

Nonsteroidal Anti-inflammatory Drugs and 5-HT₃ Serotonin Receptor Antagonists as Innovative Antipsychotic Augmentation Treatments for Schizophrenia

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Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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ABSTRACT

Antipsychotic treatment is the mainstay in the management of schizophrenia. However, despite optimum use of antipsychotic drugs, many schizophrenia patients continue to exhibit residual positive, negative, cognitive, and other symptoms. Various antipsychotic augmentation strategies have been studied using non-antipsychotic augmenting agents; 2 innovative classes of drugs examined have been nonsteroidal anti-inflammatory drugs (NSAIDs) and 5-HT₃ serotonin receptor antagonists. Meta-analysis of the NSAID studies in schizophrenia patients with positive symptoms (8 randomized controlled trials [RCTs], pooled N = 774) shows that NSAID augmentation is associated with a significant decrease in positive symptom ratings (standardized mean difference [SMD] = 0.19), with no significant change in negative or total symptom ratings. Meta-analysis of the 5-HT₃ antagonist studies in stable schizophrenia patients (6 RCTs, pooled N = 311) shows that 5-HT₃ antagonist augmentation is associated with significant reduction in negative symptom (SMD = 1.10), general psychopathology (SMD = 0.70), and total symptom (SMD = 1.03) ratings without reduction in positive symptom ratings. Neither NSAID nor 5-HT₃ antagonist augmentation increases the dropout rate. Whereas the benefits with NSAID augmentation are, perhaps, too small to be clinically meaningful, antipsychotic augmentation with 5-HT₃ antagonists may be a possible strategy to reduce persistent negative symptoms in schizophrenia. Both fields of inquiry require further investigation.

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Clinical Problem

Mr C is a 23-year-old student with a 9-month history of schizophrenia. He has responded only partially to antipsychotic drug treatment, developing adverse effects at higher doses of whatever antipsychotic he receives. Mr D is a 41-year-old clerk with a 20-year history of schizophrenia. He is stable on maintenance antipsychotic medication; however, he is withdrawn and shows no interest in leisure and pleasure activities. Are there non-antipsychotic augmentation agents that might improve outcomes in these 2 patients?

Introduction

Typical and atypical antipsychotic drugs are effective treatments for schizophrenia. However, despite best attempts to optimize therapy, fewer than 15% of treated patients recover.¹ Most patients continue to exhibit a mix of positive, negative, and cognitive symptoms, and some are considerably impaired by these. Raising (or lowering) the antipsychotic dose, switching antipsychotics, and augmenting with a second antipsychotic are examples of pharmacologic interventions that are antipsychotic-based. For patients in whom antipsychotic approaches fail, and for those who do not tolerate antipsychotic drugs well, are there augmentation approaches involving non-antipsychotic drugs? A previous article in this column suggested that famotidine augmentation may not be of much benefit.² The present article examines 2 other innovative augmentation treatments: nonsteroidal anti-inflammatory drugs (NSAIDs) and 5-HT₃ serotonin receptor antagonists.

Mechanisms

Inflammatory markers have been identified in plasma as well as brain before and during the onset of psychotic symptoms in schizophrenia^{3–5}; if these contribute to the disease process, then anti-inflammatory treatments may attenuate the severity of schizophrenia.⁶

5-HT₃ receptors are widely distributed in the brain, including in limbic and frontal cortical areas. These receptors result in downstream modulation of many neurotransmitters, including dopamine. These receptors also influence auditory gating in schizophrenia.⁷ 5-HT₃ receptors probably do not modulate basal dopamine release but facilitate reward-related phasic dopamine release in the nucleus accumbens. 5-HT₃ antagonists reduce dopaminergic activity in the nucleus accumbens.⁸ 5-HT₃ antagonists have been used to treat different dopaminergic disorders such as tardive dyskinesia,⁹ Tourette's disorder,¹⁰ and schizophrenia.¹¹ Finally, 5-HT₃ antagonists have a calming effect and improve cognition in animal models.^{12,13} Drugs acting on 5-HT₃ receptors may therefore moderate the symptoms of schizophrenia.

NSAIDs for Schizophrenia

Many randomized controlled trials (RCTs) have examined whether NSAID augmentation is an effective treatment strategy in schizophrenia;

- Some schizophrenia patients may require antipsychotic augmentation treatments to manage residual positive, negative, or other symptoms. In this regard, nonsteroidal anti-inflammatory drugs (NSAIDs) and 5-HT₃ antagonists are 2 novel augmentation strategies that have been studied and meta-analyzed.
- The results with NSAIDs in patients with acute illness and those with persistent positive symptoms have been mostly disappointing; only improvements in positive symptoms have been found, and the pooled effect size is probably too small to be clinically relevant.
- The results with 5-HT₃ antagonists in stable patients are more promising; negative symptoms, general psychopathology, and total symptom ratings have all been shown to attenuate. However, the literature in the field is insufficient for definitive recommendations to be made.

not all outcomes were favorable. Nitta et al¹⁴ therefore examined the subject in a systematic review and meta-analysis. The authors searched electronic databases, clinical trial registries, reference lists, and other sources and identified 8 relevant placebo-controlled RCTs (pooled N=774), including 3 that had not been published. These RCTs examined acutely ill schizophrenia patients and those with positive symptoms. The mean age of the pooled sample was about 34 years. The sample was two-thirds male. Risperidone was the commonest antipsychotic that was augmented. Six RCTs examined celecoxib (400 mg/d; N=504) and 2 examined aspirin (1,000 mg/d; N=270) augmentation. The trials were 5 to 16 (median=8) weeks in duration.

Nitta et al¹⁴ found that NSAID augmentation of antipsychotic drugs was associated with a statistically significant reduction in positive symptoms scores; however, the standardized mean difference (SMD) was only 0.19, representing an effect size of questionable clinical significance. The SMD for Positive and Negative Syndrome Scale (PANSS) total scores narrowly missed statistical significance; this effect was also small and likely to be of doubtful clinical value. There were no other treatment gains evident. Dropout was not increased by NSAID augmentation.

Many subgroup analyses suggested possible areas of benefit, but these results are best considered preliminary because the analyses were exploratory and not corrected for type II errors. The results of the meta-analysis are summarized in Table 1. In brief, the findings do not encourage the use of anti-inflammatory treatments for schizophrenia unless inflammatory or other biomarkers can be identified that reliably define subpopulations of patients who might benefit from the intervention. In such an event, long-term studies are desirable to determine whether reducing inflammation improves the course of the illness.

Table 1. Important Findings From a Meta-Analysis¹⁴ of Placebo-Controlled RCTs of NSAID Augmentation in Schizophrenia

1. NSAIDs did not significantly improve PANSS total scores (SMD = -0.24; 95% CI, -0.48 to 0.01). There was, however, significant heterogeneity identified in this analysis. In subgroup analyses of PANSS total scores, aspirin (SMD = -0.29; 95% CI, -0.52 to -0.05), but not celecoxib (SMD = -0.21; 95% CI, -0.57 to 0.15), was superior to placebo. NSAID augmentation was also effective in first-episode patients and inpatients, but not in chronically ill patients or outpatients. Lower negative symptom scores at baseline, but not PANSS total or positive symptom scores, predicted greater PANSS total improvements with NSAIDs.
2. NSAIDs were associated with a small but statistically significant decrease in PANSS positive symptom ratings (SMD = -0.19; 95% CI, -0.37 to -0.01).
3. NSAIDs did not significantly improve PANSS negative symptom ratings (SMD = -0.03; 95% CI, -0.17 to 0.12).
4. NSAIDs were not associated with higher all-cause dropout (relative risk = 1.13; 95% CI, 0.79 to 1.60). Meta-analysis was not possible for other adverse outcomes, including individual adverse effects.

Abbreviations: NSAID = nonsteroidal anti-inflammatory drug, PANSS = Positive and Negative Syndrome Scale, RCT = randomized controlled trial, SMD = standardized mean difference.

Table 2. Important Findings From a Meta-Analysis¹¹ of Placebo-Controlled RCTs of 5-HT₃ Antagonist Augmentation in Schizophrenia

1. 5-HT₃ antagonist augmentation was associated with a significant attenuation of PANSS total scores (5 RCTs; N=261; SMD, -1.03; 95% CI, -0.36 to -1.70).
2. 5-HT₃ antagonist augmentation was associated with a significant attenuation of PANSS negative symptom scores (5 RCTs; N=261; SMD, -1.10; 95% CI, -0.39 to -1.82).
3. 5-HT₃ antagonist augmentation was associated with a significant attenuation of PANSS general psychopathology scores (5 RCTs; N=261; SMD, -0.70; 95% CI, -0.17 to -1.23).
4. 5-HT₃ antagonists did not significantly reduce PANSS positive symptom scores (5 RCTs; N=261; SMD=0.12; 95% CI, -0.12 to 0.36).
5. Constipation was more common with 5-HT₃ antagonists (risk ratio = 2.05; 95% CI, 1.07-3.91; NNH = 11).
6. In one study, extrapyramidal symptom ratings were significantly lower with ondansetron, and in another study, nausea and vomiting were significantly lower with ondansetron.
7. Dropout due to inefficacy, adverse events, and all causes was similar in treatment and control groups.

Abbreviations: NNH = number needed to harm, PANSS = Positive and Negative Syndrome Scale, RCT = randomized controlled trial, SMD = standardized mean difference.

5-HT₃ Antagonists for Schizophrenia

Kishi et al¹¹ presented a systematic review and meta-analysis of selective 5-HT₃ antagonist augmentation of antipsychotic medications in schizophrenia. These authors searched electronic databases, clinical trial registries, reference lists, and other sources and identified 6 relevant placebo-controlled RCTs (pooled N=311), only 5 of which contributed data to efficacy outcomes. The mean age of the sample was about 37 years. Patients in these studies were, in general, clinically stable and on stable doses of antipsychotic medication. The RCTs ranged from 10 days to 12 weeks (median, 8 weeks) in duration. Three RCTs studied tropisetron (5-10 mg/d), 2 studied ondansetron (8 mg/d),

and 1 studied granisetron (2 mg/d). One ondansetron RCT augmented haloperidol; the remaining 5 RCTs augmented risperidone. One RCT reported only a completer analysis. None of the RCTs was industry-driven.

The results of the meta-analysis are summarized in Table 2. 5-HT₃ antagonists were associated with significant reductions in PANSS total scores, negative symptoms, and general psychopathology scores; the SMDs were medium to large. All 3 analyses, however, were characterized by statistical heterogeneity. 5-HT₃ antagonists did not significantly reduce positive symptoms. Dropout rates were not increased by 5-HT₃ antagonists.

These results should, at best, be considered preliminary because of the small number of studies, the small size of the pooled sample, and the considerable heterogeneity detected in the analyses. However, the large effect sizes across several outcome measures imply that the field is worthy of further study.

Conclusions

Nonsteroidal anti-inflammatory drugs seem to hold little promise as antipsychotic augmentation agents in acutely ill schizophrenia patients or those with persistent positive symptoms. However, these drugs may merit investigation in samples of patients in whom biomarkers of neuroinflammatory pathology suggest the possibility of benefit. 5-HT₃ antagonists may improve negative symptoms, general psychopathology, and overall symptom ratings in schizophrenia patients who are on a stable dose of antipsychotic medication; the field, however, requires stronger evidence before definitive conclusions can be drawn.

Where does this leave the 2 patients who were described at the start of this article? At best, a 5-HT₃ antagonist may be trialed in each patient as an experimental, off-label augmenting agent for a period of about 8 weeks. The data suggest that, whereas there can be hopes of improvement, the risks (except for constipation) are no greater than with placebo.

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