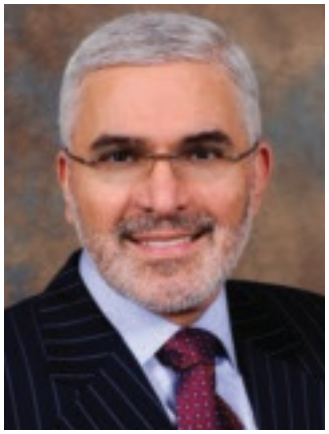

Henry A. Nasrallah, MD
Editor-in-Chief

Contrarian patients in clinical trials

Lessons from exceptions

The complex process by which psychiatric medications are discovered, developed, and tested culminates in "evidence-based medicine"—the backbone of psychopharmacology. Large controlled clinical trials are designed to demonstrate under highly controlled conditions that a newly synthesized molecule has sufficient efficacy and a reasonable side-effect profile to warrant FDA approval. Results are published, and the pharmaceutical company launches the approved medication in the community.

Unexpected drug response patterns or adverse effects may provide insights with practical applications

Not usually recognized is that a treasure trove of information may be buried in a preapproval clinical trial's massive database. The pharmaceutical company might not "mine" this information without the likelihood of revenue enhancement, but the raw data may hold clinically useful revelations.

These may include clues about which patients are likely to respond (or not) or experience a serious side effect with the drug (or placebo). Sometimes examining contrarian psychopharmacology—unexpected patterns of response or adverse effects—provides valuable insights with clinical applications. Here are some questions we could explore beyond the efficacy-safety-tolerability data published on atypical antipsychotics.

Drug efficacy

- What are the demographic, biologic, and clinical profiles of rapid responders vs delayed responders vs nonresponders?
- How do full responders differ from partial responders or complete nonresponders? Can we identify them in clinical settings?
- Can we predict who will respond or not to a particular antipsychotic? Why not report whether the nonresponders in a clinical trial responded to some other antipsychotic after the trial was completed? That information would be tremendously useful and cost-effective in clinical practice.

continued on page 18

To comment on this editorial or other topics of interest, contact Dr. Nasrallah at henry.nasrallah@currentpsychiatry.com or visit CurrentPsychiatry.com and click on the "Send Letters" link.

From the Editor

continued from page 16

Placebo efficacy

- How do placebo responders differ from non-responders?
- Are placebo nonresponders similar in some ways to drug nonresponders?
- Would placebo nonresponders respond to the active drug after the controlled trial is completed?

Side effects

Each atypical has common side effects, but we know little about patients who buck the trend. Consider the potentially useful insights from studying patients who:

- lose weight on olanzapine
- gain weight on ziprasidone
- get sedated with aripiprazole
- develop insomnia or extrapyramidal symptoms with quetiapine
- continue to menstruate regularly on risperidone.

Patients such as these are reported in clinical trials but not monitored or compared for their response rates.

Placebo

- What would we learn if we compared psychotic patients who developed sedation with those who developed insomnia while receiving placebo in a clinical trial? Would these 2 groups differ in their response to the antipsychotic?
- Some psychotic patients gain substantial weight (>7%) on placebo, whereas others lose quite a bit of weight. Do they differ in response rates or other traits?

Individualized therapy

Contrarian patients who develop unexpected responses (such as strong improvement on placebo or side effects the opposite of what is expected) represent missed opportunities for research to elucidate the heterogeneity of psychosis (as well as mania, depression, or anxiety). Understanding individual differences could enable practitioners to predict efficacy and tolerability and to match patients with the most suitable medications from the start. These insights could save time, reduce duration of illness, predict likely side effects, and ultimately reduce the costs of treatment.

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