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

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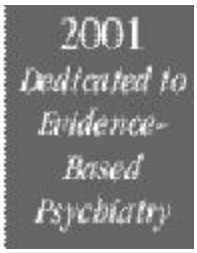

Medication treatment of severe mental illness has been advanced and complicated by the introduction of numerous therapeutic agents. Practice guidelines based on research evidence have been developed to help clinicians make complex decisions. Studies of usual care suggest an important potential role for 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 incorporate 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

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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 categories 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.

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.

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), 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 schizophrenia. 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 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.

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

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 guidelines. 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. ♦

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