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On the Value of Evidence-Based Psychopharmacology Algorithms

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Lucian Leape raised awareness of the high error rate in medicine (1). These errors may be due to "slips" (unintentional mistakes) or may result from not obtaining key facts about the patient's history or from not knowing or applying the best evidence for optimal care of the patient. The remedy for the latter is said to be the practice of Evidence-Based Medicine (EBM) – which has been defined by Sackett and colleagues as "…integrating clinical expertise with the best available external clinical evidence from systematic research" (2).

However, EBM is easier said than done. For psychopharmacology, it requires a laborious process of activity and thinking. First one must make a criteria-based Diagnostic and Statistical Manual diagnosis, identifying subtypes, specifiers, and comorbidity that may affect what treatment will be preferred. This is necessary because almost all of the psychopharmacology evidence is derived from studies of patients that are carefully diagnosed by these criteria. The treatment history must then be explored in detail for adequacy and outcomes of trials in order to avoid repeating ineffective or harmful approaches used in the past. Finally, it is necessary to search for, find, read, and interpret the pertinent literature. This idealized approach to clinical practice is impractical because it takes far too much time and requires use of cognitive processes that may be unfamiliar to some clinicians. These barriers have limited the usefulness of EBM in the day-to-day practice of medicine and psychopharmacology.

Instead of using EBM, clinicians often resort to quicker but more error-prone processes of decision-making (3). Reflexive decisions are decisions made without consciously considering any alternative, usually because you are in a hurry. Under this heading there are bias-driven judgments, which are decisions motivated by overconfidence based on some bias. Also there is the availability heuristic, which is grabbing the first idea that comes to mind (4,5). Another cause of errors is the affective heuristic which is the tendency of affect-laden practice experiences (either positive or negative) to be far more influential than considerations based on the scientific evidence. For example, if you once had a patient who had a Stevens-Johnson syndrome from lamotrigine, you may be reluctant to prescribe that medication again even if it is a preferred option for preventing recurrence of bipolar depression. If statistics are presented on the low frequency of this syndrome, you will not believe them.

These quick, intuitive decisions are sometimes excused (or praised) as being part of the art of medicine. Faith in this art is part of the culture of medicine, with deep historical roots. For thousands of years, the apprentice model dominated training in medical practice. The art is initially conveyed by more experienced mentors, and then augmented by personal experience as the emerging practitioner makes his/her own mistakes. As Groopman has noted, we do not want airline pilots to learn from their mistakes – we want them to make the right decisions every time. However, the healthcare system continues to be built on a foundation of mistakes followed by "corrective action plans" (3).

Busy physicians typically do a limited review of the patient's history and mental status, focusing on certain symptoms or historical details that seem likely to explain the patient's chief complaint, after which the treatment plan just "falls into place" (6). Practice is centered on faith in a collection of "rules of thumb" that can be applied rapidly and confidently. However, Michael O'Donnell, M.D., former editor of the British Medical Journal, quipped that this kind of clinical experience ran result in "… making the same mistakes over and over with increasing confidence over an impressive number of years" (7).

There is a neurobiology of how people react to information and experience. Risk-taking tendency, for example, is a strongly heritable personality trait (0.58 heritability in twins (8)). Thus, while some psychiatrists will rarely use clozapine even when clearly indicated because of fear of its risks, others may have minimal fear and even overlook necessary monitoring. This is not the only reason that clozapine is under-prescribed, however: it has been found that when scientifically validated, well-evidenced treatment approaches take more time than what physicians do now and believe works well, they will not provide the time-consuming treatment (9).

Other problems with using clinical experience as the primary basis for practice are the generally small Ns of the experience, and sampling differences: i.e., the patient to be treated now may not in fact be at all similar to the dimly-recollected previous patients.

Drug companies are also shaping decision-making, sometimes against EBM, taking advantage of "novelty preference bias," "familiarity effect" and "overoptimism bias" (10). Their representatives provide education that may be neither objective nor comprehensive but is quick, easy, and often accompanied by free samples. The pharmaceutical firms (usually in collaboration with academic psychiatry) produce most of the psychopharmacological studies and influence their design, interpretation, and publication in ways that tend to encourage excessive valuation of new expensive products (11,12). These studies are typically done for short lengths of time in otherwise healthy and uncomplicated patients who are not representative of the more difficult patients seen in typical practice who may be suicidal, use substances, and have much medical comorbidity. This has undermined confidence in the applicability of much of the evidence-base (13), and at the least requires that EBM practitioners become sophisticated in their ability to detect the flaws and biases of studies so that they will not draw false conclusions from them.

This brings us to the proposed solution to these problems in teaching and learning psychopharmacology: psychopharmacology algorithms that are informed by the evidence and that distill and synthesize the available research and organize it into a coherent blueprint for practice. The algorithms should be developed and updated frequently by consensus among respected EBM experts who have distanced themselves from drug-company support. They should clearly indicate best or preferred practice for cases of progressive complexity, and from initial treatment through very treatment-resistant scenarios. They should provide a scaffolding structure for organizing the data relevant to specific kinds of patients. Thus, if a new study is published, or a new medication becomes available, information about these developments can be combined with and compared with the other knowledge on the shelf for that decision point. The clinician can decide if the new information should change practice for a typical patient at that node of the algorithm – or wait for the expert consensus update. Experts have argued that healthcare desperately needs such syntheses, and the production of them needs to be recognized as a methodology and field in its own right (14,15).

What are some of the qualities of these algorithms/guidelines that would indicate that they are valid enough for clinical use? The Institute of Medicine has proposed a comprehensive set of standards (16). Few existing guidelines meet all the criteria, which include authors (a) having few to no conflicts of interest, (b) providing explanations of the reasoning behind each recommendation, (c) obtaining rigorous external review before publication, and (d) updating frequently. To these it there should be added that evidence of short and long term safety are considerations that are just as important as efficacy evidence in motivating the sequencing of medication recommendations (17). Further, there should be acknowledgement of other published algorithms with different conclusion and an analysis of the basis for the differences with attempts to resolve them (17). The impact of comorbidity, medical and psychiatric, including the effect if the patient is a woman of child-bearing potential, should be assessed and recommendations offered.

Finally, it should be emphasized that algorithms, no matter how well-constructed, should not be followed rigidly as if they represent absolute truth. They are aids to judgment, and practitioners should be free to determine whether or not they are suitable for application to an individual patient. Despite this caveat, it is worth noting that evidence from other fields (e.g. - engineering) suggests that when algorithm-based decisions and individual expert judgment have been compared, the results have favored algorithm adherence (18, 19). Occasionally, the expert makes a "brilliant" judgment when deviating from the algorithm that proves correct, but more often when the expert deviates, the result is an error. A good algorithm or guideline will offer and discuss some of the alternatives that could be considered at each node and why they are not favored first-line but could be reasonable under some circumstances.

What is the evidence that following psychopharmacology algorithms improves outcome? While standardized care driven by evidence-supported algorithms is a model that has produced good outcomes with other illnesses such as diabetes, pneumonia, and heart disease (20), there have not been very many studies in psychiatry and the results have been modest. Bauer examined tests of guidelines up to the year 2000 and found that 6 of 13 studies reported improved outcomes associated with guideline adherence (21). More recent psychopharmacology algorithm studies in depression were reviewed by Adli and colleagues (22) who found that patients treated with the algorithm initially benefitted more than the control group but further separation from "treatment as usual" did not necessarily occur over time (23). The early benefits could have been due to more intensive patient involvement with the project coordinator in the algorithm group. Studies in schizophrenia have found small advantages from following an algorithms (Texas Algorithm Project and German Society for Psychiatry guideline), including reduced side effects and less polypharmacy with antipsychotics (24,25). The differences were not robust perhaps because all controlled studies to date have compared use of an entire algorithm versus treatment as usual. In an algorithm there are multiple recommendations. Clinicians in the treatment-as-usual arms also usually do most of them. Of the recommendations that clinicians do not follow so often, the alternatives chosen will sometimes produce a significant difference in outcome and some may not. In the schizophrenia studies, physicians rarely complied with the algorithm recommendation to use clozapine after two adequate trials of antipsychotics. The control groups also did not use much clozapine. This may account for the lack of strong outcome differences: the algorithm-following physicians did not choose to follow the recommendation with the greatest likelihood of producing a better overall outcome for their patients!

The Texas and German algorithm groups did find that regular intensive educational discussions about the guidelines (which requires support by hospital and clinic leadership) can overcome some of these barriers. Discussions with patients to convince them of the value of the algorithm recommendations may be another critical factor.

A recent objection to EBM in general and the algorithms/guidelines derived from the evidence has come from the new emphasis on the potential for "personalized medicine (PM)" (26). Since evidence is gathered from studies of heterogeneous patient populations (e.g. – major depression) it can only give an average or typical response rate in such a group. However, this conflict between EBM and PM appears to be based on a false dichotomy. When specific biological markers or other tests enable the delineation of subgroups with specific treatment, this will be added to the diagnostic process that precedes the application of the algorithm, and the personalized treatment will be applied to those eligible for it. Then, the others in the population will be appropriate candidates for the general recommendations.

An unsolved problem with the clinical use of even the best algorithms is that some clinicians may feel pressed to make hasty consultations with the algorithm's summary flowchart rather than reading the full text and appreciating all the nuances of the reasoning. The result can be grossly inaccurate appreciation of what is recommended and significant patient care errors. On the other hand, caveat emptor (let the buyer beware) is an appropriate aphorism to warn those too eager to utilize algorithms. Some of the algorithms that have been presented in a variety of publications are oversimplified, subject to significant biases, or may give bad advice due to reasoning errors.

The Psychopharmacology Algorithm Project at the Harvard South Shore Program based at the VA Boston Healthcare System, Brockton Division, has been publishing and revising psychopharmacology algorithms for over 20 years. The more recent ones seem to meet many but not all of the IOM guidelines for quality (27-33). Most are available on the project's web site www.psychopharm.mobi. Their strongest feature is that the facts cited, analysis of the literature, and reasoning are examined in a blinded peer review process by up to 5 content experts selected by the journal editors. If the reasoning, based on the evidence interpretations provided, was plausible to all reviewers, then it was retained. When there were differences of opinion, adjustments were made or further exploration of pertinent evidence was done until consensus was achieved or a stronger argument in support of the authors' interpretation was composed.

Algorithms will be of more practical value when their most important advice – advice that differs from usual practice and may give better results – can be provided to the prescribing clinician at the point of care as part of a computerized medical record and order-entry system. Computerized expert systems are not yet common in psychiatric practice, though they are in many other complex endeavors such as flying airplanes, piloting boats, driving cars to reach a specific destination, complying with tax laws, and analyzing case law to come up with the best legal arguments. Patient cutcomes could improve if algorithm-based computer applications to aid the practice of psychopharmacology were to be developed and then utilized by clinicians.

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