Adjuvant Aspirin Therapy Reduces Symptoms of Schizophrenia Spectrum Disorders: Results From a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: Inflammatory processes may play a role in the pathophysiology of schizophrenia. The aim of this study was to determine the efficacy of adjuvant treatment with aspirin (acetylsalicylic acid) in schizophrenia spectrum disorders.

Method: This randomized, double-blind, placebo-controlled study was conducted between May 2004 and August 2007. Seventy antipsychotic-treated inpatients and outpatients from 10 psychiatric hospitals in The Netherlands with a *DSM-IV*–diagnosed schizophrenia spectrum disorder were included. Patients were randomized to adjuvant treatment with aspirin 1000 mg/d or placebo. During a 3-month follow-up, psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS). Other assessments included cognitive tests and immune function. The primary efficacy outcome was the change in total PANSS score. Secondary outcomes were changes in the PANSS subscales and cognitive test results.

Results: Mixed-effect models showed a 4.86-point (95% CI, 0.91 to 8.80) and 1.57-point (95% CI, 0.06 to 3.07) larger decrease in the aspirin group compared to the placebo group on the total and positive PANSS score, respectively. Similar but not statistically significant results were observed for the other PANSS subscale scores. Treatment efficacy on total PANSS score was substantially larger in patients with the more altered immune function ($P = .018$). Aspirin did not significantly affect cognitive function. No substantial side effects were recorded.

Conclusion: Aspirin given as adjuvant therapy to regular antipsychotic treatment reduces the symptoms of schizophrenia spectrum disorders. The reduction is more pronounced in those with the more altered immune function. Inflammation may constitute a potential new target for antipsychotic drug development.

Trial Registration: controlled-trials.com Identifier: ISRCTN27745631

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Current antipsychotic drug treatment focuses on blockade of the dopamine and serotonin receptors.[1] Although this treatment is effective in a large number of patients with schizophrenia, still around two-thirds of cases will have at least 1 relapse, and for each relapse, 1 in 6 will not remit from that episode.[2] In addition, present antipsychotic drugs are still associated with several adverse effects[1] and have not been shown to prevent cognitive decline in schizophrenia.[3] Indeed, the urgent need for discovering new, safe, and effective drugs for chronic schizophrenia was emphasized in a recent editorial.[4] Consequently, there is ample interest in pathophysiologic mechanisms other than those involving the dopamine or serotonin receptor. One of these mechanisms is inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are candidate adjuvant drugs in schizophrenia for at least 2 reasons. First, an evolving body of evidence points to altered immune function, in particular helper T cell (T_H) changes with a relative shift to anti-inflammatory T_H2 cell activity over proinflammatory T_H1 cell activity.[5,6] Nonsteroidal anti-inflammatory drugs may restore this balance by inhibition of prostaglandin E_2 synthesis and regulating anti-inflammatory cytokine production, thereby increasing the T_H1/T_H2 cytokine ratio.[6–8] Second, NSAIDs may ameliorate symptoms through antagonizing dysfunction of the N-methyl-D-aspartate (NMDA) receptor, a key feature of a well-established neurochemical model of schizophrenia.[9,10] This action is possible because prostaglandins are intermediates in the postsynaptic signal transduction cascade of cells with NMDA-type glutamate receptors, and prostaglandins inhibit astrocytic reuptake of glutamate. Both mechanisms potentiate glutamatergic transmission and may underlie the excitotoxic neuronal cell death observed in schizophrenia.[11] As NSAIDs inhibit prostaglandin synthesis, they potentially attenuate both mechanisms.[12,13]

To date, only 3 randomized studies of NSAIDs in schizophrenia have been published, all using the selective

For Clinical Use

- Adjuvant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) helps to reduce the symptoms of schizophrenia spectrum disorders.
- Among the NSAIDs, aspirin has the advantage of having favorable cardiovascular effects compared to cyclooxygenase-2 (COX-2) inhibitors.
- There is no evidence on the long-term effect of aspirin on symptoms of schizophrenia spectrum disorders.

cyclooxygenase-2 (COX-2) inhibitor celecoxib. The first study, conducted by Müller et al[14] in 50 patients treated with risperidone, showed that addition of celecoxib reduced total psychopathology over a 5-week period as compared to placebo. Subsequently, in 35 patients, Rapaport et al[15] did not find an effect after 8 weeks of celecoxib supplementation, while in a similar study, Akhondzadeh et al[16] showed a considerable positive add-on effect in 60 patients. Unfortunately, celecoxib and other COX-2 inhibitors have repeatedly been associated with an elevated cardiovascular risk.[17,18] As cardiovascular disease is a major threat to patients with schizophrenia,[19] the cardioprotective aselective COX inhibitor aspirin (acetylsalicylic acid) is arguably preferable. Furthermore, because aspirin unselectively inhibits both COX-1 and COX-2 enzymes, it potentially has a wider range of action. It is presently unknown whether unselective COX inhibition reduces symptoms of schizophrenia and whether an effect is dependent on immune function. It is also unknown whether COX inhibition improves cognitive functioning in schizophrenia.

In a randomized, double-blind, placebo-controlled trial, we investigated the efficacy of aspirin for reducing symptoms of schizophrenia spectrum disorders over a 3-month period in addition to regular antipsychotic therapy. As the active disease process underlying schizophrenia is thought to be progressive,[20] we expected to see the largest effect in those with the shortest disease duration. Furthermore, the most pronounced effect was anticipated in patients with the lowest T_H1/T_H2 balance because we expected that aspirin would down-regulate anti-inflammatory T_H2 cytokines in favor of proinflammatory T_H1 cytokines.

METHOD

Patients

Inpatients and outpatients from 10 psychiatric hospitals in The Netherlands were eligible for the screening procedure. After receiving a complete explanation of the study, all patients to be screened gave written informed consent. For inclusion, patients had to be between 18 and 55 years of age and be diagnosed with a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, or schizophreniform disorder) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*). In addition, patients had to be at least moderately ill, as determined by a minimal total score of 60 on the Positive and Negative Syndrome Scale (PANSS)[23] with a score of at least 4 on 2 items. Exclusion criteria were illness duration longer than 5 years, contraindications for aspirin or pantoprazole, significant somatic illness, chronic NSAID use, corticosteroid use, pregnancy, or change of type or doses of antipsychotic drugs in the last 2 weeks. Because of slow enrollment, the maximum disease duration of 5 years specified in the original protocol was lengthened to 10 years after inclusion of 26 patients.

The study was approved by the medical ethics review board of the University Medical Center Utrecht, The Netherlands.

Procedures

The study procedures have been described earlier in detail.[21] In brief, we performed a randomized, double-blind, placebo-controlled add-on trial. Patients showing greater than 80% compliance during a 2-week placebo run-in entered the 3-month double-blind treatment period and were randomized 1:1 to either aspirin 1000 mg or identical-appearing placebo daily. As stratification on prognostic factors is known to increase statistical power in relatively small trials,[22] patients were randomized in strata of psychiatric center (referral or nonreferral) and relative T_H1/T_H2 cytokine activity, the latter defined by the median interferon-γ (IFN-γ)/interleukin-4 (IL-4) ratio. For gastric protection, all patients received pantoprazole 40 mg daily.

At each visit, a PANSS interview was performed to assess psychopathology. The PANSS is a well-established and reliable scale for the assessment of severity of symptoms of schizophrenia.[23] Change in total PANSS score from baseline to follow-up was the primary outcome, and changes on the positive, negative, and general psychopathology PANSS subscales were secondary outcomes.

During baseline and final visits, patients underwent the following cognitive tests: the Rey Auditory Verbal Learning Test[24] assessing memory, the HQ Continuous Performance Test[25] measuring attention, the Purdue Pegboard Test[26] quantifying fine locomotor skills, and the Trail Making Test[27] assessing psychomotor skills. Changes in these tests were additional secondary outcomes. At baseline and months 2 and 3, a blood sample was taken for

immunologic measurements. To determine the T-cell cytokines IL-4 and IFN-γ, the blood samples were stimulated with anti-CD2/28.[28] For the monocyte cytokines IL-12 and IL-6, the blood samples were stimulated with lipopolysaccharide and recombinant IFN-γ.[28] Cytokines were analyzed using ELISA-assays. All outcome assessments were performed blind to the randomized treatment status.

Patients continued their regular antipsychotic treatment. Psychiatrists were requested to delay any changes in antipsychotic treatment until after the trial. A record was kept of all medication prescribed. At each visit, patients were asked about bleeding and dyspeptic complaints, which were scored on an 8-item questionnaire.[29]

We planned to include 80 patients in this trial, 40 in each arm. If one assumes 10% loss to follow-up, this is sufficient to show intermediate or larger effect sizes (Cohen $d \geq 0.67$) with an α of .05 and power $(1 - \beta)$ of 0.80. Our sample size agrees with the recommended 40 to 100 patients for drug augmentation studies in schizophrenia.[30]

Statistical Methods

Analyses were performed on an intention-to-treat basis. If a patient dropped out, all outcome measures were assessed within a week. We first examined baseline differences between the randomized groups.

To assess the efficacy of aspirin, we used linear mixed models for fixed and random effects with the scores on the PANSS and the cognitive tests as the dependent variables. Time and group were entered as a continuous and dichotomous independent variable, respectively. The 3-month treatment efficacy of aspirin compared to placebo on each outcome was estimated by entering a group-by-time interaction term. Mixed models are superior for the analysis of longitudinally correlated data with missing values.[31] These models make use of all available data and consequently have optimal statistical power. Dependency of the repeated assessments of the outcome scores was taken into account by including random effects for patients with an unstructured variance-covariance structure. Effect sizes (Cohen *d*) were calculated based on the coefficients for the group-by-slope interaction term from the mixed models and the standard deviations of the outcome parameters at baseline. Model-estimated marginal means for each follow-up visit were calculated according to treatment group. Cognitive test results were analyzed after transformation to *z* scores,[32] with higher scores indicating better cognition. Since cognitive tests were performed twice, no random slope could be included in these analyses and only a random intercept was considered. In addition, we performed a more conservative analysis of the PANSS scores, using the last-observation-carried-forward (LOCF) method for those who dropped out during follow-up. In these analyses, differences in score changes between the randomized groups were evaluated using unpaired *t* tests.

To demonstrate modification of treatment efficacy by immune function, we repeated the analyses of the PANSS scores in subgroups of patients defined by the median T_H1/T_H2 cytokine ratio. Multiple imputation techniques using Markov chain Monte Carlo methods were used in this analysis to estimate values for missing immunologic data (n = 24). Multiple imputation is the preferred method of dealing with missing data.[33]

In addition, analyses were repeated for subgroups according to mean disease duration. Variations in treatment efficacy by immune status and illness duration were statistically evaluated by testing the significance of the interaction term of the corresponding continuous variables with treatment group.

Analyses, blind to treatment status, were done using the SAS statistical package (SAS Institute Inc, Cary, North Carolina). The 2-sided level of significance was set at .05. Means with corresponding 95% confidence intervals (CIs) are given where appropriate.

RESULTS

Eighty-five patients treated with antipsychotics were included in the run-in period (Figure 1). Of those 85 patients, 70 were eligible and were randomly assigned. Baseline characteristics are displayed in Table 1. In the placebo group, the proportion of males was somewhat higher, the duration of illness slightly shorter, and the proportion of those treated with clozapine slightly higher. Other baseline characteristics showed no material differences. Notably, the scores on the total PANSS and PANSS subscales were equally distributed among the randomized groups. Twelve patients (17%), 6 in each group, did not complete follow-up. In the placebo group, 5 lacked motivation, and 1 was referred to a nonparticipating hospital. In the aspirin group, 3 lacked motivation, and 3 stopped because of clinically insignificant gastrointestinal complaints. The average compliance from randomization to last follow-up, as estimated by pill count, was 91% in the aspirin group and 89% in the placebo group. Patients were included from May 2004 to May 2007. Follow-up ended in August 2007.

The group-specific model-estimated marginal means of the PANSS scores at each follow-up visit are illustrated in Figure 2. It shows that decreases in all PANSS subscales with time were more pronounced in the aspirin group than in the placebo group, most so for the total PANSS score. Table 2 shows the mean change in the PANSS scores from baseline to last follow-up (LOCF) according to treatment group and estimates of treatment efficacy. Mixed models demonstrated larger mean decreases in the aspirin group compared to the placebo group and statistically significant differences for the total PANSS score (4.86 [95% CI, 0.91 to 8.80]) and the positive PANSS score (1.57 [95% CI, 0.06 to 3.07]). The differences in the total and positive PANSS scores were of medium size. Also, decreases in the negative and general PANSS subscale scores during follow-up were substantially larger in the aspirin group than in the placebo

Figure 1. Flow of Antipsychotic-Treated Patients Through the Trial

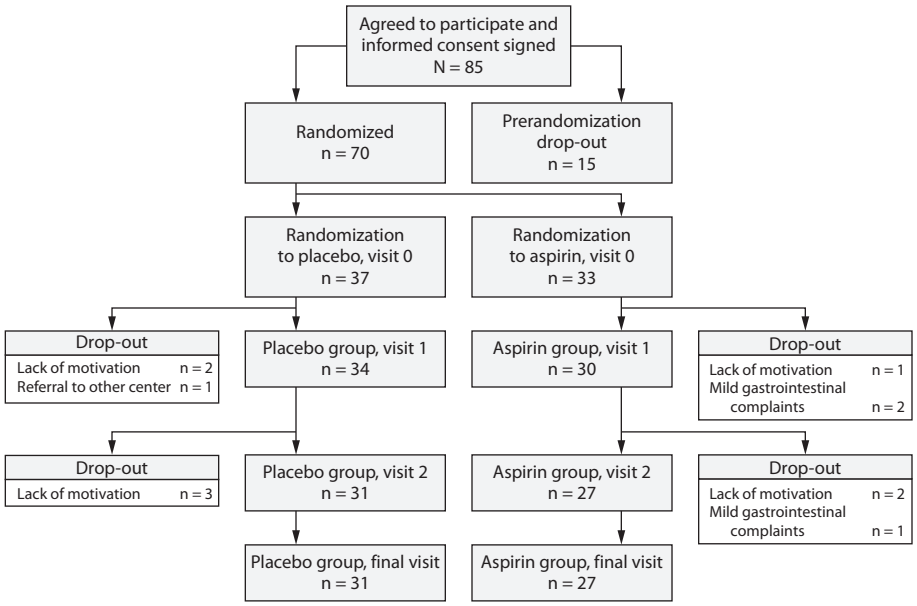


Table 1. Baseline Characteristics of Patients Treated With Antipsychotics (N = 70)

Variable	Placebo, n = 37 (53%)	Aspirin, n = 33 (47%)
Male gender, n (%)	33 (89)	25 (76)
Age, mean ± SD, y	30.6 ± 9.2	31.6 ± 8.9
Duration of illness, mean ± SD, y	3.4 ± 2.5	4.1 ± 3.0
Comedication, n (%)		
Olanzapine	7 (19)	10 (30)
Clozapine	11 (30)	5 (15)
Risperidone	9 (24)	7 (21)
DDD of antipsychotic drugs,[a] mean ± SD	1.04 ± 0.67	0.93 ± 0.62
Adherence during run-in, %	96.6	96.9
PANSS scores, mean ± SD		
Total	73.1 ± 10.3	71.1 ± 10.6
Positive	17.6 ± 3.7	16.5 ± 4.2
Negative	18.8 ± 5.2	18.4 ± 4.4
General	36.6 ± 5.5	36.3 ± 5.7
Cognitive tests, mean ± SD		
Rey Auditory Verbal Learning Test	19.2 ± 6.9	20.5 ± 7.8
HQ Continuous Performance Test	91.6 ± 10.6	85.3 ± 21.3
Purdue Pegboard Test	45.1 ± 6.4	45.4 ± 8.7
Trail Making Test	91.6 ± 45.1	82.1 ± 38.0
Blood sample taken, n (%)	24 (65)	22 (67)
T_H1/T_H2 ratio, mean ± SD	302.1 ± 268.8	290.2 ± 260.2

[a]WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2010. Available at: http://www.whocc.no/atcddd. Accessed March 17, 2010.
Abbreviations: DDD = defined daily dose, PANSS = Positive and Negative Syndrome Scale, T_H = helper T cell.

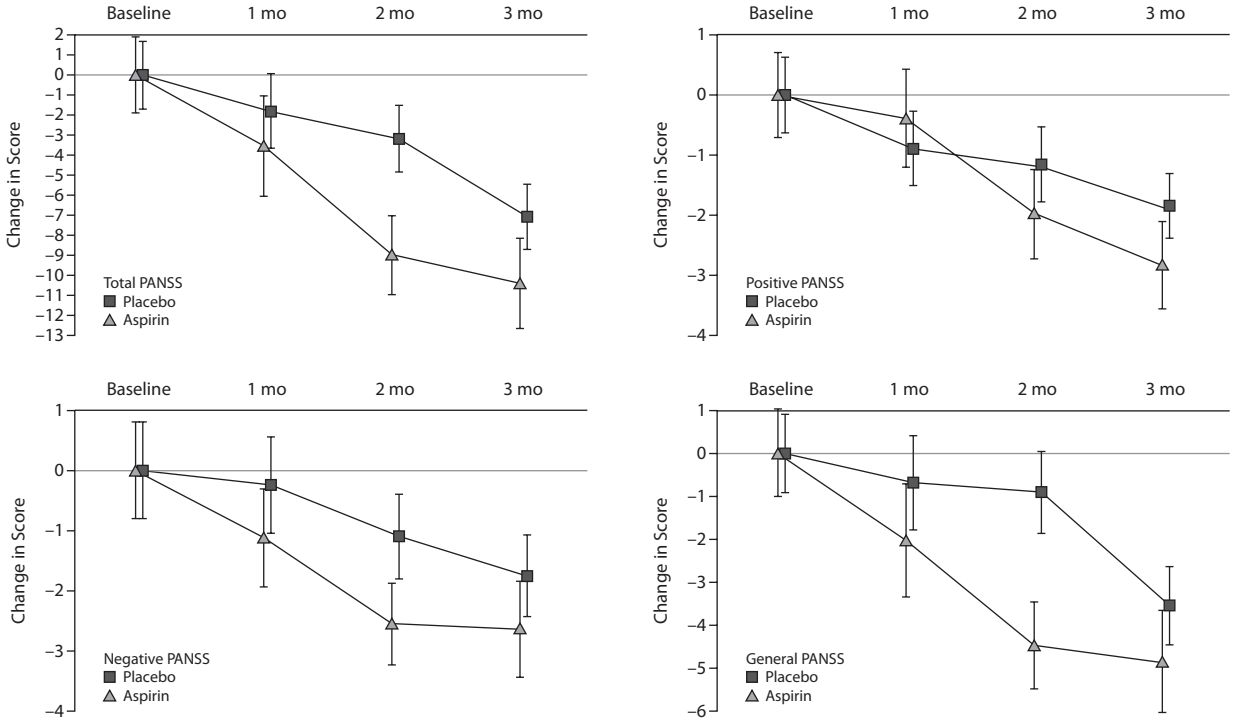
group, but these differences were small and statistically not significant. Group differences in mean changes using the LOCF approach showed the same pattern for all PANSS subscales, but according to the conservative *t* test-based CIs, these differences were not statistically significant.

Adjustment for clozapine use, by including it as a confounding variable in the multivariate mixed model, did not materially alter the results. The treatment efficacy on the total PANSS score from the mixed model changed to 4.77 (95% CI, 8.73 to 0.83). Clozapine use was therefore not included in the final analyses. An additional analysis including the stratification factors as covariates did not materially alter the efficacy estimates.

Aspirin borderline significantly increased T_H1/T_H2 cell cytokine production during follow-up ($P = .05$). Treatment efficacy for total PANSS was 7.47 (95% CI, 1.97 to 12.98) in the lowest T_H1/T_H2 cell cytokine balance, ie, highest anti-inflammatory cytokine production group, and 2.39 (95% CI, −3.50 to 8.28) in the group with the highest T_H1/T_H2 cytokine ratio, ie, those with the lowest anti-inflammatory cytokine production. This difference in treatment efficacy was statistically significant ($P = .018$). For the PANSS subscales, similar trends of larger treatment efficacy with lower T_H1/T_H2 activity were observed, but none of them were statistically significant. The separate immune values (IL-4, IL-10, and IFN-γ) did not substantially modify treatment efficacy. When analyzed in subgroups delineated by the mean disease duration (3.7 years), treatment efficacy on total PANSS score was 6.90 (95% CI, 1.80 to 11.99) in the group with the shortest duration and 3.63 (95% CI, −2.50 to 9.75) in the group with the longest disease duration. This difference was not statistically significant ($P = .66$).

Aspirin treatment did not significantly affect the results of any of the cognitive tests, and the effects were small and inconsistent (Table 3). Five serious adverse events were registered during the trial, none of them gastrointestinal. Two patients, 1 from the placebo group and 1 from the aspirin group, attempted suicide. One patient was admitted to a closed ward before randomization because of relapse of

Figure 2. Model-Estimated Marginal Means of Positive and Negative Syndrome Scale (PANSS) Total and Subscale Scores Relative to Baseline Values According to Treatment Group and Follow-Up Visit[a]



[a]Error bars indicate standard errors of the means.

Table 2. Change in the Positive and Negative Syndrome Scale (PANSS) Scores From Baseline to Last Follow-Up According to Treatment Group and Estimates of Treatment Efficacy

Variable	Total PANSS	Positive PANSS	Negative PANSS	General PANSS
Placebo group mean ± SD[a]	−5.46 ± 11.23	−1.32 ± 3.67	−1.51 ± 4.30	−2.62 ± 6.20
Aspirin group mean ± SD[a]	−9.27 ± 9.11	−2.24 ± 4.29	−2.58 ± 3.16	−4.46 ± 5.36
Group difference mean (95% CI)[b]	3.81 (−1.10 to 8.73)	0.92 (−0.98 to 2.82)	1.06 (−0.76 to 1.88)	1.83 (−0.95 to 4.61)
3-month treatment efficacy estimate, mean (95% CI)[c]	4.86 (0.91 to 8.80)	1.57 (0.06 to 3.07)	1.24 (−0.31 to 2.79)	2.17 (−0.15 to 4.48)
Effect size (Cohen *d*)[c]	0.47	0.39	0.26	0.39

[a]Using last observation carried forward.
[b]From unpaired *t* tests.
[c]From linear mixed model.

Table 3. Cognitive Tests' Treatment Effect Estimates for Linear Mixed Models With 95% CIs[a]

Treatment Effect	Total	Rey Auditory Verbal Learning Test	HQ Continuous Performance Test	Purdue Pegboard Test	Trail Making Test
Treatment effect, *z* score	0.06	0.18	−0.24	0.00	0.12
Treatment effect, 95% CI	(−0.59 to 0.71)	(−0.14 to 0.50)	(−0.62 to 0.14)	(−0.29 to 0.28)	(−0.23 to 0.48)

[a]For all treatment effects, a positive value indicates an improvement in cognitive functioning in the aspirin relative to the placebo group.

psychotic complaints. One patient from the aspirin group and 1 from the placebo group were admitted to a closed ward because of suicidal thoughts, and 1 patient from the placebo group was admitted to an open ward for daily routine restructuring. No dyspeptic complaints needing medical attention were observed. In the placebo group, 11 patients reported "moderate" dyspeptic complaints, 2 reported "serious" dyspeptic complaints, and no patients reported "very serious" dyspeptic complaints, as evaluated by the dyspepsia questionnaire.[29] In the aspirin group, these numbers were 10, 0, and 1, respectively.

During follow-up, 8 patients from the placebo arm and 5 patients from the aspirin arm changed dose or type of antipsychotics with no systematic differences between groups.

No trend of change to or from a specific antipsychotic drug was observed.

DISCUSSION

In this randomized, placebo-controlled, double-blind trial, addition of aspirin to regular antipsychotic treatment substantially reduced symptoms of schizophrenia spectrum disorders. The strongest and most statistically significant effects were observed on the total and positive (sub)scales of the PANSS. Over the 3-month treatment period, the effect size (Cohen *d*) for the total PANSS scale was approximately 0.5, which is considered a medium effect.[34] This effect size agrees with those observed in previous double-blind, placebo-controlled, parallel, add-on antipsychotic augmentation drug trials in schizophrenia.[30] The effect was most marked in those with the lowest T_H1/T_H2 cytokine balance, suggesting that the reduction of psychotic symptoms is larger among those with a relatively high anti-inflammatory cytokine production, as hypothesized. An effect on cognitive function could not be demonstrated.

To appreciate these findings, some aspects of the study need to be addressed. Although groups were well balanced at baseline, the placebo group included more patients taking clozapine than the aspirin group. This imbalance needs, however, not to have affected prognosis. Although clozapine is often prescribed to more therapy-resistant patients, it is also particularly effective in reducing symptoms in these patients.[35] Moreover, when treatment estimates were adjusted for clozapine use, conclusions did not change.

By including 70 patients rather than the planned 80, the study was slightly underpowered for the primary outcome. However, our sample size calculation was based on the most conservative analysis, ie, the unpaired *t* test of a group difference in the change in total PANSS score. As mixed models have substantially more statistical power,[31] we consider the sample size of the present study still adequate.

Although the present trial on anti-inflammatory drugs efficacy in schizophrenia spectrum disorders had the largest sample size and longest time of follow-up to date, the effects on the negative, general, and possibly cognitive symptoms are inconclusive. Perhaps a larger trial or a trial with longer follow-up could show unequivocal effects on these outcomes as well. Finally, the results do not address the long-term effects of aspirin. Yet, it is, in our view, very unlikely that the beneficial effects we observed from aspirin would remain limited to 3 months. To our knowledge, there are no published trials investigating the effect of a COX inhibitor on cognitive symptoms of schizophrenia spectrum disorders. Therefore, we are unable to compare our cognitive findings to other similar trials.

Studies by Müller et al[14] and Akhondzadeh et al[16] demonstrated significant effects of the NSAID celecoxib on schizophrenic symptoms. Both studies showed a more marked effect of celecoxib than we observed for aspirin. Patients in these studies underwent an antipsychotic wash-out period of respectively 2 and 7 days prior to administration of risperidone and randomization to either placebo or celecoxib. Patients in these studies therefore showed a considerably higher baseline PANSS score than those in our study. For this reason, there was more to gain in the celecoxib studies from the start, and comparison with our study is difficult.

Our findings on aspirin agree with those of Müller et al[36] in that the effect of the NSAID was most pronounced in those patients with the shortest disease duration, although the interaction term for treatment by disease duration was statistically not significant. Indeed, the smaller overall treatment effect in our trial could be explained by Müller's study comprising more patients with short disease duration.

The larger symptom amelioration we observed in those patients with the lowest T_H1/T_H2 ratio was in accordance with our expectation and supports the hypothesis on the pathophysiologic role of dysbalance in pro- and anti-inflammation in schizophrenia.[6] The role of inflammatory cytokines was further suggested in a recent case-control study in which several intronic haplotypes and missense variants in cytokine receptors were found to be associated with schizophrenia.[37] Nevertheless, aspirin may also reduce symptoms through other mechanisms, eg, by antagonizing dysfunction of the NMDA receptor.[9] We cannot exclude the possibility that aspirin exerts its effect in interaction with antipsychotics. Yet, we view this as unlikely because the mechanism of action of aspirin is essentially different from that of antipsychotics, the latter antagonizing dopamine and serotonin receptors. In our view, the efficacy of aspirin as a single treatment cannot be estimated, since it would be unethical to randomly assign patients with schizophrenia spectrum disorders to placebo alone.

No significant differences in changes in cognition were observed between groups. However, as cognitive functioning appears to be stable over time in schizophrenia[38] and current antipsychotics hardly improve these functions,[3] it may be difficult to actually alter these functions during a relatively short period.

Given the considerable effect of aspirin over 3 months, the refractory character of symptoms while on antipsychotics alone, and the safety of aspirin, this drug might become a useful addition to regular treatment.

Celecoxib and other COX-2 inhibitors have been associated with an elevated cardiovascular risk.[17,18] Because aspirin has well-established cardioprotective effects[39] and patients with schizophrenia already have a markedly elevated cardiovascular risk,[19] aspirin is, in our view, a better choice than a COX-2 inhibitor.

Chronic use of high doses of NSAIDs is associated with gastric side effects such as bleeding. However, these side effects can be effectively countered by concomitant use of proton pump inhibitors. At least 2 randomized, controlled trials have demonstrated that mucosal gastric injury from

aspirin at similar or higher doses than those used in our study can be abolished by adjuvant use of the proton pump inhibitor omeprazole.[40,41] We therefore take the position that the gastrointestinal bleeding risk of high-dose aspirin is acceptable, provided that a proton pump inhibitor is additionally prescribed. This was supported by the fact that no serious gastric or bleeding events requiring medical attention were observed in our trial.

The largest effect of adjuvant aspirin was demonstrated for those with the most altered immune balance and the shorter disease durations, although the latter was not statistically significant. These findings could mean that, if confirmed in future studies, anti-inflammatory treatment in schizophrenia might be particularly recommended for patients with recent onset of disease and the more disturbed immune functions.

Due to the limited follow-up time in our study, we cannot make firm recommendations for the optimal duration of aspirin treatment. Nevertheless, on the basis of our findings, a duration of at least 3 months seems reasonable. Further research will need to address this issue.

Despite its limitations, the results of this 3-month randomized trial indicate that aspirin in combination with antipsychotic drugs is a potentially useful therapy for schizophrenia spectrum disorders.

Drug names: celecoxib (Celebrex), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), pantoprazole (Protonix and others), risperidone (Risperdal and others).
Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, celecoxib is not approved by the US Food and Drug Administration for the treatment of schizophrenia.
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