Antipsychotic Polypharmacy, Part 1: Shotgun Approach or Targeted Cotreatment?

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The combination of medications is common in the management of many, if not most, chronic disorders. Being among the most severe mental disorders, schizophrenia is predisposed to the concurrent use of more than 1 medication. This article is the first of 2 related CORNER articles that discuss antipsychotic polypharmacy in the treatment of schizophrenia. Part 1 explores the reasons, concerns, and rationales relating to combined antipsychotic use. In part 2, data regarding the efficacy and safety of this commonly used approach will be presented.

Antipsychotic Polypharmacy in the Treatment of Schizophrenia

Different from bipolar disorder, in which several medications with different mechanisms or, at least, different target symptoms or domains can rationally be combined, in schizophrenia the data for the utility of adding medications to antipsychotic monotherapy have either been negative or are limited. Adjunctive treatments have been tested for positive, negative, and cognitive symptoms.[1] However, except for electroconvulsive therapy added after antipsychotic nonresponse,[2] these strategies have been neither robustly nor consistently effective.[3]

One strategy aiming to improve efficacy after partial response or nonresponse to antipsychotic monotherapy is the addition of a second antipsychotic. Depending on the country, year, clinical setting, patient population, and study methodology, occurrence of the combined use of more than 1 antipsychotic has been reported to be between less than 10% and more than 50% of patients, with modal rates of between 10% and 30%.[4–6] In descriptive studies, antipsychotic polypharmacy has been associated with schizophrenia/schizoaffective disorder, greater illness severity, longer illness duration, comorbid substance abuse and depression, white/non-Latino ethnicity, treatment with first-generation antipsychotics and with quetiapine, and shorter follow-up periods.[3]

Treatment guidelines for schizophrenia recommend antipsychotic monotherapy and reserve combined antipsychotic use for treatment-refractory patients after multiple monotherapy attempts have failed; these attempts should include clozapine,[7] which has the best evidence for being effective in treatment-refractory patients.[8–10] However, in clinical practice, it appears that antipsychotic polypharmacy is frequently used instead of clozapine. This is suggested by the fact that while about one third of patients with schizophrenia are refractory to treatment, clozapine usage is generally below 10% (IMS Health; Plymouth Meeting, Pa.; April 2006). In addition, the rate of clozapine use is clearly less than the rate of antipsychotic polypharmacy.

Reasons for and Concerns Regarding Antipsychotic Cotreatments

Reasons for combined antipsychotic use include ongoing cross-titration; aborted cross-titration due to temporary or sustained improvement; successful or unsuccessful attempts at speeding up or augmenting efficacy for core symptoms of the primary disorder or for associated features and comorbidities, including anxiety and insomnia; the desire to lower the dose and/or reduce side effects of the first antipsychotic; combination of different routes of antipsychotic administration; prescriber habit/preference; and/or patient/family preference.[3]

On the other hand, concerns include increased total dosage; acute or chronic side effects, possibly including even greater cardiac mortality; loss of "atypicality" when combining a first-generation antipsychotic with a second-generation antipsychotic; use of a second antipsychotic at low doses instead of safer and cheaper alternatives for relatively easy to treat conditions, such as insomnia and agitation and anxiety; known and unknown drug-drug interactions; increased risk for nonadherence; difficulty determining cause and effect when a patient's symptoms or adverse effects improve or worsen (i.e., whether it is due to the second antipsychotic or to the interaction of the 2 antipsychotics); greater cost; and, especially, the lack of an evidence base that might justify taking any of these risks.

Potential Rationale for Antipsychotic Polypharmacy

One of the greatest criticisms of antipsychotic polypharmacy is the lack of data that show sufficient efficacy and safety of this frequently utilized strategy. Another frequently cited criticism is the lack of a theoretical rationale that could explain the potential benefits of combined antipsychotic use. Since antipsychotic action is still believed to be tied to blockade of the dopamine D_2 receptor, it is unclear what advantage combining 2 antidopaminergic drugs may have that could not also be achieved by either increasing the dose of the first antipsychotic or switching to a different antipsychotic at doses that adequately block dopamine in the mesolimbic system. Nevertheless, when criticizing the "polypharmacy" of combined antipsychotic use, it is important to realize that most psychotropic drugs affect multiple receptor systems, constituting a form of "polypharmacy" at a molecular level, even if given as monotherapy.[11]

Theoretically, mechanisms involved in increasing (or decreasing) the efficacy of one antipsychotic by adding a second antipsychotic could involve additive, complementary, or counteractive effects on global or regional dopamine transmission and/or on nondopaminergic receptors and related downstream effects. Dopaminergic rationales may include the combination of an antipsychotic with strong affinity to the D_2 receptor with an antipsychotic with weaker D_2 binding, or a full antagonist with a partial agonist at the D_2 receptor. Nondopaminergic rationales are even less well justified due to the fact that it is unknown which additional receptor systems modulate positive, negative, or cognitive symptoms of schizophrenia. Similarly, increased or reduced adverse effects as a result of combined antipsychotic use could also be due to additive, counteractive, or complementary effects on dopaminergic or nondopaminergic receptor systems. Strategies may include combining antipsychotics at opposite ends of the spectrum regarding sedation, extrapyramidal side effects, or change in prolactin levels. It is important to note, however, that all of these considerations are theoretical.

Conclusions

The combined use of antipsychotics is common in the treatment of schizophrenia. This clinical strategy has been based mostly on pragmatic evidence and, as such, has ecologic validity, being adopted by clinicians who are faced with the common

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clinical problem of suboptimal symptom response. Although there is at least some theoretical support for combining antipsychotics, there are also valid concerns about this practice. Therefore, well-designed and controlled studies of specific combinations are required that test theoretical assumptions and refute potential risks of antipsychotic polypharmacy. Next month's CORNER will discuss the current and emerging evidence for the efficacy and safety of antipsychotic polypharmacy in the treatment of schizophrenia.

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