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Risk of Hyperprolactinemia and Sexual Side Effects in Males 10–20 Years Old Diagnosed with Autism Spectrum Disorders or Disruptive Behavior Disorder and Treated with Risperidone

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Abstract

Objective: The aim of this study was to investigate the long-term treatment effects of risperidone on prolactin levels and prolactin-related side effects in pubertal boys with autism spectrum disorders (ASD) and disruptive behavior disorders (DBD).

Method: Physical healthy 10–20-year-old males with ASD ($n = 89$) and/ or DBD ($n = 9$) chronically treated (mean 52 months, range 16–126 months) with risperidone (group 1, $n = 51$) or not treated with any antipsychotic (group 2, $n = 47$) were recruited to this observational study from the child psychiatry outpatient clinic. Morning non-fasting serum prolactin levels were measured and prolactin-related side effects were assessed by means of questionnaires and physical examination. Group differences were tested with Student's t, χ^2, Fisher exact, and Mann–Whitney tests, and logistic regression analysis, according to the type and distribution of data.

Results: Hyperprolactinemia was present in 47% of subjects in group 1 but only in 2% of subjects in group 2 (odds ratio 71.9; 95% CI, 7.7; 676.3). Forty-six percent of subjects in group1 had asymptomatic hyperprolactinemia. Current risperidone dose and 9-OH risperidone plasma level were significant predictors of hyperprolactinemia ($p = 0.035$ and $p = 0.03$, respectively). Gynecomastia and sexual dysfunction were present in 43% and 14% of the subjects in group1, respectively, compared with 21% and 0% of subjects in group 2 ($p = 0.05$ and $p = 0.01$). Gynecomastia was not significantly associated with hyperprolactinemia.

Conclusions: Hyperprolactinemia is a common side effect in young males treated over the long term with risperidone. Young males treated with risperidone are more likely to report diminished sexual functioning than are those not treated with antipsychotics.

Introduction

Second-generation antipsychotics (AP) are increasingly prescribed to children and adolescents with psychiatric disorders and have been used successfully to reduce maladaptive behaviors, such as irritability, self-injury, stereotypies, and hyperactivity in children and adolescents with autism spectrum disorders (ASD), and irritability and aggressive behavior in children and adolescents with disruptive behavior disorder (DBD) (Aman et al. 2009; McDougle et al. 2008).

Although risperidone and aripiprazole have been approved by the United States Food and Drug Administration (FDA) for the treatment of children and adolescents with irritability associated with ASD (Research Units on Pediatric Psychopharmacology Autism Network 2002, Stigler et al. 2006, Wink et al. 2010), these drugs have not yet been approved for this indication in Europe. APs are also frequently used, off-label, to treat severe aggression in children and adolescents with DBD. Despite their efficacy (Wink et al. 2010), there are concerns about the widespread use of these drugs given their side effects, such as, weight gain, metabolic

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adverse effects (dyslipidemia, hyperglycemia, and diabetes), cardiac side effects (QTc prolongation), extrapyramidal side effects, and increased prolactin levels (Molitch 2005, Correll 2008a, Vitiello et al. 2009). The side effects of APs are well described in adults, but less well studied in children and adolescents. There are indications that children are more sensitive than adults to the metabolic adverse effects of APs (Correll and Carlson 2006) and tend to gain proportionately more weight and do so more rapidly during treatment than do adults (Correll et al. 2006).

This study investigated the prevalence of hyperprolactinemia and prolactin-related side effects in children and adolescents on long-term risperidone treatment. Hyperprolactinemia is caused by dopamine 2 blockade in the tuberoinfundibular pathway, and may decrease gonadotropin levels and thereby estrogen and testosterone concentrations (Halbreich et al. 2003, Haddad and Wieck 2004). Estrogen and testosterone have important roles in sexual functioning, bone mineralization, and puberty (Saranac et al. 2010, Graham et al. 2011), such that decreased levels may result in disorders of sexual functioning (Cutler 2003, Knegtering et al. 2003), and may delay puberty. One study reported AP-induced hyperprolactinemia not to affect puberty, in prepubertal children (Reyes et al. 2006), whereas another reported diminished bone mineral density in boys on long-term prolactin-elevating APs (Calarge et al. 2010). It is not known what the threshold prolactin level is for adverse effects on sexual functioning, puberty, and bone mineralization.

Little is known about the consequences of persistently elevated prolactin levels in children and adolescents, and in particular about the effects of elevated but still subclinical levels of prolactin. A systematic review showed that maintenance treatment of children and adolescents with risperidone results in persistently elevated prolactin levels for up to 2 years (Roke et al. 2009).

When investigating the effects of AP-induced hyperprolactinemia, it is important to be able to distinguish between the effect of the mental condition for which the AP is used and the effects of hyperprolactinemia on sexual functioning, puberty, and bone mineralization. For this reason, it is important to recruit a psychiatric control group that is not treated with APs to monitor side effects before and during treatment, to use validated instruments, to physically examine participants, and to use appropriate age- and gender-based reference data for endocrine variables. Self-report data are less appropriate, because children and adolescents may feel embarrassed or are not able to express problems of sexual functioning, and they might not notice physical changes, such as gynecomastia or galactorrhea.

In this study, we investigated the consequences of long-term treatment with risperidone on prolactin levels and sexual functioning in males with ASD and DBD. We add to the current literature by recruiting a sample of patients using risperidone for >16 months, using a validated questionnaire for assessing sexual dysfunction, using appropriate age- and gender-based endocrine reference values, and using a physical examination to assess gynaecomastia. We compared boys and young men with ASD and DBD treated with risperidone (group 1) with those with ASD and DBD not treated with APs (group 2).

Methods

All participants were recruited from the total patient population of the outpatient adolescent clinic of the GGz Central Psychiatric Centre, The Netherlands, from October 2006 to November 2009. The GGz Central Psychiatric Centre hardly ever sees children and adolescents with psychotic or bipolar disorders, because these individuals tend to be referred to the nearby university hospital.

Inclusion criteria for the medication group (group 1) were: 1) age between 10 and 20 years, 2) diagnoses of any psychiatric disorder, 3) intelligence quotient (IQ) >85, and 4) treatment with any AP medication continuously for >16 months. Inclusion criteria for the comparison group (group 2) were the same except for the use of AP medication; this group had to be AP naïve. Participants were excluded if they had a history of thyroid disorders, had syndromes or other chronic diseases affecting puberty, had endocrine disorders, used oral corticosteroids or anticonvulsants, or had a known cause of hyperprolactinemia (Verhelst and Abs 2003, Melmed et al. 2011).

The first author contacted all children and adolescents who met the inclusion criteria by telephone and letter.

Most (80%) of the contacted group 1 patients (56 males, 6 females) participated in the study compared with 50% of the group 2 patients (47 males, 10 females). All participants had a diagnosis of ASD or DBD. The main reason for not participating was fear of venipuncture.

Data for female participants (16 in a total study sample of 119), 2 boys in the AP group using concomitant serotonin reuptake inhibitor (SSRI) medication, and 3 boys treated with pimozide instead of risperidone were not analyzed. Therefore, the risperidone group (group 1) consisted of 51 males with ASD or DBD treated long-term with risperidone and the comparison group (group 2) consisted of 47 males with ASD or DBD but never been treated with an AP.

Use of other concomitant medication, such as psychostimulants, melatonin, and atomoxetine was permitted (Table 1). The Local Medical Ethics Committee approved this study, and written informed consent was obtained from the patient and the subject's parents/legal guardians after a clear explanation of the study procedures.

Procedures

The clinical diagnosis was obtained from the patients' chart.

Pubertal stage was established by showing the subjects different Tanner stage photographs of genitals (G stage) and pubic hair (P stage) and then asking them to select the photographs that most accurately reflected their appearance (Duke et al. 1980). One of the parents/ legal guardians was present during the self-assessment and confirmed the stages pointed out. Sexual functioning was investigated using the items (change in sex interest, change in orgasm ability, change in erection ability, and change in the amount of ejaculate) of the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) (Wolters et al. 2003). This instrument has been developed and validated to study AP-related sexual side effects. The first author explained what change in orgasm, change in erection, change in sex interest, and change in amount of ejaculate meant. If the subjects did not remember or did not know if there was a difference, then relevant items were scored as unknown.

The first author, who was not aware of the prolactin data, systematically investigated prolactin-related side effects with the help of a checklist for children and adolescents (Saito et al. 2004) and with a physical examination (breast palpation), after first being trained by a pediatric endocrinologist to detect the presence of gynecomastia and galactorrhea. The first author also measured the participants' height (without shoes to the nearest 0.1 cm using a

Table 1. Characteristics of Male Children and Adolescents with Autism Spectrum Disorders or Disruptive Behavior Disorders Treated with Risperidone over the Long Term (n = 51) and Without Antipsychotic Treatment (n = 47)

	Cases (n = *51*)		*Comparison subjects* (n = *47*)		
	n *(%)*	*Mean (SD; range)*	n *(%)*	*Mean (SD; range)*	p *value*
Age, years		14.7 (2.1; 10,19)		15.1 (1.6; 11,18)	0.27[b]
Height *z*-score		0.40 (1.1; −2.4, 2.1)		0.35 (0.9; −1.5, 2.9)	0.79[b]
Weight *z*-score		0.49 (1.1; −2.5, 3.2)		0.34 (1.2; −2, 3.9)	0.52[b]
BMI		20.3 (3.3; 14.6, 29.5)		20.4 (4; 15,32)	0.94[b]
Underweight	3 (6)		6 (13)		
Normal	41 (80)		32 (68)		
Overweight	7 (14)		8 (17)		
Obese	0		2 (4)		
BMI *z*		0.21 (0.87; −1.8, 1.8)		−0.0.9 (1.2; −3.3, 2.3)	0.16[b]
Tanner stages					
I	0		0		
II	7 (14)		9 (19)		
III	15 (29)		13 (28)		
IIII	21 (41)		20 (43)		
V	8 (16)		6 (13)		
Primary diagnosis					
ASD	49 (96)		40 (85)		0.11[a]
DBD	2 (4)		7 (15)		0.05[c]
Risperidone (mg/day)		1.5 (0.9; 0.25,4)			—
RIS μg/L		2.7 (5; 0,28)			—
9-OH RIS μg/L		8.4 (7.5; 0–36)			—
Duration of use (months)		53 (27.8; 16–126)			—
Concomitant medication					
Melatonin	4 (8)		3 (6)		
Psychostimulants	10 (20)		13 (30)		
Atomoxetine	2 (4)		0		
Total	13 (25)		13 (30)		0.17[c]
Caucasian ethnicity	49 (96)		45 (96)		0.44[a]

[a]Chi square.
[b]Student *t*-test.
[c]Fisher Exact test.
BMI, body mass index; ASD, autism spectrum disorders; DBD, disruptive behavior disorder; RIS, plasma levels of risperidone; 9-OH RIS = plasma levels of 9-OH risperidone.

stadiometer, Seca 206, the Netherlands) and weight (participant wearing underwear, to the nearest 0.1 kg using an analogue scale, Seca 761, the Netherlands). Age- and gender-specific height, weight, and body mass index (BMI) *z*-scores were calculated using normative data for Dutch children (Fredriks et al. 2000 a,b).

A non-fasting morning blood sample was obtained at approximately 9.30 a.m. after subjects had eaten a light breakfast at approximately 7.30. Serum prolactin was measured with an automated chemiluminescence assay system (Immulite 2000, Siemens Healthcare Diagnostics) calibrated on the third IS 84/500. As macroprolactin, a complex of prolactin and immunoglobulin G (IgG) without biological activity, accounts for 10% of cases of hyperprolactinemia (McKenna 2009), seven samples with prolactin concentrations >37 ng/mL were assessed for the presence of macroprolactin. Polyethylene glycol 6000, 200 μL, (25% w/w) was added to 200 μL of serum and, after thorough vortex mixing, the mixture was centrifuged at 2200*g* for 30 minutes at 4°C. Subsequently, prolactin was measured in the supernatant and the untreated serum. The recovery of prolactin after precipitation with polyethylene glycol 6000 was 101.4 ± 9.6 (mean ± SD), which excluded the presence of macroprolactin. Thyrotropin (TSH) was measured to exclude subjects with hyperprolactinemia caused by thyroid disorders. Plasma levels of risperidone and 9-hydroxyrisperidone were measured to evaluate compliance.

Data analysis

To test for differences between groups 1 and 2, Student's *t* test, χ^2, Mann–Whitney test, Fisher Exact test, and logistic regression were used according to the type and distribution of data. Hyperprolactinemia was defined as a prolactin level above the 97.5th percentile based on normative data for age and gender (Emlinger et al. 2002) (see Table 2).

Logistic regression analysis was used to investigate whether risperidone was associated with hyperprolactinemia. The following covariates were examined based on previous literature: age, BMI *z*-score, and Tanner stage. A subsequent logistic regression analysis was performed to evaluate the influence of type of medication, duration of AP use, use of dosage, risperidone levels, and 9-OH risperidone levels on hyperprolactinemia in the patients using risperidone, corrected for age and BMI *z*-score.

Sexual dysfunction was measured with four items of the ASFQ, scored 0–5 as follows: unknown (0), strongly diminished (1),

Table 2. 97.5th Percentile of Prolactin for Age and Gender in ng/mL (Emlinger et al. 2002)

Age, (years)	n	*Female*	*Age (years)*	n	*Male*
		97.5th			97.5th
11	23	44.20	11	22	16.37
12	18	15.47	12	17	12.93
13	25	22.78	13	21	18.63
14	30	31.13	14	32	17.55
15	48	20.52	15	40	19.81
16	40	20.71	16	31	15.09
17	30	17.78	17	22	16.51
18–19	12	39.53	18–19	8	15.71
17–19	42	32.78	17–19	30	16.23

diminished (2), unchanged (3), increased (4), and strongly increased (5). The ASFQ item scores were grouped, to increase power, as follows: unknown or not applicable, diminished, unchanged, and increased.

Sexual dysfunction was present if a patient scored ''diminished'' on one or more of the four ASFQ items.

Results

Ninety-eight males with ASD or DBD took part in the study. There was no difference in mean height *z*-score, BMI *z*-score, pubertal stage, ethnicity, and use of concomitant medication between those in groups 1 and 2: however, there were more subjects with DBD in group 2 than in group 1 (15% versus 4%, $p = 0.05$). Forty-seven subjects were not using an AP, but 51 were using risperidone (mean ± SD daily dose, 1.5 ± 0.9 mg, range 0.25–4 mg) long term (mean ± SD duration, 53 ± 27.8 months, range 16–126 months), and 36 had used risperidone continuously for ≥ 3 years.

At the time of measurement, 14 (27%) of all subjects in group 1 had undetectable levels of risperidone (0 μg/L) and 4 (8%) of these had also undetectable 9-OH risperidone levels (Table 1).

Table 3 presents data on prolactin levels and the prevalence of hyperprolactinemia, asymptomatic hyperprolactinemia, and prolactin-related side effects in the two groups, as well as the number of males in each Tanner stage. Hyperprolactinemia was significantly more common among those treated with risperidone than among those not treated with an AP (24 versus 1, 47% versus 2%, respectively, $p < 0.0001$). In none of the subjects was hyperprolactinemia caused by macroprolactin or thyroid disorders.

The prolactin levels of the subjects with hyperprolactinemia were, in 18 out of 24 patients (75 %), between the 97.5th percentile level and 30 ng/mL, in 2 out of 24 (8%) between 30 and 50 ng/mL, and in 4 out of 24 (17%) > 50 ng/mL.

Among the subjects treated with risperidone, hyperprolactinemia was present in 5 of 7 in Tanner stage II (71%), in 6 of 15 in Tanner stage III (40%), in 8 of 21 in Tanner stage IV (38%), and in 5 of 8 in Tanner stage V (63%).

Hyperprolactinemia was asymptomatic in 11 subjects (46%). The odds ratio (OR) of having hyperprolactinemia with risperidone treatment was 71.9 (95% CI 7.7, 676.3). Adjustment for age and BMI *z*-score did not influence the results. Gynecomastia was detected in 24 (47%, measured by questionnaire) and 22 (43%, measured by physical examination) males in group 1 and in 10 (21%) in group 2 ($p = 0.05$): this difference remained after

Table 3. Prevalence of Hyperprolactinemia and Prolactin-Related Side Effects in Male Children and Adolescents with Mainly Autism Spectrum Disorders Treated with Risperidone (n = 51) Compared with Male Patients Without Antipsychotic Treatment (n = 47)

	Cases n = *51*		*Comparison subjects* n = *47*		
	n *(%)*	*Mean (SD, range)*	n *(%)*	*Mean (SD, range)*	p *value*
Prolactin ng/mL[a]		19.3 (16.8, 2.4–92.5)		8.0 (2.8, 3.8–15.1)	< 0.0001[b]
Tanner stage II		21.2 (10.4, 11.8, 41.0)		7.7 (2.5, 5.7, 10.8)	
Tanner stage III		18.9 (21.2, 5.7, 92.4)		7.3 (3.3, 3.8, 15.1)	
Tanner stage IV		17.9 (16.9, 2.3, 77.8)		8.5 (4.7, 5.2, 13.2)	
Tanner stage V		21.7 (13.7, 6.6, 48.6)		8.5 (3.5, 5.2, 15.1)	
Hyperprolactinemia	24 (47)		1 (2)		< 0.0001[c]
Tanner stage II/III/IV/V	5/6/8/5		0/1/0/0		
Asymptomatic hyperprolactinemia	11 out of 24 (46)		1 out of 1 (100)		< 0.0001[c]
Tanner stage II/III/IV/V	3/4/2/2		0/1/0/0		
Prolactin related side effects					
Gynecomastia					0.01[c]
Questionnaire	24 (47)		10 (21)		
Tanner stage II/III/IV/V	3/5/12/4		2/4/4/0		
Gynecomastia physical examination	22 (43)		10 (21)		0.05[c]
Tanner stage II/III/IV/V	1/8/11/2		3/4/3/0		
Galactorrhea	0		0		-
Diminished sexual functioning	7 (14)		0		0.013[d]
-sex interest	2 (4)		0		
-orgasm	4 (8)		0		
-ejaculate	5 (10)		0		
-erection	1 (2)		0		

[a]Reference value changes with age and gender (Emlinger et al. 2002), see Table 2.
[b]Mann–Whitney.
[c]Chi square.
[d]Fisher exact test.

Table 4. Predictors of Hyperprolactinemia in Children and Adolescent Population Using Risperidone

	Hyperprolactinemia *No,* n = *27* *Mean (SD)*	*Yes,* n = *24* *Mean (SD)*	*OR (CI)*	p-*value*
Current dose of risperidone (mg/day)	1.25 (0.84)	1.83 (0.95)	2.42 (1.07,5.50)	0.035[a]
RIS μg/L	1.48 (2.14)	4.30 (6.86)	1.19 (0.97, 1.44)	0.090[a]
9-OH RIS μg/L	6.26 (5.32)	11.35 (8.70)	1.15 (1.02, 1.29)	0.030[a]
Mean dose of the treatment period (mg/day)	1.41 (0.76)	1.68 (0.53)	1.98 (0.79, 4.97)	0.14[a]
Duration of treatment (months)	50.21 (27.24)	55.67 (28.51)	0.99 (0.97, 1.01)	0.40[a]

[a]Logistic regression, corrected for age and body mass index (BMI)-z.
OR, odds ratio; CI, 95% confidence interval; RIS, plasma levels of risperidone;9-OH RIS, plasma levels of 9-OH risperidone.

adjustment for age and BMI *z*-score ($p = 0.02$). Of the subjects with hyperprolactinemia, 8 (36 %) had gynecomastia on physical examination (OR = 2.86, 95% CI 1.16, 7.06, $p = 0.26$).

Sexual functioning was diminished in seven of the males in group 1 (14%), with two (4%), four (8%), five (10%), and one (2%) reporting diminished sexual interest, diminished ability to have an orgasm, diminished ejaculation, and lower ability to have an erection, respectively, compared to none in group 2 ($p = 0.01$). Five of the seven scored their sexual functioning as strongly diminished, and four of these were Tanner stage IV. Fifteen males in group 1 (29%) reported their change in sexual functioning as unknown and 10 (20%) as unchanged compared with 19 (40%) unknown and 5 (10%) unchanged in group 2.

Sexual dysfunction tended to occur more often in subjects with hyperprolactinemia ($n = 27$) (21% vs. 8%, $p = 0.07$). Five of the seven males with sexual dysfunction had hyperprolactinemia.

Table 4 shows predictors of hyperprolactinemia in males treated with risperidone. The current dose of risperidone and the 9-OH risperidone plasma level both predicted hyperprolactinemia (OR = 2.4 95%, CI 1.1, 5.5, $p = 0.035$ and OR = 1.15, CI 1.02, 1.09, $p = 0.03$, respectively), whereas the mean dose of risperidone over the period, the risperidone plasma level, and the duration of treatment did not.

Discussion

Almost half of the subjects treated over the long term with risperidone, but only 2 % of those not treated with an AP agent had hyperprolactinemia. Although prolactin levels were only measured once, it is very likely that hyperprolactinemia is a common side effect in children and adolescents treated with risperidone over the long term. Previous short-term studies have shown a steep increase in the prolactin level within the first 6 weeks, with levels stabilizing in the first 3 months (Aman et al. 2002, Snyder et al. 2002, Findling et al. 2004, Biederman et al. 2005), followed by a slow decline after 1 year (Turgay et al. 2002, Findling et al. 2004, Croonenberghs et al. 2005, Stevens et al. 2005, Anderson et al. 2007). Average prolactin levels were found to be above the reference value after 2 (Reyes et al. 2006, Staller 2006) and 3 years of continued risperidone treatment (Calarge et al. 2010), although two studies reported that prolactin levels tended to normalize after 12 months (Migliardi et al. 2009) and 22 months (Anderson et al. 2007) of AP use. Our results, obtained for pubertal boys and young men using risperidone over the long term, show that half of the patients still had hyperprolactinemia after 53 months. In previous studies, hyperprolactinemia was defined using adult reference ranges, primarily 0–18 ng/mL and 0–30 ng/mL for male and female patients, respectively. Our study is the first to use age- and gender-appropriate reference ranges (Emlinger et al. 2002, see Table 2) to define hyperprolactinemia. This is important because prolactin levels change during childhood and adolescence.

Gynecomastia was five times more common in our study than in other studies (Sikich et al. 2004, Reyes et al. 2006, Staller 2006) (Table 3). Previous studies included mainly prepubertal children, and used spontaneous self-report, rather than physical examination, to establish the presence of gynecomastia, which probably led to underestimation of the prevalence of gynecomastia. The prevalence of gynecomastia in the AP-naïve subjects was 21% (10 of 47) comparable to the prevalence of gynecomastia in healthy pubertal boys, indicating that it is a normal transient phenomenon in pubertal boys; the lifetime prevalence of gynecomastia in males is ~50% (Bembo and Carlson 2004, Hanavadi et al. 2006). None of our subjects had galactorrhea, consistent with earlier findings from a systematic review showing that galactorrhea does not occur in pubertal boys, whereas it occurs in 0.5% of postpubertal females (Roke et al. 2009).

Our study is the first to use a validated and standardized instrument to assess sexual dysfunction in male adolescents using long-term APs. We found that 1 in 8 reported sexual dysfunction in relation to risperidone treatment. An earlier study that used a specific questionnaire for sexual adverse events showed a similar prevalence of sexual dysfunction among adolescents (Staller 2006). In studies of adults with schizophrenia or mood disorders, the rate of diminished sexual functioning caused by hyperprolactinemia was ~40% (Bobes et al. 2003, Knegtering et al. 2004, 2006). The boys and young men with ASD included in our study may have different sexual behavior than did the patients with schizophrenia or mood disorders. The mean dose of risperidone used in our study population was similar to that used in other studies (weighted average 1.6 mg per day) (Roke et al. 2009). However, as our participants were older than those in most previous studies (mean age 14.5 in this study vs. weighted average of 9.7 years in earlier studies) (Roke et al. 2009), the dose corrected for age was probably lower in our study.

Limitations

This study had some limitations that should be taken into account when interpreting the results, and which should be addressed in future studies. First, our sample size was relatively small, but our findings are in agreement with those of larger studies (Calarge et al. 2010). In addition, prolactin-elevating concomitant medication was permitted, such as, atomoxetine and melatonin (Blaicher et al. 1999, Molitch 2005, Coker and Taylor 2010), which could have influenced the prolactin levels. However, use of these medications was similar in the two groups and appears not to have confounded

our results. The prolactin-elevating effect of this concomitant medication is considered to be minor compared with that of the AP used (Coker and Taylor 2010).

Another limitation was the cross-sectional design of the study, so that we cannot establish causality and also do not know what baseline prolactin levels were. Instead, we compared subjects treated with risperidone and subjects not treated with APs. Fourteen (27%) had undetectable risperidone levels, and four of these (8%) had also undetectable 9-OH risperidone levels. Risperidone has a short half-life of 3 hours compared with the longer half-life of at least 23 hours (dependent on the patients' CYP2D6 polymorphism) of 9-OH risperidone, explaining the difference in blood level detectability. These data suggest that these 14 subjects did not take their risperidone as prescribed. The 4 subjects with undetectable risperidone and 9-OH risperidone levels did probably not take their medication at all whereas the 10 with undetectable risperidone but detectable 9-OH risperidone levels probably did not take their AP as prescribed.

These adherence problems could have led to an underestimation of the actual prevalence of hyperprolactinemia and prolactin-related side effects in our study.

The ASFQ data on sexual functioning may have been biased by recall and time. The children and adolescents had to think back to the time when they did not use risperidone. Moreover, some of them may have started risperidone before puberty and may have become sexually mature since; therefore, they might have considered their sexual functioning as unchanged (20% cases and 10% comparison group) or unknown (30% cases and 40% comparison group) whereas it was, in fact, suppressed. Moreover, subjects who were sexually inexperienced or inactive could not make a before and after comparison. Another limitation was the self-assessment of pubertal stage. However, self-assessment has proven to be a valid and reliable method in comparison with physical examination, especially in nonobese adolescent boys in mid to late adolescence (Duke et al. 1980, Wacharasindhu et al. 2002, Leone and Comtois 2007, Chan et al. 2008). We found that staging of pubic hair development was less reliable than staging of genital development; therefore, we used genital development as the main measure. Self-assessment of puberty has not been investigated before in adolescents with autism, but has proven reliable in adolescents with other chronic diseases such as Crohn's disease and diabetes mellitus (Schall et al. 2002, Stephen et al. 2008). The prevalence of gynecomastia could have been confounded by the presence of overweight/obesity; however, the subjects' breasts were palpated to distinguish between fat and glandular tissue.

Conclusions

Continuous use of risperidone for ≥ 16 months induced hyperprolactinemia in $\sim 50\%$ of the subjects and might have diminished their sexual functioning. Although gynecomastia was two times more common in the risperidone group, hyperprolactinemia was not associated with gynecomastia. However, 46% (11 out of 24) of the subjects with risperidone-induced hyperprolactinemia did not have prolactin-related side effects. The long-term consequences of asymptomatic hyperprolactinemia are unknown, but theoretically, high prolactin levels could result in diminished bone mineral density, changes in sexual maturation, or an increased risk of benign prolactinomas (Sfarzman et al. 2006) during periods of critical maturation. Long-term studies are needed to investigate the relevance of asymptomatic hyperprolactinemia.

Some experts recommend a ''wait and see approach'' for asymptomatic hyperprolactinemia and advise that prolactin levels should be monitored in the event of prolactin-related side effects, such as sexual disorders, menstrual disturbances, gynecomastia, or galactorrhea (Haddad and Wieck 2004, Correll et al. 2006, Anderson et al. 2007, Correll 2008b). Others suggest proactive monitoring of prolactin levels and possible side effects before and during treatment with prolactin-elevating APs (Staller 2006, Citrome 2008, Ho et al. 2011).

Clinical Significance

This study provides further support for the monitoring of prolactin levels in symptomatic patients only. Diminished sexual functioning was associated with long-term hyperprolactinemia, whereas gynecomastia may be a normal phenomenon. Therefore, sexual function should be addressed before and during treatment, using a standardized questionnaire.

If symptomatic AP-induced hyperprolactinemia occurs, the AP should be stopped, if this is clinically feasible. Prolactin levels should normalize within days, depending upon the half-life ($T_{1/2}$) of the drug (Pollock and McLaren 1998, Turrone 2002). Alternatively, the dosage should be reduced as there is a dose-response relation with prolactin levels (Knegtering and Baselmans 2005), or another AP agent without prolactin-elevating qualities should be tried (e.g., quetiapine, aripiprazole, clozapine) (Stevens et al. 2005, Greenaway and Elbe 2009). If the hyperprolactinemia persists despite these steps, further investigation of the patient is necessary (Ho et al. 2011).

Disclosures

Dr. van Harten has given lectures at symposia sponsored by Lilly, Bristol Meyers Squibb, and Glaxo Smith Kline, for which he received an honorarium. Dr. Buitelaar has been, during the past 3 years, a consultant to/member of the advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Medice, and Servier. Drs. Roke, Boot, and Tenback have nothing to disclose.

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