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Editor-in-Chief

Clozapine, known as having the highest efficacy, had the lowest mortality risk in an 11-year study of 66,881 patients

Paradigms shift rapidly in antipsychotic treatment

Like the “paradigm shift” Thomas Kuhn coined in his seminal book, *The Structure of Scientific Revolutions*,¹ paradigm shifts have been occurring at a breathless pace in psychiatry. Thanks to ongoing research, changes in the clinical standard of care for schizophrenia in the past 20 years are a case in point.

Old paradigm: Clozapine is ‘last resort’

Let’s take 1988 as a starting point. That’s when clozapine was “resurrected” as the only drug with proven efficacy in refractory schizophrenia after several first-generation antipsychotics (FGAs) had been tried.² However, because of its potentially fatal side effect (agranulocytosis), clozapine was designated as an absolute last-resort agent. It also was stigmatized for its many other side effects, including serious metabolic complications.

In the 1990s, several more-tolerable second-generation antipsychotics (SGAs) modeled after the clozapine receptor-binding paradigm with “broader efficacy” were launched and quickly became the standard of care. Then in 2000, the field was jolted by a meta-analysis claiming that SGAs are not superior to FGAs in either efficacy or tolerability.³ The 5-year Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, completed in 2004, confirmed that FGA and SGA discontinuation rates were not different,⁴ but it also showed that clozapine’s superior efficacy to FGAs also extended to SGAs.

Emerging research into neuroplasticity and neurogenesis later indicated that SGAs are neuroprotective, whereas FGAs are not.⁵ As a class, SGAs appeared to have repaired their tarnished image but still suffered from the fact that several are associated with metabolic syndrome risk factors,⁶ which are linked to early mortality.

New paradigm: Clozapine should be ‘first-line’

Then a report by Ray et al⁷ showing a significant increase in sudden cardiac death associated with both FGAs and SGAs appeared in January 2009. This put all antipsychotics in a negative light again. But in July 2009, a massive 11-year study by Tiihonen et al⁸ of 66,881 schizophrenia patients in Finland introduced yet another paradigm shift. It strongly suggested

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that clozapine was the safest antipsychotic, with the lowest mortality from all causes compared with any FGA or SGA, and that it should be considered as first-line treatment! That study also reported that mortality in antipsychotic-treated patients was lower than in untreated ones, which neutralized the cardiac death findings of Ray et al.

The greatest paradigm shift from the Tiihonen et al⁸ study is the stunning conclusion that clozapine should be a first-line antipsychotic, not a last resort for refractory patients. Clozapine has not only the highest efficacy (a very important outcome measure) but also the lowest mortality (death is the most important outcome measure in medicine!). Not a single practice guideline has ever recommended clozapine as a first-line antipsychotic. It is puzzling why the obesity, hyperglycemia, and hyperlipidemia observed with clozapine do not increase mortality. The low suicide rate with clozapine is not surprising, however, because clozapine received FDA approval for the treatment of suicidality in schizophrenia based on the InterSePT study.⁹

The bottom line: Evidence-based research leads to paradigm shifts in treatment that can shatter clinical dogmas. Stay tuned; ongoing psychiatric research will certainly generate new paradigms, and our patients will be better for it.



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