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Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: A meta-analysis ☆

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ABSTRACT

Objective: The use of dopaminergic antagonist antipsychotics is associated with hyperprolactinemia, but some studies have found increased prolactin concentrations in antipsychotic-naive patients with schizophrenia and related disorders. We conducted a systematic review and meta-analysis of studies of prolactin in antipsychotic-naïve patient with these disorders (PRISMA No. CRD42015016337).
Data sources: PubMed (Medline), PsycInfo, and Web of Science were searched for articles from 1950 to the present in English.
Study selection: Seven studies of males (N = 141 for patients, N = 191 for control subjects) and five studies of females (N = 67 and N = 116) met criteria for inclusion: data on blood prolactin concentrations for both control subjects and antipsychotic-naive patients with schizophrenia or a related disorder, with data available separately for males and females.
Data extraction: Data was extracted from the papers by one author and independently verified by a second.
Results: The mean effect size for males was 1.02 (95% CI, 0.77, 1.26; $p < 0.001$) and 0.43 for females (95% CI 0.11, 0.76; $p < 0.01$). Meta-regression analyses for age, smoking, body mass index (BMI), year of publication, and cortisol were not significant. Funnel plots did not suggest the presence of a publication bias.
Conclusions: Our meta-analyses found significantly increased prolactin levels in both male and female antipsychotic-naïve patients with schizophrenia and related disorders. The small number of studies and limited matching for potentially confounding variables in some of the studies were limitations of this analysis. Prolonged hyperprolactinemia may lead to sexual dysfunction and osteoporosis, and some antipsychotics cause additional elevation of prolactin concentrations.

1. Introduction

Prolactin, a polypeptide hormone secreted by lactotroph cells of the anterior pituitary gland, is involved in many biological functions including reproduction, pregnancy and lactation, and growth and development. Gender, sexual activity, childbirth, stress, smoking, and some medications are among the factors that can affect blood prolactin concentrations (Ranabir and Reetu, 2011; Ohta et al., 2011). The inhibitory effect of dopamine is important in the control of prolactin release (Engler et al., 2009), and blood concentrations of prolactin are increased by many current antipsychotics, which act as antagonists or partial agonists of dopamine receptors. Hyperprolactinemia is associated with a variety of adverse effects: amenorrhea and galactorrhea, an acceleration of osteoporosis in women, and a lack of libido and erectile dysfunction in men, and may increase the risk of breast cancer in women (Rajkumar, 2014).

Some recent studies have found increased prolactin concentrations in antipsychotic-naïve psychotic patients (Albayrak et al., 2014; Aston et al., 2010; Garcia-Rizo et al., 2012; Lee and Kim, 2006; Segal et al., 2007; Song et al., 2014), while other studies of previously treated but drug-free patients reported concentrations that are normal or lower

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than those of control subjects (Chatterjee, 1998; Kleinman et al., 1982; Kuruvilla et al., 1986). While this area has been reviewed before (Rajkumar, 2014), there has not been a systematic, quantitative review of these studies. We performed a systematic review and meta-analysis of blood prolactin concentrations in male and female antipsychotic-naïve patients with schizophrenia and related disorders compared to control subjects.

2. Materials and methods

2.1. Protocol registration

The analysis was registered under the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (Moher et al., 2009; PRISMA registration number CRD42015016337).

2.2. Study selection

Studies of prolactin and antipsychotic-naïve patients with schizophrenia and related disorders were systematically searched using PubMed (Medline), PsycInfo, and Web of Science in February 2016. The primary search strategy was (schizophrenia or psychosis) and (untreated or naïve or antipsychotic naïve or antipsychotic free) and (prolactin). Our searches included articles from 1950 to the present in English. This combination of terms yielded 124 articles from PubMed, 46 from PsycInfo and 121 from Web of Science, and the three lists were examined for duplications. From these sources, as well as manual review of reference lists, we identified 188 potential studies for inclusion.

The *inclusion* criteria for the meta-analysis were: 1) a study of blood prolactin concentrations that included both control subjects and antipsychotic-naive patients with a psychotic disorder in the schizophrenia spectrum (delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder), and 2) a maximum cumulative (lifetime) antipsychotic exposure of 1 week, and no antipsychotic use in the 30 days prior to the study. *Exclusion* criteria were: 1) the study did not present means and standard deviations (SDs) for prolactin data separated by gender, and this data could not be obtained by attempting to contact the study authors, 2) the study was a second publication with a significant overlap in study population, and the new data could not be clearly distinguished, and 3) patients or control subjects were known to have a pituitary microadenoma.

After independent searches, review of study methods by two authors (AMG and LGB), and attempts to contact authors as noted, 7 studies met the inclusion criteria; 4 were cross-sectional studies and 3 were longitudinal (we included baseline data from the longitudinal studies as the patients had been treated by the time of follow-up). The two reviewers agreed on study inclusion and exclusion. The number of studies excluded and the reason for exclusion are shown in Fig. 1.

Only one study had any subjects with a diagnosis of schizoaffective disorder (Rao et al., 1990). The total number of patients in that study was 20, while the total number of patients in all the studies was 208. We were not able to obtain the number of schizoaffective patients or the prolactin values from only the schizophrenic patients from that study.

2.3. Data extraction and statistics

One author (LGB) extracted all data, which was independently verified by another (AMG). Sample sizes and prolactin values (mean and standard deviation [SD]) were extracted separately for males and females. Data was available for males from 7 studies, and for females from 5 studies. Effect size (ES) estimates (Hedges' g) were calculated for prolactin concentration. Random effects, pooled ES estimates and 95% confidence intervals were calculated using the method of DerSimonian and Laird (1986). Separate meta-analyses were performed for prolactin in male and female subjects; p-values were considered statistically significant at the $p = 0.05$ level. The statistical analyses were performed in the Stata 13.1 software program.

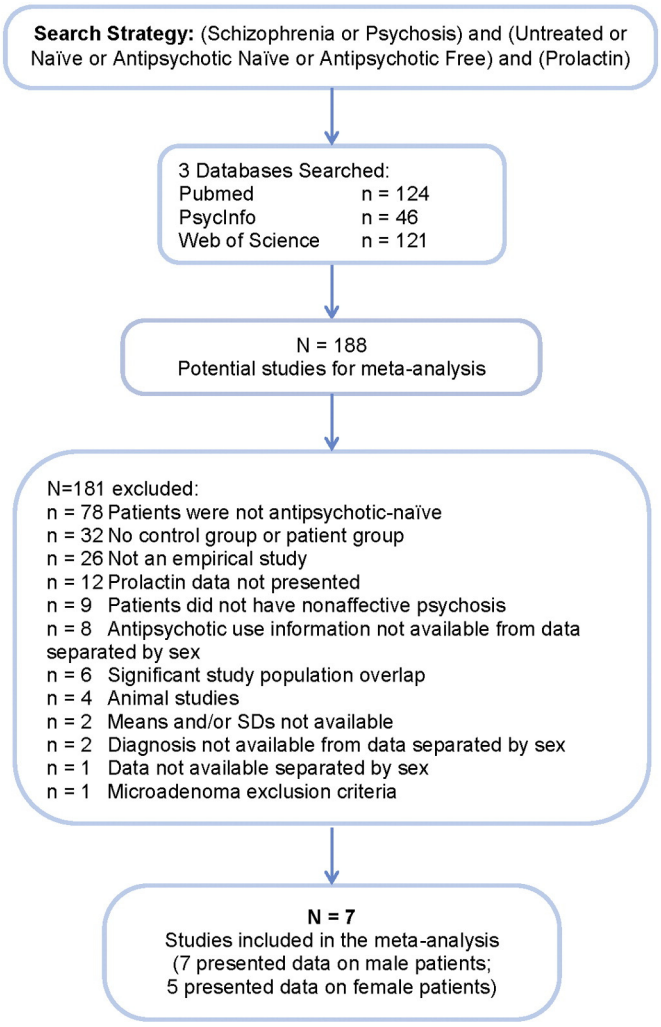

Fig. 1. Study selection.

We examined heterogeneity in the ES estimates using chi-square (Cochran, 1950). We also performed a sensitivity analysis separately for males and females. The sensitivity analyses were done by removing one study at a time and repeating the meta-analysis for that parameter to examine the impact on the ES estimate (Higgins and Green, 2011). To assess possible publication bias we examined a funnel plot separately for males and females.

3. Results

3.1. Males

Prolactin was significantly increased in male patients versus male control subjects [ES = 1.02, 95% CI 0.77, 1.26; $p < 0.001$; Fig. 2]. The heterogeneity was significant with all of the studies included in the analysis (I-squared = 81%, $p < 0.001$). Heterogeneity remained significant after removal of each of the studies individually, including the most divergent study (I-squared = 73%, $p < 0.01$; Bicikova et al., 2011); the ES also remained significant ($p < 0.001$) with each of the studies removed individually ($p < 0.001$ for each of these comparisons). When the two most

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