Consensus Guidelines in the Treatment of Major Depressive Disorder

A. John Rush, M.D.; M. Lynn Crismon, Pharm.D.;
Marcia G. Toprac, Ph.D.; Madhukar H. Trivedi, M.D.; William V. Rago, Ph.D.;
Steve Shon, M.D.; and Kenneth Z. Altshuler, M.D.

The number of available antidepressant medications has increased dramatically in the last 10 years. Furthermore, no single medication is a panacea for all depressed patients—a fact underscored by randomized, controlled trial evidence showing that when one medication fails, an alternative may succeed. Thus, a key issue in the treatment of depression is how to optimally orchestrate available medication options to maximally benefit the greatest number of patients most rapidly. One approach is the use of consensus guidelines or medication algorithms. This paper discusses the rationale for and critical issues in the development of medication algorithms, and the timely use of symptom measures to ensure proper implementation. Once developed, guidelines must be appropriately implemented by clinicians, adhered to by patients, and supported by administrators. These three stakeholder groups often need education, incentives, and ongoing support to implement such guidelines. Whether guidelines actually improve outcome is largely uninvestigated, although a recent study of depressed patients in primary care found that using guidelines did improve outcome but at an increased treatment cost. The clinical and economic impact of guideline-driven treatment for the severe and persistently depressed deserves study. *(J Clin Psychiatry 1998;59[suppl 20]:73–84)*

The past several decades have witnessed the introduction of a wide variety of antidepressant medications, with improved safety and tolerability and different mechanisms of action. Thus, we have moved from a position of having only one group of medications in wide use (i.e., tricyclic medications) to having a more complex set of clinical decisions confronting practitioners: namely, which among a variety of medications is best to start a patient on first, and secondarily, should that medication fail (true for roughly 50% of patients, on the basis of evidence from randomized, controlled trials),[1] what is the next best step?

To address these issues, a variety of reports outlining different options or providing more specific guidance in the form of clinical practice guidelines or medication treatment algorithms have recently become available. The philosophical and scientific rationale for such guidelines has been outlined.[2,3]

Simultaneous with the development of a larger number of treatment options, there has been a shift in the culture surrounding treatment of depression. Table 1 summarizes key elements in this cultural shift. These elements include an emphasis on effective and/or restorative care as opposed to simply humane custodial treatment; a shift from nearly exclusive reliance on psychosocial and rehabilitation services to a greater reliance on pharmacologic interventions; a shift from symptom control to specific treatment for particular syndromes; and a move from divided to integrated care and to patient-driven rather than provider-driven care. Also among the changes is an increasing recognition that simple symptom response is not preferred when symptom remission can be obtained, because the latter is associated with better overall functional restoration and long-term prognosis.[4]

Table 1. A Paradigm Shift in the Management of Depression

Evaluation of processes	→	Evaluation of outcome
Divided care	→	Integrated care
Provider driven	→	Patient driven
Acceptance of symptomatic response	→	Recognition of the importance of remission
Family blame	→	Family collaboration
Custodial/humane treatment emphasis	→	Emphasis on restoration of normal function
Exclusive reliance on social rehabilitation	→	Combining pharmacologic and psychosocial treatments
Symptom control	→	Treatment of the syndrome
Inpatient care	→	Outpatient care

These cultural shifts serve to highlight the current debate over how to deliver quality care. Quality of care may be ranked as *minimal*, which is undesirable; *preferred*, which is good for most patients; or *optimal*, which is the best treatment for each individual patient. *Excessive* care encompasses both necessary and unnecessary treatment, the latter producing little or no clinical benefit and potentially increasing risks and costs.

Most guidelines attempt to recommend preferred care (i.e., that which is good for most individuals) because guidelines are based on group data and, therefore, can make only group-based recommendations. Logically, they cannot recommend optimal care for each individual patient. Rather, practitioners utilizing guidelines while appropriately deviating from, adapting, and tailoring them to individuals can take a preferred level of care and bring it to an optimal level (see Rush and Prien[5]).

The definition of quality care can be based on scientific information, consensus of expert scientists/practitioners, or prospective evaluation. Scientific data often lag behind and fail to fully address the clinical decisions confronted by practitioners on a daily basis. Therefore, one often must rely on a combination of both scientific evidence and clinical experience to form the basis for guideline development. Of note, however, is that the more specific the guideline recommendations, the greater the role of clinical experience and the less robust the scientific data upon which to make recommendations.

A second controversy focuses on who defines quality care. Potential contenders include physicians, other health care providers, patients and/or their families, administrative contractors, contractees, and third party payors. It seems logical to involve as many of these stakeholders as possible in the initial development of guidelines but then to evaluate empirically the actual clinical and economic impact of their recommendations on individual patients and systems of care.

It is important to note that, with rare exception,[6] the clinical and economic impact of even the most conscientiously created guidelines has yet to be evaluated in routine practice. Whether guidelines actually improve the quality of care—as defined by better clinical outcomes

(e.g., greater symptom reduction or functional restoration)—and/or whether such guidelines contain or reduce costs is unknown in psychiatry.[7]

TERMS AND CONCEPTS

Various terms to describe clinical procedures for managing disorders have recently been coined, including *preferred practices*, *disease management protocols*, *guidelines*, *therapeutic pathways*, and *algorithms*. We view *guidelines* as documents that make available to practitioners rational treatment options that have been evaluated by using empirical data, clinical experience/consensus, or the combination. Guidelines that recommend more specific sequenced strategies, as well as particular tactics by which to implement these strategies, have been called *disease management protocols* or *medication algorithms*.[8] The level of specificity of these protocols or algorithms is often greater than those found in clinical practice guidelines, but as might be expected, the scientific certainty upon which these more specific recommendations are based becomes more tenuous (for more detailed discussions, see Rush and Prien[5]). For the purposes of this discussion, we use *algorithms* to identify these more specific, stepwise recommended sequences of treatment and associated tactics.

There are a variety of ways to gauge the certainty of the available scientific evidence. Designs using randomized, controlled comparisons are, of course, the gold standard in determining comparative efficacy, safety, and tolerability. One difficulty with these randomized, controlled trials is that the patient groups selected for study are not adequately representative of the usually more diverse populations to which treatments are applied in practice.[9] For example, patients in antidepressant randomized, controlled trials are usually moderately ill, young to middle-aged adults without comorbid general medical or psychiatric conditions. In addition, randomized, controlled trials often employ substantial clinical support that may not be available to many clinicians, such as research personnel, high visit frequency, regular use of symptom response measures that inform practitioners' clinical decision-making, and financial incentives. Thus, both the populations studied and the clinical procedures typical of randomized, controlled trials differ from those encountered in routine practice, which makes inferences about safety, efficacy, optimal dosage, and tolerability between these different practice settings tenuous at best.

RATIONALE FOR IMPLEMENTING ALGORITHMS

There are both clinical and administrative reasons for developing and using treatment algorithms (Table 2). The most important clinical rationale is to facilitate appropriate clinical decision-making to sustain a preferred level of

Table 2. Reasons for Using Algorithms

Clinical
   Facilitate clinical decision-making
   Improve quality of care
   Conveniently list options for appropriately tailoring treatment to
      individuals
   Make treatment plans consistent across sites and physicians
   Provide adequate clinical documentation
Administrative
   Improve cost efficiency of treatment
   Make costs more predictable
   Define where new medications fit for optimal clinical outcomes
   Provide a basis for defining when new medications are cost effective
   Define costs related to specific treatments or outcomes
   Provide adequate clinical documentation

Figure 1. Potential Benefits of Algorithms: More Rapid and More Thorough Response*

*This material is in the public domain and may be reproduced without permission. "Patient condition" refers to combination of symptom severity and psychosocial functioning. Symbols: – = patient condition at initiation of treatment, + = improvement during course of treatment.

Figure 2. Consequences of Preferred Versus Minimal Care*

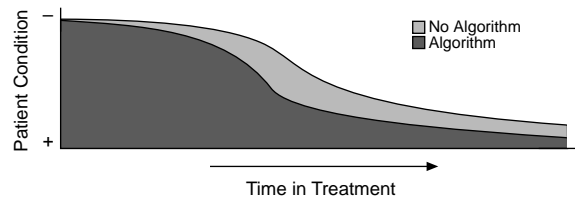*This material is in the public domain and may be reproduced without permission.

quality care. To have clinical utility, algorithms must allow for physicians to tailor them to individuals. Algorithms must be flexible enough to take into account prior treatment history, individual patient factors (such as comorbid conditions and concomitant medications), as well as—wherever possible—patient preference. Even so, some individuals are likely to be inappropriately treated if the algorithm is followed.

Another clinical reason for using algorithms is that, as lengths of hospital, day treatment, and partial hospitalization stays shrink, patients begun on medication(s) in these venues do not remain under the care of the initial prescriber long enough for him or her to determine whether the medication produces optimal results for the individual. As patients move more rapidly among treatment settings, it is critical that treatment plans are consistent across sites and physicians so that a treatment trial (which may last 4–8 weeks) can be consistently conducted and individual response can be accurately gauged.

For both clinical and administrative reasons, it is important to provide consistent and concise clinical documentation of the treatment provided—especially since one provider may inherit the patient from another and must be fully informed regarding the patient's prior treatment(s) and response to it/them so as to take the next step(s) in a timely fashion should the prior treatment have failed or have been found to be intolerable.
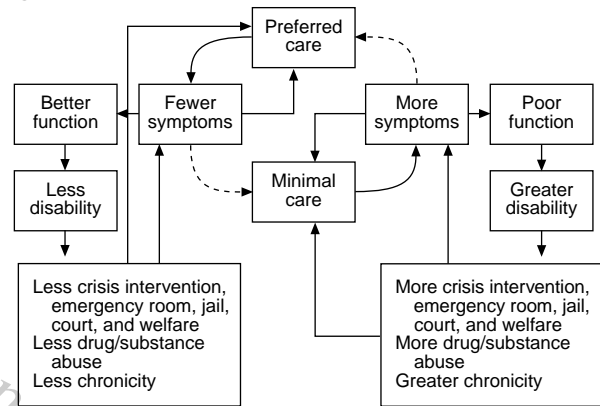
Administratively, there are a number of reasons to suggest that algorithms may be of substantial utility. Ultimately, algorithms should serve to make optimal use of finite resources (i.e., improve the cost efficiency of treatment) as well as to make costs more predictable. Furthermore, once a baseline practice is established with a particular algorithm, then one can insert new medications into the recommended sequence of treatment steps at various points to provide empirical data regarding the most cost-efficient use of the medication. Finally, algorithms provide—at least in theory—a mechanism by which to relate costs to specific treatments or particular outcomes. That is, algorithms can be used as a framework for pharmacoeconomic analyses.

The hope is that algorithms will produce a more rapid and/or a more thorough response (symptom reduction, functional restoration) with better tolerability for patients than treatment-as-usual. Figure 1 illustrates these hoped-for benefits for patients treated with compared to those treated without an algorithm.

Figure 2 illustrates the potential benefit of moving from minimal to preferred care from a system perspective. Minimal care may result in more symptoms, poorer function, and greater disability, which in turn results in greater chronicity, greater use of the treatment system—particularly hospital, emergency, and crisis intervention—as well as potentially greater reliance on nontreatment system resources (e.g., courts, jails, prisons, or the welfare system). Depression—when inadequately treated—may be associated with greater drug abuse,[10,11] chronicity, or other complications (e.g., suicide or morbidity from concurrent general medical conditions).

On the other hand, preferred care, perhaps facilitated by algorithms, should reduce symptoms and improve function, thereby resulting in less disability, with secondarily reduced utilization of hospital, crisis, and emergency services—as well as courts, jails, prisons, and the welfare

system—and a reduced risk of chronicity and secondary complications. Not shown in Figure 2, but another hypothetical benefit of algorithms, as preferred replaces minimal care, is reducing family burden.

RISKS OF USING ALGORITHMS

Hypothetical benefits of algorithms have not yet been empirically established in psychiatry. Furthermore, algorithms (or guidelines) have inherent risks. First, they may simply be wrong—that is, the recommendations, even if largely based on randomized controlled trials and other scientific evidence and even when interpreted with substantial clinical experience, may recommend incorrect or inadequate treatments. For example, participants involved in guideline development may be biased and, therefore, recommend inappropriate treatments. Plus, adequate scientific evidence rarely exists for treatment decisions beyond the second treatment stage, adding to the possibility that clinical consensus may not be correct.

Second, the nature of the disorders, the treatments, and the clinical contexts are all heterogeneous. While currently constituted guidelines have struggled with issues of which patient groups, which types (or subtypes) of disorders, and which treatments or clinical contexts should be addressed by guidelines, it is uncertain that these issues of heterogeneity have been properly resolved.

Third, because algorithms often make rather explicit recommendations, those who are clinically inexperienced or unfamiliar with basic pharmacology, physiology, and pathology may misconstrue the apparent transparency of recommendations for simplicity of implementation. Administrators may erroneously decide that insufficiently trained or inexperienced personnel should implement these algorithms, which in turn can lead to poor or even tragic outcomes.

A fourth danger is the rush to reification of recommended guidelines without empirical evaluation.

Finally, as noted by the Institute of Medicine,[7] guidelines may improve the quality of treatment and clinical outcomes but with increased costs (i.e., improved value but increased cost). Then a moral or ethical question emerges: within a fixed budget, do we dispense less-than-preferred care (e.g., minimal care) to serve more people, or do we reduce the numbers served in order to provide preferred care to all those whom we do serve? Politically, it is desirable to appear to serve everyone in need, while medically, it is essential that those we serve are cared for properly. If the preferred treatment actually results in the hypothesized benefits shown in Figure 2, then administrators can partially solve this dilemma by reinvesting dollars saved from decreased emergency room or crisis intervention and hospital days into preferred outpatient treatment. However, if the budget available does not match the needs after these shifts, either new dollars are needed or the numbers served must be decreased.

AN OVERVIEW OF AVAILABLE GUIDELINES FOR DEPRESSION

In 1993, a panel commissioned by the Agency for Health Care and Policy Research (AHCPR) issued clinical practice guidelines for the management of major depressive disorder in primary care settings.[1,2] These guidelines relied on randomized, controlled trials and other kinds of evidence to evaluate the efficacy of available medications, psychotherapies, and other treatments for depression for acute, continuation, and maintenance phase treatments and provided indications for maintenance treatment. They also specified principles by which to select among treatments.

Shortly thereafter, the American Psychiatric Association[3] (APA) recommended depression guidelines aimed at psychiatrists. These, too, were evidence-based, in which options were listed along with the scientific evidence recommending each, although clinical opinion was also added to these judgments. The AHCPR and APA guidelines are quite compatible, but neither recommend specific sequences of particular treatments.

Next, the University of Minnesota summarized a March 1995 consensus conference.[12] These recommendations used clinical consensus combined with scientific evidence to address particular practical questions. For example, they specified the parameters by which to select among available antidepressant medications, including tolerability, safety, prior history of response or nonresponse, current general medical or psychiatric comorbidities, patient preference, and other patient factors such as age, potential drug interactions, and ease of use—parameters already largely established in the AHCPR guidelines. This consensus statement also tried to answer specific questions germane to optimizing acute phase treatment. For example, one question posed was, "How long should we maintain patients with minimal response on a specific medication?" The consensus was that if at least a 25% reduction in symptoms was not seen following at least 4 weeks at a therapeutic dose, the chance of response is relatively low, although not zero, for subsequent medication response.[13,14] Like the AHCPR guidelines, this consensus statement also recommended including maintenance phase treatment to prevent recurrences or new episodes for patients who have had three episodes or for those who have experienced two episodes and are at risk for a third episode; risk factors include a positive family history, poor prior interepisode recovery, early age at onset of the first episode, and a short time interval between the onset of the first and second episodes. This consensus statement also offered more specific recommendations regarding when to switch medications or to augment one medication with another should the first medication be ineffective or intolerable and when to refer patients from primary to specialty care.

In December 1996, the American Pharmaceutical Association published specific protocols for the treatment of depression.[15] These specific protocols are evidence-based and were developed using a three-tier, consensus-driven review process. The protocols provide a detailed decision tree to guide clinicians through treatment decisions and also make some consideration for comorbidity. One potential shortcoming is a lack of specificity in defining the clinicians for whom the protocols are intended.

More recently, the Texas Medication Algorithm Project (TMAP) held a consensus conference in July 1996. A series of specific, sequenced medication treatment strategies with options for individualizing treatment were recommended based on both scientific evidence and clinical consensus. As with the University of Minnesota consensus statement, the serotonin selective reuptake inhibitors (SSRIs) were recommended as first-line treatments. In addition, given the equivalent efficacy, safety, and tolerability of other newer medications such as bupropion, nefazodone, and venlafaxine, these too were recommended as first-line treatments by the consensus conference. However, since dose adjustments are modest and once-a-day dosing is typical with all three SSRIs (paroxetine, fluoxetine, and sertraline),[16] these agents were viewed as preferable in many clinical situations by this consensus group. In addition, this consensus conference recommended particular tactics with regard to dosing, treatment duration, and outcome assessment. Key strategic decision points in the course of the sequenced medication treatment plans were noted. A grade was also provided as to the level of evidence supporting each recommendation.

MAJOR ISSUES CONFRONTING ALGORITHM DEVELOPERS

Available guidelines range in the specificity of their recommendations and the degree of their reliance on scientific data to support such recommendations. AHCPR guidelines for the treatment of depression in primary care,[1,2] as well as the APA guidelines for the treatment of depression,[3] relied heavily on the available scientific evidence and then noted the inferences that had to be made and weighed on the basis of clinical consensus.[17] Evidence-based guidelines, while constituting the foundation upon which algorithms are based, almost always contain significant gaps since scientific data are unlikely to address all the possible clinical questions and nuances that practitioners must face in applying nomothetic (group) data to idiographic (individual) situations.[5] Thus, the assumptions upon which guidelines are based must be explicitly stated.

Another major tension in guideline development is the need to provide enough specificity but also to allow for flexibility. Recommended strategies that tell what to do without giving salient tactical suggestions describing how to do it are often insufficiently specific. For example, the appropriate medication(s) but not the proper dose or the proper length of treatment may be recommended by a guideline. Tactical recommendations must also be flexible so that practitioners can tailor them to individual patients. Thus, some optional tactics must be included in order for algorithms to be useful in diverse clinical situations.

Also inherent within guideline development is the struggle to define the population for which the algorithm is recommended. Is it for all patients, the average patient, or specific subgroups? In general, the choice of target population is one of an average patient with common comorbidities but who is in otherwise good general medical health. For major depression, guidelines often separate patients into those with and without psychotic features, since evidence suggests that the combination of an antidepressant and an antipsychotic is more effective than an antidepressant alone in those with psychotic features.[1] Another aspect of the target population question is whether recommendations should differ for the same condition in patients seen in psychiatric as opposed to primary care settings. In general, while the parameters and structural elements of care often differ between those two venues (e.g., length of visits, amount of time given to diagnostic evaluation, frequency of visits), there is a recommendation throughout medicine that primary care patients should otherwise receive the same quality of treatment as that provided by specialty care. When the treatment elements that are called for by the algorithms cannot be delivered in the primary care setting (e.g., due to structural limitations or because procedures called for exceed the skills of primary care providers), then specialty care is recommended.

Because algorithms are usually more specific than guidelines, which simply list options and the associated scientific evidence, they require more frequent revisions. Algorithm developers confront such issues as: How much evidence is enough to recommend revisions? What type of evidence (e.g., clinical impression versus scientific evidence) is required? Whose clinical impression should be relied upon? For example, when a new medication becomes available for depression, algorithm developers must ponder questions such as how wide the exposure should be before including the new medication in revised algorithms and at what stage in the algorithm it should be inserted.

A final consideration of algorithm developers is whether the design allows one to reach a rational conclusion with regard to cost-effectiveness in specific practice settings? For example, do modelling studies using clinical trial data provide any useful information for practice decisions? Naturalistic health care database studies frequently use no or imprecise indicators (e.g., length of time patients take a drug, number of refills) to define successful treatment outcomes. Is this information adequate for making cost-effectiveness decisions, and can it be successfully extrapolated from one practice setting to another? Systematic

prospective outcome evaluations of algorithm-based treatments are needed to assess the therapeutic benefit of interventions as well as costs to the health care system.

ELEMENTS OF ALGORITHM FORMULATION

To implement guidelines or the more specific algorithms, the recommended strategies must have sufficient options, such that they are applicable to a large number of patients. Selected tactical recommendations are helpful. Some tactical recommendations are relatively specific (e.g., they give the amounts for a therapeutic dose range), while others are more general (e.g., they simply say a response is expected between 4 and 6 weeks at "a therapeutic dose" in most patients).

It is often advisable to engage the clinicians who will use the guidelines or algorithms in the development process.[18] Adaptation to specific populations (e.g., public sector patients or primary care patients) or delivery systems depends in part on clinicians' working knowledge and experience, which sometimes necessitates tactical modification of algorithms more suitable for other systems. For example, some audiences may be highly sophisticated with regard to the nuances of psychopharmacology and, therefore, require less specific tactical directions, whereas others may be only modestly familiar with one or two medications and, therefore, may benefit from more specific recommendations. Conversely, details as to treatment nuances that are not of essential clinical significance should be eliminated from guidelines. In addition, especially in the public sector, it is useful to engage administrators and advocates in the formulation of guidelines, as these persons are stakeholders in the recommendations and should inform the choices confronting guideline developers.

To reduce inappropriate variance among providers, we suggest that brief, clinically agreed-upon methods by which to assess symptom response and side effects be described in the algorithms, because some physicians may accept a partial response as sufficient, whereas others may be less satisfied with a partial response, and still others may change treatments prematurely before full benefit can be gauged. Coming to some consensus as to what is a sufficient level of symptom response, when it is expected, and how to gauge it should reduce inappropriate interprovider variation.

To gauge patient response to each treatment stage, an assessment of symptom severity is recommended; whether the assessment is clinician-rated or self-reported depends in part on the patient's cognitive capacity. For example, psychotic symptoms may reduce the accuracy of self-ratings, whereas nonpsychotic, moderately depressed outpatients probably can self-report symptoms. In addition, it should be noted that cognitive changes (e.g., less pessimism) appear to follow somatic improvement (e.g., appetite or energy growth) so that rating scales with substantial cognitive loading may reveal improvement later than self-reports with less cognitive loading.[19] A practical issue is when to measure response to the algorithm. In general, the recommendation is to conduct response measurements only when needed (i.e., at key decision points such as after 4–6 weeks of medication treatment)[1,13] or when there is an unclear accounting of the degree of response based on the practitioners' global evaluation. Conversely, one cannot make clinical decisions based only on rating scale numbers. That is, symptom ratings provide additional information but do not supersede clinical judgment. For example, a patient who shows improvement on a rating scale but does not remit may represent a therapeutic victory if he or she has failed on five different prior treatments, but such a response may not be acceptable for a less chronically ill, previously drug-naive patient.

Both the Depression Guideline Panel[1] and the TMAP conference recommend that patient preference play a key role in selecting among otherwise medically-equivalent treatments (i.e., those that are equally effective, safe, and tolerable). Some medically-equivalent treatments have different side effect profiles. We know that some patients may prefer to risk developing certain types of side effects (e.g., sexual dysfunction) if they can absolutely avoid others (e.g., sedation). Allowing patients to participate in selecting among medically-equivalent but side-effect differentiable treatments may increase patient adherence, and mention of this should be made in treatment algorithms.

In addition, since clinicians have to weigh and select among options at various stages in the algorithm, the strength of evidence supporting each option should be provided. Finally, algorithms should advocate beginning with the simplest, least complicated treatments and moving to more complicated treatment combinations only when patients have failed to respond to the less complicated interventions. Prototype or exemplar algorithms are provided in Figure 3, which shows strategic recommendations, and Figure 4, which shows tactical recommendations.

ESSENTIAL ELEMENTS OF GUIDELINE IMPLEMENTATION IN THE PUBLIC SECTOR

The following suggestions are based on our experiences to date with the existing literature (e.g., Katon et al.[20]) evaluating guideline-based disease management protocols for depression in primary care settings and with TMAP. Katon et al.[20] noted four essential elements in a chronic disease management program pertinent to the management of depression: practice design features, patient education, expert care, and information. The practice design features necessary for chronic disease management include appropriate appointment-setting, reminders to patients to keep appointments, and follow-up procedures for missed appointments. Also, the roles of diverse providers in the multidisciplinary team need to be specified. Patient education

Figure 3. Exemplar Algorithm Showing Strategic Recommendations*
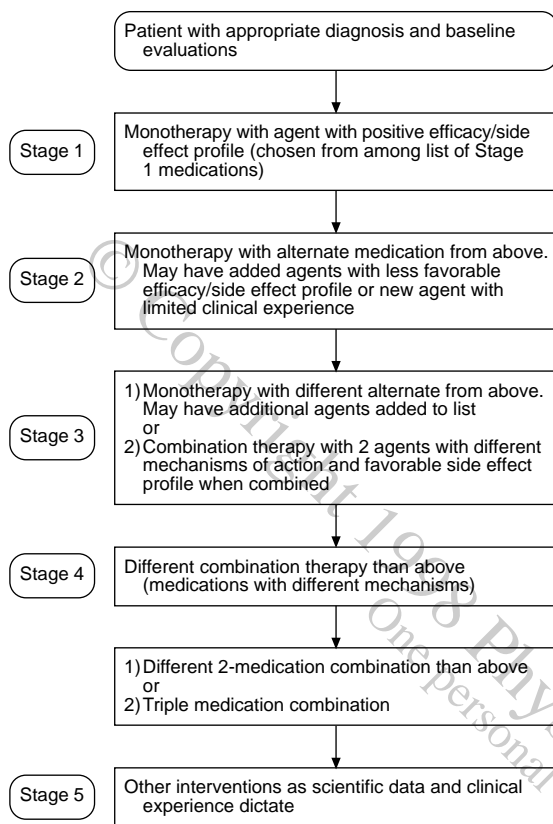
*This material is in the public domain and may be reproduced without permission.

involves helping patients develop self-management skills, change their behavior, utilize psychosocial support, and, most importantly, participate in the overall management of their condition. Expert care requires education and decision support for providers, easy access to consultation should problems or obstacles be encountered, and information systems to give reminders and feedback to providers and patients. Information systems may be, for example, a simplified method of outcome measurement that gives feedback to providers and patients, leading to timely revisions in care plans, with communication of that information to all providers.

TMAP is an ongoing project that aims to develop, feasibility test, and prospectively evaluate the clinical and economic impacts of algorithm-based treatment for depression, schizophrenia, and bipolar disorder in three phases (Figure 5). Phase 1 included the development by consensus, with a focus on empirical scientific evidence of medication algorithms for each disorder.

Phase 2—a feasibility trial completed in September 1997—involved nearly 40 physicians at more than one dozen sites and engaged patients with one of the three target disorders in order to determine whether the strategic and tactical recommendations were suitable, applicable, and acceptable. This uncontrolled trial allowed us to gauge response rates to each step; to revise, where appropriate, the strategies and tactics; and to evaluate which of several potential symptom outcome measures were most useful for implementing the algorithms.

Only a prospective (preferably randomized but at least matched) comparison of algorithm-driven treatment versus treatment-as-usual can determine whether algorithms actually improve outcomes and, if so, at what cost. This step, Phase 3, will last from September 1997 to August 2000.

Features of Practice Design

The following highlights best practices for developing and implementing medication algorithms in the public sector based on our experiences during Phases 1 and 2 and the Katon et al.[20] recommendations (Table 3). First, the algorithm should be practical (i.e., simple but with options so clinicians can tailor the algorithm(s) to individual patients). Options to deviate from the recommended stages, as well as the option of not using the algorithm at all—with proper documentation—should be provided. The algorithm should incorporate simple measures by which to gauge response at key decision points.

Second, the algorithm should have face validity and specify the scientific basis upon which it was developed. Participation by clinicians, advocates, and patient groups is not only especially helpful, since it may lead to revisions in scientific expert recommendations, but necessary if preferred treatment is the objective.

Third, public sector systems are run by administrators to whom physicians are responsible. Because algorithms may shift budget requirements (e.g., to medication formulary from other sources), endorsement and support of the algorithms by key administrative and budgetary officers are essential. Administrators, who are asked to implement algorithms—especially those advocating more expensive medications at earlier steps—must confront budgetary problems that can be created by these recommendations. Thus, administrators must be provided with education and feedback with regard to the rationale for the algorithms, the initial cost that may be encountered, and the potential benefits as well as the potential disadvantages of using this approach. Didactic information, regular feedback, and most important, an accounting of the outcomes obtained in both clinical (e.g., symptoms and disability) and budgetary (e.g., costs, health care system utilization) terms are profoundly useful to administrators who must defend and find resources in the shorter run, which may or may not be offset by reduced overall health care costs in the longer run.

Patient Education

To assist patients in implementing algorithm-based recommendations, patient and family education is essential. Patient education aims at increased adherence as well as at

Figure 4. Exemplar Algorithm Showing Tactical Recommendations*

Decision Point #1

1) Medication(s) chosen
2) Initial dosage and titration scheme
3) Monitoring parameters/time line established
4) Patient education/information

Decision Point #2

Time period to see "partial response"

1) Is patient responding?

Response
1) Was diagnosis correct?
2) Is patient tolerating medication?
3) If so, go to Continuation Stage
4) If not, adjust dose or change medications
5) Patient education

Partial Response
1) Is patient tolerating medication?
2) If not, go to next Stage[a]
3) If so, should dose be increased?
4) Patient education

No Response
1) Is patient tolerating medication?
2) If so, increase dose
3) If not, go to next Stage[a]
4) Patient education

Decision Point #3

Time period to see "clinical response"

Response
1) Is patient tolerating medication?
2) If so, go to Continuation Stage
3) If not, adjust dose or change medications
4) Patient education

Partial Response
1) Is patient tolerating medication?
2) If not, go to next Stage[a]
3) Should dose be increased?
4) Is augmentation medication indicated?
5) Patient education

No Response
1) Is patient tolerating medication?
2) If not, go to next Stage[a]
3) Either augment or go to next Stage[a]
4) Patient education

Decision Point #4

Time period when most patients should have responded

Response
1) Is patient tolerating medication?
2) If so, go to Continuation Stage
3) If not, adjust dose or change medications
4) Patient education

Partial Response
1) Did patient's symptoms worsen? If so, go to next Stage[a]
2) Is patient tolerating medication? If not, go to next Stage[a]
3) Was augmentation used at Decision Point #3?
   a) If so, optimize dose
   b) If not, augment now

No Response
Go to next Stage[a]

Decision Point #5

Maximum time period in Stage to see "clinical response"

Response
As above

Partial Response (or symptom worsening)
1) Reevaluate diagnosis
2) If conditions worsen, go to next Stage[a]

*This material is in the public domain and may be reproduced without permission.
[a]Refer to Figure 3 for the next Stage.

early side effect and relapse detection, optimal symptom resolution, and optimal reduction in disability. Patient education also informs patients of potentially early idiosyncratic reactions, thereby increasing safety. Most randomized, controlled trials in which patient education has been studied in depressed patients indicate that education markedly improves appointment attendance, the likelihood that medications are taken as recommended, and the likelihood that therapeutic blood drug levels are attained (for a review, see Basco and Rush[21]).

TMAP has developed patient and family education materials in collaboration with the Texas Alliance for the Mentally Ill (TEXAMI), the Texas Depressive and Manic-Depressive Association (TXDMDA), the Mental Health Association of Texas (MHAT), and Texas Mental Health Consumers. This work group recommended a five-step program, the first of which is a simple disorder fact sheet—a two-sided posterboard sheet with color illustrations of the nine criterion symptoms for major depression, available in English and Spanish (Appendix 1). The second element—a symptom and side effect monitoring sheet (Figure 6)—reminds patients of the criterion symptoms both in words and in pictures to help patients rate their symptoms and side effects during the week prior to each

Figure 5. Phases of Texas Medication Algorithm Project*
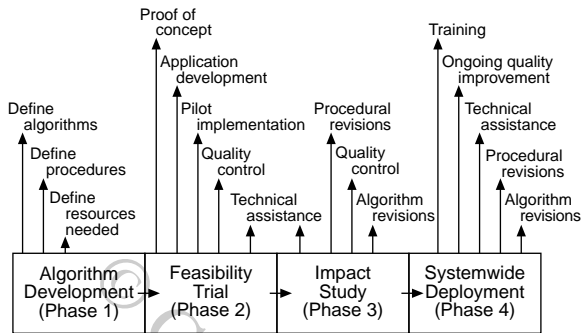
*This material is in the public domain and may be reproduced without permission.

medication visit. MedCoach® (USP) leaflets are being used to provide patients with written medication-specific information.

The third and fourth steps in the patient education program provide basic information about the disorder and its treatment, followed by more in-depth information, to both patients and their families. We have found that patient guides published by the National Alliance for Research on Schizophrenia and Depression (NARSAD)[22] and the New York State Psychiatric Association (NYSPA)[23] are extremely useful for this purpose. For depression and manic-depressive illness, the fifth step is a videotape developed by the National Depressive and Manic-Depressive Association entitled "Dark Glasses and Kaleidoscopes: Living With Manic Depression." Education is offered to patients in both individual and group formats; materials have been developed to facilitate group discussion.

By having sequenced steps, the same message is repeated but enlarged upon at each occasion—as the patient responds clinically. That is, patient education should not be a single event but rather a reiterative experience providing a growing body of knowledge based on the patient's capacity to understand and utilize the information. A patient education guide is currently in development to aid staff in the effective use of these materials for both individual and group settings.

Clinician Support

It is also important to assist clinicians in algorithm implementation. Initial educational efforts followed by ongoing consultation must be provided. Clinicians are more likely to follow the recommendations if user-friendly feedback and prompts are provided to assist them in recognizing key decision points and in considering various options.

Even the most competent clinicians are often unfamiliar with algorithms, and many may be inexperienced in the use of selected medications within an algorithm due to restrictive formularies. In addition, clinicians are often unfamiliar with symptomatic assessment or the intricacies of

Table 3. Essential Elements in Guideline Implementation in the Public Sector

Guideline Practicality
  Simple whenever possible
  Options to tailor when needed
  Options to deviate
  Measures to implement
Guideline Credibility
  Scientific basis
  Clinical face validity
  Clinician vetting
  Advocate vetting
System Endorsement
  Administrative endorsement
  Budgetary acceptance
  Resource reallocation
  Medication access
Patient-Assisted Implementation
  Education
  Family support
  Advocacy support
  Tools to gauge benefits and costs
  Help line
Clinician-Assisted Implementation
  Education
  Consultation
  Measurement of benefits
  Prompts, audits, reminders, feedback
  Participation in development and revisions
Procedural Benefits
  Simplify paperwork
  Increased patient/clinician contact
  Clinical information meets administrative needs
  Continuing medical education

patient education. We believe that clinician education should include information on the overall algorithm, each medication, patient education, symptom assessment, and problem-solving strategies when obstacles to treatment are encountered. Education should also include didactic presentations, consultation on demand, audit and feedback on algorithm adherence, evaluation of patient's clinical responses, and intermittent conferencing to discuss revisions in the algorithms.[24] We believe that optimal outcomes are facilitated by these educational efforts.

Documentation

With most traditional charting systems, it is difficult to determine past treatment response or even, in some situations, what medications have been prescribed. If algorithms are to provide consistent treatment across clinicians and treatment settings, then a systematic and informative charting system must be designed to allow different clinicians to review patients' medication history and treatment response. Such a charting system must be brief and user-friendly while allowing for the systematic recording of both medication information and ratings of the patients' symptoms and side effects. If properly designed, clinician prompts can be built into this charting system.

It is also very useful if the algorithms have an immediate payoff for clinicians (preferably in the form of simpli-

Figure 6. Symptom and Side Effect Sheet (2-sided)*

(Front)

In the last week, the symptoms of my illness were:

| Not Present (0) | Mild (1) | Moderate (2) | Severe (3) | Very Severe (4) |

List the 3 most bothersome symptoms in the last week:

1.

2.

3.

Things I did for me: _____

_____

The side effects of my medication were:

| Not Present (0) | Mild (1) | Moderate (2) | Severe (3) | Very Severe (4) |

List the 3 most bothersome side effects in the last week:

1.

2.

3.

Things I did for me: _____
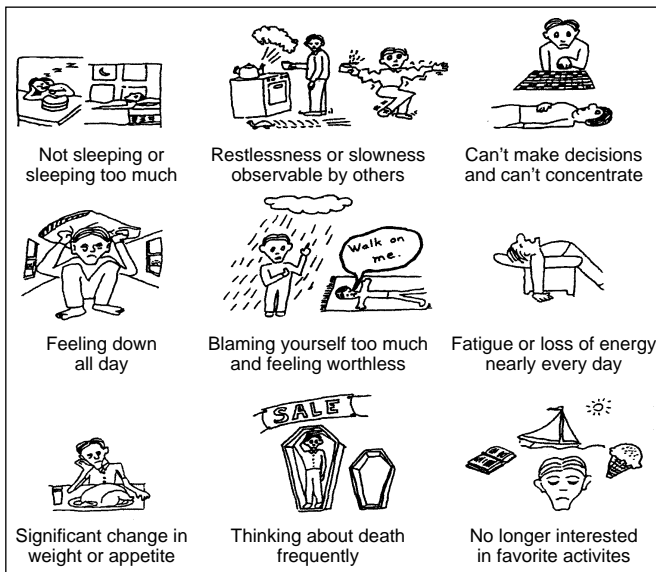
_____

List medications that you are currently taking:

1. _____ 3. _____

2. _____ 4. _____
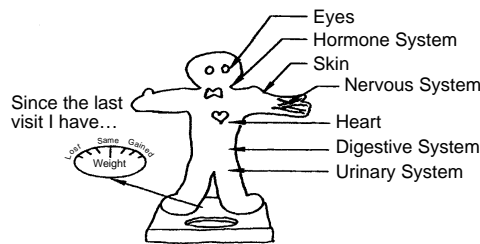
About how long have you been taking each medication?

Weeks/Months/Years

(Back)

Symptoms

- Not sleeping or sleeping too much
- Restlessness or slowness observable by others
- Can't make decisions and can't concentrate
- Feeling down all day
- Blaming yourself too much and feeling worthless
- Fatigue or loss of energy nearly every day
- Significant change in weight or appetite
- Thinking about death frequently
- No longer interested in favorite activites

Medications can cause side effects in many parts of the body. Some may go in time, others can be treated by your doctor.

Since the last visit I have…

- Eyes
- Hormone System
- Skin
- Nervous System
- Heart
- Digestive System
- Urinary System

Ask your doctor about side effects that need to be reported immediately!

Illegal drugs and alcohol may increase the side effects of medications or keep them from working.

*This material is in the public domain and may be reproduced without permission.

fied paperwork and increased patient-clinician contact time). Computer-supported platforms can assist clinicians in rapidly documenting what they are doing, provide timely prompts, and reduce paperwork. If coupled with the scientific database, they could be used to provide continuing medical education credit as well.

COSTS

How medication algorithms for psychiatric patients affect overall costs in the short- or long-run is unknown. The answer probably depends, in substantial part, on the current treatment costs in a particular system. Most pharmacoeconomic studies conducted in primary care settings[25–29] have shown that the newer generation antidepressants have greater benefits (i.e., higher adherence at the same or lower level of care or disease management costs), which argues for a shift to the formulary budget from other sources. The ultimate cost (or cost savings) of this shift depends on the baseline operating characteristics of the particular system. For example, Katon et al.[18] found that the AHCPR guidelines for depression improved outcomes in a large primary care setting but at an increased treatment cost. This increased cost may be worthwhile because of either a lower long-term treatment cost or greater work productivity for the patient (i.e., lower occupational disability).

Another major cost, more likely to be encountered with the older and less safe agents such as the tricyclics, is the catastrophic cost associated with a lawsuit filed as a result of a patient's suicide from these agents—especially when equally effective, better tolerated, and safer agents were available but not used initially. Such lawsuits will dra-

matically drive up the cost of care. Thus, safety is a major reason to recommend newer agents as first-line treatments—most importantly for the patient's sake but also for economic reasons.

SUMMARY

There are a number of clinical and administrative reasons to suggest that algorithm- or guideline-driven management of depression will increase the quality of care and reduce unnecessary and costly practice variation. There are, however, substantial subtleties and tensions in the development of such guidelines. Nevertheless, the fact that a variety of consensus and evidence-based guidelines have been produced, most of which basically agree with one another, suggests that for many patients with major depression, preferred care can be defined on the basis of both scientific evidence and clinical consensus.

Key elements are essential to implement these recommendations for the care of depressed patients. These elements include patient education, clinician education, administrative support, information system support, and often a reallocation of resources in the management of the clinic or day-to-day practice.

The only empirical evidence to date to suggest that guideline-based treatment improves outcomes comes from the primary care setting,[18] but using these guidelines, in fact, increased treatment costs. Whether such findings pertain to other practice venues or to patients with more chronic, severe, and persistent depressions—as are often found in patients in the public sector—deserves empirical study.

Note. The TMAP algorithms and individual samples of the patient/family educational materials are available at no cost from the Texas Department of MHMR, 909 W. 45th Street, Austin, TX 78751. Contact Karla Starkweather at (512) 206-4742, (512) 206-4744 (fax) or karla.starkweather@mhmr.state.tx.us (e-mail).

Drug names: fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft).

REFERENCES

1. Agency for Health Care Policy and Research. Clinical Practice Guideline, No. 5: Depression in Primary Care, vol 2, Treatment of Major Depression. AHCPR publication 93-0551. Rockville, Md: US Dept Health and Human Services; April 1993
2. Agency for Health Care Policy and Research. Clinical Practice Guideline, No. 5: Depression in Primary Care, vol 1, Detection and Diagnosis. AHCPR publication 93-0550. Rockville, Md: US Dept Health and Human Services; April 1993
3. American Psychiatric Association. Practice guidelines for major depressive disorder in adults. Am J Psychiatry 1993;150(4, suppl):1–26
4. Rush AJ, Trivedi MH. Treating depression to remission. Psychiatr Ann 1995;704–705, 709
5. Rush AJ, Prien R. From scientific knowledge to the clinical practice of psychopharmacology: can the gap be bridged? Psychopharmacol Bull 1995; 31:7–20
6. Katon W, Robinson P, Von Korff M, et al. A multifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry 1996;53:924–932
7. Field MJ, Lohr KN. Clinical Practice Guidelines: Directions for a New Program. US Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines, US Dept Health and Human Services. Washington, DC: National Academy Press; 1990
8. Diamond LH. Developing disease-specific drug treatment protocols. In: Manolakis PG, ed. APhA Guide to Drug Treatment Protocols: A Resource for Creating and Using Disease Specific Pathways. Washington, DC: American Pharmaceutical Association; 1996:6-1–6-14
9. Rush AJ. Linking efficacy and effectiveness research in the evaluation of psychotherapies. In: Miller NE, Magruder KM, eds. The Cost Effectiveness of Psychotherapy: A Guide for Practitioners, Researchers and Policymakers. New York, NY: John Wiley & Sons. In press
10. Rupp A. The economic consequences of not treating depression. Br J Psychiatry 1995;166(suppl 27):29–38
11. Lane R, McDonald G. Reducing the economic burden of depression. Int Clin Psychopharmacol 1994;9:229–243
12. Rush AJ, Clayton PJ, Galle B, et al. Consensus Conference. Length of Antidepressant Therapy. Conference Proceedings. Little Falls, NJ: Health Learning Systems, Inc; 1996:1–28
13. Rush AJ, Gullion CM, Roffwarg HP, et al. When do patients respond to tricyclic antidepressants? [abstract] Biol Psychiatry 1994;35:711
14. Nierenberg AA, McNeal NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152:-1500–1503
15. Rey JA, Crismon ML, Dopheide JA, et al. Management of major depression in adults. In: Manolakis PG, ed. APhA Guide to Drug Treatment Protocols: A Resource for Creating and Using Disease Specific Pathways. Washington, DC: American Pharmaceutical Association; 1996: MDi–MD11
16. Fava M, Rosenbaum JF. Pharmacotherapy and somatic therapies. In: Beckham EE, Leber WR, eds. Handbook of Depression. 2nd ed. New York, NY: Guilford Press; 1995:280–301
17. Hirschfeld RMA, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. JAMA 1997;277:333–340
18. Katon W, Von Korff M, Lin E, et al. Collaborative management to achieve treatment guidelines: impact on depression in primary care. JAMA 1995; 273:1026–1031
19. Prusoff BA, Klerman GL, Paykel ES. Concordance between clinical assessments and patients' self-report in depression. Arch Gen Psychiatry 1972;26:546–552
20. Katon W, Von Korff M, Lin E, et al. Population-based care of depression: effective disease management strategies to decrease prevalence. Gen Hosp Psychiatry. In press
21. Basco MR, Rush AJ. Compliance with pharmacotherapy in mood disorders. Psychiatr Ann 1995;25:269–270,276,278–279
22. National Alliance for Research on Schizophrenia and Depression. Conquering Depression. Great Neck, NY: NARSAD Research; 1996
23. New York State Psychiatric Association. Treating Major Depression: A Patient's Guide. New York, NY: New York State Psychiatric Association; 1996
24. Lin EBH, Katon W, Simon G, et al. Achieving guidelines for the treatment of depression in primary care: is physician education enough? Med Care. In press
25. McCombs JS, Nichol MB, Stimmel GL, et al. The cost of antidepressant drug therapy failure: a study of antidepressant use patterns in a Medicaid population. J Clin Psychiatry 1990;51(6, suppl):60–69
26. Sclar DA, Robison LM, Skaer TL, et al. Antidepressant pharmacotherapy: economic outcomes in a health maintenance organization. Clin Ther 1994; 16:715–730
27. Skaer TL, Sclar DA, Robison L, et al. Economic valuation of amitriptyline, desipramine, nortriptyline, and sertraline in the management of patients with depression. Curr Ther Res 1995;56:556–567
28. Simon GE, Von Korff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA 1996;275:1897–1902
29. Revicki DA, Brown RE, Keller MB, et al. Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings. J Clin Psychiatry 1997;58:47–58

Appendix 1. Depression Fact Sheet That Aids in Patient Education*

Depression

Genetics, family history, personality factors, environmental stress, and biochemical disturbances all may play a role in the onset of depression.[1] Medical research indicates that depression may be linked to imbalances of the brain's chemical messengers, called neurotransmitters.[2]
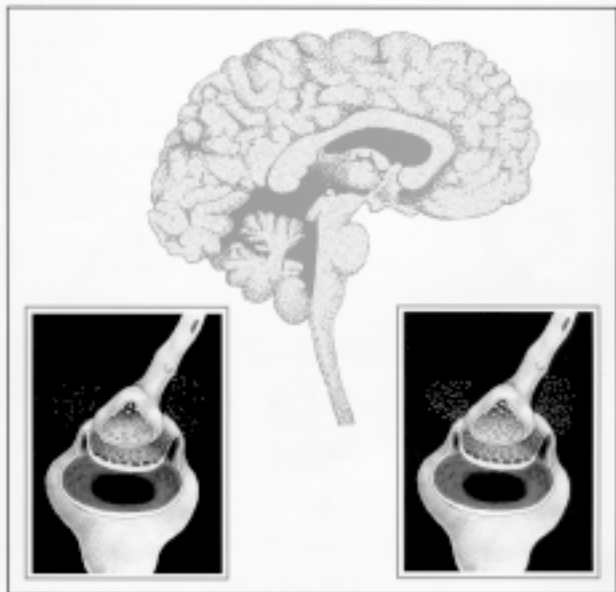
Depression may result from a chemical imbalance in the brain.

There are various therapies available, including antidepressant drugs, that can help restore chemical balance and relieve depression.

1. *Synopsis of Psychiatry. Baltimore*, MD: Williams & Wilkins, 1991:364–366.
2. *Mayo Clinic Proc.* 65(1990):1227–1236.

Depression

Diagnosis

To reach a diagnosis of major depression, at least five of the following symptoms, including depressed mood or diminished interest or pleasure in usual activities, must be present nearly every day for two weeks or longer without an alternative physical cause.[3]

Not sleeping or sleeping too much

Restlessness or slowness observable by others

Can't make decisions and can't concentrate

Feeling down all day

Blaming yourself too much and feeling worthless

Fatigue or loss of energy nearly every day

Significant change in weight or appetite

Thinking about death frequently

No longer interested in favorite activities

People do get better!

3. As defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association, 1994:285–286

*This material is in the public domain and may be reproduced without permission.

DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.