

Evidence-Based Pharmacologic Treatment for People With Severe Mental Illness: A Focus on Guidelines and Algorithms

Thomas A. Mellman, M.D.
Alexander L. Miller, M.D.
Ellen M. Weissman, M.D.
M. Lynn Crismon, Pharm.D.
Susan M. Essock, Ph.D.
Stephen R. Marder, M.D.



Medication treatment of severe mental illness has been advanced and complicated by the introduction of numerous therapeutic agents. Practice guidelines based on research evidence have been developed to help clinicians make complex decisions. Studies of usual care suggest an important potential role for guidelines in improving the quality of medication treatment for people with severe mental illness. The authors review current evidence-based guidelines for medication treatment of persons with severe mental illness. Four categories of guidelines are described: recommendations, comprehensive treatment options, medication algorithms, and expert consensus. The authors note that more research is needed on optimal next-step strategies and the treatment of patients with comorbidity and other complicating problems. They discuss barriers to the implementation of guidelines, and they observe that the potential of guidelines and algorithms to promote evidence-based medication treatment for persons with severe mental illness depends on refinement of tools, progress in research, and cooperation of physicians, nonphysician clinicians, administrators, and consumers and family members. (*Psychiatric Services* 52:619-625, 2001)

In psychiatry, as in all branches of medicine, an ever-expanding range of therapeutic options is being created. One response to this evolving complexity has been the development of guidelines intended to inform and influence clinical practice. A proximal goal of practice

guidelines is to promote the use of effective therapeutic interventions and reduce inappropriate variation in clinical practice. Guideline implementation is also expected to improve outcomes and facilitate cost management (1).

Most practice guidelines incorpo-

rate and summarize research evidence that supports their recommendations. It is a formidable challenge for busy clinicians to keep up with the high volume of research findings. Thus an additional purpose of practice guidelines is to disseminate research findings of direct relevance to clinical practice. At the systems level, practice guidelines can facilitate a systematic approach to medication management of chronic illnesses across treatment venues and prescribers.

The complexity of practice, the volume of research findings, and the advent of guidelines are trends that have become particularly germane to pharmacologic treatment of people with severe mental illness. During the past 15 years, more than ten new antipsychotic and antidepressant medications have been approved for use in the United States, and several new mood stabilizers have been identified. The comparatively favorable safety and side-effect profiles of these agents as well as their putative therapeutic advantages have raised expectations for improved outcomes with psychiatric medications.

The availability of these medications may also contribute to greater comfort with prescription of combinations of psychotropic medications. The proliferation of new agents and the resulting increase in potential medication combinations, along with elevated treatment goals, all add to

Dr. Mellman is associate professor of psychiatry at the Dartmouth Medical School, Dartmouth-Hitchcock Medical Center, Department of Psychiatry, One Medical Center Drive, Lebanon, New Hampshire 03756 (e-mail, mellman@dartmouth.edu). Dr. Miller is professor of psychiatry at the University of Texas Health Science Center at San Antonio. Dr. Weissman is assistant professor of psychiatry and Dr. Essock is professor of psychiatry at Mount Sinai School of Medicine in New York City. Dr. Crismon is professor at the University of Texas College of Pharmacy in Austin. Dr. Marder is professor of psychiatry at the University of California at Los Angeles School of Medicine

the importance and challenge of defining and implementing evidence-based psychopharmacologic practice.

Higher costs associated with new medications and polypharmacy are a growing concern for mental health administrators, policy makers, consumers and their families, and the public. The question of how the implementation of guidelines would influence medication costs and other costs related to treatment and the impact of illness is currently unanswered. Use of guidelines may reduce costs by eliminating ineffective practices. The more likely benefit of guidelines is in producing greater value per health care dollar.

In this article we discuss guidelines and algorithms as a means of addressing the complexity of pharmacologic treatment of people with severe mental illnesses and disseminating relevant research findings. Our definition of severe mental illness includes psychotic disorders, mood disorders, and certain anxiety disorders—panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. This definition is in keeping with the substantial impairment and chronicity associated with these disorders (2,3) and the range of problems typically addressed with medication treatment in mental health settings. We do not review important work on the screening and management of anxiety and depression in primary care settings. We describe relevant guidelines and discuss the nature and limitations of the supporting evidence. We then explore barriers to guideline implementation and critical components of guidelines and make recommendations for facilitating and furthering evidence-based practices in the pharmacologic treatment of people with severe mental illnesses.

Overview of current guidelines and algorithms

The current guidelines that address pharmacologic treatment of severe mental illness fall into one of four categories, according to their scope and the stringency with which they rely on empirical evidence: recommendations, comprehensive treatment options, medication algorithms, and expert consensus. All of these cate-

Editor's Note: This article is part of a series of papers on evidence-based practices being published in *Psychiatric Services* this year. Many of the papers in the series are from participants in a national demonstration project, the Evidence-Based Practices Project. The goal of the project is to develop standardized guidelines and training materials to improve client outcomes in routine mental health service settings. The project is sponsored by the Robert Wood Johnson Foundation, the Center for Mental Health Services, the National Association of State Mental Health Program Directors Research Institute, and the National Alliance for the Mentally Ill. Mental health research centers, state mental health authorities, and local mental health programs in several states are participating. Robert E. Drake, M.D., Ph.D., and Howard H. Goldman, M.D., Ph.D., are the series editors.

gories are distinct from specific, highly proscriptive protocols that might be in place in some clinical settings. Although the recommended therapeutic options tend to be consistent across the existing guidelines, they differ in scope.

Recommendations

The first category, recommendations, is exemplified by the Patient Outcomes Research Team (PORT) treatment recommendations for schizophrenia (4). The development of the PORT recommendations was initially sponsored by the U.S. Agency for Health Care Policy and Research. The PORT project was regionally based; however, three research centers participated. Methods for developing the recommendations included a literature review followed by reviews of additional experts. Rigorous requirements were established for evidence to support revision.

The PORT recommendations are supported by "substantial evidence of efficacy," and the strength of specific supporting evidence is documented in the guidelines. The PORT recommendations address antipsychotic and adjunctive medications, electroconvulsive therapy (ECT), and several psychosocial interventions. Most PORT recommendations are definitive, as embodied in statements such as "antipsychotic medications, other than clozapine, should be used as first-line treatment." The PORT guidelines also recommend use of conventional doses and maintenance on continuing treatment for at least a year for people who respond to treatment. Certain practices, such as "loading" medication treatment with "massive" doses, are discouraged. Clozapine is advocated as an approach for people who have not experienced adequate reduction in symptoms with previous antipsychotic medication treatment.

Comprehensive treatment options

Practice guidelines in the second category have been developed predominantly by professional organizations. These guidelines are comprehensive in the scope of therapeutic options presented. Thresholds for the strength of evidence required to support recommended treatment options tend to be less stringent than for the PORT treatment recommendations, and these guidelines, accordingly, are less proscriptive. The methods for developing these guidelines overlap with those described for PORT and include expert working groups, literature reviews, secondary expert review, and revision. Guidelines developed through professional organizations ultimately require organizational approval.

Pharmacologic treatment is addressed in detail by practice guidelines for the treatment of patients with bipolar disorder (5), schizophrenia (6), major depressive disorder (7), and panic disorder (8) developed by the American Psychiatric Association (APA) and practice guidelines for the treatment of posttraumatic stress disorder (PTSD) developed by the International Society for Traumatic Stress Studies (ISTSS)

(9). Except for schizophrenia and bipolar disorder, specific psychotherapies are presented as first-line alternatives to medication. Newer medications tend to be favored for initial intervention; lithium for bipolar disorder is the most notable exception.

The recently revised APA depression treatment guidelines also endorse as first-line therapeutic options the tricyclic antidepressants desipramine and nortriptyline, along with selective serotonin reuptake inhibitors (SSRIs) and antidepressants that have been marketed more recently (6). The ISTSS guidelines for PTSD give the strongest endorsement to SSRIs as a first-line medication option on the basis of data supporting their effectiveness and limited research evaluation of alternative treatments (9). For bipolar illness, lithium or the anticonvulsant valproate are endorsed for first-line therapy (5).

Algorithms

An algorithm is a rule or set of rules that is applied to solving a problem. Medication algorithms are a subset of practice guidelines. They are distinguished by an exclusive focus on medications and by a more step-by-step approach to clinical decisions. The Texas Medication Algorithm Project (TMAP) constitutes the most extensive and comprehensive development and implementation to date of medication algorithms for persons with serious mental illness. Current projects address the treatment of schizophrenia, bipolar disorder, and major depression.

TMAP was initiated by the Texas Department of Mental Health and Mental Retardation in collaboration with a consortium of Texas academic medical centers. The development of the TMAP algorithms incorporated expert panels, literature review, and consensus conferences. Development has also incorporated consumer input and revisions solicited from academic and nonacademic clinicians. Field-testing to evaluate clinical and economic impact is under way, principally in the public mental health system of the state of Texas (10,11).

The Texas Implementation of Medication Algorithms (TIMA) is the practical, clinician-targeted implementation of TMAP. TIMA and TMAP user manuals are available on the Internet (www.mhmr.state.tx.us/centraloffice/medicaldirector/tima or [tmap](http://www.mhmr.state.tx.us/centraloffice/medicaldirector/tmap)), and outlines and summaries have been presented in the literature. All the presentations feature flow diagrams that provide recommendations linked to specific stages of treatment. Like other practice guidelines described in this paper, TMAP recommends a range of stage 1, or first-line, treatment initiation strategies without prioritizing among them. For the treatment of unipolar, nonpsychotic major depression, stage 1 options are the "new-generation" antidepressants (11); for mania, stage 1 options are lithium and one of two anticonvulsants (12). All of the atypical or novel antipsychotics other than clozapine are recommended for the initial treatment of schizophrenia (13). Adequate response dictates continuation of stage 1 therapy.

The most notable aspect of TMAP may be the degree of elaboration of stepwise strategies for partial response, nonresponse, or medication intolerance. Stage 2 and subsequent stages comprise sequences of alternative medication treatment options. Staging for inadequate responders ultimately leads to recommendations such as clozapine, ECT, or combinations of medications. Initial stages of treatment usually feature monotherapy, except for the treatment of bipolar and psychotic depression. In addition to presenting the algorithms, TIMA and TMAP documents include information on dosing, side-effect profiles, and the tools used for assessment and monitoring as well as consumer education material.

Expert consensus guidelines

The fourth category, expert consensus guidelines, is quite distinct from the categories previously considered. Recommendations are based on the results of surveying a relatively broad array of experts in the treatment of the condition in question and do not rely directly on analysis of the research literature. The stated purpose

of this approach is to supplement "the first generation of treatment guidelines," and its rationale is that research literature sometimes does not adequately address critical points for treatment decisions (14). Expert consensus guidelines for the treatment of schizophrenia (15), bipolar disorder (16), obsessive-compulsive disorder (17), agitation in older persons with dementia (18), and PTSD (19) have been published as supplements in journals and are available on the Internet (www.psychguides.com). Statistical results of questionnaire-based surveys addressing the appropriateness of interventions for different stages of treatment are presented, along with guidelines synthesized from the survey results.

Other efforts

Additional examples that illustrate the scope of emerging guidelines relevant to pharmacologic treatment in psychiatry include the recent implementation of guidelines by the U.S. Department of Veterans Affairs for screening, referring, and managing depression among persons with and without PTSD and substance abuse and for treating psychosis (see www.va.gov for more information). The Canadian Psychiatric Association has developed practice guidelines for the treatment of schizophrenia that have an emphasis similar to that of the APA guidelines (20). Guidelines developed by the American Academy of Child and Adolescent Psychiatry for the treatment of disorders presenting in children and adolescents address therapeutic modalities comprehensively and provide recommendations about the role of medication (21). Texas now has a children's medication algorithm project (CMAP) that addresses the use of medication for childhood and adolescent depression and attention-deficit hyperactivity disorder and comorbid disorders (22).

Nature and limitations of the evidence

Most guideline documents include a critical appraisal of the quality of supporting evidence for each recommendation. The highest levels of confidence are assigned to recommenda-

tions supported by multiple randomized controlled clinical trials. Gradations of confidence are generally rated on considerations that include the number and quality of research studies and the consistency of findings.

Recommendations made with high confidence are those that are based on evidence supporting the efficacy of first-line acute treatments for schizophrenia, mood disorders, and most anxiety disorders as well as on evidence supporting the role in relapse prevention of continuation of these treatments. In recent guidelines, the newer psychotropic agents are preferred as first-line agents. Their use is justified principally by their safety and tolerability profiles. First-line use of the newer antipsychotic medications may also offer advantages in the areas of negative symptoms and cognition. However, as experience with newer agents has accumulated, their advantages have been debated, and unforeseen risks, such as weight gain, have been identified. As Miller and associates concluded in their review (23), clozapine is not considered a first-line option because of safety concerns and monitoring requirements.

Recommendations for next-step strategies for patients who respond only partially or who do not respond to these agents and recommendations for treating patients with complex comorbidity often rely on more limited research evidence, such as open studies and case series, and on expert opinion. Most recommendations for treatment-resistant patients with severe mental illness are not guided by a strong research base. There are a few notable exceptions. The utility of clozapine for treating persons with schizophrenia who do not respond adequately to traditional antipsychotic agents has been established by controlled trials that featured prospective determination of treatment nonresponsiveness (24).

Similar studies were not required for the approval of risperidone, olanzapine, and quetiapine by the U.S. Food and Drug Administration (FDA), and such studies are just beginning to appear in the literature. Available studies of these novel antipsychotic medications provide

more limited support (25) or are not supportive (26) of efficacy when the initial treatment strategy is ineffective. In addition, in these studies, treatment refractoriness is usually defined in the context of traditional antipsychotic medications. Because atypical antipsychotics are now being used as first-line agents, research is needed to evaluate next-step strategies for patients who are treatment resistant to atypical antipsychotics.

For patients with depression who are unresponsive or partially responsive to initial treatment, extensive evidence supports a reasonable probability that patients who have not adequately responded to or tolerated some agents will respond to others (27). The best-studied medication strategy for refractory major depression other than switching agents is lithium augmentation—the addition of lithium to existing treatment. The TMAP algorithms recommend lithium augmentation before augmentation with other medications and before combination strategies (11). It is not known how lithium augmentation compares with alternative strategies that may currently be more popular, such as the addition of bupropion to an SSRI, an intervention that is mainly supported by a theoretical rationale and uncontrolled observations (28).

Some widely used strategies for augmenting antidepressant response have not withstood the test of a randomized controlled trial (29,30). Other next-step strategies for the treatment of mood disorders that are supported by reasonable evidence include combinations of mood stabilizers in bipolar disorder (31) and ECT. ECT, which is considered more invasive than pharmacologic treatment, is a well-established approach to treatment-refractory mood disorders (32).

There are other categories of severe mental illness in which medication treatment is often used but is generally understudied. For example, research evaluating medication treatment for PTSD is limited but is gaining momentum. A large study that showed the efficacy of sertraline, an SSRI, in the treatment of PTSD recently led to FDA approval

of the addition of PTSD to sertraline's on-label indications (33). Few studies have examined second-line medication strategies and treatment of comorbid presentations that would be highly relevant to clinical practice. To our knowledge, some evidence has not yet been synthesized into guidelines. This evidence supports the apparently common practice of pharmacologically targeting mood symptoms and impulsivity in borderline and other severe personality disorders (34,35). The rationale for much of the prescribing for patients with a dual diagnosis—severe mental illness co-occurring with a substance use disorder—is extrapolated from studies of non-substance-abusing populations. Studies that specifically address efficacy and safety in younger populations are sorely needed as the use of psychotropic medications by children and adolescents increases (36).

Conformance of usual care

We are unaware of any published reports showing the impact on treatment outcomes of implementing pharmacologic treatment guidelines in mental health settings. However, a few studies have evaluated how closely usual care resembles that suggested by guideline recommendations. The PORT project included a survey of usual care for people with schizophrenia from geographically diverse public-sector settings. The rates at which usual practice conformed to medication recommendations varied. Antipsychotic medication was prescribed for 89 percent of inpatients and 92 percent of outpatients. Prescriptions conformed to dosage recommendations for 62 percent of the inpatients but for only 29 percent of the outpatients. Rates of use of adjunctive agents in cases in which they appear to have been therapeutically indicated ranged from 14 to 41 percent, depending on the setting (37).

Using criteria derived from the PORT recommendations, Young and associates (38) evaluated the adequacy of treatment for patients with schizophrenia in two large public mental health settings in Los Angeles in 1996. Inadequate treatment

was defined as the presence of either significant side effects or unresolved symptoms, with no attempt made to alter medication therapy. At the two sites, the rates of inadequate treatment not attributable to patient factors were 28 percent and 16 percent, respectively. Use of the atypical or novel antipsychotics available at the time, clozapine and risperidone, was low (38).

Published studies, however, may not adequately capture the evolving landscape of pharmacologic treatment of severe mental illness. In keeping with recent guideline recommendations, treatment with atypical antipsychotic medications appears to be becoming the modal therapy for schizophrenia. A recent analysis used data from a Medicaid prescription database for the State of New Hampshire to identify a cohort of persons diagnosed as having schizophrenia (39). Prescription of atypical antipsychotic medications other than clozapine rose from 18 percent in 1995 to 54 percent in 1999. Clozapine use remained stable at 26 percent.

Concurrent prescription of two or more antipsychotic medications appeared to be a related trend (Clark RE, Mellman TA, Bartels SJ, et al, unpublished data, 2001). Rates of coprescription of antipsychotics rose from 6 percent in 1995 to 24 percent in 1999. In most cases, the duration of coprescription exceeded that expected during a straightforward medication switch—that is, cross-tapering. Further research is needed to provide an understanding of the course of treatment, the rationales, and the outcomes associated with this and other common forms of coprescription. The practice of coprescribing appears more common than would be expected if practice conformed to TMAP and other medication guidelines, which place combinations of antipsychotic medications at or near the last step of their recommendations.

Barriers to implementation

The findings discussed here suggest that implementation of guidelines can improve the quality of medication treatment for people with schiz-

ophrenia. It seems likely that the situation is similar for the usual treatment of other severe psychiatric disorders. For implementation to be successful, the effort must address potential barriers. Implementation of medication guidelines as well as barriers to implementation can be conceptually divided into two categories, systemic and individual.

At the systemic level, there must be a commitment to providing the tools necessary for guideline implementation. Practically speaking, this means providing the resources necessary to implement guidelines, such as ensuring that the recommended medications are on the formulary

■

*It is
our experience
that practice within
appropriately constructed
guideline parameters readily
allows for consideration of
the individual and for
creative, individualized
treatment
planning.*

■

and that adequate time is provided for required assessments. In addition, documentation forms must be changed to facilitate recording and review of data used in making medication decisions, according to recommendations of the particular algorithm or guideline being implemented.

At the individual level, providers and patients must accept the guidelines as a reasonable approach to treatment that increases the likelihood of successful outcomes. Experience indicates that clinicians do not readily adhere to practice guide-

lines. Literature from nonpsychiatric medicine identifies barriers to clinicians' adherence, including lack of familiarity with guidelines, lack of agreement with or confidence in guidelines, practical limitations, and practice inertia (39). Some clinicians may view guidelines as limiting their autonomy and creativity.

Barriers specific to clinical practice in psychiatry may complicate efforts to implement guidelines. Clinical histories that are used to "stage" patients in guideline-based treatment may be inaccurate when obtained from patients with severe mental illness, who may have symptoms that limit their ability to report their past treatment response adequately and for whom collateral informants may be lacking. Psychiatrists and other treatment staff as well as patients and family members may be resistant to switching medications when the patient has a history of violence toward self or others or has gotten worse after previous medication changes. In many public-sector settings, patients who are considered stable by the treatment team continue to experience disabling symptoms. Because switching medications involves some risk of behavioral deterioration, treatment teams may forgo attempts to treat remaining symptoms in order to maintain the status quo.

Consumers and family members may fear that guidelines represent a dehumanizing trend in health care that limits consideration of individuality. Although this concern is understandable, it is our experience that practice within appropriately constructed guideline parameters readily allows for consideration of the individual and for creative, individualized treatment planning. Guideline materials developed for consumers and their families can help them understand the rationale for current medication treatments and can serve as tools for initiating discussion of alternative considerations, thereby promoting shared decision making.

Critical components, current applications, and future issues
Discussions of evidence-based practice for nonpharmacologic treat-

ments, including papers previously published and those projected for this series, emphasize implementation of underused effective practices. In contrast, pharmacologic treatment is accepted by most treatment providers and does not appear to be generally underused in the usual treatment of people with severe mental illness. Our emphasis is on using medication treatments that are evidence based and, whenever possible, on using them in sequences supported by research—that is, in conformance with the principles delineated in the guidelines and algorithms discussed in this paper.

What practices are needed for pharmacologic treatment for people with severe mental illnesses to conform to evidence-based principles? First, the clinician must make an accurate diagnosis and specify target symptoms and their initial severity. Second, the clinician should choose a medication and dosage range supported by the research evidence for the condition and target symptoms in question.

Third, the clinician should monitor changes in symptoms and the occurrence and tolerability of side effects. Determining adequacy of response and tolerance of side effects requires clinical judgment. Use of systematic rating instruments can make these determinations more precise. Determining appropriate thresholds to define adequate versus inadequate response is an important focus for continuing investigation.

Fourth, if medications are not tolerated well or symptoms do not respond after a trial of adequate duration, the clinician should consider strategies recommended by the illness-specific guidelines, such as raising the dosage, changing to another efficacious medication, or using an augmentation strategy. Fifth, similar approaches should be used to address co-occurring syndromes. Finally, the clinician must critically evaluate a patient's response to coadministered medication treatments—augmentation and combination strategies—and attempt to discontinue medications that have not improved the therapeutic response.

Although these principles may

seem self-evident, it is not clear that they are routinely applied in many practice settings. The guidelines and algorithms present options for implementing evidence-based medication treatment. For example, the more proscriptive nature of the PORT guidelines leads to identification of treatments that do not conform to the usually recommended practices. In our view, given the present state of knowledge, it would not be appropriate to uniformly prohibit treatment approaches that do not conform to medication guidelines. Rather, many nonconforming practices might be held to greater scrutiny and standards for justification.

TMAP offers clinicians a convenient, comprehensive elaboration of next-step alternatives. The recent development of consumer-oriented materials is a promising approach to facilitating clinician-consumer dialogue and shared decision making (41).

The ultimate utility of guidelines and algorithms for promoting evidence-based medication treatment for people with severe mental illness depends on continuing refinement of guideline tools and progress in research. The likelihood that a busy clinician will refer to guideline material is greatly enhanced by efficient access to the information, ideally during the clinical encounter itself. The literature on guideline implementation in nonpsychiatric medicine suggests that computerized tools for tracking clinical data and providing information offer advantages (41). The guidelines discussed in this paper address a range of problems from various perspectives. Tools that distill and synthesize key elements to educate clinicians and consumers should enhance guideline implementation. One worthwhile goal may be to integrate tools that apply to different disorders, which may facilitate comprehensive application of guidelines in public mental health settings.

Further development and dissemination of practical assessment and tracking tools would advance the implementation of evidence-based prescribing. Clinical decisions about changes in treatment after the initial intervention hinge on judgments of the adequacy of response. In research

settings, diagnosis and therapeutic response are determined by systematic assessments with standardized tools. Although it is reasonable to apply some of the available rating instruments in clinical settings, others can be complicated and time-consuming. Research is needed to establish the validity of pared-down, clinician-friendly rating instruments. For assessment and tracking tools to be more widely accepted outside of research settings, they should not substantially increase, and ideally would decrease, the burden of documentation.

Research in these areas can better inform the next generation of guidelines and algorithms. We hope that the current prioritization of effectiveness research (42) will address the more critical gaps in current evidence.

Conclusions

The potential for guidelines to improve care ultimately depends on the acceptance and commitment of administrators, consumers, and members of the treatment team. Successful implementation of guidelines requires administrative support and motivated prescribers. Nonphysician members of the treatment team have a critical role in monitoring medication compliance, affecting patients' and families' attitudes toward changes in treatment, and providing critical feedback to prescribers about a patient's clinical state and treatment response. Consumers and their family members must have an active role in discussing therapeutic options, initiating changes, and providing feedback about treatment response. Achieving the potential of improved quality of care through the use of medication guidelines founded on evidence-based practices requires collaboration between policy makers, administrators, providers, and consumers of psychiatric care. ♦

Acknowledgments

This work was supported by a grant from the Robert Wood Johnson Foundation and the Substance Abuse and Mental Health Services Administration. The authors thank Kara Comins, B.S., and Wendy Bayles-Dazet, R.N., for their assistance and Robert E. Drake, M.D., Ph.D., for comments on the manuscript.

References

- Audet AM, Greenfield S, Field M: Medical practice guidelines: current activities and future directions. *Annals Internal Medicine* 30:709-714, 1999
- Roy-Byrne PP, Stang P, Wittchen HU, et al: Lifetime panic-depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course, and help-seeking. *British Journal of Psychiatry* 176:229-235, 2000
- Kessler RC: Posttraumatic stress disorder: the burden to the individual and to society. *Journal of Clinical Psychiatry* 61(suppl 5):4-12, 2000
- Lehman AF, Steinwachs DM: Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophrenia Bulletin* 24:1-10, 1998
- American Psychiatric Association Practice Guideline for the Treatment of Patients With Bipolar Disorder. *American Journal of Psychiatry* 151(Dec suppl):1-36, 1994
- American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *American Journal of Psychiatry* 154(Apr suppl):1-63, 1997
- American Psychiatric Association Practice Guideline for the Treatment of Patients With Major Depressive Disorder. *American Journal of Psychiatry* 157:1-45, 2000
- American Psychiatric Association Practice Guideline for the Treatment of Patients With Panic Disorder. *American Journal of Psychiatry* 155:1-34, 1998
- Foa EB, Keane TM, Friedman MJ: Guidelines for treatment of PTSD. *Journal of Traumatic Stress* 13:539-588, 2000
- Gilbert DA, Altshuler KZ, Rago WV, et al: Texas Medication Algorithm Project: definitions, rationale, and methods to develop medication algorithms. *Journal of Clinical Psychiatry* 59:345-351, 1998
- Crismon ML, Trivedi M, Pigott TA, et al: The Texas Medication Algorithm Project: report of the Texas consensus conference panel on medication treatment of major depressive disorder. *Journal of Clinical Psychiatry* 60:142-156, 1999
- Suppes T, Brown A, Dennehy E, et al: Bipolar Disorders Module Guideline Procedures Manual. TMAP Procedural Manual 1:2, 1999. Available at www.nhmr.state.tx.us
- Miller AL, Chiles JA, Chiles JK, et al: The Texas Medication Algorithm Project (TMAP) schizophrenia algorithms. *Journal of Clinical Psychiatry* 60:649-657, 1999
- Frances F, Kahn D, Carpenter D, et al: The Expert Consensus Practice Guideline Project: a new method of establishing best practice. *Journal of Practicing Behavioral Health* 5:295-306, 1996
- McEvoy J, Weiden P, Smith T, et al (eds): The Expert Consensus Guideline Series: treatment of schizophrenia. *Journal of Clinical Psychiatry* 57(suppl 12B):1-58, 1996
- Kahn D, Carpenter D, Docherty J, et al (eds): The Expert Consensus Guideline Series: treatment of bipolar disorder. *Journal of Clinical Psychiatry* 57(suppl 12A):1-88, 1996
- March JS, Frances A, Carpenter D, et al (eds): The Expert Consensus Guideline Series: treatment of obsessive-compulsive disorder. *Journal of Clinical Psychiatry* 57(suppl 4):1-72, 1997
- Alexopoulos GS, Silver JM, Kahn DA, et al (eds): The Expert Consensus Guideline Series: treatment of agitation in older persons with dementia. *Postgraduate Medicine Special Report*, 1998
- The Expert Consensus Guideline Series: treatment of posttraumatic stress disorder: the expert consensus panels for PTSD. *Journal of Clinical Psychiatry* 60(suppl 16):3-76, 1999
- Canadian clinical practice guidelines for the treatment of schizophrenia. *Canadian Journal of Psychiatry* 43(suppl 2):25S-40S, 1998
- Practice parameters for the assessment and treatment of children and adolescents with schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry* 33(suppl 5):616-635, 1994
- Hughes CW, Emslie GJ, Crismon ML, et al: The Texas Children's Medication Algorithm Project: report of the Texas consensus conference panel on medication treatment of childhood major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 38:1442-1454, 1999
- Miller AL, Dassori A, Ereshefsky L, et al: Recent issues and developments in antipsychotic use. *Psychiatric Clinics of North America: Annual Review of Drug Therapy*, in press, 2001
- Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Archives of General Psychiatry* 45:789-796, 1997
- Sharif Z, Raza A, Ratakonda SS: Comparative efficacy of risperidone and clozapine in the treatment of patients with refractory schizophrenia or schizoaffective disorder: a retrospective analysis. *Journal of Clinical Psychiatry* 61:498-504, 2000
- Conley RR, Tamminga CA, Kelly DL, et al: Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. *Biological Psychiatry* 46:73-77, 1999
- Fava M: Management of nonresponse and intolerance: switching strategies. *Journal of Clinical Psychiatry* 61(suppl 2):10-12, 2000
- Nelson JC: Augmentation strategies in depression: 2000. *Journal of Clinical Psychiatry* 61(suppl 2):13-19, 2000
- Landen M, Bjorling G, Agren H, et al: A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *Journal of Clinical Psychiatry* 59:664-668, 1998
- Perez V, Soler J, Puigdemont D, et al: A double-blind randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibition. *Archives of General Psychiatry* 56:375-379, 1999
- Freeman MP, Stoll AL: Mood stabilizer combinations: a review of safety and efficacy. *American Journal of Psychiatry* 155:12-21, 1998
- Janicak PG, Davis JM, Gibbons RD, et al: Efficacy of ECT: a meta-analysis. *American Journal of Psychiatry* 142:297-302, 1985
- Brady K, Pearlstein T, Asnis GM, et al: Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 283:1837-1844, 2000
- Cowdry RW, Gardner DL: Pharmacotherapy of borderline personality disorder. *Archives of General Psychiatry* 45:111-119, 1998
- Coccaro E, Kavoussi RJ: Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Archives of General Psychiatry* 54:1081-1088, 1996
- Report of the Surgeon General Conference on Children's Mental Health, Feb 2000. Available at www.surgeongeneral.gov/cmhc/childreport.htm
- Lehman AF, Steinwachs DM: Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) client survey. *Schizophrenia Bulletin* 24:11-20, 1998
- Young AS, Sullivan G, Burnam MA, et al: Measuring the quality of outpatient treatment for schizophrenia. *Archives of General Psychiatry* 55:611-617, 1998
- Cabana MD, Rand CS, Powe NR, et al: Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 282:1458-1465, 1999
- Toprac MG, Rush AJ, Conner TM, et al: The Texas Medication Algorithm Project patient and family education program: a consumer-guided initiative. *Journal of Clinical Psychiatry* 61:477-486, 2000
- Shiffman RN, Freudigman MD, Brant CA, et al: A guideline implementation system using handheld computers for office management of asthma: effects on adherence and patient outcomes. *Pediatrics* 105:767-773, 2000
- Bridging Science and Service: A Report by the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup. Rockville, Md, National Institute of Mental Health, 1999

Treatment in Psychiatry

Treatment in Psychiatry begins with a hypothetical case illustrating a problem in current clinical practice. The authors review current data on prevalence, diagnosis, pathophysiology, and treatment. The article concludes with the authors' treatment recommendations for cases like the one presented.

Schizophrenia and Co-Occurring Substance Use Disorder

Alan I. Green, M.D.

Robert E. Drake, M.D., Ph.D.

Mary F. Brunette, M.D.

Douglas L. Noordsy, M.D.

How commonly does schizophrenia co-occur with substance use disorder? What are the implications of substance use for the course of the psychosis? What do we understand about the basis of the co-occurrence of substance use disorder and schizophrenia? How best can a psychiatrist work with this type of a patient? What medications are most likely to be helpful?

A 29-year-old Caucasian man was brought to the emergency department by the police after he was found wandering barefoot through the snow on Main Street. The police had been called after passers-by reported that the man seemed intoxicated and was acting strangely. When an officer approached the man, he became belligerent and agitated and angrily exclaimed that they had no reason to question him. Using some force, the police brought him to the emergency department. The psychiatrist who interviewed him noted a strong smell of alcohol and signs of psychosis; the man demonstrated a clear thought disorder, and he appeared to be responding to internal voices. A physical examination was unremarkable. His urine was positive for cannabis by dipstick test, and an alcohol breath test was positive. Given the absence of further information about him, the patient was admitted to the crisis service, where he promptly fell asleep. Four hours later, he was less intoxicated. A history was obtained and a mental status examination was performed. As far as could be determined, he had been receiving treatment at a local mental health center, but he had stopped taking his medication (risperidone) 4 weeks earlier and had relapsed to heavy use of alcohol and cannabis. During this period he had been essentially homeless, a situation that presented increasing difficulty for him given the recent cold weather and snow.

Overview of Schizophrenia and Co-Occurring Substance Use Disorder

This patient presents with a "dual disorder," most likely schizophrenia and co-occurring alcohol and cannabis use disorders. This is not an uncommon clinical scenario. The literature suggests that nearly 50% of patients with schizophrenia have a co-occurring substance use disorder, most frequently alcohol and/or cannabis (at a rate about three times as high as that of the general population) (1). Patients with dual diagnoses are highly prone to adverse outcomes in several domains: increased symptom severity; increased rates of hospitalization, infectious illnesses, violence, victimization, homelessness, and nonadherence to medication; and poor overall response to pharmacologic treatment (1). Co-occurring substance use disorders contribute substantially to the financial costs and emotional burdens of schizophrenia—for patients, their families, and the mental health system.

The co-occurrence of schizophrenia and substance use disorder is not seen only in patients with chronic illness. Rates of cannabis use disorder as high as 53% have been reported in some studies of patients with first-episode schizophrenic psychosis (2), and cannabis use has been associated with an earlier age at onset of schizophrenia (2), an elevated risk of developing psychosis (3), and a higher relapse rate after remission of acute psychotic symptoms in the first episode (4). Strategies to help patients decrease substance use both in their the first episode and over the course of their illness are essential if we are to achieve optimal outcomes for patients with schizophrenia.

This article is featured in this month's AJP Audio, and is the subject of a CME course.

Theories on the Co-Occurrence of Schizophrenia and Substance Use Disorder

A number of theories have been advanced to explain the elevated prevalence of substance use disorder in people with schizophrenia (5, 6). First, some authors have proposed neural diathesis-stress models, which suggest that a neurobiologic vulnerability interacts with environmental stressors (such as substance use) in vulnerable individuals to precipitate the onset of schizophrenia or relapse of psychosis (7). Support for this model has been found in studies indicating that substance abuse is associated with an earlier age at onset of schizophrenia (2, 3), the recent finding that use of cannabis by adolescents who have the "high output" catechol *O*-methyltransferase polymorphism (Val/Val) is associated with a higher risk of developing psychosis in young adulthood (8), and evidence that patients with schizophrenia experience negative clinical effects, such as relapse, after using small quantities of substances of abuse (9). Patients with schizophrenia thus appear to have a heightened vulnerability to the effects of psychoactive substances, with relatively modest levels of alcohol and drug use leading to adverse consequences.

Second, the accumulative risk factor hypothesis (5) suggests that people with schizophrenia may have a greater risk of substance use disorder because of the cumulative effects of poor cognitive, social, educational, and vocational functioning as well as poverty, victimization, and exposure to deviant and/or substance-using familial and social environments, all of which are known risk factors for substance abuse. While this model has strong face validity, research has not yet tested whether the accumulation of these risk factors underlies the higher rates of substance abuse in patients with schizophrenia.

Third, the self-medication hypothesis (see reference 10, for example) proposes that patients with schizophrenia use substances in order to reduce symptoms of the disorder or to lessen the side effects of antipsychotic medications. While this model has some commonsense appeal, most studies have reported no relationship or only a limited relationship between substance use and either positive or negative symptoms or medication-induced extrapyramidal side effects (see reference 11, for example). Studies demonstrating elevated rates of substance use disorder among patients with first-episode psychosis before any exposure to antipsychotic medication further argue against this hypothesis (2).

Our group (6, 12) and Chambers and colleagues (13) have proposed an alternative model, that of reward circuitry dysfunction. Animal and human studies indicate that the brain areas thought to be dysfunctional in schizophrenia are part of the dopamine-mediated brain reward circuitry (14). In patients with schizophrenia, substance

use may modulate this dysfunctional brain reward circuitry by producing an increase in the neuronally based signal detection of these dopamine-rich systems (15). Thus, the basis of the use of these substances may be related to the difficulty these patients have in experiencing "normal" levels of reward from the environment and to the ability of substances of abuse to ameliorate this reward circuitry deficit (6, 12).

Detection of Substance Use Disorders in Patients With Schizophrenia

Co-occurring substance use disorders are often under-detected and undertreated in mental health settings, where the traditional separation between mental health and substance use training programs and service delivery systems results in a lack of knowledge about co-occurring disorders and a seemingly inconsistent commitment to the treatment of the substance use component. Given the substantial lifetime vulnerability of patients with schizophrenia to substance use disorder, this situation is clearly problematic. Clinicians must keep possible substance use clearly in mind when evaluating and treating

"The literature suggests that nearly 50% of patients with schizophrenia have a co-occurring substance use disorder, most frequently alcohol and/or cannabis."

patients with schizophrenia. Screening and assessment can be aided by the use of standardized measures, especially instruments specifically developed for patients with severe mental illness, such as the Dartmouth Assessment of Life Style Instrument for Screening [16; <http://dms.dartmouth.edu/prc/instruments/dali.pdf>]; the Alcohol Use Scale and the Drug Use Scale (17); and the Stage of Treatment Scale for ongoing assessment (18, 19). The key ingredient, however, is for clinicians to be alert to the potential for substance use when working with patients who are unstable. Taking note of behaviors consistent with substance abuse—for example, frequent missed appointments, poor medication adherence, and financial or legal problems—and obtaining collateral information from family members, case managers, and significant others can be of great help. Honest reporting of actual use is most likely to occur if the clinician establishes a nonjudgmental therapeutic alliance when assessing a patient who may have a co-occurring substance use disorder.

Treatment and Management

Integrated Treatment

More than 50 controlled studies have established the importance of integrating the treatment of patients with co-occurring disorders—in essence, overcoming the problems inherent in the separate systems of care for these individuals (20). While the philosophical approaches of substance use treatment programs and community mental health centers may differ, patients with co-occurring disorders need to be treated in a coherent manner, ensuring

that they receive the same message from all clinicians about the importance of treatment for both their mental illness and their substance use. Programs that coordinate pharmacotherapy, psychosocial treatments, and substance abuse counseling into a single comprehensive package are most likely to have good treatment outcomes. Integrated treatment programs for dual-diagnosis patients should include staged interventions tailored to the patient's motivation for change (e.g., the use of assertive outreach to engage patients in treatment and motivational interviewing techniques to develop motivation to address substance use); comprehensive services (e.g., medication management, rehabilitation, and social support interventions); and a long-term perspective, since relapse is a common occurrence. One such well-described treatment program, integrated dual disorder treatment (21), involves multidisciplinary teams to provide a truly integrated level of care. The teams often include clinical case managers, who may serve as individual, group, or family therapists, as well as psychiatrists and other medical staff. One of the keys to success in such treatment strategies lies in ensuring that patients have access to residential services and vocational supports, which the majority of these patients need.

Patients with co-occurring disorders benefit from standard psychosocial interventions, such as assertive community treatment and supported employment, just as other patients do, but these interventions have a minimal impact on their substance use disorder. The specific integrated interventions that consistently reduce substance abuse include group counseling with cognitive behavior and motivational components (22), contingency management (23), and, for patients who do not respond to less intensive interventions, long-term residential programs (24). With treatment, the majority of these patients will become abstinent over time, but incarceration, homelessness, infection with hepatitis C and HIV, and early mortality are clear risks for those who do not become abstinent.

Pharmacologic Management

Antipsychotic Medication. While some controversy exists on the optimal antipsychotic medication for patients with schizophrenia, there is a general consensus that the first-generation (conventional) antipsychotics are not particularly helpful in the treatment of patients with schizophrenia and substance use disorder. Studies over many years have documented a high rate of substance use disorder in schizophrenia patients who have been treated with these agents and have shown that patients with dual diagnoses experience a more difficult course of illness when treated with these medications compared with schizophrenia patients who do not have a co-occurring substance use disorder. Several investigators have suggested that conventional antipsychotics may actually precipitate or worsen the abuse of substances in patients with schizophrenia (reference 25, for example). The data suggesting that haloperidol may increase cigarette smoking in patients with schizophrenia are often cited to highlight the

problems associated with the use of conventional antipsychotics in these patients (26).

Injectable Antipsychotics. Given the poor treatment adherence that is characteristic of patients with schizophrenia and co-occurring substance use disorder, it is not surprising that long-acting injectable conventional antipsychotics have often been used in these patients to enhance control over psychosis. Data on the efficacy of these medications are sparse, however. One unblinded study (27) suggests that the long-acting injectable second-generation antipsychotic risperidone may be of greater value than long-acting injectable conventional antipsychotics in these patients.

Atypical Antipsychotics. In contrast to concerns that conventional antipsychotics may worsen substance abuse, a number of (still preliminary) studies suggest that some of the second-generation (atypical) agents may be helpful for these patients (see reference 28 for detailed review). For example, there have been reports that for patients treated with clozapine and olanzapine, overall outcomes during treatment are as good among those who have a co-occurring substance use disorder as those who do not. Some researchers have suggested that the lower incidence of neurologic side effects produced by the atypical antipsychotics, along with the possibility that these agents may be more likely to decrease negative symptoms, make them a logical choice for patients with co-occurring substance use disorder (even though parameters of the metabolic syndrome must be monitored while using these agents).

Regarding nicotine, several controlled studies (reference 29, for example) have indicated that smoking cessation interventions may be more effective in patients with schizophrenia who are treated with atypical rather than conventional antipsychotics. McEvoy and colleagues prospectively studied patients switching from conventional antipsychotics to clozapine and observed spontaneous reductions in cigarette smoking, in both a small (N=12) and a larger (N=55) group of patients (review in reference 28).

A substantial portion of the available data concerning the effects of atypical antipsychotics on substance use in patients with schizophrenia is from clozapine studies. Initially, case reports and series noted reduced use (with frequent abstinence) and reduced craving for substances while taking clozapine. Two retrospective surveys of approximately 35 patients each (one by our group) reported significant reductions in use of alcohol and other substances. These findings were supported by data from a prospective trial indicating that 11 of 16 patients (70%) with co-occurring substance use disorder and schizophrenia reduced or stopped using substances during a 12-week prospective trial of clozapine (review in reference 28).

Our group also reported this unusual effect of clozapine. In a naturalistic study of 151 patients with schizophrenia and substance use disorder who were followed longitudinally for more than 3 years (30), we found that the 36 patients treated with clozapine were more than twice as likely to attain full remission of alcohol abuse than those treated with conventional antipsychot-

ics (79% versus 34%). In a 10-year follow-up report on the same patient sample (31), we noted that in patients who attained remission, use of clozapine was associated with a markedly reduced relapse rate over the subsequent year (8% of the clozapine group versus 40% of the conventional antipsychotic group). We have proposed that the effect of clozapine on substance use in these patients is related to clozapine's broad-spectrum pharmacologic effects (i.e., its weak antagonism at the dopamine D² receptor and its potent blockade of the noradrenergic α^2 receptor, coupled with its ability to release norepinephrine in the brain), which result in an amelioration of the brain reward circuit deficiency in these patients (6). However, despite the strong suggestions these studies offer on clozapine's potential, none were prospective randomized controlled trials, and thus the evidence about clozapine's value for these patients remains preliminary.

A number of other, more recently developed atypical antipsychotics have also been assessed in patients with co-occurring substance use disorder, but there is even less information about them than about clozapine. In a randomized, prospective study comparing risperidone and haloperidol, risperidone treatment decreased cue-craving and substance abuse relapse in patients with schizophrenia and co-occurring cocaine dependence (32). However, our group, in a retrospective study of 41 patients with schizophrenia and co-occurring alcohol or cannabis use disorder (33), noted that abstinence rates were considerably higher among patients treated with clozapine (54%) than among those treated with risperidone (12.5%). Moreover, a large (N=249) retrospective chart review of Department of Veterans Affairs (VA) patients (34) found that after confounding factors were controlled for, there were no differences in improvement on Addiction Severity Index scores between patients treated with atypical antipsychotics (mostly risperidone and olanzapine) and those treated with conventional antipsychotics.

Although case reports and one open-label trial (review in reference 28) have suggested that olanzapine may be associated with a reduction in substance use, results of randomized controlled trials have been mixed. Smelson and colleagues (35) reported reduced cue-craving and reduced cocaine-positive urine screens with olanzapine compared with haloperidol, but Sayers and colleagues (36) reported negative findings for olanzapine compared with haloperidol. Our group reported that although the rate of substance use appeared to decrease in patients treated with olanzapine, the same decreased rate was observed in patients treated with conventional antipsychotics (see reference 28). Finally, as noted above, in the large VA chart review, no differences were observed in improvement in substance abuse measures between those taking olanzapine or risperidone and those taking conventional antipsychotics (34).

In two open trials, treatment with quetiapine was associated with reductions in one of several measures of substance abuse in 24 patients with schizophrenia spectrum disorders and with decreased stimulant craving but not

decreased stimulant use in 24 patients with co-occurring disorders whose medications were switched from conventional antipsychotics (see reference 28). In two small pilot studies, aripiprazole has been reported to decrease craving for and use of alcohol and cocaine (see reference 28). To our knowledge, there are no reports on the use of ziprasidone in this population.

Clearly, further studies of the effects of the various atypical antipsychotics will be needed before clear recommendations can be made on optimal pharmacologic management for patients with schizophrenia and co-occurring substance use disorder.

Adjunctive Agents. A number of medications have been used adjunctively with antipsychotics in patients with schizophrenia and co-occurring substance use disorder. For example, several recent studies have suggested that bupropion may be helpful for smoking cessation in patients with schizophrenia (reference 37, for example). The tricyclic antidepressants desipramine and imipramine appear to be helpful in reducing cocaine use in patients with a co-occurring cocaine use disorder (reference 38, for example). Although a few studies have suggested that valproic acid may reduce alcohol use in patients with bipolar disorder, this agent has not been studied in patients with schizophrenia and co-occurring alcohol use disorder.

Adjunctive Alcohol Use Disorder Treatments. Three medications have been approved in the United States for the treatment of alcohol use disorders—disulfiram, naltrexone, and acamprosate. While disulfiram has been available for decades as a treatment for alcoholism and has been used safely in patients with schizophrenia and alcohol use disorders, its use in this patient group has been quite limited. This may be due to concerns about its potential ability to increase psychosis and about its potential liver toxicity. However, a recent retrospective study of disulfiram in 33 patients with alcohol use disorder and severe mental illness found that 64% developed a sustained remission from their alcohol use disorder without evidence of exacerbation of psychosis (39). A recent report (40) on the use of disulfiram in a large group of patients (N=250) with a variety of mental illnesses and co-occurring alcohol dependence (66 of whom had a diagnosis of a psychotic spectrum disorder) demonstrated that disulfiram was well tolerated and more effective than placebo in reducing alcohol use in this population, without worsening psychosis or causing liver toxicity.

Naltrexone, which has been shown to reduce drinking in patients with primary alcohol use disorders, has shown promise in patients with co-occurring schizophrenia or other psychotic disorders and alcohol use disorder. In two randomized controlled trials, one with 31 patients with schizophrenia, the other with 66 patients with a psychotic spectrum disorder, alcohol use decreased more in patients treated with adjunctive naltrexone than in those treated with adjunctive placebo (40, 41). Continued studies will be needed to fully delineate the extent of this effect and to ascertain whether naltrexone's potential liver toxicity will be problematic for routine use in this population. The avail-

ability of long-acting injectable naltrexone will provide another potential therapeutic option for these patients.

Two other medications may be of interest in the future for this population. Acamprosate, an agent with glutamatergic effects, was recently approved for use in the treatment of alcoholism. However, we are not aware of any studies of this medication in patients with schizophrenia. Finally, the anticonvulsant topiramate has shown promising results in patients with alcoholism. At the time of this writing, case reports suggest that topiramate may also have a beneficial effect on alcohol use in patients with schizophrenia (review in reference 28).

Summary and Recommendations

As we noted earlier, nearly 50% of patients with schizophrenia develop a substance use disorder in their lifetime, and this co-occurring disorder substantially worsens the course of schizophrenia by destabilizing the illness, impeding treatment adherence, and adding the problems of psychosocial instability, legal entanglements, and medical illnesses to the challenge of managing psychotic symptoms. While the basis of the high rate of substance use in this patient group is uncertain, it appears that these patients are highly vulnerable to the effects of alcohol and other drugs and that they suffer from an accumulation of known risk factors for the development of substance use disorder. We and others have hypothesized that a brain reward circuit dysfunction may underpin substance use in these patients. The emerging data suggesting that patients with schizophrenia may have a biologic basis for their substance use may be helpful therapeutically. The notion that patients have a desire to use substances in order to achieve some feelings of normalcy can help clinicians suspend judgment about substance use and adopt a pragmatic attitude that they will need if they are to work effectively with these patients and apply the techniques recommended by clinical experts in behavioral substance abuse counseling (21). In addition, careful prescription of medications to treat the psychotic illness and the substance use disorder is likely to enhance the treatment of patients with co-occurring disorders.

Although the patient described in the vignette at the beginning of this article was homeless, psychotic, and intoxicated, clinicians should be optimistic about the potential for effective treatment of his co-occurring conditions. While he is in the hospital, clinicians should conduct an assessment (in a nonjudgmental fashion), including contacting the outpatient treatment team and family or support persons for information. Psychiatric stabilization with medication should be initiated immediately. The patient should be offered a choice of antipsychotic medications that are least likely to exacerbate substance use and most likely to enhance adherence, such as one of the atypical agents (recognizing that no published data are as yet available on ziprasidone in this population). Assessment for common comorbid medical conditions, such as infec-

tious diseases and diabetes, and comorbid psychiatric conditions, such as posttraumatic stress disorder, should also be conducted and any comorbid conditions treated.

Since this patient is likely to have a very brief hospital stay, a community-based, stagewise clinical approach to treatment would be optimal. Outpatient clinicians treating a patient who has recently suffered a significant relapse, as this patient has, should reach out to him while he is in the hospital and immediately after discharge to offer practical assistance, such as help with regaining housing, reaccessing entitlements, and other concerns the patient may have. Once the patient becomes reengaged in treatment, clinicians can provide motivational counseling to enhance his motivation to participate in treatment and to consider the impact of alcohol use on his ability to attain his own personal goals. Efforts to stabilize the patient's psychiatric symptoms should continue. Ensuring that he continues to take his antipsychotic medication and engaging him in rehabilitation, such as supported employment services and social skills training, are often addressed first. As the patient becomes motivated to address his substance use, he should be encouraged to participate in a dual-disorder treatment group or a contingency management program, since these have the strongest evidence of efficacy. The treatment team should encourage the patient to develop friendships with sober peers and to become involved in activities with substantial reinforcement value that are alternatives to substance use, such as work, exercise, or a hobby. Use of an adjunctive medication aimed at decreasing substance use, such as naltrexone, should also be considered. Once remission is attained, clinicians should focus on maintaining remission over the long term while they address other key issues, such as overall physical health, employment, and ongoing symptom management.

Received Dec. 8, 2006; accepted Dec. 11, 2006. From the Department of Psychiatry, Dartmouth Medical School, Hanover, N.H. Address correspondence and reprint requests to Dr. Green, Department of Psychiatry, Dartmouth-Hitchcock Medical Center, One Medical Center Dr., Lebanon, NH 03756.

Supported in part by grants R01-DA13196 from the National Institute on Drug Abuse, R03-AA014644 from the National Institute on Alcohol Abuse and Alcoholism, and R21-MH62197 from the National Institute of Mental Health to Dr. Green.

CME Disclosure

Dr. Green has received grant support or honoraria from, or served as an adviser for, Eli Lilly, Janssen, Bristol-Myers Squibb, Forest, and AstraZeneca. Dr. Drake receives support from Johnson & Johnson for project implementation. Dr. Noordsy has received grant support or honoraria from, or served as an adviser for, Eli Lilly, Janssen, Bristol-Myers Squibb, and AstraZeneca. Dr. Brunette reports no competing interests.

APA policy requires disclosure by CME authors of unapproved or investigational use of products discussed in CME programs. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by scientific literature and clinical experience.

References

1. Dixon L: Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophr Res* 1999; 35(suppl):S93-S100
2. Green AI, Tohen M, Hamer RM, Strakowski SM, Lieberman J, Glick I, Clark WS, Group HR: First-episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res* 2004; 66(2-3):125-135
3. Hambrecht M, Häfner H: Substance abuse and the onset of schizophrenia. *Biol Psychiatry* 1996; 40:1155-1163
4. Linszen D, Dingemans P, Lenior M: Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry* 1994; 51:273-279
5. Mueser K, Drake R, Wallach M: Dual diagnosis: a review of etiological theories. *Addict Behav* 1998; 23:717-734
6. Roth RM, Brunette MF, Green AI: Treatment of substance use disorders in schizophrenia: a unifying neurobiological mechanism? *Curr Psychiatr Rep* 2005; 7:283-291
7. Fowles DC: Schizophrenia: diathesis-stress revisited. *Annu Rev Psychol* 1992; 43:303-336
8. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW: Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene x environment interaction. *Biol Psychiatry* 2005; 57: 1117-1127
9. D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH: Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 2005; 57:594-608
10. Khantzian EJ: The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv Rev Psychiatry* 1997; 4:231-244
11. Brunette M, Mueser KT, Drake RE, Xie H: Relationships between symptoms of schizophrenia and substance abuse. *J Nerv Ment Dis* 1997; 185:13-20
12. Green AI, Zimmet SV, Strous RD, Schildkraut JJ: Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? *Harv Rev Psychiatry* 1999; 6: 287-296
13. Chambers AR, Krystal JH, Self DW: A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* 2001; 50:71-83
14. Gardner EL: Brain reward mechanisms, in *Substance Abuse: A Comprehensive Textbook*. Edited by Lowinson JH, Ruiz P, Millman RB, Langrod JG. Baltimore, Williams & Wilkins, 1997
15. Nissel M, Nomikos GG, Svensson TH: Nicotine dependence, midbrain dopamine systems, and psychiatric disorders. *Pharmacol Toxicol* 1995; 76:157-162
16. Rosenberg SD, Drake RE, Wolford GL, Mueser KT, Oxman TE, Vidaver RM, Carrieri KL, Luckoor R: Dartmouth Assessment of Lifestyle Instrument (DALI): a substance use disorder screen for people with severe mental illness. *Am J Psychiatry* 1998; 155: 232-238
17. Drake RE, Mueser KT, McHugo GJ: Clinician Rating Scales: Alcohol Use Scale (AUS), Drug Use Scale (DUS), and Substance Abuse Treatment Scale (SATS), in *Outcomes Assessment in Clinical Practice*. Edited by Sederer LI, Dickey B. Baltimore, Williams & Wilkins, 1996
18. Drake RE, Osher FC, Noordsy DL, Hurlbut SC, Teague GB, Beaudett MS: Diagnosis of alcohol use disorders in schizophrenia. *Schizophr Bull* 1990; 16:57-67
19. McHugo GJ, Drake RE, Burton HL, Ackerson TH: A scale for assessing the stage of substance abuse treatment in persons with severe mental illness. *J Nerv Ment Dis* 1995; 183:762-767
20. Drake RE, O'Neal EL, Wallach MA: A systematic review of psychosocial interventions for people with co-occurring substance use and severe mental disorders. *J Subst Abuse Treat* (in press)
21. Mueser KT, Noordsy D, Drake RE, Fox M: *Integrated Treatment for Dual Disorders: A Guide to Effective Practice*. New York, Guilford, 2003
22. Bellack AS, Bennett ME, Gearon JS, Brown CH, Yang Y: A randomized clinical trial of a new behavioral treatment for drug abuse in people with severe and persistent mental illness. *Arch Gen Psychiatry* 2006; 63:426-432
23. Drebing CE, Van Ormer EA, Krebs C, Rosenheck R, Rounsaville B, Herz L, Penk W: The impact of enhanced incentives on vocational rehabilitation outcomes for dually diagnosed veterans. *J Appl Behav Anal* 2005; 38:359-372
24. Brunette MF, Mueser KT, Drake RE: A review of residential programs for people with severe mental illness and co-occurring substance use disorders. *Drug Alcohol Rev* 2004; 23:471-481
25. Voruganti LNP, Heslegrave RJ, Awad AG: Neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. *J Nerv Ment Dis* 1997; 185:463-465
26. McEvoy JP, Freudenreich O, Levin E, Rose JE: Haloperidol increases smoking in patients with schizophrenia. *Psychopharmacology* 1995; 119:124-126
27. Rubio G, Martinez I, Ponce G, Jimenez-Arriero MA, Lopez-Munoz F, Alamo C: Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. *Can J Psychiatry* 2006; 51:531-538
28. Green AI, Noordsy DL, Brunette MF, O'Keefe C: Substance abuse and schizophrenia: pharmacotherapeutic intervention. *J Subst Abuse Treat* (in press)
29. George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, Rounsaville BJ, Kosten TR: Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 2000; 157:1835-1842
30. Drake RE, Xie H, McHugo GJ, Green AI: The effects of clozapine on alcohol and drug use disorders among schizophrenic patients. *Schizophr Bull* 2000; 26:441-449
31. Brunette MF, Drake RE, Xie H, McHugo GJ, Green AI: Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 2006; 32:637-643
32. Smelson DA, Williams J, Ziedonis D, Sussner BD, Losonczy MF, Engelhart C, Kaune M: A double-blind placebo-controlled pilot study of risperidone for decreasing cue-elicited craving in recently withdrawn cocaine dependent patients. *J Subst Abuse Treat* 2004; 27:45-49
33. Green AI, Burgess ES, Zimmet SV, Dawson R, Strous RD: Alcohol and cannabis use in schizophrenia: effects of clozapine and risperidone. *Schizophr Res* 2003; 60:81-85
34. Petrakis I, Leslie D, Finney J, Rosenheck R: Atypical antipsychotic medication and substance use-related outcomes in the treatment of schizophrenia. *Am J Addictions* 2006; 15:44-49
35. Smelson DA, Ziedonis D, Williams J, Losonczy MF, Steinberg ML, Kaune M: The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. *J Clin Psychopharmacol* 2006; 26:9-12
36. Sayers SL, Campbell EC, Kondrich J, Mann SC, Cornish J, O'Brien C, Caroff SN: Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. *J Nerv Ment Dis* 2005; 193: 379-386
37. Evins AE, Cather C, Deckersbach T, Freudenreich O, Culhane MA, Olm-Shipman CM, Henderson DC, Schoenfeld DA, Goff DC,

- Rigotti NA: A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J Clin Psychopharmacol* 2005; 25:218–225
38. Siris SG, Mason SE, Bermanzohn PC, Shuwall MA, Aseniero MA: Adjunctive imipramine in substance-abusing dysphoric schizophrenic patients. *Psychopharmacol Bull* 1993; 29:127–133
39. Mueser KT, Noordsy DL, Fox L, Wolfe R: Disulfiram treatment for alcoholism in severe mental illness. *Am J Addictions* 2003; 12:242–252
40. Petrakis IL, Nich C, Ralevski E: Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophr Bull* (in press)
41. Petrakis IL, O'Malley S, Rounsaville B, Poling J, McHugh-Strong C, Krystal JH; VA Naltrexone Study Collaboration Group: Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. *Psychopharmacology* 2004; 172:291–297