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Published in:
Journal of Clinical Psychopharmacology

DOI:
[10.1097/JCP.0b013e3181a44575](https://doi.org/10.1097/JCP.0b013e3181a44575)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Laan, W., Smeets, H., de Wit, N. J., Kahn, R. S., Grobbee, D. E., & Burger, H. (2009). Glucocorticosteroids Associated With a Decreased Risk of Psychosis. *Journal of Clinical Psychopharmacology*, 29(3), 288-290. <https://doi.org/10.1097/JCP.0b013e3181a44575>

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Glucocorticosteroids Associated With a Decreased Risk of Psychosis

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Abstract: The hypothesis that chronic inflammation may play a role in psychosis receives increasing attention. In this study, we aim to investigate whether the use of steroidal anti-inflammatory drugs is associated with a decreased risk of psychosis.

A longitudinal nested case-control study was performed investigating the association of glucocorticosteroid (GCS) consumption with a new diagnosis of a psychotic disorder. Significantly reduced odds ratios of 0.52 (95% confidence interval, 0.36–0.75) were found for GCS in men only (odds ratio in women, 0.84 [95% confidence interval, 0.590–1.20]). Similar risk reductions were present for the inhaled and systemic GCSs. A dose-response relationship was present. Our finding of an inverse relation between GCS consumption and new psychotic episodes may promote further research into inflammation in schizophrenia.

Key Words: schizophrenia, psychosis, inflammation, glucocorticosteroids

(*J Clin Psychopharmacol* 2009;29: 288–290)

Current treatment in psychosis focuses on the antagonism of the dopaminergic and serotonergic receptors.¹ As many cases relapse,² there is ample interest in alternative mechanisms in psychosis, one of them being inflammation. We previously showed a protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of psychosis in male subjects.³ Moreover, 2 randomized clinical trials showed a beneficial effect of the NSAID celecoxib on schizophrenic complaints.^{4,5} There is also a direct evidence of inflammation in schizophrenia, as elevated levels of several inflammatory cytokines in patients with schizophrenia are reported.⁶ Furthermore, serum cortisol levels have shown to be elevated in schizophrenia,⁷ indicating inflammation and stress.⁸

Because glucocorticosteroids (GCSs) are potent inhibitors of inflammation, we expect these drugs to be associated with a decreased risk of psychosis. In this study, we aim to investigate this association longitudinally by linking pharmacy records from a health insurance company to data obtained from a psychiatric case register.

METHODS

We performed a longitudinal nested case-control study on the association between psychosis and GCSs. This was done by linking the database of the Psychiatric Case Register Middle Netherlands (PCR-MN) covering the midwest part of the province of Utrecht, The Netherlands, to that of a regional health insurance company. Among other characteristics, the case register recorded personal level admissions to psychiatric wards and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses made from 1999 onward. The present analysis used data collected from 60,000 persons with at least one contact with the psychiatric healthcare system. The Agis Health Insurance Company (Agis) recorded all medications used by its participants except for medications prescribed to inpatients.

In this study, we defined a new psychosis as a person in the case register with a psychotic episode in the years 2002 to 2005, where no such episode was recorded before. A psychotic episode was defined as a recorded *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis with codes 295.1 to 295.7, 293.81, 293.82, 297.1, 297.3, 298.8, or 298.9.

By linking these databases a complete representation of the medication use for the cases was made.

The control group was randomly sampled from the same source population, that is, those insured at Agis. To optimize statistical power, 4 controls were matched to each case regarding age and sex.

Data were analyzed for the index year, defined as the 365 days preceding the first psychotic episode for the cases and the same days for their matched controls.

Because social withdrawal is common during the prodrome of schizophrenia,¹ patients might be less likely to visit a physician and therefore to be prescribed any medication, including GCS. We attempted to account for this possibility by adjusting our analyses for the total defined daily doses (DDD) of all medication used during the index year.

Because schizophrenia is progressive,⁹ we expected to see the largest effect in the youngest persons. Consequently, a subgroup with age below 33 years (youngest age quartile) was analyzed separately. Further analyses were repeated by sex.

Glucocorticosteroid use was defined as any prescription of a GCS during the index year. A dose-response relation was examined in quartiles of GCS use. Because it is estimated that 40% of the inhaled GCSs are absorbed into the blood stream, these drugs also have shown systemic effects, although less pronounced than orally administered GCS.¹⁰ Consequently, they were analyzed separately.

To estimate the sensitivity of the hypothesized relation to the time span between GCS intake and psychosis, we also considered the effect of GCS consumption taken in the year preceding the index year.

Analyses were performed with SAS 9.1 (SAS Institute Inc, Cary, NC). Odds ratios (ORs), 95% confidence intervals, and *P* values were calculated using conditional logistic regression

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ISSN: 0271-0749

DOI: 10.1097/JCP.0b013e3181a44575

TABLE 1. Odds Ratios (95% Confidence Interval) of a Psychotic Episode for Corticosteroid Use and *P* value for Interaction by Sex and by Age Subgroup

	Systemic GCS	Inhaled GCS	Any GCS	Youngest Subgroup, Any GCS
Men	0.51 (0.31–0.84)	0.58 (0.36–0.94)	0.52 (0.36–0.75)	0.41 (0.17–0.98)
Women	1.07 (0.68–1.67)	0.68 (0.41–1.11)	0.84 (0.59–1.20)	0.63 (0.21–1.88)
Total	0.74 (0.53–1.03)	0.62 (0.44–0.88)	0.65 (0.51–0.85)	0.48 (0.24–0.95)
<i>P</i> for interaction by sex	0.03	0.65	0.06	0.49
<i>P</i> for interaction by age group	0.47	0.55	0.42	—

analysis while controlling for age and sex. Differences in associations across subgroups of age and sex were tested as statistical interactions in regression models.

RESULTS

Of 3872 cases from the PCR-MN case register with a psychotic episode between 2002 and 2005 and no such episode recorded before, 47.8% ($n = 1849$) could be linked to the insurance database. Cases that could and could not be linked did not materially differ on demographic characteristics. Cases were matched to 7396 controls. Subsequently, 486 cases (26.3%) and 2779 (37.6%) controls were excluded because they were not insured at Agis during the complete index year, leaving 1363 cases (median age, 41.8 years; 56.8% men) and 4617 controls (median age, 41.8 years; 61.3% men) for analysis.

The prevalence of systemic, inhaled, and any GCS used in the control population were 4.6%, 4.7%, and 5.3%, respectively, during the index years. In the cases, these percentages were 3.3, 2.9, and 4.2, respectively. Case patients were prescribed medication approximately twice the quantity of other drugs during the index year compared with the control population (1279 vs 609 DDDs).

Compared with those not using these medications, the ORs of psychosis were significantly lower in men using systemic, inhaled, or any GCS (Table 1). For women, a similar OR was observed for inhaled GCS, although this was not statistically significant. The lower ORs for psychosis associated with GCS use in the youngest subgroups seemed to be slightly more pronounced than those in the total group, but the interaction by age group was not significant ($P = 0.42$). A significant *P* value for interaction by sex is present for the systemic GCS only. Total DDD prescriptions did not confound the associations. For example, the OR for any GCS changed from 0.65 (0.51–0.85) to 0.61 (0.47–0.79). When the GCS prescriptions during the year preceding the index year only were analyzed, all ORs were closer to unity, with neither of them being statistically significant.

An increasing amount of any GCS use was associated with lower ORs of psychosis ($P = 0.017$) when analyzed on a per DDD basis. Compared with no GCS consumption, the first, second, third, and fourth quartiles showed ORs of 0.73 (0.46–1.17), 0.70 (0.41–1.20), 0.70 (0.45–1.10), and 0.47 (0.26–0.84), respectively.

DISCUSSION

This study shows that GCSs are associated with a substantially lower risk of psychosis in men, with ORs around 0.50. The associations were similar for systemic and inhaled GCSs. In women, the magnitude of the associations was smaller, and they were not statistically significant. This sex difference was statistically significant. Decreasing risks were observed with increasing dose of GCS.

Although our results suggest a beneficial effect of GCSs, the use of GCSs has also been associated with psychiatric adverse effects including psychosis.¹¹ Taken together, a complex relationship between exogenous GCSs and mental functioning is likely.

Besides a direct effect of GCS on the risk of psychosis, the observed association could have resulted from an association between a disease for which these drugs are prescribed and psychosis. However, in the absence of evidence for an inverse relation of psychosis with asthma, Crohn disorder, or other indications for GCS, this explanation seems unlikely.

Although our study provides evidence for a pathophysiological role of inflammation in psychosis, its nature remains unknown. We previously demonstrated an inverse relation between the use of NSAIDs in men and subsequent psychosis.³ The present study using a more reliable assessment of psychosis confirms a favorable effect of the inhibition of inflammation, again in men only. The sex specificity of the inverse relation might be due to the postulated protective effect of estrogen in female subjects.¹²

Because the total prescription volume of all drugs was not confounding the observed relation, we consider it unlikely that it was the result of case patients being less likely to be prescribed any medication.

Approximately half of the case patients with a new psychotic episode had a positive match with a person in the Agis database. This proportion was anticipated in view of an approximately 50% overlap between those living in the PCR-MN region and those insured at Agis. Bias from incomplete linkage seems unlikely because cases that were and were not linked to Agis did not substantially differ.

The findings from this study may promote further research into inflammation in schizophrenia.

AUTHOR DISCLOSURE INFORMATION

All authors declare that they have no competing interests. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take public responsibility for the integrity of the data and the accuracy of the data analysis.

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