Nonsteroidal Anti-Inflammatory Drugs in Schizophrenia: Ready for Practice or a Good Start? A Meta-Analysis

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ABSTRACT

Objective: Mounting evidence suggests that inflammation is involved in the pathogenesis of schizophrenia. This evidence implies that anti-inflammatory agents are potentially useful therapeutic strategies in schizophrenia. This article quantitatively summarizes the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) to augment antipsychotic treatment to reduce schizophrenia symptom severity.

Data Sources: An electronic search was performed using MEDLINE, Embase, the National Institutes of Health Web site clinicaltrials.gov, Cochrane Schizophrenia Group entries in PsiTri, and the Cochrane Database of Systematic Reviews. The following basic search terms were used: *schizophrenia*, *nonsteroidal anti-inflammatory drug*, and *NSAID* together with the name of each specific NSAID (*ibuprofen*, *diclofenac*, *naproxen sodium*, and *acetylsalicylic acid*). We applied no year or language restrictions.

Study Selection: Studies were selected if they met the following inclusion criteria: (1) randomized, double-blind, placebo-controlled trials regarding augmentation of antipsychotic medication with an NSAID, (2) patients included had a diagnosis of a schizophrenia spectrum disorder according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, and (3) studies reported sufficient information to compute common effect size statistics, or corresponding authors could supply these data upon request.

Data Extraction: The primary outcome measure was the mean change in total score on the Positive and Negative Syndrome Scale (PANSS). Secondary outcome measures included positive and negative symptom subscores of the PANSS.

Results: We could include 5 double-blind, randomized, placebo-controlled trials, reporting on 264 patients. Four studies applied celecoxib, and 1 used acetylsalicylic acid. We found a mean effect size of 0.43, which was significant at $P = .02$ in favor of NSAIDs on total symptom severity. For positive symptom severity, the mean standardized difference was 0.34 ($P = .02$). For severity of negative symptoms the mean standardized difference was 0.26 ($P = .03$).

Conclusions: These results suggest that NSAID augmentation could be a potentially useful strategy to reduce symptom severity in schizophrenia. As these are the first studies on a relatively new strategy and the included sample size is modest, these results should be interpreted with caution. However, augmentation with acetylsalicylic acid may have the additional benefit of reducing cardiac and cancer mortality in schizophrenia. We therefore believe that application of NSAIDs in schizophrenia deserves further investigation as augmentation of antipsychotic treatment and reducing comorbid somatic diseases.

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Schizophrenia is a severe mental disorder, with a worldwide prevalence of around 1%[1] placing significant burden on global health.[2] Although the introduction of antipsychotic medications in the 1950s has substantially improved clinical symptoms of schizophrenia,[3] the disease is still causing considerable morbidity and mortality.[4] Various pharmacologic therapies as adjuncts to antipsychotics have emerged over the last decades,[3,5] such as antidepressants,[6] anticonvulsants,[7] lithium,[8] benzodiazepines,[9] fatty acids,[10] and vitamins.[11] However, none have come into general clinical practice so far because of insufficient efficacy or conflicting evidence.[3,5]

The pathogenesis of schizophrenia is still far from elucidated, which hampers the rational development of novel pharmacologic therapies. Different lines of evidence now suggest that inflammation in the central nervous system is involved in the pathogenesis of schizophrenia.[11,12] These lines include the altered risk of schizophrenia patients and their relatives for specific autoimmune diseases,[13] clinical similarities between the course of schizophrenia and autoimmune disease,[14] and decreased prevalence of schizophrenia in men who have used nonsteroidal anti-inflammatory drugs (NSAIDs)[15] or glucocorticosteroids.[16] Furthermore, an infectious cause or trigger is suggested by the observed association between schizophrenia and prenatal and perinatal infections,[17] as well as by seroconversion to certain pathogens in patients with schizophrenia.[12,18] On a cellular level, inflammation of the central nervous system is suggested by an increased number of activated microglia cells in the brains of patients with schizophrenia, as visualized by positron emission tomography[19,20] and altered function of immune cells in serum.[12,21] A large, pooled, data set of single nucleotide polymorphism–based, genome-wide, association studies followed up the most significant association signals.[22] One of the most remarkable findings was a significant association with several markers spanning the major histocompatibility complex (MHC) region on chromosome 6p21.3–22.1. This genetic deviation in the MHC region is consistent with an immune component to schizophrenia risk.

Finally, immune dysregulation might be reflected by abnormal levels of cytokines and the presence of autoantibodies in serum and cerebrospinal fluid.[12,23] This mounting body of evidence suggests that anti-inflammatory drugs can be viewed as potential candidates for new augmentation therapies.

Nonsteroidal anti-inflammatory drugs are a relatively safe, well-known, and broad class of anti-inflammatory drugs that inhibit the conversion of arachidonic acid to prostaglandins by blocking the enzyme cyclooxygenase-1

Clinical Points

- Nonsteroidal anti-inflammatory drug (NSAID) augmentation to antipsychotic medication can potentially improve both positive and negative symptoms, but more research is needed before this can be implemented in clinical practice.
- The 5 randomized controlled trials included in this meta-analysis did not show increased side effects of NSAID augmentation as compared to placebo, but longer application (ie, years) may induce side effects, especially on the stomach.
- Augmentation with aspirin may have the additional benefits of reducing cardiovascular and cancer mortality, which are both increased in patients with schizophrenia.

(COX-1) and/or -2 (COX-2) (also referred to as prostaglandin synthase).[24,25] Prostaglandins and their receptors are found throughout the body and are involved in many regulatory processes, including inflammation, pain, and thermal regulation. By blocking prostaglandins, NSAIDs have anti-inflammatory effects, among many others. Several studies have applied NSAIDs to augment antipsychotic treatment in order to improve clinical outcome (see Table 1). However, sample sizes were rather modest. This meta-analysis aims to evaluate the efficacy of NSAIDs as adjunctive therapy in schizophrenia. We aim to include all double-blind placebo-controlled studies published so far. By combining these studies in a meta-analysis, we can increase power and come to a more general answer regarding the efficacy of NSAIDs in decreasing total, positive, and negative symptoms.

DATA SOURCES AND STUDY SELECTION

Literature Search

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[26] An electronic search was performed using MEDLINE, Embase, the National Institutes of Health Web site clinicaltrials.gov, Cochrane Schizophrenia Group entries in PsiTri (http://psitri.stakes.fi/EN/psitri.htm), and the Cochrane Database of Systematic Reviews. We applied no year or language restrictions. The following basic search terms were used: *schizophrenia*, *nonsteroidal anti-inflammatory drug*, and *NSAID* together with the name of each specific NSAID (*ibuprofen*, *diclofenac*, *naproxen sodium*, and *acetylsalicylic acid*). Additionally, the reference lists of the retrieved articles and relevant review articles were examined for cross-references. When necessary, corresponding authors were contacted to provide full details of study outcomes.

Inclusion

Consensus on the studies included was reached on the basis of the following criteria:

1. Studies were randomized, double-blind, placebo-controlled trials regarding augmentation of antipsychotic medication with an NSAID.
2. Patients included had a diagnosis of a schizophrenia spectrum disorder (schizophrenia, schizophreniform disorder, or schizoaffective disorder) according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*[27] (*DSM-III*, *DSM-III-R*, *DSM-IV*, *DSM-IV-TR*, or *ICD*-9 or *-10*).
3. Studies reported sufficient information to compute common effect size statistics—ie, means and standard deviations; exact *P*, *t*, or *z* values (cf Lipsey and Wilson[28]); or corresponding authors could supply these data upon request.

Crossover studies were not excluded in order to obtain as much information as possible.

DATA EXTRACTION

Outcome Measures

The primary outcome measure was the mean change in total score on the Positive and Negative Syndrome Scale (PANSS).[29] Secondary outcome measures included positive and negative symptom subscores of the PANSS or scores on the Scale for the Assessment of Positive Symptoms[30] and the Scale for the Assessment of Negative Symptoms.[31] Patient data of the last observation carried forward were used for analysis when provided. If only data of completers analyses were given, these data were used instead. Where possible, side effects were evaluated by comparing scores on the various side effects scales. Two reviewers independently extracted data from the articles; any disagreements were resolved by consensus.

Statistical Analyses

Standardized differences were calculated from the mean differences (placebo versus augmentation) of the change score (end of treatment minus baseline) mean and standard deviation values. When possible, change scores were used instead of pretreatment and posttreatment scores in order to avoid overestimation of the true effect size because of the pretreatment-posttreatment correlation. When only exact *F* or *P* values for main effect of treatment group (augmentation or placebo) were provided, these data were used. All standardized differences were calculated twice independently from the original articles to check for errors. Standardized differences of studies were pooled in meta-analyses to obtain mean standardized differences for primary and secondary outcome measures. Hedges *g* was used to quantify the mean standardized differences of combined studies using a random model.[32] A homogeneity statistic, I^2, was calculated to test whether the studies could be taken together to share a common population effect size.[33] High heterogeneity (ie, I^2 value of 50% or higher) indicates heterogeneity of the individual study effect sizes,

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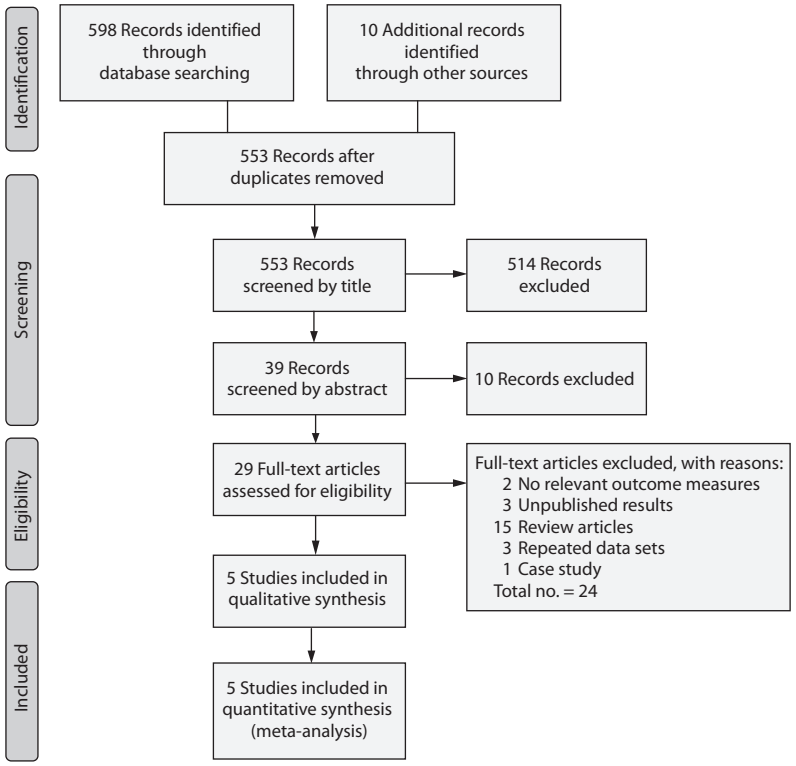
Figure 1. PRISMA Flow Diagram of the Literature Search



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Included Randomized, Double-Blind, Placebo-Controlled Trials on Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Study	Duration of Illness, Mean, y	NSAID, mg/d	Trial Duration	Subjects, n	PANSS Score[a]	Antipsychotic
Müller et al,[34] 2002	5.9	Celecoxib, 400	5 wk	50	Not provided	Risperidone (flexible dose)
Rapaport et al,[35] 2005	≤ 10[b]	Celecoxib, 400	8 wk	35	84.2	Risperidone or olanzapine (fixed dose)
Akhonzadeh et al,[36] 2007	7.9	Celecoxib, 400	8 wk	60	Not provided	Risperidone (fixed dose)
Müller et al,[37] 2010	1.3	Celecoxib, 400	6 wk	49	95.2	Amisulpride (flexible dose)
Laan et al,[38] 2010	3.7	Acetylsalicylic acid, 1000	3 mo	70	72.2	Risperidone, olanzapine, or clozapine (fixed dose)

[a]Values are provided as the mean score of both groups at baseline.
[b]No mean provided.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

which poses a limitation to a reliable interpretation of the results. Values of I^2 between 30% and 50% were considered moderate. Mean standardized differences with a P value smaller than .05 were considered significant. All standardized differences were computed using Comprehensive Meta Analysis Version 2.0.[34]

RESULTS

Inclusions

Using our search criteria, we found 598 reports (Figure 1), of which we could include 5 studies that provided augmentation of NSAIDs to antipsychotic medication in patients with schizophrenia in a double-blind, randomized, placebo-controlled fashion.[35–39] None of the included studies used a crossover design. These studies reported on 264 patients in total. Table 1 lists details of the 5 included studies.

Effect of NSAID on Symptom Severity

All studies provided enough data to calculate standardized differences for the change in symptom severity as measured with the PANSS total scores. These standardized differences were combined to calculate Hedges *g*, signifying the mean standardized difference, as shown in Figure 2.

The mean standardized difference of 0.43 was significant at $P = .02$, indicating a moderate effect. The 95% confidence interval ranged from 0.06 to 0.80. Data were highly heterogeneous, as reflected in an I^2 of 56%.

The effect of NSAID augmentation on the severity of positive symptoms as scored with the positive symptoms section of the PANSS is shown in Figure 3. The mean standardized difference was 0.34, significant at $P = .02$. The 95% confidence interval ranged from 0.05 to 0.64. There was moderate heterogeneity with an I^2 of 32%.

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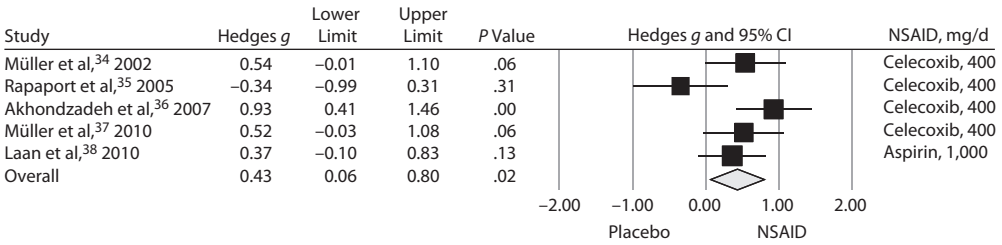
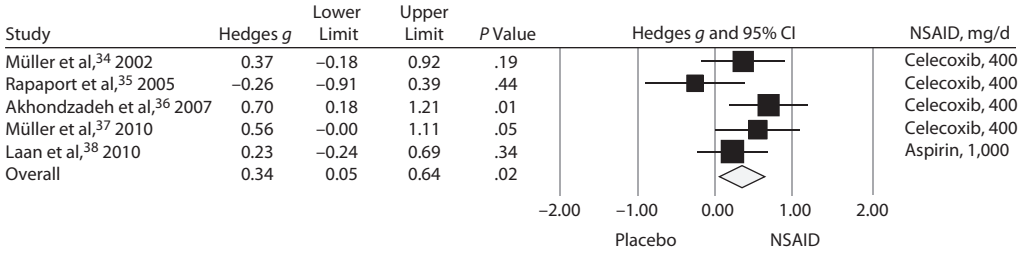
Figure 2. Meta-Analysis of Augmentation of Antipsychotic Therapy With NSAIDs Versus Placebo on PANSS: Total Scores



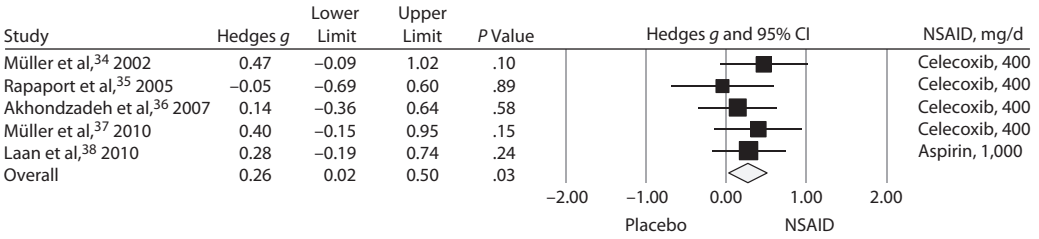
Abbreviations: NSAID = nonsteroidal anti-inflamatory drug, PANSS = Positive and Negative Syndrome Scale.

Figure 3. Meta-Analysis of Augmentation of Antipsychotic Medication With NSAIDs Versus Placebo on PANSS: Positive Scores



Abbreviations: NSAID = nonsteroidal anti-inflamatory drug, PANSS = Positive and Negative Syndrome Scale.

Figure 4. Meta-Analysis of Augmentation of Antipsychotic Medication With NSAIDs Versus Placebo on PANSS: Negative Scores



Abbreviations: NSAID = nonsteroidal anti-inflamatory drug, PANSS = Positive and Negative Syndrome Scale.

The standardized differences for the effect of NSAID augmentation on negative symptoms were combined to yield the mean standardized difference, as shown in Figure 4. The mean standardized difference for the effect of NSAID augmentation on negative symptoms was 0.26, significant at $P = .03$, indicating a small effect size. The 95% confidence interval ranged from 0.02 to 0.50. These data were homogeneous, with an I^2 of 0%.

Side Effects

Most studies excluded patients with peptic ulcers from participation. The patients generally tolerated NSAID augmentation well. Müller et al[35] and Rapaport et al[36] reported no effect of celecoxib augmentation on extrapyramidal side effects nor on safety parameters. Comedication such as biperiden and benzodiazepine was not prescribed more frequently in the celecoxib augmentation group.[35,36] Specific side effects of NSAIDs, such as gastrointestinal problem, were not reported more frequently in the celecoxib group (Müller et al[35]), nor in the acetylsalicylic acid group (Laan et al[39]), as compared to placebo.

DISCUSSION

This article provides a quantitative review of 5 randomized, double-blind, placebo-controlled trials including 264 schizophrenia patients on NSAID augmentation of antipsychotic medication. The meta-analysis demonstrated a moderate effect on total symptom severity, with Hedges $g = 0.43$, but studies were heterogeneous. The mean standardized difference for the severity of positive symptoms was 0.34, again with some heterogeneity among studies. For both total and positive symptom severity, the study by Rapaport et al[36] had findings that deviated from the rest. The reason why the results of this study are less positive than the others remains unclear. Trial duration or baseline clinical status is

not likely to explain the difference, as this study did not differ on these measures (see Table 1). It is possible that the duration of illness was somewhat longer, but the study provided no exact mean duration of illness.

Finally, the mean standardized difference for severity of negative symptoms was 0.26, which is a small but significant effect. For severity of negative symptoms, the data were homogeneous. Side effects were comparable between the augmentation and the placebo groups.

These meta-analyses show that randomized controlled trials (RCTs) on NSAID augmentation for schizophrenia that have been published so far show moderate but significant positive results. Therefore, NSAID augmentation appears to be an avenue that deserves more research, as it may provide a possibility to obtain better symptom reduction.

The main limitation of this meta-analysis is that not more than 5 studies could be included. In addition, those studies did not include very large samples. Therefore, a note of caution may be in place here. When new treatment strategies are introduced, initial reports tend to include relatively small sample sizes and provide favorable results, while small sampled studies with negative findings do not become published.[40] Indeed, in a review article, Müller and Schwarz[12] mention 2 other trials on celecoxib addition without significant effects that had not been published. In time, sample sizes tend to increase and negative findings become published as well. Such trends have led effect sizes to decrease with year of publication.[41] As this is an early meta-analysis of a relatively young field, future studies may show less positive results. Thus, although the possibility of publication bias remains, the positive effect of these initial studies does warrant further research into this direction, as NSAID augmentation could be a potential strategy to increase efficacy of pharmacologic treatment. The negative results of the study by Rapaport et al[36] may indicate that NSAID augmentation is effective only in the early stages of the disease, but more studies in different disease stages are needed to confirm this hypothesis. It is conceivable that NSAIDs are most effective in the prodromal phase, or before disease onset.[39] Therefore, another possible role for NSAID treatment would be as monotherapy in ultra-high–risk groups. Anti-inflammatory drugs could be candidates for neuroprotection,[15,16] given the emerging role of inflammation in the disease process.

We should emphasize that the reviewed RCTs have applied NSAID augmentation for a relatively short time, the longest treatment duration being 12 weeks. Much longer augmentation, for 1 or more years, could potentially yield higher symptom reductions but also carry more risk of side effects. Since NSAIDs are relatively mild and broadly acting anti-inflammatory drugs, further unraveling of the inflammatory pathways putatively involved in schizophrenia could lead to anti-inflammatory treatments that more specifically and effectively affect a dysregulated immune response. Several studies have tried to address the underlying mechanism for the positive effect of NSAID augmentation in schizophrenia. Cyclooxygenase-2 expression was not altered in the hippocampus of schizophrenia patients,[42] and celecoxib treatment did not affect cytokine profiles in peripheral blood mononuclear cells.[43] However, the positive effect of acetylsalicylic acid augmentation was associated with disturbed cytokine profiles in peripheral blood.[39]

Schizophrenia has been associated with a rate of premature mortality that is 2 to 3 times higher than that in the general population.[44] Patients with schizophrenia have a 79% increased risk to die of cardiovascular disorders.[45] By inhibiting platelet aggregation, COX-1 inhibition decreases the risk to cardiovascular events. Cancer is another source of increased mortality in schizophrenia patients.[44] Long-term treatment with acetylsalicylic acid was recently demonstrated to reduce cancer mortality, even at relative low dose.[46] Therefore, acetylsalicylic acid augmentation might reduce morbidity as well as mortality in schizophrenia patients.

Interestingly, the effect size on symptom reduction for augmentation using acetylsalicylic acid, which is a COX-1 and COX-2 inhibitor, was not superior to that of celecoxib, a selective COX-2 inhibitor. Side effects and additional beneficial effects may therefore direct the choice between those 2 classes of NSAIDs in the future. While acetylsalicylic acid may have the additional benefit of cardioprotection, celecoxib has relatively few side effects,[47] which might lead to improved compliance over acetylsalicylic acid.

In summary, we found provisional evidence from 5 RCTs reporting on 264 patients that NSAID augmentation has a moderate beneficial effect on total symptom severity as well as on positive symptoms in schizophrenia and a small effect on negative symptoms in schizophrenia. Although the efficacy of new therapeutic options tends to be overestimated at early stages of research, further investigations into this direction, especially with longer treatment duration, seems warranted.

Drug names: biperiden (Akineton), celecoxib (Celebrex), clozapine (FazaClo, Clozaril, and others), diclofenac (Zipsor, Cambia, and others), lithium (Lithobid and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

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