

Does Evidence From Clinical Trials in Psychopharmacology Apply in Clinical Practice?

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Issue: *Evidence-based medicine that derives from studies of patient populations selected to gain marketing approval for new psychopharmacologic drugs is increasingly distinct from the experience of treating patients in clinical psychiatric practice.*

Trying to use clinical trial data as a beacon to guide the use of new drugs in clinical practice can lead to errant expectations. Consider the story of the police officer who encountered a man looking for something near a street light after dark:

“What are you doing?” asked the police officer.

“Looking for the coin I dropped a little while ago down the street,” replied the man.

“Why are you looking here instead of down the street where you dropped it?” queried the police officer.

“Because this is where the light is shining,” answered the man.

Just because the light of research shines on a population of patients in a clinical trial doesn't always mean it will illuminate patients in clinical practice. Why is this so?

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You Can't Get There From Here

Getting from clinical trials to clinical practice can be difficult. Comorbidity of psychiatric disorders may be the rule rather than the exception in clinical practice today, yet such patients are generally excluded from clinical trials. In terms of health care utilization and disability, comorbid patients are clearly the most important to study, e.g., 14% of psychiatric patients have 3 or more comorbid disorders, yet they consume almost half of all medical care resources.^{1,2} These patients may be more resistant to drugs, represent a different genetic population (i.e., genotype), and require polypharmacy. Neglecting this population prior to marketing a new drug may be commercially motivated owing to methodological complexities in dealing with simultaneous and interacting conditions and treatments, fear of “niching” the drug out of the broad market, and the lack of leadership among many, but not all,^{1,2} experts who are often strangely silent about the need for such studies as part of the drug-approval process.

Come One, Come All Step Right up to the Clinical Trial

Currently, patients for clinical trials in psychopharmacology are often recruited from advertisements, sometimes with monetary incentives and no prior

relationship to the investigator, and then “purified” of comorbidity and extreme severity for randomization into placebo-controlled trials. By contrast, in years past, patients in clinical psychopharmacology trials were frequently recruited from an investigator's clinical practice by utilizing diagnostic criteria that had not necessarily been well developed, especially for numerous anxiety disorders.³ Thus, patients who had a prior relationship with the investigator and who may have had unrecognized common comorbidities, such as social anxiety disorder, panic disorder, and other anxiety disorders, were probably included in clinical trials.

As time has passed, not only has the clinical trial population morphed, but so have clinical investigators. On the one hand, patients have become more sophisticated about their illnesses, often self-diagnosing, and more knowledgeable about treatments, clinical research, and the placebo effect. They also may have participated in prior trials and present at a milder stage of illness in response to an advertisement for a study. Often excluded are not only patients with comorbidities, but also a host of other patient types: depressed patients who are psychotic, bipolar, suicidal, medically ill, taking concomitant drugs, and treatment resistant; manic

and schizophrenic patients who are too ill to consent or who abuse drugs and alcohol; Alzheimer's disease patients with early illness for whom early drug intervention may be the most valuable; children and adolescents; women taking estrogen replacement therapy; and many ethnic groups.

On the other hand, clinical investigators have been increasingly recruited from both academia and clinical practice as clinical revenues have dried up and opportunities for clinical trials have multiplied. Raters of the symptoms of patients have multiplied in number, including many with little training, experience, or demonstrated reliability. Pressure to rapidly complete trials has resulted in the migration away from proven models of the past, in which a few investigators were held accountable for the trial results and many patients were enrolled per site, to a model with many investigators and only a few patients enrolled per site.³ Enrollment rates along with placebo-response rates have increased, leading to increased variance in results such as many failed clinical trials and positive clinical trials of patients not necessarily representative of those in a clinical psychiatrist's practice.

Pharmacogenomics May Be the Long-Term Answer

It is probably unrealistic to return to the "good old days," so how can a clinician apply clinical trial data to clinical practice? For one thing, the advent of agreed-upon conventions on how to use rating scales accompanied by formalized rater training and certification is improving interrater reliability as raters and investigative sites proliferate. For another, the placebo-response phenomenon is finally being seriously studied in relation to clinical trial populations, which may lead to enrollment of patients more representative of those seen in clinical practice. Ultimately, however, patients' genes may actually be the

determining factor as to whether a drug will be approved as safe and effective (pharmacogenomics), i.e., the drug approvals of tomorrow are likely to be for psychiatric symptoms associated with a specific portfolio of genotypes and not just DSM-IV symptom clusters.^{4,5}

Indiana Jones, but not Dirty Harry, May Be the Short-Term Answer

What is a clinician to do before pharmacogenomics is a reality? In other words, to what extent can the evidence from clinical trials help the prescriber treat patients largely excluded from clinical trials once a new drug is approved for marketing?

One possibility for the modern-day prescriber is to look at the data, identify the differences between evidence based on these patients and those in practice, learn the mechanism of action of the new drug, stay vigilant to case reports and early anecdotes, and then embark on a targeted prescribing mission, patient by patient—"making it up as you go," as did the successful and serendipitous adventurer Indiana Jones in Harrison Ford films. Such a prescriber will be skeptical of the generalizability of new data,^{5,6} knowing that some patients tolerate or respond better to one drug than to another, so that the median patient's response and tolerance to a

Take-Home Points

- ◆ Clinical trials to prove safety and efficacy of new psychopharmacologic agents are increasingly being performed in "pure" clinical populations derived from advertising, rather than in "real" clinical populations derived from clinical psychiatric practice.
- ◆ Evidence from clinical trials is increasingly not reproducible in such "pure" populations, resulting in failure to consistently show differences between an active drug and placebo or between 2 active drugs; thus, using a population in which the diagnosis is more certain can make the data less valuable in clinical practice.
- ◆ The translation of information from clinical trial populations to patients in the clinical practice of psychiatry can result in surprises when new drugs are first marketed, so a prescriber must have a strategy for dealing with the unknown.

drug in clinical trials are perhaps poor predictors of any given individual's response or tolerance in clinical practice. Best avoided is a reckless approach, forging ahead, dismissing the data and hoping to be "lucky," as did the renegade cop Dirty Harry in Clint Eastwood films.

Summary

The art of psychopharmacology derives from the science of psychopharmacology, but still requires wisdom, judgment, and experience to translate findings from clinical trials of a new drug into clinical practice.

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