How Best to Make the Switch to Clozapine

By Brian Miller, MD, PhD, MPH
Clozapine is the “gold-standard” antipsychotic for treatment-resistant schizophrenia.

No previous studies have compared immediate versus gradual discontinuation of the previous antipsychotic when switching to clozapine, although a meta-analysis of non-clozapine antipsychotic switching found no differences in efficacy or tolerability[1].
Potential Risks of Antipsychotic Discontinuation

 Immediate
Withdrawal/discontinuation or “rebound” symptoms
Supersensitivity syndromes (e.g., withdrawal dyskinesias)
Symptom reemergence or exacerbation

 Gradual
Worsening or emergent side effects
Takeuchi and colleagues[2] piloted a trial of immediate versus gradual antipsychotic discontinuation in patients with schizophrenia switching to clozapine. They hypothesized that there would be no differences in efficacy or tolerability between the 2 strategies.
An 8-week, double-blind, parallel-group, randomized, controlled trial was performed in patients with schizophrenia or schizoaffective disorder who were candidates for clozapine. Exclusion criteria were active substance use disorder, medical contraindications to clozapine, and evidence of significant nonadherence.
In the gradual discontinuation group, baseline antipsychotic(s) were reduced by 25% weekly over 3 weeks and administered as unmarked capsules.

In the immediate discontinuation group, all unmarked capsules contained placebo.

In both groups, clozapine was started at 12.5 mg/d, then increased by 25 mg/d to 300 mg/d at Day 12.
The primary outcome measure was the 18-item Brief Psychiatric Rating Scale (BPRS), administered at weeks 1, 2, 3, 4, and 8.

Statistical analyses were performed using an intention-to-treat basis.

Differences in efficacy and side effect scores from baseline to endpoint were analyzed using a last-observation-carried-forward approach.
Study Results

33 patients were randomized to either immediate (n = 15) or gradual (n = 18) discontinuation

3 patients—all in the gradual discontinuation group—withdraw prematurely because of adverse events within the first 3 weeks; 30 patients completed the trial

Subjects in the immediate discontinuation group were more likely to be taking 2 antipsychotics at baseline, as well as a higher antipsychotic dose (defined as > 600 mg/d chlorpromazine equivalents)
Within each group, BPRS total scores and Clinical Global Impression-Severity scores improved.

There were no significant differences in changes from baseline to endpoint in any efficacy or side effect measures between the 2 groups.
Discussion

• This was the first known trial investigating clinical outcomes of immediate versus gradual discontinuation of the previous antipsychotic when switching to clozapine

• The primary findings were significant improvements in psychopathology upon switching to clozapine

• There was no evidence of differences in terms of efficacy or tolerability between the 2 approaches, which is broadly consistent with trials of switching to other antipsychotics[1]
Discussion

• The authors note that as a pilot study, the small sample size may have contributed to the absence of between-group differences on outcome measures.

• These preliminary findings suggest that either strategy could be used by prescribers based on clinical judgment.

• Further larger-scale trials in this area are warranted.

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