Benjamin P. Yu, MD | Gerald A. Maguire, MD

Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Schizophrenia has plagued Mr. X for most of his adult life. He finally responds to a novel antipsychotic after many failed trials, but severe negative symptoms and medication-associated sedation are stalling his progress. In their efforts to reintegrate the patient, these doctors pose the question:

Can a wakefulness-promoting agent augment schizophrenia treatment?

History **A long, losing battle**

Mr. X, 41, has had schizophrenia, paranoid type, since age 24. Unable to work, keep house, or even groom himself, he has lived his entire life with his mother, his principal advocate and caretaker. He has been hospitalized 11 times for persecutory delusions, most recently 2 years ago at our medical center..

Numerous antipsychotics, including risperidone, haloperidol, quetiapine, clozapine, and thiothixene, did not work. He has responded best to olanzapine, but some mild paranoid symptoms and significant negative symptoms (alogia, anhedonia, amotivation, hypersomnia, restricted affect) persist.

He gained 30 pounds within 6 months after starting olanzapine. He was keeping his weight at 230 pounds and his body mass index (BMI) at 31.3. (A normal BMI is <25; a BMI >30 is considered obese.)

The patient was maintained on olanzapine 20 mg/d, but higher dosages caused oversedation. At the hospital, he would sleep through breakfast, get up late in the morning, then lie around until bedtime.

As an outpatient, he had no social contact outside the home. While hospitalized, Mr. X attended a therapy group on his ward, but never participated in the discussion. His speech was profoundly deficient; he never volunteered information and never responded to questions with anything more than a barely audible "yes" or "no."

How would you help Mr. X? Would you augment the olanzapine therapy or consider another antipsychotic, even one that failed the first time? Which negative symptom would you address first?

Drs. Yu's and Maguire's observations

Benjamin P. Yu, MD

Gerald A. Maguire, MD

Compared with the older antipsychotic agents, specifically haloperidol and thiothixene in this case, the newer antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) have demonstrated the ability to comprehensively treat schizophrenia.[1-4] But these novel agents sometimes fail to remedy the negative symptoms. Thus, as is the case with Mr. X, many patients with schizophrenia whose positive symptoms are controlled realize little or no improvement in quality of life.

Olanzapine and risperidone have more effectively reduced the negative symptoms of schizophrenia than have the older antipsychotics,[1-4] but—as we see with Mr. X—their record in treating negative symptoms is far from perfect. Additionally, sedation secondary to the antipsychotic may worsen the negative symptoms.

What's more, the newer agents are associated with potential weight gain.[5-7] Mr. X's weight will need to be addressed, but with much caution. Many agents prescribed for weight loss, notably amphetamines, are avoided in psychotic patients because of the potential for abuse and worsening psychosis.[8]

Augmentation with modafinil, a wakefulness-promoting agent, is being considered for Mr. X. Although modafinil's efficacy against obesity has not specifically been tested, studies have shown that this agent, which has actions similar to those of sympathomimetic agents, offers a lower abuse potential. Gold and Balster found that the medication was 250 times less potent than amphetamine and 15 times less potent than ephedrine in producing cocaine-like discriminative stimulus effects in rats.[9] Single oral doses of modafinil did not cause elation or euphoria in healthy volunteers or those with substance abuse disorders.[10,11] And compared with amphetamines, modafinil has a limited side-effect profile, with weak peripheral sympathomimetic activity and minimal effects on hemodynamics.[12]

Though it is best to minimize both the number of medications and the dosage for each patient, augmentation is still needed in some cases.[13-15]

Treatment augmentation

An agent is added

Mr. X's olanzapine was increased to 30 mg/d. Modafinil, 100 mg/d, was then added to reduce the sedation associated with the higher olanzapine dosage.

Within a week, Mr. X's negative symptoms had begun to improve. He started to speak more often and more clearly; his previously monotone voice exhibited a small degree of intonation and inflection. His fatigue decreased, and he was able to stay awake through breakfast and throughout the day.

That first week, he exhibited a brightened affect and more energy. He began to socialize to some extent with other patients in the hospital therapy group and was less isolated than before.

This slight but sudden improvement encouraged us. While he still showed slight paranoid ideations, he looked forward to a safe discharge and returning home to his family.

At this point, would you increase the dosage of either modafinil or olanzapine, or stay the course and monitor the patient's improvement?

Drs. Yu's and Maguire's observations

Modafinil is a novel compound indicated for narcolepsy treatment. Though its precise mechanism is unknown, modafinil is neither a direct- nor indirect-acting dopamine receptor agonist and is inactive in several in vivo preclinical models capable of detecting enhanced dopaminergic activity.[16] Therefore, the agent's pharmacologic profile may be favorable for off-label

use in treating negative symptoms of schizophrenia. Modafinil also has been shown to be effective as an augmentation therapy in depression, especially with treating fatigue symptoms.[17]

In your view, what should be the next step toward reintegration for Mr. X?

Continued treatment

Improving symptoms

After 1 month, we increased Mr. X's modafinil dosage to 200 mg/d and olanzapine to 40 mg/d. Both were well tolerated. No extrapyramidal symptoms were noted.

Over the next 4 months, his negative symptoms improved to the point where he had some concept of self-image. He was more alert, less isolated, and better groomed.

Once too sleepy to even eat breakfast, Mr. X began to participate in an exercise program, performing aerobic exercise including regular use of a treadmill, at a local gymnasium 3 days a week. This may have contributed to his loss of 20 pounds across 4 months. Over the next 6 months, the patient maintained his weight at 210 pounds, with a resultant BMI of 28.5. (He has lost slightly more weight since then.)

His socialization skills, while still far from mainstream levels, also improved. His mother began taking him to support group meetings at the local office of the National Alliance for the Mentally Ill (NAMI). There, he interacted with persons with schizophrenia and other psychiatric disorders.

During this time, his psychiatric condition remained stable, and his paranoia showed a mild improvement. Whereas Mr. X once required hospitalization every 6 months to 2 years, he has now been an outpatient for more than 2 years.

The modafinil dosage was titrated to 400 mg/d to further improve his negative symptoms and prevent antipsychotic-associated sedation. Mr. X has noted a continued increase in his alertness. He is still exercising, remains well groomed, and has begun taking vacations with his family. His mother, an active NAMI member, has continued to be his advocate and encourage his improvement.

Overall, we estimate that Mr. X is now functioning at about 65% of normal human capacity. When we began olanzapine with modafinil augmentation 2 years ago, he was functioning at barely one-half that level.

Drs. Yu's and Maguire's observations The olanzapine/modafinil regimen brought about great improvement, but pharmacologic therapy only goes so far. As of this writing, Mr. X has never held a job or lived independently. Also, socialization beyond the family and NAMI support group meetings remains nonexistent.

Behavioral strategies may be just as important as medication treatment for patients with schizophrenia. We would consider behavioral therapy for Mr. X, employing token economies and social skills training to increase social abilities, self-sufficiency, practical skills, and interpersonal communication—skills that may further improve his negative symptoms and lessen the chance of relapse. Social skills training through the use of videotapes, role playing in therapy, and homework assignments to practice specific skills may allow Mr. X to improve his maladaptive behaviors.

Educating the patient and his family would help them understand what to expect in the course of his illness and can enhance treatment. NAMI is one useful referral source. NAMI and similar organizations offer emotional and practi-

Bottom Line

Novel antipsychotics offer unprecedented effectiveness against the positive symptoms of schizophrenia, but do little to remedy the potentially debilitating negative symptoms. Exploration of behavioral and pharmacologic augmentation therapies is key to reintegrating these patients.

Related resources

- National Alliance for the Mentally Ill. www.nami.org
- The Center for Reintegration. www.reintegration.com
- National Alliance for Research on Schizophrenia and Depression. www.mhsource.com/narsad/ or www.narsad.org

DRUG BRAND NAMES

Clozapine • Clozaril
Ephedrine • Rynatuss
Haloperidol • Haldol
Modafinil • Provigil
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

AUTHOR AFFILIATIONS

Benjamin P. Yu, MD
Resident physician
Gerald A. Maguire, MD
Assistant dean for continuing medical education, Director of residency training, Associate clinical professor

Department of psychiatry and human behavior
University of California-Irvine Medical Center

DISCLOSURE

Dr. Yu reports that he serves on the speaker's bureau of Cephalon Inc.

Dr. Maguire reports that he receives research/grant support from, serves as a consultant to, and is on the speaker's bureau of Eli Lilly & Co.

cal advice about obtaining care in today's complex health care delivery system.

A case manager also plays an invaluable role, ensuring that efforts are coordinated and that the patient keeps appointments and complies with treatment plans. The case manager may make home visits and even accompany the patient to work. The program's success depends on the educational background, training, and qualifications of the case manager, which are variable.

Other behavioral strategies that could help Mr. X and other patients with schizophrenia include:

- Group therapy, which focuses on real-life plans, problems, and relationships. Group therapy effectively reduces social isolation, increases cohesiveness, and improves reality testing. Groups led in a supportive rather than interpretative manner appear to be most helpful in schizophrenia.
- Cognitive-behavioral therapy, which has been used in schizophrenia to improve cognitive distortions, reduce distractibility, and correct errors in judgment.
- Individual psychotherapy, which has been shown to effectively complement pharmacologic treatment.[18]

As patients' symptoms improve, we as psychiatrists can help by encouraging them to gradually reintegrate into society, often by offering resources such as NAMI or referrals to appropriate rehabilitation programs.

We plan to continue Mr. X's olanzapine/modafinil regimen to keep positive and negative symptoms at bay while improving his chances at reintegration. Careful monitoring of medications during reintegration is key to preventing relapse. We will continue to see Mr. X once a month.

References

1. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997;58:538-46.
2. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry* 1997;42:233-46.
3. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry* 1998;55:250-8.
4. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol* 1997;17:407-18.
5. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 1999;60(6):358-63.
6. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* 1997;7(2):125-37.
7. Blackburn GL. Weight gain and antipsychotic medication. *J Clin Psychiatry* 2000;61(suppl 8):36-41.
8. Gawin FH, Khalsa ME, Ellinwood E. Stimulants. In: Galanter M, Kleber HD, eds. *The American Psychiatric Press textbook of substance abuse treatment*. Washington, DC: American Psychiatric Press, 1994.
9. Gold LH, Balster, RL. Evaluation of the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil. *Psychopharmacology (Berl)* 1996;126(4):286-92.
10. Warot D, Coruble E, Payan C, et al. Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo. *Eur Psychiatry* 1993;8:201-8.
11. Duteil J, Rambert FA, Pessonnier J, et al. Central alpha1-adrenergic stimulation in relation to the behaviour stimulating effects of modafinil: studies with experimental animals. *Eur J Pharmacol* 1990;180:49-58.
12. Wong YN, Simcoe D, Hartman LN, et al. A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 1999;39:30-40.
13. Purdon SE. Cognitive improvement in schizophrenia with novel antipsychotic medications. *Schizophr Res* 1999;35(suppl):S51-S60.
14. Beasley CM Jr., Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacol* 1996;124(1-2):159-67.
15. Marder SR. Management of treatment-resistant patients with schizophrenia. *J Clin Psychiatry* 1996;57(suppl 11):26-30.
16. *Physician's Desk Reference* (55th ed). Montvale, NJ: Medical Economics, 2001.
17. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry* 2000;61(5):378-81.
18. Maguire GA. *CNS News*. Supplement August 2001:6-10.