

Antipsychotic Polypharmacy: Update and Guidelines for Practice

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Despite scanty empirical support, the concurrent use of two or more antipsychotic medications is fairly common in real-world clinical settings. The limited data available on this practice provide little support for its utility, except for the potential value of adding a second antipsychotic agent to clozapine in patients with otherwise treatment-refractory schizophrenia. A number of adverse associations of antipsychotic combinations have been reported, including higher mortality, an increased risk of a range of adverse effects, dangerous drug interactions, decreased treatment adherence, and greater costs. We evaluate the appropriateness of the many rationales for antipsychotic combinations and outline recommendations for its place in antipsychotic therapy.

Reasons for concurrent use of two or more antipsychotic agents

Clinicians describe a range of different objectives as to why they combine two or more antipsychotic agents. Their logic and relevant data are briefly examined:

1. Proper and interrupted cross-titration during switching between antipsychotic medications

During the process of switching from one antipsychotic agent to another, the strategy of cross-titration over several weeks is often recommended. During cross-titration, patients appropriately receive both antipsychotic medications. Switching is a time-limited process, however, and should generally be completed within 8 weeks.

Cross-titration is often interrupted because patients appear to look better during the switch process leading to the impression that the

combination of two agents may be responsible for the improvement. It is more likely that the second agent by itself or the process of discontinuing the first agent explained the improvement. **Once switching is initiated, it should be completed.**

2. Failure of antipsychotic monotherapy (number of agents, dose, duration, clozapine)

Effectiveness of antipsychotic medications is determined by appropriateness of their dosing and the adequacy of the trial duration. Before concluding that antipsychotic monotherapy “will not work” in a given patient, the patient should have received adequate trials of at least three antipsychotic agents for at least 6 weeks each, including clozapine for at least 12 weeks. Recent studies indicate that clinicians frequently resort to antipsychotic polypharmacy without trying an adequate number of antipsychotics or exploring the suitable dose range of individual agents. (Please refer to the Florida Schizophrenia Treatment Guidelines for details).

3. Different mechanism of action of the different antipsychotic agents

The nineteen antipsychotic agents available in Florida differ in their pharmacological attributes. The only mechanism definitively linked to antipsychotic efficacy, however, is their effect on the dopamine D-2 receptor. Whereas the relationship between other pharmacological properties and risk of side-effects is reasonably well understood, their relevance to efficacy is unknown. Therefore from an efficacy perspective, no rationale currently exists for combining multiple antipsychotic agents.

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4. To enhance effect or accelerate speed of response

There is no evidence that combining antipsychotic agents achieves a faster response than optimal use of a single agent. With the exception of some data suggesting the utility of adding a second antipsychotic agent to clozapine in select populations, there is little evidence for multiple antipsychotics being more effective than single agents.

5. To reduce side-effects of a single agent

Data from the few clinical trials to evaluate this hypothesized benefit of antipsychotic combinations yield mixed results, but generally suggest that the addition of a second antipsychotic agent rarely reduces side effects or allows a dose reduction of the first.

6. To treat comorbid conditions

A frequent justification for using antipsychotic combinations is that one of the agents is being utilized for its antipsychotic effect and that the second agent is targeting a comorbid condition such as insomnia or agitation. Several complications accompany this practice, and **the use of a non-antipsychotic agent for the comorbid condition** (eg., benzodiazepine or other hypnotic for insomnia, benzodiazepine for agitation) is recommended- more targeted, fewer side-effects, less costly.

7. Different route of administration

Transition to appropriate monotherapy is the preferred option, but targeted use of two antipsychotic agents with different routes of administration may occasionally be appropriate. However, its use should generally be time limited.

Guidelines

In view of the absence of evidence indicating its efficacy or safety, the use of antipsychotic combinations is discouraged and warrants critical scrutiny. Better proven treatment strategies (outlined in the Florida Schizophrenia and Bipolar Disorder Treatment Guidelines) should be utilized before a trial of antipsychotic polypharmacy is implemented. If a combination of antipsychotic medications is being considered, this should be done only after finding that optimal use of each component of the combination is ineffective without the other. If a combination of antipsychotic agents is being employed, its utility should be monitored on an ongoing basis, ideally using measurement-based psychiatry, including simple clinician and/or self-rating scales. Based on recent data, conversion of patients treated with two antipsychotics to antipsychotic monotherapy should be possible in at least two-thirds of the patients without loss of efficacy. Thus, conversion to monotherapy should be considered, unless a very good rationale for continued antipsychotic polypharmacy exists, and this needs to be properly documented.

References

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