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High-Dose Olanzapine for Treatment-Resistant Schizophrenia

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In this issue of the *Journal,* Meltzer et al.[1] present provocative results from a randomized, double-blind study showing that larger-than-typically-prescribed doses of olanzapine appear to be equivalent to conventional doses of clozapine in treatment-resistant schizophrenia. Although the sample size is relatively small (total N = 40), the data are consistent with the notion that high-dose olanzapine might be effective in treatment-resistant schizophrenia. These findings are important because they open up the possibility of a new approach to treatment-resistant schizophrenia.

Previous studies have examined the potential of high-dose olanzapine therapy for treatment-resistant schizophrenia, with mixed results. Two prior controlled studies—one in adolescents[2] and another in adults[3]—demonstrated that clozapine was superior to higher-dose olanzapine, while other more naturalistic studies suggest that high-dose olanzapine might be equi-effective.[4–6] Because it is known that the effects of clozapine in treatment-resistant schizophrenia tend to increase with time (with effects at 6 months exceeding those at 6 weeks[7]), it is possible that prior studies failed to note equivalency because of their relatively short time courses.

Although clozapine and high-dose olanzapine did not differ on most measures of psychopathology and cognition in the study by Meltzer et al.,[1] clozapine displayed superiority on the Global Assessment of Functioning at 6 months, while olanzapine demonstrated superiority on the Wechsler Intelligence Scale for Children-Revised Mazes and Verbal List Learning-Delayed Recall tests of cognitive functioning. On all other measures, clozapine and high-dose olanzapine were equivalent. In terms of side effects, at the 6-month timepoint olanzapine was associated with a higher body mass index and greater weight gain—data consistent with prior studies. Taken together, though, these results indicate that for treatment-resistant individuals for whom clozapine treatment is not possible, high-dose olanzapine is an option.

If we accept the notion that clozapine and high-dose olanzapine are equivalent (or nearly so) for treatment-resistant schizophrenia, how can such findings be explained? Two likely possibilities relate to pharmacodynamics and pharmacokinetics.

In terms of pharmacodynamics, a careful examination of the receptor pharmacology for both olanzapine and clozapine indicates that they have similar affinities for most relevant biogenic amine receptors,[8] with significant affinity differences only at 5-HT_7 receptors[9] and some muscarinic receptor subtypes.[10] Importantly, clozapine's active metabolite *N*-desmethylclozapine is a potent M_1-receptor agonist[10] and dopamine D_2/D_3 partial agonist.[11] Thus, one explanation for the apparent equivalency of high-dose olanzapine and clozapine is that high-dose olanzapine results in plasma levels of olanzapine (or an olanzapine metabolite) that interact with critical receptors essential for the actions of clozapine in treatment-resistant schizophrenia. The notion that antipsychotic drug metabolites might be essential for the unique actions of their respective drugs is supported by our recent finding that *N*-desalkylquetiapine is a potent antidepressant that inhibits norepinephrine reuptake—which would explain its unique efficacy in treating depression.[12] Thus, a careful examination of the pharmacology of various olanzapine metabolites could shed light on the mechanism of action of olanzapine in treatment-resistant schizophrenia.

A more trivial explanation is that a subset of treatment-resistant schizophrenia patients rapidly metabolize olanzapine. Thus, high-dose olanzapine is needed to achieve adequate plasma levels of the parent compound to achieve therapeutic equivalence. To date, no studies have adequately addressed the possibility that the apparent effectiveness of high-dose olanzapine can be explained by pharmacokinetics.

A third explanation relates to pharmacogenetics. It is possible that treatment-resistant schizophrenia patients

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possess single nucleotide polymorphisms (SNPs) that interfere with the actions of olanzapine, and that higher doses than usual are required to overcome this. Indeed, we have demonstrated recently that some SNPs in the 5-HT_{2A} serotonin receptor—a major target for clozapine and olanzapine—modulate olanzapine's activity.[13] Further study will be required to fully explore this possibility.

Whatever the explanation, the current findings are intriguing because they imply that high-dose olanzapine could be effective in individuals with treatment-resistant schizophrenia. Clearly, however, larger double-blind, controlled studies will be needed to support this hypothesis. Additional mechanistic studies will be needed to provide a scientific rationale for this provocative new approach for schizophrenia treatment.

Drug names: clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa).

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