd behavior or isolation.⁷

There is increasing evidence that motivational enhancement and skills training¹¹ may encourage patients to attempt substance control, and these techniques can be applied to inpatients during an acute hospitalization.¹² Psychological interventions should consider the patient's level of cognitive deficits, the patient's need for environmental structure, and the availability of longer-term social support. Medications can play an important role in treating target symptoms, but there are few studies of patients with comorbid substance abuse. There is some evidence that appropriate antipsychotic treatment results in reduced use of tobacco, alcohol, and cocaine,⁷ but pharmacologic management of nicotine, alcohol, and opioid dependence should be combined with other treatment modalities. Even though an integrated treatment program is more effective,¹³ health delivery systems often separate substance abuse and other mental health disorders, so astute providers may need to take extra steps to monitor substance issues and create a treatment plan that is geared toward the patient with severe mental illness.

Medical comorbidities have been receiving increased attention because patients with schizophrenia have higher-than-expected rates of morbidity and mortality for several medical conditions.^{14–16} The average life expectancy for an individual with schizophrenia is up to 2 decades less than for the general population. A large study¹⁷ of psychotic patients found an increased odds ratio for diabetes, hypertension, heart disease, gastrointestinal disorders, and malignancy. It has been reported that more than two thirds of patients with schizophrenia will die of coronary heart disease, compared with 50% of the general population.³ Cardiovascular disease is thus a much more prevalent cause of death than suicide,¹⁴ and in women with schizophrenia, is the leading cause of excess deaths.¹⁴ In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study's comparison of 10-year cardiac risk estimates in schizophrenia patients, the impact of cigarette smoking on cardiovascular risk was quite evident, while further clarifications need to be made on the role of diet, exercise, quality of care, or specific antipsychotic agents.¹⁸ Programs for smoking cessation need to be implemented within the care

model, since studies have shown that smoking is stopped or reduced when nicotine replacement products or bupropion are offered in conjunction with a behavioral program.^{19,20}

The physical health of patients with schizophrenia is also of concern because of the accumulated evidence that relates weight gain, diabetes, lipid dysregulation, metabolic syndrome, and sexual side effects to use of atypical antipsychotics.^{16,21} Patients with schizophrenia have a higher prevalence of abdominal obesity, elevated triglycerides, and high blood pressure, all of which are components of the metabolic syndrome.²¹ In the United States, individuals with schizophrenia are still 2 to 3 times more likely to meet metabolic syndrome criteria than the general population, a finding seen in other countries such as Finland and Canada.^{21,22} Public health interventions are particularly challenging in this mentally ill population because they require lifestyle changes, such as increased physical activity, improved diet, and smoking cessation. The recent Mount Sinai Conference on the Pharmacotherapy of Schizophrenia has reiterated the fact that clinicians need to closely monitor blood pressure, waist circumference, and laboratory measures of serum glucose and lipids in order to make appropriate clinical decisions that consider physical as well as psychiatric symptoms.²³

In addition to health problems that increase risk for cardiovascular disease, individuals with severe mental illness, such as schizophrenia, are more likely to have infectious diseases such as human immunodeficiency virus (HIV) and hepatitis B and C because of elevated rates of injection drug use, homelessness, and high-risk sexual activity.²⁴ The prevalence rates of HIV, hepatitis B, and hepatitis C are estimated to be approximately 8, 5, and 11 times those in the general U.S. population, respectively.²⁵ A comprehensive screening program at Oregon State Hospital found that approximately 20% of the patients screened for hepatitis C were seropositive.²⁴ In particular, because symptoms of the hepatitis C virus may not appear until many years after infection, patients often fail to receive treatment that could limit liver damage and prevent further spread of the disease. Thus, patients with schizophrenia may benefit from primary or secondary interventions through routine screenings for HIV and hepatitis B and C viruses; vaccinations for hepatitis A and B in those who are hepatitis-C seropositive; and educational programs aimed at risk reduction, especially for HIV.

Multimodal Treatment of Schizophrenia

Much can be learned from psychosocial rehabilitation models that include social-skills training, cognitive-behavioral therapy, or cognitive remediation.^{11,26} These techniques of reframing negative thoughts and behaviors may be extended to targeting physical as well as mental outcomes. The goals are to improve functioning in the social, occupational, and independent-living domains and to

minimize environmental factors such as substance abuse. Specific focus has recently been given to cognitive rehabilitation, in that it predicts later functional outcome. However, the roles of psychosocial, educational, and vocational services are understudied in many trials.²⁷ Proposed methods to improve the effectiveness of standard cognitive rehabilitation include individualizing treatments (basing them on current cognitive neuroscience) and addressing motivation, affective factors, self-esteem, and experience of the self.²⁸ Standard medical treatments for substance abuse, cardiovascular disease, metabolic syndrome, and infectious diseases may not work for patients with schizophrenia because they do not address the cognitive and psychological limitations of patients with a chronic mental illness.

Among the psychosocial services, vocational rehabilitation cannot be overlooked, because it has been shown to decrease disability, reduce costs to society, and improve subjective ratings of quality of life.^{29,30} Despite limited research on vocational rehabilitation, employment programs, such as Individual Placement and Support, that are integrated within mental health settings have produced successful outcomes compared with traditional programs.²⁹ Housing and family support also play an important, integral part in long-term treatment outcomes. Psychoeducational interventions for families have produced improvement in clinical symptoms and social functioning.³¹ Reviews of family interventions that reduce levels of expressed emotions, criticism, hostility, and over-involvement suggest that they may help decrease frequency of relapse and improve medication compliance and social functioning. However, these data are statistically heterogeneous, and further studies need to be done to examine whether and how much such interventions augment routine care.³²

Treatment With Pharmacotherapy

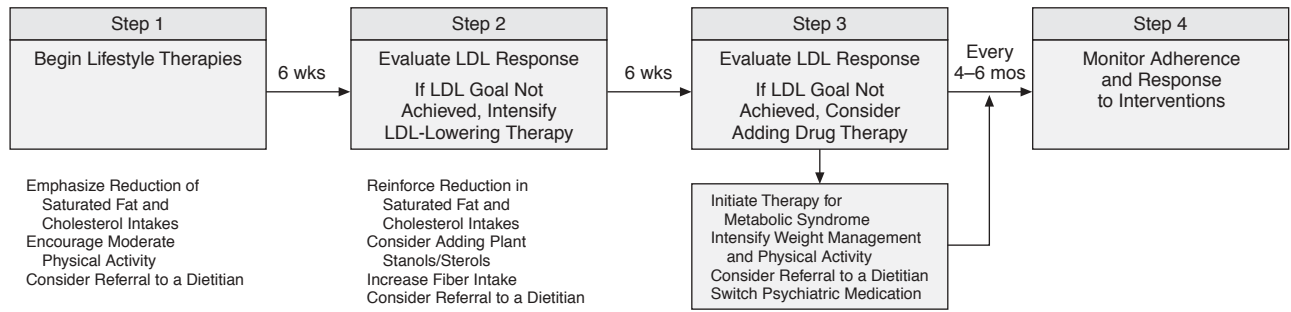
Medications are considered the mainstay of treatment in schizophrenia. They are necessary for adequate control of symptoms and for maximizing the likelihood of improved functioning. Nonadherence to medication treatment is a primary barrier to successful care. Purely educational approaches are less helpful at improving medication adherence than are those that also include behavior and affective strategies.³³ This integrated approach also decreases relapse rate, symptoms, and hospitalizations. In addition to education that advances understanding of the purpose and side effects of the medication, specific social-skills training and behavioral interventions assist by using external reminder cues or devices, reframing negative attitudes, and helping patients be more effective consumers. In trials, integrated interventions that were longer in duration, with increased sessions for more patients, resulted in better medication adherence.³³

Given that weight gain is a common side effect of antipsychotic medications, subjective distress over weight gain and body mass index (BMI) can predict noncompliance.³⁴ In a study by Weiden et al.,³⁴ obese schizophrenia patients were 2.5 times more likely to stop their medications than normal-weight respondents. Clinicians need to consider a patient's current weight and concern about obesity, along with other side-effect profiles, when discussing medication options. Prior to the advent of atypical antipsychotics, clinicians had to consider the benefits and risks of conventional agents that caused tardive dyskinesia and extrapyramidal symptoms at significantly higher rates than current medications. Accumulating evidence suggests that, when using atypical antipsychotics, efforts must be made to minimize the adverse effects of weight gain, metabolic syndrome, and sexual side effects that may lead to noncompliance and poor health outcomes.

Lessons Learned From CATIE Phases 1 and 2

The CATIE schizophrenia effectiveness trial can inform us about long-term treatment strategies because it was designed as a practical clinical trial to determine the real-world effectiveness of antipsychotics. It examined the final outcome of multiple inputs that lead to the decision to discontinue or switch treatment, rather than examining simply a standard primary endpoint for efficacy in a circumscribed study population. In phase 1, 74% of the patients discontinued the study medication before 18 months.³⁵ The time to discontinuation was longer in the olanzapine group compared with the quetiapine and risperidone groups but not when compared with the perphenazine or ziprasidone groups. Although there were no significant time differences for intolerability, the rates of side effects differed. Discontinuation rates due to weight gain and metabolic effects were highest with olanzapine, and for extrapyramidal effects, with perphenazine. In the intolerability arm of phase 2, the time to treatment discontinuation was longer for patients treated with risperidone and olanzapine than for patients treated with quetiapine and ziprasidone.³⁶

The lessons learned about physical health outcomes and the high prevalence of metabolic abnormalities in schizophrenia patients are striking. The CATIE study showed that, overall, 42% (51.6% of women and 36% of men) fulfilled criteria for metabolic syndrome at study baseline.²¹ After controlling for BMI differences, men had a nearly 85% greater risk and women had a 140% greater risk for metabolic syndrome than the general population.²¹ Antipsychotic medications and lifestyle patterns may increase the risk for metabolic syndrome, but there may also be inherent predispositions related to pathophysiology of visceral adiposity and endocrine changes that occur with the onset of schizophrenia.²¹ It has been asserted that physical health care cannot be ignored because the number of medical problems may independently contribute to

Figure 1. Model of Steps in Therapeutic Lifestyle Changes^a

^aAdapted from the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.⁴³

Abbreviation: LDL = low-density-lipoprotein cholesterol.

worse perceived physical health status, more severe psychosis and depression, and an increased likelihood of a suicide attempt.³⁷ In the CATIE study, those with metabolic syndrome rated themselves with lower physical health and higher somatic preoccupation on standardized measures, even after controlling for age, gender, race, ethnicity, and site variation.²

Another result from the CATIE baseline sample reveals that common metabolic disturbances are not only underdiagnosed but are also undertreated. In the CATIE trial, ranges of nontreatment were 30% to 88% for diabetes, hypertension, and dyslipidemia.³⁸ This illustrates that even with regular access to diagnosis and care, routine medical screening is not being performed, with the end result that medical treatments for common conditions are not received. Long-term treatment requires careful clinical monitoring over time and is becoming the standard of care. Cost-effective ways to monitor risk are fairly straightforward, and simple measures such as waist circumference and blood pressure are very sensitive at identifying individuals at high risk for cardiovascular disease.³⁹ In this medically underserved population, psychiatrists often need to oversee or take care of physical health issues.²³ Currently, many psychiatrists are neither treating routine or iatrogenic medical conditions, nor working closely with primary care physicians to make sure their patients get the same level of medical care available to the general population.⁴⁰

AN INTEGRATED CARE MODEL FOR MEDICAL AND MENTAL HEALTH

Based on the 2004 Consensus Report on Antipsychotics,⁴¹ screening for metabolic disturbances should be done at baseline and during follow-up; this screening should include personal and family histories, weight and BMI, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile.⁴² If screening measures

are positive, what should clinicians do next? According to the summary report of the National Cholesterol Education Program (NCEP), as shown in Figure 1,⁴³ therapeutic lifestyle changes are the first step in addressing elevated low-density-lipoprotein (LDL) cholesterol (> 100 mg/dL with coronary heart disease and > 160 mg/dL with 0–1 risk factors). Therapeutic lifestyle changes include reducing saturated fats and cholesterol, weight reduction, and increased physical activity. Referrals to a dietitian or nutritionist should be considered in order to start and follow up on lifestyle change over 3 months. If changes are not noted within 3 months, the next step is considering drug therapy to achieve LDL-cholesterol goals. The Diabetes Prevention Program has demonstrated a 58% reduction in rate of progression to diabetes through a 16-session program that combines individual and group strategies for weight loss, physical activity, clinical support, and flexible maintenance interventions or “restarts”; addresses ethnic differences; and personalizes a toolbox of adherence strategies.⁴⁴

There is limited research on behavioral interventions for weight management in schizophrenia, but at least 10 studies have reported weight loss or posttreatment differences in weight or BMI.⁴⁵

What is the next step if therapeutic lifestyle changes do not reduce LDL cholesterol or metabolic disturbances to an appropriate level within the 3-month time frame? The treatment team now needs to consider switching to an antipsychotic medication that is more weight neutral. Currently, ziprasidone and aripiprazole treatments are generally associated with minimal mean weight gain and have the lowest risk for more significant increases after switching.⁴² Patients who were switched from olanzapine to ziprasidone lost a mean of 3.9 lb over 6 weeks,⁴⁶ and there is further evidence for weight and metabolic benefits in a 1-year follow-up study.⁴⁷ In a post hoc analysis of switching from olanzapine to risperidone in a multicenter study of overweight patients with schizophrenia, the prevalence

of metabolic syndrome was decreased from 53.5% of patients at baseline to 36.6% of patients after 20 weeks.⁴⁸ Although clinicians frequently use a crossover strategy in switching antipsychotics, empirical evidence does not support the idea that gradual versus abrupt discontinuation and replacement decreases adverse events with olanzapine, aripiprazole, and ziprasidone.⁴⁹ In studies in which medications were switched for nonmetabolic reasons, moving from more sedating to more activating agents resulted in trouble with insomnia and reports of worsening psychotic symptoms.⁴⁶ When switching in an inpatient setting, clinicians may be more comfortable with higher doses to target symptoms more quickly. It is important to note that the mean dose of ziprasidone is 60 mg b.i.d. with food, because its bioavailability is reduced by 50% without food. If obesity and metabolic disturbances continue to be a problem after trying therapeutic lifestyle changes and more weight-neutral medications, it is important to pursue appropriate treatment for the metabolic disorder. The NCEP⁴³ suggests initiating LDL-cholesterol-lowering drug therapy, such as statins, bile acid sequestrants, or nicotinic or fibric acids, and dosing appropriately with 6-week follow-ups. If LDL-cholesterol goals are not reached, referring to a lipid specialist should be considered. Similarly, appropriate follow-up is needed for blood glucose control. Clinicians need to monitor the side effects and interactions of added medications by including liver function tests with some of these agents.

CONCLUSIONS

Psychiatrists are well-versed in the importance of long-term treatment-related risk and the need to reassess benefits and risks of treatment options over time. Typical antipsychotics forced clinicians to consider long-lasting motor effects, such as tardive dyskinesia. In schizophrenia research, there has been the hope that identifying or treating individuals at risk or in early phases of the illness will alter and diminish a potentially severe course. Early intervention must be extended to somatic as well as mental disease, shifting from short-term symptom management to a broader view of health issues across the life span. Because schizophrenia is a complex disorder, biological treatments must be integrated into a multimodal therapeutic plan that addresses social, family, financial, housing, and overall health needs. Patients with schizophrenia appear to have both intrinsic and extrinsic factors that make them vulnerable to increased morbidity and mortality, and they are often marginalized from traditional medical systems. The mental health team is often their primary asset and advocate for navigating complex health and social systems. Clinicians need to broaden their scope of care to identify and facilitate treatment for the whole patient and minimize dichotomies between mental and physical treatments.

Drug names: aripiprazole (Abilify), bupropion (Zyban and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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