Differences in Prolactin Elevation and Related Symptoms of Atypical Antipsychotics in Schizophrenic Patients

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Objective: The aim of this cross-sectional study was to investigate the degree and frequency of prolactin (PRL) elevation and related symptoms in patients treated with 3 different atypical antipsychotics: clozapine, olanzapine, and risperidone.

Method: Twenty-eight patients receiving clozapine, 29 patients receiving olanzapine, and 18 patients receiving risperidone (all meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder) were studied. The median daily dose was 400 mg of clozapine, 10 mg of olanzapine, and 3 mg of risperidone. Fasting morning blood samples were analyzed for PRL, and the occurrence of hyperprolactinemic symptoms in the patients was evaluated.

Results: Elevated PRL levels were found in 16 (89%) of the patients receiving risperidone and in 7 (24%) of the patients receiving olanzapine, but in none of the patients receiving clozapine. In addition, there was a significant difference in median PRL level among the treatment groups ($p < .0001$), in that the PRL level was higher both in the patients treated with risperidone and in the patients treated with olanzapine, compared to those treated with clozapine. Moreover, hyperprolactinemic symptoms—menstrual disturbances, galactorrhea, impotence, oligospermia, and decreased libido—were reported in 8 (44%) of the risperidone-treated patients and in 1 (3%) of the olanzapine-treated patients, but in none of the clozapine-treated patients.

Conclusion: Treatment with risperidone was frequently associated with hyperprolactinemia and related symptoms, whereas the occurrence of PRL elevation and related symptoms was modest in patients receiving olanzapine and nonexistent in those receiving clozapine. Thus, atypical antipsychotics in therapeutic doses differ with regard to effect on PRL secretion.

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Antipsychotic medications have been found to be the most common drugs in the etiology of persistent hyperprolactinemia.[1] The antipsychotic-induced hyperprolactinemia in turn may cause hypogonadism in both men and women with symptoms like impotence, menstrual disturbances, decreased libido, and infertility.[2–5] It may also give rise to galactorrhea and gynecomastia, and long-term, it may increase the risk for osteoporosis and cardiovascular disease.[2,6–12] Thus, it is important to take this hormonal-related side effect into serious consideration.

The hormone prolactin (PRL) is produced by the lactotrophs in the anterior pituitary gland.[13] Its main physiologic action is to initiate and maintain lactation, but it may also act at tissues other than the mammary glands.[13,14] In hypothalamus, elevated PRL levels inhibit the pulsative secretion of gonadotropin-releasing hormone, with impaired gonadotropin secretion and inhibited gonadal function as a consequence.[13,14] Excessive hyperprolactinemia may also inhibit hypophyseal growth hormone (GH) secretion, leading to reduced hepatic production of the GH-dependent, insulin-like growth factor I (IGF-I).[15,16]

The most important PRL-regulating factor is dopamine, which reaches the pituitary via the hypothalamic-hypophyseal portal system and acts at the dopamine$_2$ (D_2) receptors on the lactotrophs, resulting in inhibition of PRL synthesis and secretion.[17] Antipsychotic drugs, which are dopamine antagonists, may, through blockade of the D_2 receptors on the lactotrophs, more or less abolish the dopamine-inhibiting effect on the PRL release, leading to hyperprolactinemia and related symptoms.[17]

The frequency as well as the degree of PRL elevation among patients on treatment with conventional antipsychotics differs between studies.[18–21] This probably depends on both the type of conventional agent used and the dosages. Moreover, the sex-related difference in PRL re-

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sponse has to be taken into account, as hyperprolactinemia induced by conventional antipsychotics has been shown to be more common in women than in men, despite lower dosages in the women.[18,21–23]

The effect on PRL secretion of conventional antipsychotics, rather than of newer, so-called atypical agents, has been extensively examined earlier. The aim of this study was therefore to investigate the degree and frequency of PRL elevation and related symptoms in male and female patients treated with 3 different atypical antipsychotics: clozapine, olanzapine, and risperidone. In addition, the influence of these atypical agents on gonadotropic and sexual steroid hormone levels, as well as on the GH-IGF-I axis, was evaluated.

METHOD

Patients

Consecutive outpatients on therapy with clozapine, olanzapine, or risperidone, and with diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria,[24] were asked to participate in the study. The study was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden, and all patients participated after giving informed consent. Patients with physical illness, substance-related disorder, or drugs other than the current antipsychotics that could influence the hormonal evaluation were excluded. Taken together, 28 patients (16 men and 12 women) receiving clozapine, 29 patients (17 men and 12 women) receiving olanzapine, and 18 patients (9 men and 9 women) receiving risperidone were included.

Data on the age, diagnosis, duration of disease, duration of therapy with current antipsychotic, and daily dose as well as serum concentration of antipsychotics for the patients are given in Table 1. The patients received either clozapine, olanzapine, or risperidone, and the only concomitant medications used were benzodiazepines, β-blockers, biperiden hydrochloride, lithium, orphenadrine hydrochloride, zolpidem, and zopiclone. The median daily dose was 400 mg (range, 25–600 mg) of clozapine, 10 mg (range, 5–20 mg) of olanzapine, and 3 mg (range, 1–8 mg) of risperidone. All patients had been receiving the current antipsychotic for at least 2.5 months, although the treatment time was longer for the patients receiving clozapine than for those receiving olanzapine or risperidone (Table 1). Within groups, no significant gender differences were found in treatment time, daily dose, or serum concentration of antipsychotics (Table 1).

Assays and Clinical Evaluation

Fasting blood samples were collected between 8 and 10 a.m. prior to medication, and serum was stored at –20°C until analysis. In addition, all patients were inter-

Table 1. Age, Diagnosis, Duration of Disease, Duration of Therapy With Current Antipsychotic, and Daily Dose as Well as Serum Concentration of Antipsychotics for the Patients in the 3 Treatment Groups[a]

Treatment Group	Age, y	DSM-IV Diagnosis	Duration of Disease, y	Duration of Therapy With Current Antipsychotic, y	Daily Dose of Antipsychotic, mg	Serum Concentration of Antipsychotic, nmol/L
Clozapine (N = 28: 16 men, 12 women)	All: 40 (26–58)	Schizophrenia, paranoid type (N = 9)	All: 18.0 (3.5–42.1)	All: 6.5 (0.6–16.3)*	All: 400 (25–600)	1308 (150–2810)
	Men: 39 (29–58)	disorganized type (N = 4)	Men: 14.0 (5.0–33.1)	Men: 7.0 (0.6–16.3)**	Men: 425 (200–600)	1275 (150–2810)
	Women: 43 (26–58)	undifferentiated type (N = 15)	Women: 21.0 (3.5–42.1)	Women: 6.1 (1.3–10.1)***	Women: 375 (25–600)	1308 (150–2370)
Olanzapine (N = 29: 17 men, 12 women)	All: 39 (23–60)	Schizophrenia, paranoid type (N = 15)	All: 11.5 (0.3–34.0)	All: 0.9 (0.2–5.5)	All: 10 (5–20)	105 (42–280)
	Men: 39 (23–60)	disorganized type (N = 1)	Men: 10.8 (1.0–21.4)	Men: 0.8 (0.3–5.1)	Men: 12.5 (7.5–20)	121 (44–280)
	Women: 39 (30–57)	undifferentiated type (N = 7)	Women: 11.7 (0.3–34.0)	Women: 1.0 (0.2–5.5)	Women: 10 (5–20)	99 (42–198)
		Schizophreniform disorder (N = 3)				
		Schizoaffective disorder (N = 3)				
Risperidone (N = 18: 9 men, 9 women)	All: 41 (30–59)	Schizophrenia, paranoid type (N = 2)	All: 12.0 (2.0–22.0)	All: 1.0 (0.2–8.8)	All: 3 (1–8)	57 (7–261)[b]
	Men: 40 (30–42)	undifferentiated type (N = 13)	Men: 14.0 (9.0–17.2)	Men: 1.0 (0.2–3.4)	Men: 4 (1–8)	62 (7–261)[b]
	Women: 42 (31–59)	Schizoaffective disorder (N = 3)	Women: 5.5 (2.0–22.0)	Women: 1.0 (0.4–8.8)	Women: 3 (2–4)	50 (24–123)[b]

[a]The data are given as median and range.
[b]Sum of risperidone and 9-hydroxyrisperidone, i.e., the active moiety of risperidone.[25]
*Significantly different from the olanzapine-treated and risperidone-treated patients, $p < .0001$.
**Significantly different from the olanzapine-treated and risperidone-treated men, $p = .0001$.
***Significantly different from the olanzapine-treated and risperidone-treated women, $p = .002$.

viewed about potential hyperprolactinemic symptoms by a psychiatrist (K.M.).

The laboratory investigation included analyses of PRL, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (in the women), testosterone (in the men), GH, and IGF-I.

Prolactin was measured by a commercial fluoroimmunometric assay kit (Delfia Prolactin, Wallac Inc., Turku, Finland). With this method, the upper limit of normal for PRL was < 10 μg/L for men and menopausal women and < 20 μg/L for fertile women. LH, FSH, estradiol, testosterone, and GH as well were measured by commercial fluoroimmunometric assay kits (Delfia: LH, FSH, Oestradiol, Testosterone, and hGH; Wallac Inc., Turku, Finland). Insulin-like growth factor I was determined according to the radioimmunoassay method of Bang et al.[26] and expressed as age-correlated standard deviation scores, based on samples from healthy men and women.[27] The detection limit was 8 μg/L. Including the extraction step, the intra-assay and interassay coefficients of variation were 4% and 11%, respectively.

Statistics

As the different variables were assumed to be non-normally distributed, nonparametric statistical methods were used. Data are described as median and range. In the statistical analysis, the Kruskal-Wallis analysis of variance on ranks was employed to evaluate differences among groups. When a significant difference among the groups was detected, pair-wise comparisons between medians were performed as described.[28] To be able to compare frequencies of variables between groups, the Fisher exact test was used, and to evaluate differences within groups, the Mann-Whitney test was employed. A p value of less than .05 was considered statistically significant. All calculations were made with the statistical program Statistica for Windows (Statsoft, Inc., Tulsa, Okla.).

RESULTS

Prolactin

Elevated PRL levels (men and menopausal women ≥ 10 μg/L, fertile women ≥ 20 μg/L) were found in 89% of the patients (7 men and 9 women) receiving risperidone and in 24% of the patients (2 men and 5 women) receiving olanzapine, but in none of the patients receiving clozapine. The frequency of elevated PRL level was significantly higher both in the patients receiving risperidone compared to those receiving olanzapine ($p < .0001$) or clozapine ($p < .0001$) and in the patients receiving olanzapine compared to those receiving clozapine ($p = .01$). In addition, there was a significant difference in median PRL level among the treatment groups ($p < .0001$), in that the PRL level was higher both in the patients treated with risperidone and in the patients treated with olanzapine, compared to those treated with clozapine, $p = .00001$ and $p = .001$, respectively (Table 2).

Hyperprolactinemia was also statistically more frequent in the women than in the men treated with atypical antipsychotics (14/33 [42%] vs. 9/42 [21%], $p = .04$).

Hyperprolactinemic Symptoms

Hyperprolactinemic symptoms (i.e., amenorrhea, oligomenorrhea, galactorrhea, impotence, oligospermia, or decreased libido related to hyperprolactinemia) were found in 5 (56%) of the 9 women receiving risperidone, in 3 (33%) of the 9 men receiving risperidone, and in 1 (8%) of the 12 women receiving olanzapine (Table 3). However, no significant difference in frequency of hyperprolactinemic symptoms was found between the women and men treated with atypical antipsychotics (women vs. men: 6/33 [18%] vs. 3/42 [7%], $p = .14$; fertile women vs. men: 6/27 [22%] vs. 3/42 [7%], $p = .08$).

Of the patients with normal PRL levels, 1 clozapine-treated man reported decreased libido and 1 clozapine-treated woman had oligomenorrhea (Table 3).

LH, FSH, and Sexual Steroid Hormones

The median and range of LH, FSH, estradiol, and testosterone in the treatment groups are given in Table 2. No significant differences were found in median levels of LH, FSH, estradiol, or testosterone, either between the men or between the women in the treatment groups (Table 2).

All men had levels of LH and FSH within normal reference ranges, except 3 clozapine-treated men, 2 olanzapine-treated men, and 1 risperidone-treated man, all of whom had slightly deviating LH or FSH values, despite no hyperprolactinemia or clinical symptoms (Table 2). Three of these men with slightly decreased LH also had corresponding decreased testosterone values (5.9, 6.3, and 8.2 nmol/L), whereas the other 3 men had normal testosterone values. Of all men who had LH and FSH within normal reference ranges, 1 clozapine-treated and 1 risperidone-treated man had decreased testosterone (7.1 and 5.1 nmol/L) but normal PRL levels and no clinical symptoms.

Among the women, 1 risperidone-treated woman with hyperprolactinemia (81 μg/L) and oligomenorrhea exhibited a distinct suppression in LH, FSH, and estradiol levels (0.4 IU/L, 0.8 IU/L, and 86.1 pmol/L), and another risperidone-treated woman with hyperprolactinemia (58 μg/L) and amenorrhea showed a decreased estradiol level (70.2 pmol/L) (Table 2). However, all other women had LH, FSH, and estradiol within normal limits, except 2 clozapine-treated women who had slightly decreased estradiol levels (92 and 104 pmol/L), despite no hyperprolactinemia or clinical symptoms.

GH-IGF-I Axis

Slightly increased or decreased IGF-I values were observed in 4 clozapine-treated patients, 2 olanzapine-treated

Table 2. Median and Range of Prolactin (PRL), Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Estradiol, Testosterone, Growth Hormone (GH), and Insulin-Like Growth Factor I (IGF-I) in the 3 Treatment Groups

	Clozapine			Olanzapine			Risperidone		
Component (reference range)	All (N = 28)	Men (N = 16)	Women (N = 12)[a]	All (N = 29)	Men (N = 17)	Women (N = 12)[b]	All (N = 18)	Men (N = 9)	Women (N = 9)[c]
PRL, μg/L (men, menopausal women < 10; fertile women < 20)									
Median	4.5*	3.9**†	7.3***	7.1	6.6††	18.7	27.5	17.7†††	53.0
Range	2.7 to 16.0	2.7 to 6.7	3.6 to 16.0	5.0 to 38.0	5.7 to 14.6	5.0 to 38.0	8.5 to 84.0	8.5 to 30.6	21.4 to 84.0
LH, IU/L (men 2–10, fertile women 1–100, menopausal women 15–65)									
Median	4.8[d]	4.0†	6.6[e]	5.5[f]	3.6[g]††	18.8[h]	3.4	3.1	5.1
Range	1.2 to 20	1.2 to 8.6	4.1 to 20.0	0.6 to 36.0	0.6 to 7.1	5.5 to 36.0	0.4 to 40.0	1.5 to 6.2	0.4 to 40.0
FSH, IU/L (men < 10, fertile women 1–23, menopausal women 30–150)									
Median	3.7[d]	3.1†	6.6[e]	3.4[i]	2.5[j]††	8.9[k]	3.3	2.2	7.4
Range	0.9 to 38.6	0.9 to 6.7	1.8 to 38.6	1.0 to 90.3	1.0 to 19.3	2.8 to 90.3	0.8 to 29.0	1.6 to 7.1	0.8 to 29.0
Estradiol, pmol/L (fertile women 110–1470, menopausal women < 400)									
Median			232[k]			138[h]			138
Range			41.4 to 506			69.6 to 562			70.2 to 966
Testosterone, nmol/L (men 10–30)									
Median		17.1			21.6[g]			15.7	
Range		5.9 to 30.9			10.9 to 33.2			5.1 to 22.1	
GH, μg/L (< 15)									
Median	0.07[d]	0.03†	0.38[e]	0.05	0.03††	0.25	0.07	0.05†††	0.73
Range	0 to 6.39	0 to 5.35	0.06 to 6.39	0 to 6.74	0 to 0.21	0.02 to 6.74	0.01 to 14.0	0.01 to 0.58	0.05 to 14.0
IGF-I (± 2SD)									
Median	0	–0.6	0.3	0.2	0.2	0.1	–0.8	–0.9	–0.3
Range	–2.8 to 2.4	–2.8 to 1.3	–2.8 to 2.4	–2.1 to 2.2	–2.1 to 1.3	–1.3 to 2.2	–2.0 to 2.2	–2.0 to 0.4	–1.1 to 2.2

[a]Of whom 2 were menopausal; [b]of whom 3 were menopausal; [c]of whom 1 was menopausal.
[d]N = 27; [e]N = 11; [f]N = 21; [g]N = 12; [h]N = 9; [i]N = 23; [j]N = 13; [k]N = 10.
*Significantly different from the olanzapine-treated and risperidone-treated patients, p < .0001.
**Significantly different from the olanzapine-treated and risperidone-treated men, p < .0001.
***Significantly different from the risperidone-treated women, p < .0001.
†Significantly different from the clozapine-treated women, p = .0003.
††Significantly different from the olanzapine-treated women, p = .008.
†††Significantly different from the risperidone-treated women, p = .0003.

patients, and 1 risperidone-treated patient. The median IGF-I level was, however, normal in all 3 treatment groups, and the GH concentration was below the upper limit of normal in all patients (Table 2). Moreover, no significant differences were found in median levels of IGF-I or GH between the treatment groups (Table 2).

DISCUSSION

In this study regarding patients on treatment with therapeutic doses of 3 different atypical antipsychotics, elevated PRL levels were present in 89% of risperidone-treated patients and in 24% of olanzapine-treated patients, but in none of the clozapine-treated patients. Both the patients receiving risperidone and those receiving olanzapine had in addition significantly higher PRL levels than the patients receiving clozapine. Taken together, these findings clearly support the view that the atypical agents clozapine, olanzapine, and risperidone differ in effect on PRL secretion.

Since antipsychotic drugs exert their main effect on PRL secretion through blockade of the D_2 receptors on the lactotrophs in the pituitary,[17] it is reasonable to assume that the differences in PRL elevation of clozapine, olanzapine, and risperidone can be explained by differences in these drugs' binding affinity (K_i values) for the D_2 receptor.[29,30] Clozapine, which has a higher K_i value for the D_2 receptor than olanzapine, risperidone, and conventional antipsychotics,[29–31] and thus a weaker D_2 blocking effect,[32] was in this study associated with no PRL elevation, which is in accord with earlier studies, showing no or only small, brief PRL increases of clozapine.[33–35] A further explanation of the limited PRL elevation during clozapine treatment may be clozapine's ability to give rise to a compensatory increase in dopamine release in the tuberoinfundibular system in hypothalamus, leading to restored PRL inhibition at the pituitary level.[36,37] With olanzapine, on the other hand, which has a K_i value for the D_2 receptor that is lower than that for clozapine, but higher than those for risperidone and most conventional antipsy-

Table 3. The Occurrence of Amenorrhea, Oligomenorrhea, Galactorrhea, Impotence, Oligospermia, and Decreased Libido in Men and Women in the 3 Treatment Groups

	Clozapine		Olanzapine		Risperidone	
Variable	Men (N = 16)	Women (N = 12)	Men (N = 17)	Women (N = 12)	Men (N = 9)	Women (N = 9)
Amenorrhea (+ hyperprolactinemia)	…	…	…	…	…	3
Oligomenorrhea (+ hyperprolactinemia)	…	…	…	…	…	1
Oligomenorrhea + galactorrhea (+ hyperprolactinemia)	…	…	…	1	…	1
Impotence (+ hyperprolactinemia)	…	…	…	…	1	…
Oligospermia (+ hyperprolactinemia)	…	…	…	…	1	…
Decreased libido (+ hyperprolactinemia)	…	…	…	…	1	…
Oligomenorrhea (+ normal prolactin level)	…	1	…	…	…	…
Decreased libido (+ normal prolactin level)	1	…	…	…	…	…

chotics,[30,31] thus having an intermediate D_2 blocking effect,[38] the occurrence of PRL elevation and related symptoms in this study was modest. This is in line with other studies comparing the PRL elevating effect of olanzapine with that of risperidone or haloperidol,[39–41] but in contrast to a few studies extant comparing the PRL elevating effect of olanzapine with that of clozapine,[41,42] which show less divergence in PRL effect between these 2 agents than in this study. However, in those studies,[41,42] only men were included, which may have influenced the results. Regarding risperidone, in contrast, both risperidone and its metabolite 9-hydroxyrisperidone have low K_i values for the D_2 receptor, each of the compounds having only 2 to 4 times less affinity for the D_2 receptor than the conventional agent haloperidol.[29] The PRL response to risperidone therapy has even been reported to be twice as high as the response induced by the same dose of haloperidol, probably due to a contributive effect of the active metabolite 9-hydroxyrisperidone at the D_2 receptors on the lactotrophs.[25] Accordingly, the present results showed that risperidone therapy causes hyperprolactinemia and related symptoms, at least to a similar if not to a greater extent than is found in patients treated with conventional antipsychotics.[21] These results are also consistent with other reports.[43–46]

Additionally, the atypical antipsychotic–induced hyperprolactinemia was in this study more common in women compared with men, despite no differences in doses or serum concentrations of antipsychotics. This finding, which is in line with earlier results for conventional antipsychotics,[18,21–23] may also point to a sex-related difference in the sensitivity to atypical antipsychotics in the hypothalamic-pituitary PRL regulation. Moreover, the lack of a parallel statistically significant difference in hyperprolactinemic symptoms between men and women in this study possibly is explained by too small a number of patients in the subgroups compared.

Regarding the hypothalamic-pituitary-gonadal axis, decreased levels of gonadotropic and/or sexual steroid hormones were found in 2 (9%) of all 23 patients with hyperprolactinemia and in 9 (17%) of all 52 patients without hyperprolactinemia, suggesting that secretion of LH, FSH, and sexual steroid hormones is not markedly affected by the slight to moderate hyperprolactinemia that is induced by therapeutic doses of atypical antipsychotics. This is also in accord with previous results for conventional antipsychotics.[20–21,47] It is, however, to be noted that, although only 9% of the patients with hyperprolactinemia in this study had decreased LH, FSH, and/or sex steroid hormone levels, 39% of the hyperprolactinemic patients exhibited clinical symptoms related to their elevated PRL levels, pointing to some existing influence as well of slight to moderate antipsychotic-induced hyperprolactinemia on secretion of gonadotropic and sexual steroid hormones. This assumption is confirmed by others who, in contrast to this cross-sectional study, compared LH, FSH, and testosterone levels in schizophrenic men before and during treatment with conventional antipsychotics and found significant declines in LH and FSH levels during treatment, although the levels remained within normal limits.[48] Abnormal LH and FSH responses to luteinizing hormone–releasing hormone stimulation tests in conventional antipsychotic–treated women have also been found, despite basal LH and FSH serum concentrations within normal ranges.[49] Consequently, the secretion of LH, FSH, and sexual steroid hormones might have been influenced by the hyperprolactinemia also in those of our patients who had basal levels of these hormones within normal limits. In addition, the LH, FSH, and estradiol levels in the fertile women in this study were interpreted without regard to menstrual cycle phase, which may have contributed to an underestimation of "true" decreased levels.

Through analyzing IGF-I, and using it together with GH as an indirect parameter of GH secretion, no GH deficiency was found in the patients on treatment with clozapine, olanzapine, or risperidone. The finding indicates that therapeutic doses of these 3 atypical antipsychotics do not heavily influence the GH-regulating systems in hypothalamus, and this is also consistent with previous results for conventional antipsychotics at doses adjusted according to therapeutic efficiency.[21] Moreover, the slight to moderate hyperprolactinemia found in the patients in this study probably explains the lack of correlation between hyperprolactinemia and low IGF-I levels,

which usually is found in states of excessive hyperprolactinemia.[15,16]

In conclusion, we found that treatment with risperidone was frequently associated with hyperprolactinemia and related symptoms, whereas the occurrence of PRL elevation and related symptoms was modest in patients receiving olanzapine and nonexistent in those receiving clozapine. Thus, atypical antipsychotics in therapeutic doses differ with regard to effect on PRL secretion. Therefore, it is recommended that patients treated with atypical agents, especially risperidone, but also olanzapine, be monitored for PRL elevation and related symptoms and subjected to individualized therapeutic interventions if and when such side effects occur.

Drug names: biperiden (Akineton), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), orphenadrine (Norflex and others), risperidone (Risperdal), zolpidem (Ambien).

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