PRACTICAL PSYCHOPHARMACOLOGY

New Data Blur Typical-Atypical Drug Distinctions

The line between typical and atypical (first- and second-generation) antipsychotic medications is becoming ever more blurred, with numerous investigators suggesting that the distinction is no longer valid or useful in designing clinical trials, or even in selecting the best agent to treat an individual patient.

Safety studies drawing attention to serious side effects attributable to drugs that have been traditionally categorized as "atypical" antipsychotics have shaken the long-held paradigm that these drugs, as a class, are safer than "typical" antipsychotics.

In addition, new evidence about the risk of sudden cardiac death with drugs in both classes, along with mounting concern about the long-term consequences of weight gain and metabolic irregularities, has made many experts take a critical look at the safety of second-generation antipsychotics.

The jury is out even about extrapyramidal motor side effects, which were once thought to be less of a risk with second-generation antipsychotics.

A recent study by researchers in the working group, Drugs in Psychiatry (German acronym, AGATE), found heterogeneity in drugs within both classes in terms of rates of extrapyramidal side effects in 6,061 inpatients, leading to the conclusion that the odds of inducing such effects were "not distinguishable" by class (Neuropsychobiology 2008;57:80-7).

The study findings characterized "the misleading dichotomy," showing that rates of extrapyramidal side effects rose continuously with use of both typical and atypical agents and detailing class-busting performances of specific drugs.

For example, the AGATE researchers reported that the "atypical" drugs amisulpride and zotepine (not approved for use in the United States) and risperidone were indistinguishable from "typical" fluphenazine in terms of the risk of extrapyramidal side effects, whereas perazine, a "typical" antipsychotic available in Europe, had a risk profile lower than most drugs in the "atypical" class.

Preventing the development of potentially irreversible tardive dyskinesia, also presumed to be more likely with atypical antipsychotic medications, also is not as clear-cut as once believed.

A 2009 comparative review of antipsychotic drugs for first-episode schizophrenia revealed that most studies have compared the high-potency typical antipsychotic haloperidol with newer antipsychotics (CNS Drugs 2009;23:837-65).

Dr. Kayvon Salimi, lead author of the review, said in an interview that preclinical findings and clinical experience have indicated that mid- and lower-potency older generation antipsychotic medications might compare well with the newer generation antipsychotics with regard to neurologic effects. This was supported to some degree by the results of the 1,460-patient Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies, which should in Dr. Salimi's view be followed by similar well-designed clinical trials aimed at addressing remaining gaps in knowledge about how the drugs compare in terms of efficacy, tolerability, and overall effectiveness.

For example, there is insufficient knowledge to stratify the drugs according to risk for tardive dyskinesia, said Dr. Salimi, associate director of the clinical research unit at Dorothea Dix Hospital in Raleigh, N.C., and a clinician in the Schizophrenia Treatment and Evaluation Program in Chapel Hill, N.C. Both sites are divisions of the department of psychiatry at the University of North Carolina at Chapel Hill.

In addition, more knowledge is needed to better understand how the range of mid- and lower-potency older generation antipsychotics and the newer generation antipsychotics compare with one another when it comes to risk for metabolic impairments such as weight gain, dyslipidemia, and diabetes. "This is critical, because in the context of antipsychotic treatment, metabolic changes can happen quickly and in many cases can be difficult to reverse," Dr. Salimi said.

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More safety data emerged last year, with the publication of a large Medicaid database study that detailed a sharply elevated, dose-related risk of sudden cardiac death in patients who were using antipsychotic drugs, with the risk in atypical antipsychotic users at least as high as, if not higher than, that in patients prescribed typical antipsychotic drugs (N. Engl. J. Med. 2009;360:225-35).

In an accompanying editorial to that report, Dr. Sebastian Schneeweiss and Dr. Jerry Avorn warned about the widespread use of either class of medications in "vulnerable populations and outside the labeled indications" because of the risk of a fatal side effect.

They called for a formal decision-making algorithm to clarify the risk-benefit equation in light of the new findings (N. Engl. J. Med. 2009;360:294-6).

Efficacy and cost data further muddy the waters, because of wide variations within the classes of first- and second-generation drugs that might have obscured differences between individual drugs in studies such as CATIE.

Dr. Jan Volavka and Dr. Leslie Citrome, for example, argued that choosing perphenazine as a representative of a first-generation antipsychotic to compare with four second-generation drugs (olanzapine, quetiapine, risperidone, and ziprasidone) in CATIE might have set the stage for a stand-off in the study, because perphenazine has similar side-effect and receptor-binding profiles, and similar efficacy to second-generation drugs (Expert Opin. Pharmacother. 2009;10:1917-28).

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DR. CITROME

Indeed, "none of the 4 SGAs [second-generation antipsychotics] demonstrated statistically significant superiority" to the first-generation drug in CATIE, Dr. Volavka and Dr. Citrome asserted, although research generally, and a number-needed-to-treat analysis by Dr. Citrome and another of his colleagues, Dr. T. Scott Stroup, support the idea that olanzapine demonstrates a clear advantage over other drugs in terms of patient retention in therapy (Int. J. Clin. Pract. 2006;60:933-40).

Another individual atypical drug, clozapine, stood out in a Finnish population-based cohort study as conferring a 26% relative mortality advantage over perphenazine over an 11-year period (Lancet 2009;374:620-7).

If genetic testing could identify patients at low risk for agranulocytosis, a feared side effect of that drug, clozapine might edge its way upward on treatment decision trees, Dr. Citrome said.

"It may no longer be useful to draw a clear distinction between these two classes of drugs based on class alone," said Dr. Citrome, director of the clinical research and evaluation facility at the Nathan S. Kline Institute for Psychiatric Research, a division of the New York State Office of Mental Health in Orangeburg, in an interview.

With regard to the weight gain conundrum, which he argues is of great importance in considering drug alternatives, Dr. Citrome advised individualizing therapy.

"Although some medications are associated with the possibility of gaining more weight than others, this is highly variable among individuals.

"Children, youth, and first-episode patients with schizophrenia almost always gain weight, no matter what the medicine is," he said.

For early monitoring and ongoing assessment, Dr. Citrome said he keeps a scale in his private office, and weighs patients at every session, regardless of which medication or medications someone is receiving.

"It shows that we are serious about making an impact," he said, noting that only one patient has ever objected to the practice.

A patient's previous response to a drug and previous weight gain are often helpful in guiding therapy, he said.

But for newly diagnosed patients with acute psychosis, the way ahead is less clear.

Efficacy might weigh more heavily in his decision about a medication choice in such a patient, whereas long-term safety issues might hold more sway in his follow-up care of the patient, he said.

Such nuanced management will require resources and continuity of care, along with the need to integrate evolving knowledge about efficacy and safety by drug and not just by class, Dr. Salimi said.

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Dr. Salimi reported no relevant financial disclosures. ■

By Betsy Bates. Share your thoughts and suggestions at cpnews@elsevier.com.