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, 0.59–1.20]). Similar risk reductions were present for the inhaled and systemic GCs. 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

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Current treatment in psychosis focuses on the antagonism of the dopaminergic and serotonergic receptors. As many cases relapse, 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. Moreover, 2 randomized clinical trials showed a beneficial effect of the NSAID celecoxib on schizophrenic complaints. There is also a direct evidence of inflammation in schizophrenia, as elevated levels of several inflammatory cytokines in patients with schizophrenia are reported. Furthermore, serum cortisol levels have shown to be elevated in schizophrenia, indicating inflammation and stress.

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 GCs. 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, 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 (DDDs) of all medication used during the index year.

Because schizophrenia is progressive, 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 GCs are absorbed into the blood stream, these drugs also have shown systemic effects, although less pronounced than orally administered GCs. 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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analysis while controlling for age and sex. Differences in asso-
ciations across subgroups of age and sex were tested as statisti-
cal interactions in regression models.

**RESULTS**

Of 3872 cases from the PCR-MN case register with a psy-
chotic episode between 2002 and 2005 and no such episode
recorded before, 47.8% (n = 1849) could be linked to the in-
urance 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 med-
ication 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, in-
haled, or any GCS (Table 1). For women, a similar OR was ob-
served 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 ex-
ample, 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 sub-
stantially 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 GCSs.

Although our results suggest a beneficial effect of GCSs,
the use of GCSs has also been associated with psychiatric ad-
verse effects including psychosis. 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
indicators for GCS, this explanation seems unlikely.

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

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 psy-
chotic episode had a positive match with a person in the Agis
database. This proportion was anticipated in view of an approx-
imately 50% overlap between those living in the PCR-MN re-
igion 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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