Review: non-steroidal anti-inflammatory drugs may reduce schizophrenia symptom severity in the short term when added to antipsychotics

QUESTION

Question: Are non-steroidal anti-inflammatory drugs (NSAIDs) effective at reducing schizophrenia symptom severity when given in addition to antipsychotic medication?
Outcomes: *Primary outcome:* mean change in total score on the Positive and Negative Syndrome Scale (PANSS). *Secondary outcomes:* positive and negative symptom subscores of the PANSS or scores on the Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms.

METHODS

Design: Systematic review and meta-analysis.
Data sources: MEDLINE, EMBASE, the National Institutes of Health website (ClinicalTrials.gov), Cochrane Schizophrenia Group entries in PsiTri and the Cochrane Database of Systematic Reviews were searched (search date not reported) with no year or language restrictions. Reference lists of retrieved articles and additional relevant review articles were hand searched for additional studies.
Study selection and analysis: Double blind randomised controlled trials (RCTs) that augmented antipsychotic medication with an NSAID for patients with schizophrenia spectrum disorder (defined according to the Diagnostic and Statistical Manual of Mental Disorders criteria) were included. For inclusion studies also had to report sufficient information to calculate effect sizes, or study authors had to be able to supply this data on request. Crossover studies were included. Two reviewers independently extracted information from studies with disagreements resolved by consensus. For the meta-analysis, standardised differences were calculated from the mean differences of the change scores from baseline. The standardised differences were then pooled to calculate Hedges *g*. Heterogeneity between studies was assessed using I^2. High heterogeneity was regarded as an I^2 of 50% or above, and moderate heterogeneity was considered as an I^2 between 30% and 50%.

MAIN RESULTS

Five small RCTs met the inclusion criteria (n=264). Four studies used the NSAID celecoxib (400 mg daily) and one used acetylsalicylic acid (1000 mg daily). The studies lasted between 5 weeks and 3 months. NSAIDs were found to have a moderate effect on reducing total symptom severity compared with placebo with an overall mean effect size of 0.43 (95% CI 0.06 to 0.8, p=0.02). Substantial heterogeneity was identified across studies for this estimate (I^2=56%). There was a moderate effect of NSAIDs on positive symptom severity with a mean overall effect size 0.34 (95% CI 0.05 to 0.64, p=0.02). Moderate heterogeneity was identified across studies for this estimate (I^2=32%). For severity of negative symptoms, the overall mean effect size was 0.26 (95% CI 0.02 to 0.50, p=0.03) indicating a small but significant effect and homogenous data (I^2=0%).

CONCLUSIONS

There is preliminary evidence to suggest that use of an NSAID to augment antipsychotic drugs has a moderate beneficial effect on symptom severity for people with schizophrenia in the short term.

NOTES

For both total and positive symptom severity, heterogeneity appeared to be due to one study which had less positive results than the other studies. The authors noted the possibility of publication bias, as another review had mentioned two studies of NSAID augmentation that had found no significant benefit that had not been published.

ABSTRACTED FROM

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COMMENTARY

Immune dysfunction and inflammation have been described in patients with schizophrenia. For example, findings from our group suggested that markers for inflammation, including elevated blood levels of C reactive protein[1] and white blood cell count[2] are associated with negative symptoms in patients with schizophrenia. Furthermore, nuclear factor κB activation may play a pivotal role in schizophrenia through interaction with cytokines.[3]

This meta-analysis was based on five double-blind, randomised, placebo-controlled trials with a total number of 264 patients. Four studies examined celecoxib and one used aspirin. The studies included were heterogeneous in terms of the chronicity of illness and the choice of study drugs; in addition, the study time periods were relatively short (up to three months). Despite these limitations, the analysis provided further evidence suggesting that non-steroidal anti-inflammatory drug augmentation treatment could be beneficial in reducing schizophrenia symptoms.

Celecoxib and other cyclooxygenase-2 (COX-2) inhibitors are associated with an elevated risk of cardiovascular disease, which is a serious comorbid medical condition in patients with schizophrenia. The cardioprotective non-selective COX inhibitor aspirin is arguably preferable. However, it is well established that aspirin, especially when used in a relatively high dosage, is associated with a significant risk for gastrointestinal bleeding.

Continued effort should be made to identify potential anti-inflammatory agents with a better side effect profile, and also examine the longer term effect of anti-inflammatory treatment in schizophrenia. Future studies focusing on the early stage of schizophrenia are particularly valuable because pharmacological treatment during the early phase could improve the course and overall prognosis of the disease.

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Competing interests None.

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