Combined Anti-Psychotic Treatment in Acute Manic Psychosis

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Overview: A successful use of two antipsychotics in the treatment of severe psychosis highlights the potential value of a partial agonist alongside a typical dopamine agonist.

Problem: In the treatment of acute psychosis, literature review and clinical practice reassert the common wisdom that multiple antipsychotics have a limited role. Nonetheless, acuity and urgency often necessitate trials with multiple antipsychotic agents to affect the resolution of psychosis. We specifically investigated the literature to guide the treatment of acute psychotic mania to address a severely psychotic geriatric patient requiring seclusion to avoid self-harm. In this case, trials with second-generation antipsychotics had failed and limited compliance hindered achieving proper levels of anti-manic agents. We sought to maximize the potential value of antipsychotic agents.

Goal: We sought to maximize the potential value of antipsychotic agents in terms of increased efficacy and decreased side effects, especially those that hinder optimal treatment.

Background: Given urgent safety concerns, we transitioned from prior treatment to haloperidol (HAL), a high-potency antipsychotic emphasizing selective D2R full antagonism. We optimized treatment with haloperidol until EPS hindered further adjustment despite typical EPS interventions. Short-acting benzodiazepines were slowly increased with some benefit but eventually halted due to benzodiazepine-induced delirium in this geriatric patient. There is limited data on the effectiveness of third-generation antipsychotics such as aripiprazole (ARI) alone in such a patient. A potential explanation and cause for concern is the potential up-regulation of D2 receptors (D2R).

Treatment Strategy: To proceed, we investigated adjunctive antipsychotic medications with multiple trials and this necessitated focusing on medications with longer-term usage and multiple investigations. Given aripiprazole's partial dopamine D2R agonism and haloperidol's selective dopamine D2R full antagonism the combination was the most logical to consider. In fact, haloperidol value alongside aripiprazole has been reported for emotional dysregulation, treatment-resistant schizophrenia, and antipsychotic-induced hyperprolactinemia. There are other logical combinations of high-potency antipsychotics and partial agonists; however, the combination we utilized was the most studied and reported.

A second psychiatric opinion was obtained to assure that more favorable options did not exist. Burke and Lincoln, identify a risk of a higher dose of ARI (30mg/day) given its lower Ki; thus, an initial lower dose was chosen.

After adding aripiprazole at a low dose, despite weeks of uncontrolled mania on an inpatient basis, the psychosis resolved. Safety measures could be discontinued and compliance improved sufficiently to achieve proper anti-manic medication levels.

Case Analysis: Our experience mirrors others who emphasize the usage of a high potency typical antipsychotic to its most reasonable dose followed by low dose partial agonist such as aripiprazole at a low dose. A potential explanation is the countering role of aripiprazole's stronger binding affinity toward D2R [ARI (Ki = 0.34 nM) and HAL (Ki = 1.0 nM)] and slower dissociation kinetics versus haloperidol. Although the proper dose requires further investigation; in our case, a low dose was sufficient and appropriate.

Discussion: The decades-long advice of utilizing a single anti-psychotic agent in the treatment of psychosis should be reassessed in light of novel antipsychotic agents that provide partial agonism at the D2R. Rather than as a primary treatment, their role may be to augment a more typical D2R antagonist with the goal of increasing effectiveness while decreasing side effects. This is the benefit seen in this case and described elsewhere

Our case only investigated the role of a specific partial agonist, aripiprazole, in combination with haloperidol, primarily because of available evidence. There may be value in investigating other combinations.

Our treatment was provided on a secure inpatient psychiatric unit with a second case review by another psychiatrist to ensure maximal safety. We recommend a similar strategy given the limited data to guide the use of two antipsychotics in the treatment of acute psychosis.

Implication: Additional basic science research is needed to clarify the role of partial agonism and to guide treatment in terms of the most optimal dosage of two antipsychotics and the proper ratio of the two.

Additional clinical case descriptions especially with younger, adult, and other geriatric patients can further help elucidate the potential benefits in terms of positive and negative symptoms of psychosis and risks as well as provide additional guidance regarding the optimal strategy.

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Acknowledgments & Disclosure: The findings and strategy discussed are an individual case and should not be utilized as a guide to treatment more broadly. The authors have no relationship or specific financial investment in the pharmaceutical companies that sell the medications identified in this poster.

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