Texas Medication Algorithm Project: Definitions, Rationale, and Methods to Develop Medication Algorithms

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Background: The Texas Medication Algorithm Project (TMAP), a public-academic collaborative effort, is a 3-phase project to develop, implement, and evaluate medication treatment algorithms for public sector patients with schizophrenia, major depressive disorders, or bipolar disorders.

Discussion: This paper, the first in a series describing the activities of the TMAP, focuses on the various definitions and reasons why guidelines have gained popularity. Also discussed are their strengths, the limitations of the various methods used to develop them, and potential barriers to their implementation.

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Clinical practice guidelines are a response to behavioral health care's growing concern with access, quality, and the cost of care. An increasing number of organizations have developed such guidelines. The Agency for Health Care Policy Research (AHCPR) guidelines aid the primary care practitioner in treating depressed patients likely to be encountered in general practice.[1] The several treatment guidelines of the American Psychiatric Association[2] use thorough reviews of the literature to organize medication and psychosocial treatment choices according to the levels of the scientific certainty on which they are based, while the Tri-University guidelines[3,4] aim at a comparable goal through expert consensus. The protocols of managed behavioral health care organizations appear to take a different approach and focus on medical necessity as a tool primarily to manage costs rather than the disease.[5,6] Other guidelines limit which medications are allowed or in what order they are selected, again often as a cost saving effort.

The vast majority of this work focuses on acute care and not on patients with serious and persistent mental illnesses (SPMI) who largely receive services in the public sector. Yet, the public sector, with its limited resources and social pressures to increase quality and serve more people, is perhaps the most in need of methodologies that reliably align clinical knowledge and therapeutic interventions so that patient outcomes are based on the best possible care, delivered as efficiently as possible.

In the only effort of its kind to our knowledge, the Texas Department of Mental Health and Mental Retardation (TDMHMR) has entered into a collaborative relationship with Texas' medical schools and universities, led by the Department of Psychiatry at the University of Texas Southwestern Medical Center, Dallas, and the University of Texas at Austin College of Pharmacy, to develop, apply, and evaluate medication treatment algorithms for the 3 major disease groups receiving mental health services in the public sector—schizophrenia, major depressive disorders, and bipolar disorders. This paper, the first in a series describing the Texas Medication Algorithm Project (TMAP), provides an overview of algorithms in general, identifying many of the important issues in algorithm development that the TMAP methodology addresses, including definitions, methods of development, benefits, potential dangers, and barriers to implementation.

PRACTICE GUIDELINES, DISEASE MANAGEMENT PROTOCOLS, AND ALGORITHMS

It has been estimated that more than 30,000 articles are entered into the National Library of Medicine's database each month.[7] Achieving the benefit of this explosion in

knowledge would require clinicians to sort through the research, evaluate its quality, integrate the findings into a coherent model, and incorporate this into their practices. Practice guidelines, appropriately developed and regularly updated, could aid clinicians in this otherwise unwieldy and unrealistic task.

The most widely used definition of *clinical practice guidelines* is that used by the Institute of Medicine,[8] which states, "clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." *Appropriate health care*, as defined by Park and colleagues,[9] occurs "when the clinical benefit obtained outweighs the harms and costs involved."

There are other definitions as well. Woolf[10] defines *practice guidelines* as "the official statements or policies of major organizations and agencies on the proper indications for performing a procedure or treatment or the proper management for specific clinical problems." The American Psychiatric Association,[11] in the preface to its publication of the first practice guideline to be approved by the society, defines the term as "a set of patient care strategies developed to assist physicians in clinical decision making."

Not only is there variation in how practice guidelines are defined, but, according to Woolf,[10] authors refer to them with different terms, including *practice standards*, *protocols*, *policies*, and *practice parameters*. Jobson and Potter,[7] in their introduction to the International Psychopharmacology Algorithm Project, differentiate between *guidelines* and *algorithms*. In their understanding, guidelines consider a wide range of possibilities and seem to demand of themselves that they be multifaceted and provide enough information to be generalized.

Algorithms, on the other hand, are rule-based deductive systems that operate with inputs, sequences, time frames, and outputs. They specify certain features of information management that help the clinician select from large databases information relevant to decision making. Algorithms, as cognitive tools, are intended to assist, not limit, clinical decision making. A clinical algorithm, therefore, can be represented by a flowchart that identifies what clinical process might follow from a patient's clinical status and response to prior treatments, thereby providing a more specific statement of priority, or what to do next if the initial treatment is not effective, than the options recommended by guidelines.

TMAP embraces elements of both definitions and entails the development or modification of existing algorithms (guidelines) for the treatment of the 3 major disease groups that receive the bulk of services in TDMHMR's service system. The algorithms provide a choice of medications in treatment and support clinical decision making at 2 levels: (1) strategic decisions and (2) tactical decisions.[12]

WHY ALGORITHMS?

Algorithms not only provide the framework for vast amounts of information, but can also shape the database in response to certain clinical questions around disease management or utilization of medical procedures.[13] The several reasons why algorithms have grown in popularity include the following:

Reduce unnecessary variation in clinical practice patterns. Research by Wennberg and colleagues[14–16] documented large inconsistencies in the rate in which specific procedures are performed by physicians in different geographic areas. These results led Wennberg[17] to argue that providing clinicians with guidelines would be useful in reducing the magnitude of this variation, thus improving the quality of treatment. Andersen and Mooney[18] found that clinician uncertainty in the use of medical practices led to substantial variations, not only in practice, but also in the development of appropriate clinical policies. Other researchers have shown, also, that a significant portion of care is inappropriately provided[19]; that is, incorrect treatment is provided for the diagnoses, treatment is provided when not needed, or treatment which is needed is not provided. Indeed, recognizing the clinical variation in medical practices, and the costs associated with it, was part of the impetus for the U.S. Congress to create the Agency for Health Care Policy Research in 1989.[20] In its activity, AHCPR has significantly advanced the development of practice guidelines.

Facilitate clinical decisions: strategic and tactical decision making. According to Roche and Durieux,[13] the main goal of clinical algorithms is to facilitate decisions by practitioners who cannot integrate into their daily practice all the published data concerning new technologies and knowledge. Rush and Prien[12] categorize decision making into strategic and tactical decisions. Strategic decisions focus on the "what" of treatment and include a concern for (1) what is wrong, (2) what are the treatment objectives, and (3) what treatment to use first. Since the knowledge for making strategic decisions comes from group-based research, e.g., randomized controlled safety and efficacy trials (RCT), the physician is also faced with making practice decisions that tailor the treatment strategy to the individual patient. These tactical decisions focus on such "how to" issues as (1) dosage, (2) titration scheme, (3) monitoring parameters, and (4) patient response in relation to treatment timelines. Guidelines should provide direction for making both types of decisions.

Make clinical decisions explicit. In his early work on the application of algorithms to diagnostic reasoning, Feinstein[21] recognized the importance of using algorithms to make explicit the "traditional art" of diagnostic reasoning. Algorithms do this by allowing clinicians to identify the components and pathways of their clinical judgments, thereby preserving the vitality of diagnostic reasoning

while enhancing its scientific effectiveness. To improve the quality of diagnostic reasoning, Feinstein says clinicians must explore its constituents and directions and convert its logic into algorithmic outlines.

Improve the quality of treatment. By providing the best treatment knowledge to clinicians, clinical guidelines intend to achieve a faster and more complete patient response to treatment than would occur with treatment uninformed by the guidelines, i.e., treatment as usual.

Algorithm-based treatment should reduce symptoms and increase a patient's psychosocial functioning faster than non–algorithm-guided treatment. There are 3 ways that algorithm-based treatment might improve the quality of treatment: (1) the patient reaches remission or a satisfactory treatment response faster, (2) the patient's improvement is more complete, and (3) response is both faster and more complete.

Consider the impact of algorithms in a clinical environment where hospital stays are getting shorter. This means that the physician is unlikely to know at discharge whether the treatment selected is the best one for the patient. A strategy to address this increasingly prevalent occurrence is to have a consistent medication plan that moves with the patient across different treatment venues, e.g., inpatient, day hospital, outpatient, and across doctors. Algorithms provide a mechanism for communicating these treatment plans across treatment venues and physicians.

One treatment is not best for all patients. Quality in medication treatment for the individual patient necessitates an informed trial and error approach. It is logical for the treating physician to begin simply yet, not stop when partial benefits have been obtained. Treatment must aim for full remission, and this requires a coherent medication strategy that identifies full treatment benefits and side effects in a stepwise medication treatment plan.

Increase the cost efficiency of treatment. A more rapid response may cost less if fewer visits result, but it may cost more for medication compared to treatment as usual. If the patient's improvement is more complete (even if it takes longer), the efficiencies gained from the algorithm may lie in other areas. These may be in direct costs such as decreased clinic and emergency room visits and hospitalization, or they may be related to decreased indirect costs, such as the patient's faster return to work, and enhancing the positive impact for nonmedication treatments.[22]

Rush and Trivedi[23] summarize studies indicating that the more complete the depressed patient's response is to acute phase treatment, the better the outcome in longer term follow-up studies. By measuring symptom severity during acute phase treatment, one can determine whether or not full remission or improvement, rather than a simple response without remission, has occurred. Thus, even though the immediate cost of medication treatment may increase (depending on the algorithm recommendation), there is a strong possibility that the enhanced benefits of treatment will achieve longer term cost efficiencies. This potential benefit is particularly likely to accrue to patients with illnesses that have an otherwise unremitting, chronic course.

Provide a metric to compare patient progress. In treating the SPMI patient, the cause-effect relationship that exists between treatments and outcomes may be more tenuous than that which typically exists in general medical or acute mental health care. This is because of the inherent waxing and waning in the natural course of the illness and the increased likelihood that unforeseen environmental events may occur over the longer periods involved in chronic illness. This distortion of the clinical cause-effect relationship that chronic mental illness produces most likely introduces substantial variation into clinical decision making.

To the extent that algorithms associate patient outcomes with clinical strategies as delineated by a sequence of steps derived from a preconstructed decision tree, clinicians can compare the progress of their patients with that identified in the algorithm's decision points. Though the comparison of an individual patient with a group-derived description of patient progress may have limited applicability, it may be an opportunity to improve quality and realize cost efficiencies.

Provide important and self-correcting feedback to augment our knowledge. RCTs generally compare results of 1 medication with placebo or with a reference medication. Rarely do they compare the efficacy of 2 or more options after failure or suboptimal response to a first treatment, and virtually never are RCTs undertaken to determine what is best to do after 2 failures. Moreover, RCTs are usually performed on pure samples from which most of the comorbidities and complications commonly encountered in real-life treatment conditions are eliminated; that is, RCTs look at the efficacy of treatments rather than the effectiveness in actual clinical situations.

Thus, in the clinical environment, science usually runs out at the third decision point, and even what we think we know is uncertain when applied to the SPMI patient receiving care in the public sector because they are often members of the population screened out of RCTs. Well-designed guidelines will provide scientifically based, consensus-driven choices at each of the key decision points. Collation of data on patient improvement can, over time, identify the points in treatment associated with improvement for which patients and under what circumstances.

Provide a metric for evaluating when and whether to adopt new medications. The last decade has witnessed the introduction of 6 new antidepressants, 3 new antipsychotics, and 2 new antimanic mood-stabilizing medications. One can expect more psychotropic agents to be forthcoming in the next decade. At least theoretically, some medications represent such dramatic advances that they re-

place others in priority almost immediately, e.g., a new drug that is twice as safe and twice as effective as the standard. Rarely, however, is such a clear-cut case presented. Rather, new agents often have equal efficacy but may be better tolerated, safer in overdose, or effective for patients failing to respond to other agents. A system proceeding from a clearly articulated, multistep medication plan can define empirically where, in the sequence of steps, the new agent may afford the most clinical benefit.

POTENTIAL DANGERS OF GUIDELINES

There are potential dangers in the development of practice guidelines of which developers and clinicians must be cognizant. Among these are the following:

Insufficient evidence. Well-developed guidelines should include a rigorous review of scientific literature and empirical evidence. Guidelines based upon only 1 aspect of evidence or a very narrow set of parameters may not lead to the best quality of care and outcomes for the patient. For example, guidelines heavily influenced by the comparative cost of medications may sacrifice long-term beneficial outcomes for short-term financial savings.

Biased opinions. Guidelines developed by consensus panels may not always reflect a broader consensus of experts, depending upon which experts were selected for the panel. Also, within the panel the results may not reflect a true consensus of the group, but instead the opinions of the person or persons who were most articulate, vocal, or unyielding.

Increased costs and utilization of services. The use of guidelines may have the opposite results from those intended, especially if lower utilization of certain types of services is an objective of the guidelines.[24]

Substitute for clinical judgment. Psychiatrists know that every individual is unique and that, while they might fit certain categories, they will also differ to greater or lesser degrees. If a guideline is too rigid and inflexible, the psychiatrist may not be able to use appropriate expertise and judgment in making decisions in the best interest of the patient. Guidelines that shackle the psychiatrist in such a manner could actually do more harm than good. On the other hand, if the guideline is too flexible, it will not be effective in guiding or directing care.

Poor standard of care. Guidelines may eventually become 1 of the instruments used by various entities including those that provide funding and oversight. Ill conceived guidelines may be used to incorrectly judge psychiatrists' practice. The development and use of appropriate guidelines and, as always, good documentation will be paramount.

METHODS FOR DEVELOPING ALGORITHMS

Questions relevant to the construction of algorithms include: (1) how is the topic chosen, (2) who participates in the algorithm's development, (3) how to evaluate the quality of the scientific literature used in constructing the algorithm, (4) how are the gaps in research filled in when constructing the algorithm, (5) how is agreement achieved among the participants, (6) how are the tradeoffs between cost and clinical effectiveness addressed, and (7) what is the role of expert clinical judgment?

The methods used to develop algorithms vary according to how they address these and similar questions. Woolf[25] classifies methods for guideline development into 4 categories: (1) informal consensus, (2) formal consensus development, (3) evidence-based guideline development, and (4) explicit guideline development.

Informal consensus. In this method, an expert panel meets and reaches consensus through open discussion. Basically, participants simply decide on what to recommend. Eddy[26] has characterized this method as "global subjective judgment." A significant problem with this approach according to Woolf is that the guidelines it produces are often of poor quality.

Formal consensus development. This method was pioneered in 1977 by the National Institutes of Health (NIH) Consensus Development Program. In following it, an expert panel reaches consensus on guideline recommendations in a structured, $2^1/_2$-day conference.[27] Its sequenced development begins with a plenary session with presentations by experts and open discussion. Following this is a closed session with an invited panel to produce the guidelines. The process ends when the panel's recommendations are presented to an audience of peers.

The Harvard Community Health Plan, since 1986, has followed a variation of the NIH method that includes the participation of local practitioners in the development of the guidelines. This enables clinicians who are going to use the algorithms to review the evidence upon which they are to be based.

Another variant of the NIH's formal consensus method was introduced by the RAND Corporation in the 1980s[9] and has since been used, though in modified form, by the Tri-University consortium. In this method, an expert panel is provided with background articles that review existing scientific evidence relevant to the topic of the guideline to be developed. A 2-step Delphi technique follows where, before the first meeting, each panel member is asked to assess the appropriateness of several possible procedures for each of a series of indications, using a 9-point score, with 1 representing extremely inappropriate; 5, equivocal; and 9, extremely appropriate. When the panel meets, it uses the scores to identify areas of disagreement. After thorough discussion, the panel rescores the evidence, revising their scores on the basis of the discussion. This method can produce a long list of appropriateness scores which, according to Woolf,[25] can be a problem because it is difficult for clinicians to actually apply the results in practice.

Evidence-based guideline development. In this method, the strength of the recommendations contained in the algorithm is graded to reflect the quality of the evidence. Rules are established in an a priori fashion for evaluating the quality of the evidence. This provides practitioners with weighted guidance as to the expected effectiveness of a particular step in the algorithm. Woolf[25] says that, while this approach has increased the scientific rigor of guidelines, it has often been unable to produce recommendations in the absence of acceptable evidence such as gaps in the research literature. Thus, neutral recommendations, neither for nor against a treatment, are often issued. The American Psychiatric Association's guidelines use a modification of this process, whereby levels of scientific credibility (e.g., RCTs, uncontrolled series, anecdotal reports, clinical opinion) are denoted for each recommendation; the method also employs panels of experts to review the evidence and design the guideline followed by several levels of review by practitioners and organizations involved in the area. Thus, evidence based on guideline development can be a component of a formal consensus development process.

Explicit guideline development. Work by Eddy[28,29] has led to the use of more explicit methods of guideline development. In this approach, guideline developers specify the benefits, harms, and costs of potential interventions and derive explicit estimates of the probability of each outcome. Critics of this method argue that it is too complex and requires too much time to develop the guidelines.

The American Psychological Association's template for the construction of clinical practice guidelines[30] designs the guideline along 2 axes. The first orders the scientific evidence relevant to the topic of the algorithm based on results from systematic evaluations of the interventions in a controlled, clinical research context. The second axis addresses the feasibility of applying the intervention in the local setting where it is to be delivered.

Wilson et al.[31] recommend a strategy for the practitioner to use in determining the viability of practice guidelines. Clinicians involved with implementing guidelines should ask the following questions:

- Are practical, clinically important recommendations made?
- How strong are the recommendations?
- What is the impact of uncertainty associated with the evidence and values used in the guidelines?
- Will the recommendations help you in caring for your patients?
- Are the recommendations applicable to your patients?

ALGORITHM DEVELOPMENT IN TMAP

The following provides a brief overview of algorithm development in TMAP. The first algorithm developed was for major depressive disorder. Using the formal consensus conference method, a consensus panel was convened that included national experts, TDMHMR practitioners who were going to implement the algorithm, administrators, patients, and family members.

The development of the schizophrenia and bipolar algorithms took a different course. For these disorders, TMAP used the results of the Tri-University Project [3,4] as the basis for algorithm development. These consensus guidelines, utilizing a modified RAND survey methodology of large numbers of academic experts and clinicians, attempted to add additional specificity to treatment recommendations and to fill gaps in the existing literature, including the American Psychiatric Association's evidence-based guidelines.

To use these documents, 2 conferences were held, 1 for bipolar and 1 for schizophrenic disorders. The Tri-University investigators presented to an audience of TDMHMR practitioners who had volunteered to implement 1 of these 2 algorithms in a Phase 2 feasibility trial, as well as academic experts, administrators, families, advocates, and patients. Based on feedback from these participants, we adapted the guideline recommendations into algorithms for the Phase 2 bipolar and schizophrenic modules.

Table 1. Potential Barriers to Using Guidelines

Physician reluctance to being "told" what to do
Initial physician training and ongoing consultation required to implement guidelines
Additional work required to use the guidelines
Perceived "static" nature of guidelines
Patient adherence to the guideline-directed treatment

BARRIERS TO USING GUIDELINES

Table 1 identifies barriers to implementing guidelines. The degree to which any 1 of these barriers will be realized depends on the sophistication of the guidelines. TMAP's algorithms are sophisticated and potentially intimidating to physicians. This has led to an initial concern on the part of physicians that the algorithms will "tell" them how to practice medicine, an issue, which in turn, raised concerns about how to make clinical decisions when the algorithms appear silent on treatment issues pertaining to a specific patient.

When the treatment guidelines require documentation and/or assessment information, the significant issue of physician time becomes an important issue. In TMAP's algorithms for example, tactical decisions require diagnostic and clinical information such as regular monitoring of symptom severity and functioning as assessed through measures to include Brief Psychiatric Rating Scale, Inventory for Depressive Symptomatology-Clinician rated, Inventory for Depressive Symptomatology-Self-Report,

and global ratings of patient functioning. In preliminary data from TMAP Phase 2, the average time for patient visits was 45–60 minutes for the initial visit and about 30 minutes thereafter (Rush AJ, Crismon ML. 1997. Unpublished data).

Physician training can place a burden on the clinic since the time required for training reduces physician availability and requires juggling of patient appointments. Once training has occurred, TMAP's experience has shown that a physician will be reluctant to use the algorithms unless there is an opportunity for ongoing consultation about how individual patients fit within the algorithm. Even when training and consultation barriers have been resolved, physicians must have confidence that the algorithms will be continuously updated as new medications and research become available. Otherwise, they find it hard to invest the time required to learn the algorithms if they perceive that they will become outdated with the release of the next medication.

The last barrier concerns patient adherence with the guideline-directed treatment regimen. Even when guidelines are seen as efficacious, and physicians are willing to use them, if patients do not adhere to treatment such as keeping appointments or if they do not take the medications as prescribed because of unwanted side effects, then what treatment value do the guidelines have? TMAP's algorithms incorporate patient choice in that where scientific or expert clinical evidence suggests equally efficacious medications at a particular step, patient choice determines which medication to take. To support patient choice, the algorithms have an extensive patient/family education component providing education on the course of the disease, the content of the algorithms, and its medications, including potential side effects.

CONCLUSION

Practice guidelines possess the potential to improve the quality of medication treatment. Realizing this potential requires a sophisticated development process that recognizes that poorly constructed guidelines can have detrimental effects.

While there are various methodologies for the development of guidelines, even the most sophisticated stop before implementation begins. Thus, the process of guideline development, no matter how scientifically sophisticated, remains essentially an intellectual exercise in which a new "whole" is created without evaluation of its intended effects.

The Texas Medication Algorithm Project has developed medication algorithms for the treatment of SPMI patients with schizophrenia, major depressive disorders, and bipolar disorders. Recognizing that it is one challenge to design but another to implement (a recognition that arises from gaps in the scientific knowledge and lack of agreed-upon outcomes for public sector SPMI population), TMAP, in the only effort of its kind to our knowledge, has designed into its project 2 evaluation phases. The first evaluates the feasibility of using these algorithms in the public sector environment; that is, can the algorithms, as designed, be implemented by physicians working in public sector mental health clinics and hospitals, and how might they be modified so as to make them most user-friendly and likely to be followed? The second phase will evaluate the clinical and economic impact of the algorithms in a controlled, prospective research design. This evaluation will determine if algorithm-based treatment generates more positive outcomes than treatment as usual. TMAP and its 3 phases are detailed in "TMAP-2: Medication Treatment of the Seriously and Persistently Mentally Ill" (Rush AJ, Crismon ML, Toprac MG, et al. Manuscript submitted).

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