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Original Article

Antipsychotic Medication in Children and Adolescents: A Descriptive Review of the Effects on Prolactin Level and Associated Side Effects

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Abstract

Objective: This review reports the incidence of hyperprolactinemia, its relationship with genotype, and prolactin-related side effects in children and adolescents treated with antipsychotics.

Method: Data on prolactin levels were available for haloperidol, pimozide, risperidone, olanzapine, clozapine, ziprasidone, and quetiapine. Twenty-nine studies were selected after a literature search in the English Medline/Embase/Psychinfo/EBM databases (1965 to August, 2008).

Results: All antipsychotics, except clozapine, ziprasidone, and quetiapine, increase the mean prolactin level from baseline values of 8.0 ng/mL to 25–28 ng/mL after 4 weeks of treatment (reference range 0–15 ng/mL). The most and best data are available for risperidone. Five risperidone studies ($n = 577$) show an increase of prolactin level from 7.8 ng/mL to 17.7 ng/mL after 1 year of treatment, and two risperidone studies ($n = 60$) show an increase from 7.4 ng/mL to 24.9 ng/mL after 2 years of treatment. Aggregated over all antipsychotics, prolactin-related side effects, such as gynecomastia, galactorrhea, irregular menses, and sexual dysfunction, were reported by 4.8% of the children and adolescents. No data are available on bone mineral density in relation to antipsychotic-induced hyperprolactinemia in children and adolescents. Prolactin levels may be influenced by the genetic differences that influence prolactin metabolism and D2 dopamine receptor density.

Conclusion: Persistent elevation of prolactin for periods up to 2 years has been documented in maintenance treatment with risperidone. Very limited long-term data of pimozide, olanzapine, and quetiapine prohibit drawing conclusions for these antipsychotics. Systematic long-term observational studies, including specific questionnaires as well as physical examination, are needed to investigate prolactin-related side effects of antipsychotic treatment in children and adolescents.

Introduction

THE NUMBER OF PRESCRIPTIONS for antipsychotics to treat children and adolescents with both schizophrenia and other psychotic conditions and with nonpsychotic conditions such as autism spectrum disorders, disruptive behavioral disorders, tic disorders, and behavioral problems associated with mental retardation has increased significantly (Schirm et al. 2001; Zito et al. 2003; Cooper et al. 2004; Correll 2008a). This increase can be attributed largely to the introduction of new antipsychotics with fewer extrapyramidal side effects (Correll et al. 2004), greater efficacy for broader target symptoms (Buckley 2001), and possibly improved compliance (Dolder et al. 2002; Menzin et al. 2003).

In particular, low dosages of risperidone and olanzapine appear to be effective in the treatment of behavioral problems in autism spectrum disorders (Malone et al. 2002; McCracken et al. 2002), conduct disorders (Findling et al. 2000; Aman et al. 2002; Snyder et al. 2002), and acute psychotic symptoms (Arango et al. 2004; Sikich et al. 2004). However, risperidone and olanzapine may have potential long-term side effects. There is increasing awareness of the impact of long-term side effects of antipsychotics in children and adolescents. Because these children and adolescents are in a continuous state of

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development and maturation, they may be more vulnerable to these side effects than adults. The understanding of the complex interaction of these drugs with neurochemical systems, such as pre- and postsynaptic receptor systems and binding to transporter sites or to secondary or tertiary messenger systems in the brain, would explain these potential long-term side effects. Many of these interactions have not yet been clarified. Our knowledge about these medication–brain interactions has been quite limited.

One side effect of antipsychotics is hyperprolactinemia. The secretion of prolactin by the anterior pituitary gland is inhibited by the tuberoinfundibular dopamine system. Hyperprolactinemia is caused by blocking of the D2 dopamine receptor at the anterior lobe of the pituitary gland, resulting in high prolactin levels. This may cause a decline in gonadotropins and a decrease in estrogen- and testosterone concentrations (Halbreich et al. 2003; Haddad and Wieck 2004). Strong D2 dopamine-receptor blocking antipsychotics, such as amisulpiride, cause frequent hyperprolactinemia in adults (Paparrigopoulos et al. 2007), but data in children and adolescents are not available.

The tuberoinfundibular D2 dopamine receptors are known to react more sensitively and faster to the D2-blocking effects of antipsychotics than the D2 receptors in the mesolimbic and mesocortical dopamine systems (Langer et al. 1977; Halbreich et al. 2003). Prolactin is secreted intermittently, which may result in variation between single samples.

Hyperprolactinemia associated with antipsychotic medication may be more prevalent in children and adolescents than in adults because the density of D2 dopamine receptors in the central nervous system is higher in children and adolescents than in adults (Seeman et al. 1987). Hyperprolactinemia may cause gynecomastia, galactorrhea, irregular menses, and amenorrhea in women, sexual dysfunction (decreased sexual desire, erectile/ejaculatory dysfunction, orgasmic dysfunction, vaginal dryness), and reduced fertility (Bobes et al. 2003; Knegtering 2003; Knegtering et al. 2004; Knegtering et al. 2006; Costa et al. 2007; Nakonezny et al. 2007). The induced hypogonadotropic hypogonadism together with low estrogen and testosterone levels may cause low bone mineral density and osteoporosis (Abraham et al. 2003a; Abraham et al. 2003b; Meaney et al. 2004; Hugenholtz 2005; O'Keane and Meaney 2005; Becker and Epperson 2006; Howard et al. 2007). This effect may be even more marked in adolescents because puberty is an important period for the attainment of peak bone mass (Davies et al. 2005).

Serum prolactin levels vary in time and between individuals. There is reasonable consensus regarding the upper limit of the normal range (hyperprolactinemia) being 500 mU/L in both men and women at adult age, which is approximately 15 ng/mL (Bevan 1991). However, some authors suggest an upper limit of 25 ng/mL for adults (Lenton et al. 1979; Marken et al. 1992). Studies in children and adolescents show slightly lower values (Gässler et al. 2000). There is individual variation in the plasma prolactin level at which symptoms appear. Some symptoms, for example galactorrhea, reflect raised prolactin acting on target tissue, whereas other symptoms, such as amenorrhea, are due to secondary hypogonadism. Amenorrhea usually appears at prolactin levels above 60 ng/mL (Haddad and Wieck 2004).

A previous review on antipsychotic-induced hyperprolactinemia in children and adolescents was published in 2004 and included 14 studies (Pappagallo and Silva 2004). Eighteen studies were published hereafter and are include in our review. Pappagallo and Silva (2004) reported an overall incidence of 20%. Our review reports an incidence of, respectively, 90%, 80%, 62%, 31%, and 12% with haloperidol, pimozide, risperidone, olanzapine, and quetiapine during treatment. Recent reviews on hyperprolactinemia did not include children and adolescents and were not comparable to the incidence numbers of this review (Byerly et al. 2007). The objective of this review was to evaluate the incidence and severity of antipsychotic-induced hyperprolactinaemia, the incidence of prolactin-related side effects, and the role of genetic vulnerability factors among children ≤12 years of age) and adolescents (12–18 years of age).

Methods

A search was conducted in the English Medline/Embase/Psychinfo/EBM databases (1965 to August, 2008) using the following terms: "risperidone," "olanzapine," "pimozide," "clozapine," "quetiapine," "haloperidol," "aripiprazole," "amisulpiride," "ziprasidone," "(a)typical antipsychotics," "adverse effects," "side effects," "hyperprolactinemia," "bone mineral density," "children," "adolescents," "prolactinoma," "osteoporosis," "prolactin," "hypogonadism," "bone density," "sex hormone," "androgen," "estrogen," "metabolic," "endocrine," "puberty disorders," "delayed puberty," "polymorphism," "genetic," and "puberty." The terms were used alone or in various combinations. Data appearing only in abstracts of scientific meetings or in journals written in languages other than English were excluded. The results were based upon studies carried out with children and adolescents. All reports (except single-case reports) with a duration longer than 3 weeks were included. Data about prolactin levels were available for haloperidol, pimozide, risperidone, olanzapine, clozapine, ziprasidone, and quetiapine. Antipsychotics were converted to chlorpromazine-equivalent doses (CPZ) (Woods 2003).

Results

Data

Twenty-nine publications with study durations longer than 3 weeks were found: risperidone ($n = 20$), olanzapine ($n = 7$), quetiapine ($n = 5$), haloperidol ($n = 4$), pimozide ($n = 3$), clozapine ($n = 2$), and ziprasidone ($n = 1$). These studies varied in terms of the duration of treatment, which ranged from 3.3 to 106 weeks. Six papers were based on the same clinical sample and study (Wudarsky et al. 1999; Alfaro et al. 2002; Aman et al. 2002; Findling and McNamara 2004; Croonenberghs et al. 2005; Reyes et al. 2006). The samples included children with disruptive disorders, conduct disorder, oppositional defiant disorder, autism, schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorders not otherwise specified (NOS), Tourette's syndrome, bipolar affective disorder with psychotic features, depression with psychotic features, and children with normal and subnormal intelligence. The design of the studies varied. Seventeen studies had an open-label design, four studies had an observational design (Frazier et al. 1999; Masi et al. 2003; Stevens et al. 2005; Staller 2006), and eight studies were double blind (Sallee et al. 1996; Wudarsky et al. 1999; Snyder et al. 2002;

Alfaro et al. 2002; Aman et al. 2002; Sikich et al. 2004; Hellings et al. 2005; Luby et al. 2006). Seven risperidone studies (Turgay et al. 2002; Findling and McNamara 2004; Croonenberghs et al. 2005; Stevens et al. 2005; Reyes et al. 2006; Staller 2006; Anderson et al. 2007) monitored prolactin for a period of 48–106 weeks. For olanzapine, quetiapine, and pimozide, one long-term study has been performed (Suwa et al. 1984; Staller 2006). Clozapine and ziprasidone were studied for 6 weeks (Alfaro et al. 2002; Malone et al. 2007).

The total number of patients studied for risperidone, olanzapine, quetiapine, haloperidol, pimozide, clozapine, and ziprasidone were 1390, 170, 72, 56, 46, 30, and 12, respectively. The weighted average of the percentage of boys included in the studies ranged from 63 to 82.5%. Ten of the 29 studies used a prospective design with prolactin as the principal outcome variable (Simeon et al. 1979; Sallee et al. 1996; Wudarsky et al. 1999; Masi et al. 2001; Alfaro et al. 2002; Masi et al. 2003; Saito et al. 2004; Hellings et al. 2005; Anderson et al. 2007; Troost et al. 2007). Two studies had no medication-free baseline measurement (Saito et al. 2004; Sikich et al. 2004), and six studies had no prolactin baseline measurement (Hardan et al. 1996; Frazier et al. 1999; McConville et al. 2000; Fegert et al. 2003; Stevens et al. 2005; Anderson et al. 2007). Co-medication was permitted in 19 out of 29 studies. In five studies (Wudarsky et al. 1999; Shaw et al. 2001; Alfaro et al. 2002; Anderson et al. 2007; Dittmann et al. 2008), the use of co-medication was unknown and in six studies co-medication was not allowed (Simeon et al. 1979; Suwa et al. 1984; Sallee et al. 1996; Masi et al. 2001; Masi et al. 2003; Luby et al. 2006). Eleven studies (Frazier et al. 1999; McConville et al. 2000; Shaw et al. 2001; Snyder et al. 2002; Findling and McNamara 2004; Saito et al. 2004; Sikich et al. 2004; Hellings et al. 2005; Stevens et al. 2005; Reyes et al. 2006; Staller 2006) allowed co-medication that can cause modest elevations of prolactin levels such as antidepressants (Molitch 2005) and melatonin (Blaicher et al. 1999) and five studies allowed other co-medication, such as psychostimulants, benzodiazepines, and anticholinergics (Hardan et al. 1996; Aman et al. 2002; Turgay et al. 2002; Croonenberghs et al. 2005; Troost et al. 2007).

Most studies (17) used 0–18 ng/mL for boys and 0–30 ng/mL for girls, but four studies used 0–15 ng/mL for boys and girls (Frazier et al. 1999; Masi et al. 2001; Masi et al. 2003; Stevens et al. 2005), while eight studies did not give a reference value (Suwa et al. 1984; Shaw et al. 2001; Aman et al. 2002; Fegert et al. 2003; Sikich et al. 2004; Luby et al. 2006; Anderson et al. 2007). All the data are summarized in Tables 1–4. The weighted averages were calculated by multiplication of the number of patients and the matching variable of the same study. The amounts of the different studies were added and then divided by the total number of patients. Medication-free prolactin baseline values were missing in two studies, and seven studies had no prolactin baseline value measurement; these studies were left out of the prolactin baseline weighted average calculation.

Prolactin Level

All antipsychotics, except clozapine, ziprasidone, and quetiapine, increased the prolactin level from baseline values of 8.0 ng/mL to 25–28 ng/mL after 4–8 weeks of treatment. Eight short-term risperidone studies ($n = 739$) with an average duration of 4.6 weeks showed an increase of prolactin from 7.9 ng/mL at baseline to 27.6 ng/mL at end point (Masi et al. 2001; Aman et al. 2002; Snyder et al. 2002; Turgay et al. 2002; Fegert et al. 2003; Croonenberghs et al. 2005; Anderson et al. 2007; Troost et al. 2007). Further treatment showed a decrease to 17.7 ng/mL (male 15.8 ng/mL and female 20.8 ng/mL) after 1 year of treatment (Turgay et al. 2002; Findling and McNamara 2004; Croonenberghs et al. 2005; Stevens et al. 2005; Anderson et al. 2007) and to 24.9 ng/mL (male 24.6 ng/mL and female 27.6 ng/mL) after 2 years of treatment (Reyes et al. 2006; Staller 2006). Long-term prolactin level was still elevated compared to baseline and compared to reference value after 1 year and 2 years of treatment. A pimozide study ($n = 13$) showed an increase after 1 year of treatment from 12.4 ng/mL to 24.5 ng/mL (Suwa et al. 1984), but one olanzapine study ($n = 7$) showed no increase of prolactin level after 1 year of treatment (Staller 2006). The possibility of drawing conclusions is limited by the small sample size, however. Thus, persistent elevation of prolactin has been clearly documented in the maintenance treatment with risperidone for up to 2 years. As shown in Tables 1–4, the incidence of hyperprolactinaemia during treatment with haloperidol, pimozide, risperidone, olanzapine, and quetiapine was, respectively, 90%, 80%, 62%, 31%, and 12%.

It is not likely that the prolactin elevation is illness related, as comparative populations, namely the one with disruptive disorder, conduct disorder, and oppositional defiant disorder ($n = 1060$) treated with risperidone and the one with autism treated with risperidone ($n = 158$) showed no difference with respect to the severity or incidence of prolactin elevation. It is not possible to draw conclusions about illness-related prolactin elevation for the populations with affective, tic, and psychotic disorders because of their small sample size.

Prolactin-Related Side Effects

Sex hormones

As far as we know, no attention has yet been given on the prolactin-raising effect on sex steroid levels in children or adolescents receiving antipsychotic medication.

Pubertal development

Only two studies with duration of 1 year investigated the association between risperidone and the progression of puberty (Reyes et al. 2006). No effect was found on the progression of Tanner stages after 1 year of follow-up.

Neuroendocrine and sexual side effects

Tables 1–4 show that children and adolescents treated with olanzapine, haloperidol, quetiapine, and risperidone report, respectively, 13.8%, 13.5%, 5.7%, and 5.1% symptoms related to hyperprolactinemia. Most frequently reported are gynecomastia (risperidone 3.0%, olanzapine 6.2%, haloperidol 6.7%) and irregular menses (risperidone 6.2%, haloperidol 15.4%, quetiapine 11.8%). In a prospective study of hyperprolactinemia in children and adolescents, 25% (10/40) reported a decrease in sexual performance, and, in double-blind randomized 8-week trial, 22% of 50 adolescents treated with prolactin-raising atypical antipsychotics reported sexual side effects (Sikich et al. 2004; Saito et al. 2004). Unfortunately, many studies did not report on sexual side effects.

TABLE 1. EFFECT OF RISPERIDONE (N = 1390) ON PROLACTIN LEVEL AND PROLACTIN-RELATED SIDE EFFECTS

Author	n Baseline	n End point	Design	Diagnosis	Duration weeks (SD)	Mean age in years (SD)	% of males	Mean dose mg/day (SD)	CPZ eq. (mg)	Prolactin Baseline ng/mL (SD)	Prolactin End point ng/mL (SD)	Hyperprolactinemia (%)	Total	Gynaeco-mastia	Galactor-rhea	Irregular menses	Sexual disturbance
Fegert et al. (2003)	319	298	OL	ADHD, DBD, S-IQ	4 (0) d	9.6 (0.1)	83	1.6 (0.04)	80	c	21.8	c	5	3.1	0.3	3.8	0.3
Snyder et al. (2002)	53 / m 41 / f 12	47 / c / c	DBPCT	DBD, S-IQ	6 (0)	8.6 (0.3)	77	1.0 (0.06)	50	8.0 (2.7) / m 7 (0.63) / f 11.5 (4.14)	27.8 (3.9) / m 27.1 (3.1) / f 30.4 (5.2)	c	11.3 / c	c	c	c	c / c
Aman et al.†^ (2002)	55 / m 47 / f 8	41 / m 34 / f 7	DBPCT	DBD, S-IQ	6 (0)	8.7 (2.1)	85	1.2 (0.6)	60	7.2 (4.1) / m 6.7 (3.6) / f 9.7 (5.6)	27.1 (21.2) / m 29 (22.3) / f 18.1 (12.6)	13 / c	0 / c	0	0	0	0
Biederman (2005)	16	15	OL	MD, DBD, ADHD	8 (0)	5.3 (0.8)	75	1.4 (0.5)	70	12 (10.4)	47.7 (21.9)	c	0	0	0	0	0
Sikich et al. (2004)	19	10	DBRT	PD, MD	8 (0)	14.6 (2.9)	68	3.3 (1.5)	165	a	37.2 (19.8)	c	21	10.5 / c	5.3 / c	16.7 / c	0 / c
Masi et al. (2001)	25	25	OL	ASD	10 (0)	4.9 (0.8)	88	0.5 (0.2)	25	9.8 (3.9)	25.9 (13.9)	76	c	c	c	c	c
Saito et al. (2004)	21	21	OL	ASD, MD, DBD, PD	11.2 (2.2)	13.4 (3.4)	55	2.2 (2.0)	110	a	46.8 (33.3)	71	23.8 d	c	c	c	c
Troost (2006)	25	15	OL	ASD	24 (0)	8.6 (2.2)	92	1.7 (0.6)	85	7.8 (8)	28.8 (13.6)	76	0 d	0	0	0	0
Frazier et al. (1999)	28	11	RCR	BD	26 (36)	10.4 (3.8)	96	1.7 (1.3)	85	c	32.8 (12.5)	82	7.1	0	3.6 (f)	100	3.6 (m)
Luby et al. (2006)	11	11	DBPCT	ASD	26.1 (0)	4.1 (0.9)	82	1.14 (0.32)	57	8.1 (4.6)	41.5 (18.3)	c	0	0	0	0	0
Hellings et al. (2005)	10	7	DBPCT	ASD, S-IQ	33 (4.2)	12.5 (3.5)	90	1.25 (c)	63	13.2 (8.6)	37.9 (10.4)	100	c	0	0	0	0
Masi et al. (2003)	37	25	PCS	ASD	34.4 (29.6)	4.6 (0.7)	85	0.55 (0.2)	28	13.3 (7.8)	28.4 (22.5)	65	0 d	0	0	0	0
Hardan et al. (1996)	20	20	OL	ASD, S-IQ, DBD	39 (19)	13.4 (2.5)	65	3.0 (2.1)	150	c	c	c	10 (f)	0	10 (f)	14.3	0
Findling and McNamara (2004)	107 / m 86 / f 21	50 / c	OL	S-DBD, S-IQ	48	9 (2.0)	80	1.5 (0.07)	75	7.2 (4.1) / c	15.9 (c) / m15.6 (c) / f16.9 (c)	c	0	0	0	0	0
Turgay et al. (2002)	77 / m 57 / f 20	60 / c / c	OL	DBD, S-IQ	48 (0)	8.7 (0.2)	74	1.4 (0.06)	70	6.5 (c) / m 5.9 / f 8.3	19.3 (c) / m 18.6 / f 21.3	20 / c / c	2.6 / 0	0	0	10 / 0 / 10	0
Anderson et al. (2007)	50	50	OL	ASD	51.4 (8.7)	13.5 (2.8)	100	2.4 (1.6)	120	c	20.3 (9.7)	68	0 d	0	0	0	0
Stevens et al. (2005)	50	50	CSS	PD, BPD, DBD	51.4	13.5 (2.8)	100	2.4 (1.6)	120	c	20.3 (9.7)	68	0	0	0	0	0
Croonenberghs et al. (2005)$	504 / m 419 / f 85	367 / c / c	OL	DBD, S-IQ	52	9.7 (2.5)	83	1.6 (0.03)	80	8.1 (7.3) / m 7.7 (7.1) / f 10.1 (8.1)	17.0 (14.2) / m 16.1 (11.9) / f 21.6 (22.0)	62.9 / c / c	6.4 / c	5.0 / 5.3 / 3.5	0.2 / c / c	7.1 / 0 / 7.1	c / c / c
Reyes et al. (2006)$^	48 / m 42 / f 6	38 / m 33 / f 5	OL	DBD, S-IQ	104	9.9 (2.3)	88	1.83	92	8.0 (8.0) / m 7.7 (8.3) / f 10.1 (5.0)	26.6 (51.5) / m 25.5 (55.1) / f 34.0 (14.0)	c	8.3 / c	6.3 / 9.1	0	20 / 0 / 20	0 / 0
Staller (2006)£	18 £ / m 10 £ / f 8 £	22 / m 19 / f 3	CSS	BD, PD, DBD, ADHD, AD	106.3 (121)	12.7 (2.3)	83	1.5 (1.4) / m 1.5 (1.5) / f 1.8 (1.4)	75 / m 75 / f 90	6.4 (1.5) / m 5.6 (1.4) / f 7.4 (0.94)	22 (1.9) / m 22.9 (1.9) / f 17.0 (0.33)	c / c / c	9.1 d / 0	9.1	0	0 / 0	0 / 0
Weighted average					**34.8**	**9.7**	**82.9**	**1.6**	**80**	**8.2**	**21.6**	**61.7**	**5.2**	**3.0**	**0.5**	**6.2**	**0.3**

aNo medication-free baseline was available.

bProlactin levels were measured at 4 weeks, the total study duration was 52 weeks.

cNot reported.

dSymptoms were measured by questionnaire: m = male, f = female.

$ Reyes performed an extended study using the same population as Croonenberghs et al.

^ Finding et al. used the same population as Aman et al. and included 52 new patients.

†Studies without a which included populations of other studies ($ and ^) are left out of the calculations, except for Reyes et al (2006) at end point prolactin measurement.

£ Used a control group at baseline and a patient group at end point.

Abbreviations: SD = Standard deviation; CPZ eq = chlorpromazine equivalent dose; OL = open label; ADHD = attention-deficit/hyperactivity disorder; (S)DBD = (severe) disruptive behavior disorder; S-IQ = subaverage Iintelligence (IQ 36–84); DBPCT = double-blind placebo-controlled trial; BD = bipolar disorder; PD = psychotic disorder; PCS = prospective cohort study; AD = anxiety disorder; MD = mood disorder; DBRT = double-blind randomized trial; CSS = cross-sectional study; RCR = retrospective chart review.

TABLE 2. EFFECT OF OLANZAPINE ($N=170$) ON PROLACTIN LEVEL AND PROLACTIN-RELATED SIDE EFFECTS

Author (year)	n Baseline point	n End point	Design	Diagnosis	Duration weeks (SD)	Mean age in years (SD)	% of males	Mean dose mg/day (SD)	CPZ Eq. (mg)	Prolactin ng/mL (SD) Baseline (SD)	Prolactin ng/mL (SD) End point (Sd)	Hyperprolactinemia (%)	Total	Gyneco-mastia	Galactor-rhea	Irregular menses	Sexual disturbance
Alfaro et al. (2002); Wudarsky et al. (1999) $^	12	12	DBRT	PD	6 (0)	14.5 (3.2)	58	17.5 (2.8)	350	10.4 (4.4)	34 (22)	70	8.3	0	8.3	0	0
	m 7 / f 5	m 7 / f 5						m 18.2 (1.9) / f 16.5 (3.8)	364 / 330	m 10 (4.9) / f 11.3 (3.8)	m 25 (10) / f 48 (27)	b / b	0 / 20	0 / 0	0 / 20	0 / 0	0 / 0
Biederman (2005)	15	9	OL	MD DBD ADHD	8 (0)	5.0 (0.8)	67	6.3 (2.3)	126	7.6 (4.1)	19.5 (9.7)	b	0	0	0	0	0
Sikich et al. (2004)	16	14	DBRT	PD MD	8 (0)	14.6 (3.1)	56	12.3 (4.5)	246	a	30 (12.9)	b	19	12.5	6.3	0	0
Saito et al. (2004)	13	13	OL	ASD PD MD DBD	11.2 (2.2)	13.4 (3.4)	55	7.8 (4.2)	156	a	24.5 (17.8)	39	23.1c	b	b	b	b
Dittman et al. (2008)	96	34	OL	PD	24 (0)	15.9 (1.4)	70.8	14.0 (0)	280	12.7 (7.5)	22.2 (11.2)	25	13.5	6.3	2.1	3.6	3.1
	m 68 / f 28	m 26 / f 8								m 10.5 (10.9) / f 28.3 (25.9)	m 13.4 (7.3) / f 24.9 (10.1)						
Staller (2006)£	18 £	7	CSS	DBD ADHD BD	54 (113.3)	14.4 (3.4)	86	10 (2.5)	200	6.4 (1.5)	10.4 (2.0)	b	28d	14	0	0	14
	m 10 £ / f 8 £	m 6 / f 1						m 10 (0) / f 7.5 (0)	200 / 150	m 5.6 (1.4) / f 7.4 (0.94)	m 8.2 (1.4) / f 23.6 (1.8)	b / b	28 / 0	16.7 / 0	0 / 0	0 / 0	16.7 / 0
Weighted average		28			28	14.4	68.6	12.7	254	11.1	24.2	31	13.8	6.2	2.8	2.4	2.7

[a] No medication-free baseline was available.
[b] Not reported.
[c] Symptoms where measured by questionnaire: m = male f = female.
$ Alfaro et al. used the same population as Wudarsky et al. and included 5 new patients.
^ Studies that included populations of other studies.
($) are left out of the calculations.
£ Used a control group at baseline and a patientgroup at end point.
Abbreviations: SD = Standard deviation; DBRT = double-blind randomized trial; PD = psychotic disorder; OL = open label; MD = mood disorder; (S)DBD = (severe) disruptive behavior disorder; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorders; BD = bipolar disorder; CSS = cross-sectional study.

TABLE 3. EFFECT OF HALOPERIDOL (N=56) ON PROLACTIN LEVEL AND PROLACTIN-RELATED SIDE EFFECTS

| | n Baseline | n End point | Diagnosis | Design | Duration weeks (SD) | Mean age in years (SD) | % of males | Prolactin ng/mL (SD) | | | | Hyperprolactinemia (%) | % Symptoms related to hyperprolactinemia | | | | |
Author (year)								Mean dose mg/day (SD)	CPZ Eq. (mg)	Baseline (SD)	End point (Sd)		Total	Gyneco-mastia	Galactor-rhea	Irregular menses	Sexual disturbance
Alfaro et al. (2002); Wudarsky et al. (1999) $^	15	15	PD	DBRT	6 (0)	13.8 (1.5)	60	15.4 (8.1)	770	9.2 (4.2)	47.9 (30.6)	90	0	0	0	0	0
	m 9 f 6	m 9 f 6						m 15 (6.9) f 16.1 (10.3)	750 805	m 8.6 (4.2) f 10.2 (4.4)	m 34.7 (13.2) f 67.7 (39.5)	b	0 0	0 0	0 0	0 0	0 0
Sallee et al. (1996)	26	19	TS	DBPCT	6 (0)	10.5 (2.6)	81	3.5 (2.2)	175	6.8 (2.5)a	12.9 (8.4)	b	b	b	b	b	b
Sikich et al. (2004)	15	8	PD MD	DBRT	8 (0)	15.4 (2.2)	53	5.3 (1.7)	265	32.2 (29)	b	27	13.3	0	28.6	0
Weighted average					6.5	12.7	65.2	7.2	360	7.7	29.1	90	13.5	6.7	0	15.4	0

a No medication-free baseline was available.
b Not reported.
d Symptoms where measured by questionnaire: m = male, f = female.
$ Alfaro et al. used the same population as Wudarsky et al. and included 5 new patients.
^ Studies that included populations of other studies ($) are left out of the calculations.
Abbreviations: SD = Standard deviation; DBRT = double-blind randomized trial; PD = psychotic disorder; DBPCT = double-blind placebo-controlled trial; TS = Tourette's syndrome; MD = mood disorder.

Bone mineral density

So far no studies have examined the effect of prolactin-raising antipsychotic medication on bone mineral density (BMD) in adolescents.

Discussion

The main conclusion from this review is that all antipsychotics, except clozapine, ziprasidone, and quetiapine, cause a rise in prolactin level to levels higher than two times the upper normal limit after 4–8 weeks of treatment. Furthermore, long-term studies with adequate sample size have only been performed with risperidone, and limited long-term data are available for pimozide, olanzapine, and quetiapine, leading to cautiousness in drawing conclusions about these latter medications. In any event, available data show that risperidone and pimozide induce a persistent elevation in prolactin levels above the upper limit, whereas the prolactin level normalizes to baseline value with olanzapine. Quetiapine did not increase the mean prolactin level (Shaw et al. 2001; Staller 2006). The actual percentage of children or adolescents that had hyperprolactinemia was measured in a few studies (Tables 1–4). The weighted average incidence of 12% hyperprolactinemia in the quetiapine group was reported in the text of three studies. No baseline measurements were available, thus pre-existing hyperprolactinemia could not be excluded. Furthermore, prolactin-elevating co-medication was used in two out of three studies (Saito et al. 2004; Stevens et al. 2005). Prolactin levels were averaged across the whole sample studied, including those whose prolactin levels were not raised. Therefore, group mean data shown in Tables 1–4 are lower than the mean data of the subgroup of children and adolescents with prolactin levels above the upper limit. Little is known about the clinical consequences of a sustained higher prolactin level over years among children and adolescents.

Only two studies with a duration of 1 year investigated the association between risperidone and the progression of puberty (Dunbar 2004; Reyes et al. 2006). Although no effect was found on the progression of Tanner stages, a 1-year follow-up may be too short to draw conclusions about the effect of pubertal development or later developmental processes. It is known that hyperprolactinemia due to prolactinoma is associated with delayed puberty, but in those patients prolactin levels were much higher, in the range of 200 ng/mL or above, than in the child and adolescent psychiatric samples included in this study (Patton and Woolf 1983; Sack et al. 1984; Greenspan et al. 1986; Howlett et al. 1989; Kawano et al. 2000). It is also known that prolactinoma-induced hyperprolactinemia induces a decrease in testosterone levels in men and pubertal boys, but no studies have been performed to examine the effect of antipsychotic-induced hyperprolactinemia on the sex hormone levels. Studies in adult males show that the prolactin-raising effect of antipsychotics leads to a significant decline in luteinizing hormone, follicle-stimulating hormone, and testosterone, although the levels remained within the normal range (Siris et al. 1980; Carter et al. 1982). Prolactin-related side effects, such as gynecomastia, galactorrhea, irregular menses, and sexual side effects, were reported by 4.8% of the total number of patients. In several adult studies, 30–60% of adult patients using prolactin-raising antipsychotic medication reported sexual side effects, such as erection and ejaculatory and menstrual disturbances, compared to about

TABLE 4. EFFECT OF QUETIAPINE (N = 72), CLOZAPINE (N = 30), ZIPRASIDONE (N = 12), AND PIMOZIDE (N = 46) ON PROLACTIN LEVEL AND PROLACTIN-RELATED SIDE EFFECTS

	n Baseline	n End point	Design	Diagnosis	Duration weeks (SD)	Mean age in years (SD)	% of males	Treatment	Mean dose mg/day (SD)	CPZ Eq. (mg)	Baseline (SD)	End point (Sd)	Hyperprolactinemia (%)	Total	Gynecomastia	Galactorrhea	Irregular menses	Sexual disturbance
McConville et al. (2000)	10	10	OL	PD	3.3 (0)	13.7 (1.2)	50	Quetiapine	800 (0)	1067	b	b	b	0[c]	0	0	0	0
Shaw et al. (2001)	15	15	OL	PD	8 (0)	15.1 (1.2)	53	Quetiapine	467 (b)	623	11.3 (5.1) [a]	11.1 (4.7)	0	0	0	0	0	0
Saito et al. (2004)	6	6	OL	ASD DBD PD MD	11.2 (2.2)	13.4 (3.4)	55	Quetiapine	283.3 (222.9)	378		16.7 (10.1)	17	33.3[c]	b	b	b	b
Stevens et al. (2005)	20	20	CSS	PD BD DBD	65.4	13.5 (2.4)	100	Quetiapine	317.5 (238)	423	b	8.5 (5.7)	20	0	0	0	0	0
Staller (2006) £	18 £	21	CSS	DBD ADHD BPD	98 (107.6)	13.8 (3.6)	76	Quetiapine	200 (300)	267	6.4 (1.5)	6.7 (1.7)	b	10	0	0	40	0
	m 10 £	m 16						Quetiapine	200 (300)	267	m 5.6 (1.4)	m 6.3 (1.8)	b	0	0	0	0	0
	f 8 £	f 5						Quetiapine	350 (300)	467	f 7.4 (0.94)	f 8.0 (0.83)	b	10	0	0	40	0
Weighted average					49.6	13.9	72.5		378.5	505	8.4	9.3	12.2	5.7	0	0	11.8	0
Alfaro et al. (2002); Wudarsky et al. (1999) $^	30	30	DBRT	PD	6 (0)	14.5 (3.2)	63	Clozapine	269.9 (173.3)	208	9.6 (4.8)	11.6 (4.8)	0	0	0	0	0	0
	m 19	m 19						Clozapine	m 295.3 (194.8)	227	m 9.5 (5.2)	m 10.3 (3.6)		0	0	0	0	0
	f 11	f 11						Clozapine	f 226.1 (124.4)	174	f 10 (3.4)	f 13.9 (5.8)		0	0	0	0	0
Weighted average					6	14.5	63		269.9	208	9.6	11.6	0	0	0	0	0	0
Malone et al. (2007)	12	11	OL	ASD	6	14.5 (1.8)	80	Ziprasidone	98.3 (40.4)	164	8.6 (6.6)	12.0 (8.0)	0	0	0	0	0	0
Weighted average					6	14.5	80		98.3	164	8.6	12.0	0	0	0	0	0	0
Sallee et al. (1996)	26	25	DBPCT	TS	6 (0)	10.5 (2.6)	81	Pimozide	3.4 (1.6)	113	6.8 (2.5)	21.6 (19.5)	b	b	b	b	b	b
Simeon et al. (1979)	7	5	OL	PD DBD ADHD	12 (0)	11.9 (2.3)	100	Pimozide	6.4 (2.2)	213	13.1 (5.1)	40.3 (33.7)	80	b	b	b	b	b
Suwa et al. (1984)	13	13	OL	DBD	56.6 (22.7)	9 (3)	69	Pimozide	2.9 (1)	97	12.4 (3.2)	24.5 (4.2)	b	b	b	b	b	b
Weighted average					21.2	10.3	80.5		3.7	123	9.3	24.7	80	b	b	b	b	b

a No medication-free baseline was available.
b Not reported.
c Symptoms were measured by questionnaire: m = male, f = female.
$ Alfaro et al. used the same population as Wudarsky et al. and included 5 new patients.
^ Studies which included populations of other studies ($) are left out of the calculations.
£ Used a control group at baseline and a patient group at end point.
Abbreviations: SD = Standard deviation; CPZ eq = chlorpromazine equivalent dose; (S)DBD = (severe) disruptive behavior disorder; OL = open label; PD = psychotic disorder; ASD = autism spectrum disorders; CSS = cross-sectional study; DBRT = double-blind randomized trial; MD = mood disorder; ADHD = attention-deficit/hyperactivity disorder; BPD = bipolar disorder; TS = Tourette's syndrome; DBPCT = double-blind placebo-controlled trial.

10% of patients using prolactin-sparing antipsychotic medication (Knegtering et al. 2003). In The Outcomes Research Study in schizophrenia (EIRE) (Bobes et al. 2003), the prevalence of sexual dysfunction and reproductive side effects was investigated in 365 adult schizophrenic Spanish patients using the prolactin-raising antipsychotics risperidone and haloperidol, compared to 43 patients using quetiapine. The prolactin-raising antipsychotic treatment was associated with 40% sexual dysfunction compared to 18% in the quetiapine group. Several studies show a relationship between serum prolactin level and sexual functioning, strength of sex drive, penile erection, and sexual arousal (Knegtering et al. 2003; Knegtering et al. 2004; Knegtering et al. 2006; Costa et al. 2007; Nakonezny et al. 2007). The 4.8% of the total number of patients in this review that reported sexual dysfunction is low in relation to the percentage of adult patients that report these side effects. This discrepancy can be partly explained by comparing the method of the different studies, spontaneous self-report in adolescents and children versus questionnaires used in adult studies. Besides the method, the age of sexual development and the diagnosis also play an important role. The adults were mainly adults with psychotic disorders, whereas the children and adolescents had autistic or behavioral disorders.

The effect of antipsychotic-induced hyperprolactinemia on BMD has not been studied in children and adolescents. Several adult studies have investigated antipsychotic-induced hyperprolactinemia, and possibly related hypogonadism, and related effects on BMD. These studies show a relation between antipsychotic-induced hypogonadism and a decrease in BMD (Abraham et al. 2003a; Abraham et al. 2003b; Meaney and Keane 2003; Meaney et al. 2004; O'Keane and Meaney 2005; Becker and Epperson 2006). Furthermore, two large case–control studies (44,500 patients and 16,341 patients) showed that prolactin-raising antipsychotic medication was associated with a two-fold increased risk of hip or femur fractures. The validity of this finding was supported by a dose increase relationship, i.e., the longer duration of antipsychotic use, the higher the risk (Hugenholtz 2005; Howard et al. 2007).

The relation between hyperprolactinemia and BMD loss in adolescents was studied in patients with prolactinomas. The effect of hyperprolactinemia on BMD was studied by comparing the results for two groups of patients with prolactinomas, one group of 20 adolescents and one group of 20 adults. The adolescents had more severe bone loss than the adults. After 2 years of treatment with dopaminergic drugs, the bone mass and bone turnover in the adolescent group were still not restored to normal values (Colao et al. 2000). Prolactin levels above 60 ng/mL are likely to be associated with hypogonadism in adult studies (Haddad and Wieck 2004). The occurrence of osteopenia or osteoporosis correlates with the presence and duration of hypogonadism rather than the degree of hyperprolactinemia (Greenspan et al. 1989; Misra et al. 2004; O'Keane and Meaney 2005). Adolescence is an important period for the attainment of peak bone mass (Davies et al. 2005), and disturbances in this process during puberty may influence the risk of osteoporosis later in life. The bone cortical thickness was reported to be significantly reduced in 75 boys, aged 4–8 years, with autism or autism spectrum disorders, indicating that bone development should be monitored in these patients (Hediger et al. 2008).

Besides the dose and duration of antipsychotic medication, prolactin levels may be influenced by the genetic differences that influence prolactin metabolism and D2 receptor density. However, the genetic studies performed so far by Anderson et al. (2007) and Troost et al. (2007) included small numbers of patients, respectively, 42 and 26. In 2004, another review on prolactin and antipsychotic agents in children and adolescents was published (Pappagallo and Silva 2004), and in 2007 a review on prolactin elevation and antipsychotic treatment in adult patients with schizophrenia and bipolar disorders was published (Byerly et al. 2007). Pharmacovigilance studies indicate that, although very rarely, hyperprolactinemia due to D2-blocking antipsychotics may be associated with increased risk for pituitary tumors (Szarfman 2006).

Prolactin level and mediators

Postpubertal status (Duval et al. 2007), female gender, higher relative doses of antipsychotic medication, and genetic differences are all known risk factors for prolactin elevation. Adolescent women of reproductive age have greater prolactin response to antipsychotics than prepubertal girls or males. Estrogen stimulates prolactin synthesis and enhances prolactin response to neuroleptic medication (Alfaro et al. 2002; Saito et al. 2004). Age-related decrease in dopamine receptors (Seeman et al. 1987) also gives a more pronounced effect in postpubertal adolescents and children compared to adults (Wudarsky et al. 1999). Genetic differences may explain individual variation in whether hyperprolactinemia leads to clinical consequences. The Taq1 A1 allele of the D2 dopamine receptor gene (DRD2) is associated with a significantly reduced density of D2 receptors. Also, the metabolization rate of prolactin-inducing antipsychotics may influence prolactin levels.

Limitations

The conclusions of this review are limited by the design and limitations of the original studies such as: the use of concomitant prolactin-elevating medication; the short overall study duration of most studies; differences in the diagnosis, age, and pubertal status; and the lack of prolactin baseline values in 7 out of 29 studies (Hardan et al. 1996; Frazier et al. 1999; McConville et al. 2000; Fegert et al. 2003; Stevens et al. 2005; Anderson et al. 2007); and an overlap in populations or the missing of medication-free baseline values in 2 out of 29 studies (Sikich et al. 2004; Saito et al. 2004), which were excluded from the analysis. Furthermore, publication bias likely exists in that not all data on prolactin levels available in drug companies' files have been published.

Furthermore, because prolactin-related side effects were based mainly on spontaneous self-report, the actual percentage of prolactin-related side effects may have been underestimated. In addition, it may be impossible in some patients to distinguish between prolactin-related side effects and common physiological processes such as gynecomastia in early pubertal boys and irregular menstrual cycles in females during the first few years after menarche (Bembo and Carlson 2004; Hanavadi et al. 2006).

Higher age, postpubertal status (Duval et al. 2007), female gender, and higher relative doses of antipsychotic medication are all known risk factors for prolactin elevation. The mean age of the risperidone and pimozide studies was 9.7 and 10.3 years, respectively, of which most patients were prepubertal, while the mean age in the olanzapine, quetiapine, haloperidol, pimozide, ziprasidone, and clozapine studies was, respectively, 14.4, 13.9, 12.7, 14.5, and 14.5 years and the patients were mainly postpubertal. The relative CPZ dose of the antipsychotic used was 80 mg for risperidone versus 254 mg, 123 mg, 505 mg, 208 mg, 164 mg, and 360 mg for olanzapine, pimozide, quetiapine, clozapine, ziprasidone, and haloperidol, respectively. The percentage male versus female among the different studies was also roughly the same for quetiapine, olanzapine, clozapine, and haloperidol, whereas the percentage of males was slightly higher for risperidone, ziprasidone, and pimozide. Lower overall age, low relative CPZ dose, higher percentage of males, and prepubertal status may have masked an actual higher elevation of prolactin in the risperidone group.

The CPZ dose varied among the different studies. The overall quetiapine and haloperidol dose used was five and four times higher, respectively, than the risperidone dose used. The dose of olanzapine and clozapine was two-fold higher and of pimozide one and a half times higher than the risperidone dose. This may have biased the comparison of these medications in terms of side effects and elevation of prolactin.

Prolactin reference values differed among the studies, and that influenced the percentage of hyperprolactinemia. Most studies (17) used 0–18 ng/mL for boys and 0–30 ng/mL for girls, but four studies used 0–15 ng/mL for boys and girls (Frazier et al. 1999; Masi et al. 2001; Masi et al. 2003; Stevens et al. 2005); eight studies did not give a reference value (Suwa et al. 1984; Shaw et al. 2001; Aman et al. 2002; Fegert et al. 2003; Sikich et al. 2004; Luby et al. 2006; Anderson et al. 2007). Furthermore, only 15 out of 29 studies reported the incidence of hyperprolactinemia (Tables 1–4).

Clinical implications

The clinical value is related to the consequences of long-term hyperprolactinemia such as a decline in sexual function (Knegtering 2003; Knegtering et al. 2004; Knegtering et al. 2006; Costa et al. 2007; Nakonezny et al. 2007) and decreased BMD (Abraham et al. 2003a; Abraham et al. 2003b; Meaney and O'Keane 2003; O'Keane and Meaney 2005; Becker and Epperson 2006; Meaney and O'Keane 2007). Children and adolescents may be more vulnerable to the adverse effects of hyperprolactinemia.

Therefore, prolactin-related side effects should be systematically investigated, e.g. with the help of a side-effect checklist for children and adolescents (Saito et al. 2004) and with a physical examination.

This review suggests that prolactin levels should be monitored in children or adolescents with sexual dysfunctions, gynecomastia, galactorrhea, or hypogonadotrophic hypogonadism. The antipsychotic-induced hyperprolactinemia can be treated by lowering the dose or by switching to a prolactin-sparing antipsychotic. If both strategies fail, a dopamine agonist (amantadine, carbergoline) may be added (Correll 2008b).

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