Can Clinical Practice Guide a Research Agenda?

by Stephen R. Marder

Abstract

Articles from this issue of the Bulletin indicate that clinicians are frequently adopting clinical practices that have not been supported by an evidence base. Examples of these practices are prescribing more than one antipsychotic and reserving clozapine for patients who have had multiple antipsychotic trials. This commentary suggests that these practices can be used to define important research questions.

Keywords: Schizophrenia, antipsychotic, clozapine, evidence-based practice, polypharmacy.


The articles in this issue of the Bulletin provide valuable information about how clinicians are treating psychotic illnesses in the public sector. A number of these practices either deviate from evidence-based practices or have not been adequately studied. This commentary will focus on two of these practices: the use of more than one antipsychotic and the low incidence of clozapine prescribing. I will take the position that current controlled trials do not provide guidance for many common clinical situations. The problem is that even clinicians who religiously follow the dictates of evidence-based practice often end up with unsatisfactory results. This is where the road map of treatment guidelines ends and uncharted territory begins.

Although polypharmacy can include the prescribing of multiple psychotropics, the supplementation of an antipsychotic with other agents such as mood stabilizers, antidepressants, and benzodiazepines is an accepted practice for patients with complex disorders. The combining of antipsychotics—as reported by Miller and Craig in this issue (2002)—has virtually no support from controlled trials. The report by Covell and colleagues (2002) suggests some of the concerns that lead to this practice. They report that 45 percent of patients had their medications changed during a 2-year period, indicating that clinicians (and patients) are dissatisfied with the results of pharmacotherapy with at least one agent. Unfortunately, the available information is unable to tell us whether this dissatisfaction is a result of a poor clinical response or side effects. The high prevalence of combining second generation antipsychotics (SGAs) with conventional agents or with other second generation drugs suggests that extrapyramidal side effects are not the main reason. The finding from the Italian Collaborative Study (Italian Cooperative Study Group on the Outcome of Severe Mental Disorders 1999) that this form of polypharmacy was associated with higher overall doses provides further support for the interpretation that this practice tends to occur in treatment-refractory patients.

Clinicians may also be combining antipsychotics as a means of managing side effects. For example, higher doses of clozapine may be associated with seizures, hypotension, sialorrhea, and other dose-related effects. Lowering the dose of clozapine (or another antipsychotic with a dose-related side effect) and adding another drug with a different side effect profile makes intuitive sense, although—as noted by Miller and Craig (2002)—this practice has never been adequately studied. Unfortunately, it is unclear if this form of polypharmacy is very common.

Covell and colleagues’ data also indicate that relatively few patients (10%) stay on more than one antipsychotic. For example, by 1 year, 82 percent of patients on more than one antipsychotic had stopped taking more than one. This finding suggests a number of possibilities. Conceivably, clinicians give up on polypharmacy because (1) they find that it is relatively ineffective, (2) they find that it is effective only during times of more symptoms (or a relapse), or (3) they are cross-titrating antipsychotics very slowly. Covell’s study was done in a large urban mental health center. It is possible that patients remain on

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more than one antipsychotic for longer periods of time in other settings. It is also important to point out that adding a second antipsychotic when the first is suboptimal is relatively easy to do and makes intuitive sense. For other illnesses—including bipolar disorder, seizure disorder, and hypertension—combining agents is the accepted practice. Moreover, just as there is no evidence that polypharmacy works, there is also no evidence that it does not work.

The paper by Weissman (2002) documents that clozapine use is relatively uncommon in a selected Department of Veterans Affairs (VA) network. Moreover, clozapine use appears to be decreasing. This is understandable in that there is evidence that patients who are treatment refractory may improve on second generation agents that are much better tolerated than clozapine (Breier and Hamilton 1999; Wirshing et al. 1999). In addition, the available SGAs provide alternatives for patients who have difficulty tolerating the side effects of one or more agents. On the other hand, the rates of changing medications documented in Covell and colleagues’ report (2002) suggest that clinicians are making changes but may be avoiding clozapine. That is, they may be changing to another SGA or adding a second agent rather than selecting clozapine. They may be doing this because (1) they are unaware that the evidence indicates that clozapine is probably the most effective agent for treatment-refractory patients, (2) they are unfamiliar with using clozapine, or (3) they lack the time to change to clozapine. It is also likely that some patients in the Weissman and Covell reports had had clozapine trials that they failed.

The clinicians who combine antipsychotics or delay clozapine in favor of an agent that is easier to administer must believe that their patients are benefiting from the practice. However, the history of medicine has demonstrated that the instincts of physicians are not always correct. Practices such as “rapid neuroleptization” and mega-dose treatment were widely accepted by many excellent clinicians until they were proven ineffective by carefully designed clinical trials. As Miller and Craig (2002) point out, there is virtually no level 1 evidence to tell us if polypharmacy is harmful or helpful. As mentioned by Clark and colleagues, not knowing is a serious problem because these practices may be harmful, because other practices may work better, or because these practices require resources that could be used more effectively to support other practices.

One of the most useful functions of medical research is exposing accepted clinical practices to the scrutiny of a controlled trial. Studies of this type are relatively uncommon in psychiatry for a number of reasons. First, studies that emerge from the clinic may not excite those review committees who place high value on the logical progression of research ideas that appear innovative and that have a clear rationale. Also, the questions that are in the minds of clinicians may be difficult to answer using the relatively small, highly homogenized samples that are commonly examined in single center clinical trials. And finally, clinical researchers in psychiatry may not be interested in or even aware of practice patterns in public psychiatric settings.

Translating an important clinical question into a well-designed research study can also be a serious challenge. As mentioned earlier, combining antipsychotics is not a single strategy but an intuitive clinical practice that is used for a number of reasons. As a result, there are a series of questions that could be addressed by clinical trials: Should clozapine be supplemented in partial responders or individuals with dose-related side effects? If a patient is a partial responder to risperidone at 4 milligrams, is it better to raise the dose or to add olanzapine or another second generation drug? The questions selected for study should be derived from what is actually occurring in clinical practice. Each of these separate research questions can be addressed by a number of designs that can be implemented through randomized, double-blind trials in academic research centers or through effectiveness studies that can be carried out in the setting of routine care. It is neither feasible nor vital to study all of the possible combinations. Studies that test a specific strategy can be used to develop principles of clinical practice that can, in turn, permit clinicians to make more informed decisions.

The National Institute of Mental Health has accepted the importance of addressing compelling issues in the pharmacotherapy of schizophrenia in the implementation of a large multicenter trial comparing second generation agents with older agents. This study—known as CATIE (Clinical Trials of Intervention Effectiveness)—will not address the issue of combining antipsychotics, although it may provide information about clozapine’s place in a treatment algorithm. But even for clozapine, it is unlikely that any single study—regardless of size—will completely resolve these complex issues. Rather, the enhancement of clinical practice is likely to occur when vital questions that emerge from clinical practice are tested by well-designed clinical studies.

References


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