

Risperidone and Risk of Gynecomastia in Young Men

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Abstract

Objective: The purpose of this study was to quantify the risk of gynecomastia with risperidone in adolescent and young adult males.

Methods: We created a cohort of males 15–25 years of age from the IMS LifeLink database, and conducted a case–control study within the cohort by identifying all new cases of gynecomastia. For each case, 10 controls were selected and matched to the cases by age, follow-up, and calendar times (cases and controls had the same follow up time and cohort entry date). Rate ratios (RR) for current use of risperidone were computed adjusting for potential confounding variables.

Results: First diagnosis of gynecomastia was made based on International Classification of Diseases, 9th revision (ICD-9) for gynecomastia. There were 401,924 males ages 15–25 in the primary cohort. There were 1556 cases of gynecomastia and 15,560 corresponding controls. Current users of risperidone had approximately four times the risk of developing gynecomastia than non-users (RR = 3.91, 95% CI = 2.01–7.62). When the analysis was stratified to children and adolescents (≤ 18 years of age) taking risperidone, the risk of gynecomastia was five times higher than for non-users (RR = 5.44, 95% CI = 1.50–19.74).

Conclusions: Risperidone is associated with an increase with the risk of gynecomastia in adolescent and young adult males.

Introduction

RISPERIDONE IS a commonly used psychotropic medication prescribed for a wide range of mental health conditions including schizophrenia and bipolar and autism spectrum disorders. Risperidone is a strong antagonist for dopamine-2 (D2) receptors (Markowitz et al. 1999; Leucht et al. 2013). D2 blockade has been shown to increase prolactin release (Calarge et al. 2009), leading to gynecomastia in boys and men (Markowitz et al. 1999). Some studies have examined the risk of gynecomastia with risperidone (Findling et al. 2004; Roke et al. 2012). Most have been small, uncontrolled studies (Roke et al. 2012). Five prospective clinical trials of risperidone included 489 boys 5–15 years followed for up to 55 weeks. Incidence of gynecomastia was reported as 3.7%, based on the entire primary analysis population of males and females; however, the appropriate incidence with only males as the denominator would be 4.5% (22/489) (Findling et al. 2004). The population-based health examination survey in the United States found the prevalence of gynecomastia to be 2.6% of 608 15-year-olds, 2.9% of 553 16-year-olds, and 1.6% of 486 17-year-olds (Harlan et al. 1979). We have previously shown, using a nested case–control study, an increase in the risk of gynecomastia with risperidone in geriatric men, but no epidemiologic study has quantified this risk in adolescent boys or younger men (Etminan et al. 2014). Gynecomastia carries a high psychological burden in young men (Kinsella et al. 2012). Given the availability of other antipsychotics with a lower propensity for gynecomastia, the

risk of gynecomastia in adolescent boys and younger men must be quantified so that clinicians can make a more informed decision when considering prescribing risperidone to this patient population.

Methods

Data sources and cohort description

We used the IMS Lifenlink™ health claims database as the main data source for this study. Lifenlink is a comprehensive health claims database that captures health claims information for ~150,000,000 de-identified Americans with fully adjudicated medical claims (LifeLink Health Plan Claims Database 2010). The database represents a balanced demographic sample of all geographic regions in the United States.

The original cohort for this study was composed of all subjects 15–60 years of age randomly selected from the entire Lifenlink™ database for the period from January 2006 to March 2014, who had at least 1 year of prescription drug data. The database captures all prescription drugs, physician visits (through International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]). From the original cohort, we created a subcohort defined as dispensing of any prescription drug in males 15–25 years of age. Cohort members were followed to the first diagnosis of gynecomastia or termination of a health claim (physician visit, hospitalization or dispensing of a prescription drug).

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Study design

We used a nested case-control study to quantify the risk of gynecomastia with risperidone in young men. This design has been shown to be efficient in quantifying rare adverse events with an exposure that changes over time, such as prescription drugs. A density based-sampling approach was used to select 10 controls for each case. Controls were matched to cases by age, calendar time (month of cohort entry for both cases and controls) and follow-up time (cases and controls had the same duration of follow-up). This approach has shown to generate an odds ratio (OR) that closely approximates a rate ratio (RR) from a cohort study (Essebag et al. 2003).

Case and control definition

Gynecomastia cases were identified as the first physician visit for the following conditions: Hypertrophy of the breast (611.1), breast atrophy (611.4), breast mass (611.72), breast ptosis (611.81). The index date was deemed the first date for any of the aforementioned physician visits. A risk set of all controls who had the same length of follow-up, cohort entry time, and age as the case was created. From the risk set, we randomly selected 10 controls and matched them to the index date of the case.

Exposure definition

Information on all oral and injectable forms of risperidone prescriptions before the index date was obtained. We defined *any use* of risperidone as the use of at least one prescription in the year before the index date. Subjects who were in the *any use* category and whose last prescription and its day supply overlapped with the index date were deemed as *current users*. All RRs for the study drug were compared with non-users of a study drug.

Ethics approval

The study was approved by the University of British Columbia behavioral ethic board.

Results

Among a cohort of 401,924 subjects, there were 1556 cases and 15,560 corresponding controls (Table 1). The average age for the cases and controls was 21 (Table 1) with an average follow up of 1.60 years (± 1.56). The average time from the last risperidone prescription to the diagnosis of gynecomastia was 62 days (± 73). Any use of risperidone was associated with three times higher risk of gynecomastia compared with non-users (RR = 3.25, 95% CI = 1.98–5.33) whereas this risk was approximately four times higher among current users of risperidone (RR = 3.91, 95% CI = 2.01–7.62) (Table 2). When we stratified our analysis to children (≤ 18 years) taking

TABLE 1. CHARACTERISTICS OF CASES AND CONTROLS

	Cases	Controls
Number	1,556	15,560
Age in years (mean \pm SD)	21.07 \pm 2.54	21.11 \pm 2.56
Follow-up in years (mean \pm SD)	1.60 \pm 1.56	1.60 \pm 1.56
Gynecomastia confounders 1 year before cohort entry		
Cimetidine use	0.06	0.06
Ketoconazole use	1.74	1.03
Klinefelter syndrome	0.26	0.06
Testicular cancer	0.00	0.02

TABLE 2. CRUDE AND ADJUSTED RATE RATIOS OF RISPERIDONE AND ARIPIPRAZOLE

Study drug	Cases	Controls	Crude RR	ARR and 95% CI
<i>n</i>	1556	15,560	—	—
No use of risperidone	1535	15,494	1.00	1.00 1.00
Any use	21	66	3.23	3.25 1.98-5.33
Current use	12	31	3.90	3.91 2.01-7.62
Past use	9	35	2.62	2.64 1.26-5.52

RR, rate ratio; ARR, adjusted rate ratio.

risperidone, the risk of gynecomastia was five times higher than for non-users (RR = 5.44, 95% CI = 1.50–19.74).

Discussion

This is the first large epidemiologic study that demonstrates an increase in the risk of gynecomastia with risperidone in adolescent and young adult males. Gynecomastia is an adverse event that may occur with many antipsychotics (Szarfman et al. 2006), depending upon their propensity for blocking D2 receptors. Risperidone is the strongest blocker of D2 receptors (Markowitz et al. 1999), and, in turn, prolactin release, and is a potential cause of gynecomastia. Recently, Leucht et al. (2013) conducted a meta-analysis involving 12 randomized trials totalling 43,049 subjects. Different adverse events for all antipsychotics were pooled across the trials. Risperidone and its active metabolite paliperidone had the highest risk of prolactin increase compared with other antipsychotics (RR = 1.23 [95% CI = 1.06–1.40], RR = 1.30 [95% CI = 1.08–1.51], respectively) although hyperprolactinemia does not always correlate with gynecomastia (Roke et al. 2012). The prospective trial by Findling et al. (2003) that examined the risk of gynecomastia with risperidone in 489 boys, found an incidence of 4.5%, but risk assessment could not be assigned in the absence of a control group of non-users of risperidone.

In a clinical study of 489 boys 5–15 years of age, gynecomastia was observed in 4.5% of the subjects (Findling et al. 2003). Another study used the United States Food and Drug Administration (FDA)'s adverse drug reaction reporting database and examined the proportion of reported events for all prolactin-related adverse events including gynecomastia for atypical antipsychotics compared with the same events for all other prescription drugs. In this study, risperidone had the highest reported case incidence for gynecomastia (RR = 2.7, 95% CI = 2.3–3.1) compared with olanzapine (RR = 0.80, 95% CI = 0.6–1.2) and quetiapine (RR = 0.7, 95% CI = 0.3–1.3) (Szarfman et al. 2006).

Our study has several strengths and limitations. The large sample size in our study allowed for quantification of this rare adverse event. The age range of our study population also controlled for confounding by puberty, as we only included adolescent and young adult males (Marshall and Tanner 1970). Gynecomastia cases were ascertained through ICD-9 CM codes. As with all pharmacoepidemiology studies that utilized health claims databases, we only had information on prescription dispensings and could not verify prescription intake by study subjects. We did not have information on prolactin levels, although studies have shown that the risk of gynecomastia is not always correlated with prolactin levels (Kleinberg et al. 1999). Finally, the small number of exposed cases did not allow for examination of a dose response relation between the study drugs and gynecomastia.

Conclusions

Our study showed a strong association between risperidone use and gynecomastia in young adult males. Clinicians who are prescribing risperidone to this demographic may need to consider this adverse event in their therapeutic decision-making process.

Clinical Significance

Our study results suggest an increase in the risk of gynecomastia in adolescent and young adult males. Given that this condition carries a high psychological burden, clinicians might want to consider prescribing antipsychotics with a lower propensity for gynecomastia to young or adolescent males.

Disclosures

Dr. Etminan has been a consultant on risperidone and gynecomastia litigation. The other authors have nothing to disclose.

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