

Impact of a switch from typical to atypical antipsychotic drugs on quality of life and gonadal hormones in male patients with schizophrenia

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Abstract

OBJECTIVES: We investigated the effects of a switch from typical to atypical antipsychotic drugs (olanzapine, n=8; perospirone, n=9; or quetiapine, n=13) on quality of life and hypothalamo-pituitary-gonadal axis hormones.

METHODS: The subjects were 30 male chronic schizophrenia inpatients. The assessment was done before and after the switch.

RESULTS: After the switch, (i) scores of the Brief Psychiatric Rating Scale total and three factors (anxiety-depression, anergia, and thought disturbance) decreased, (ii) the overall severity score of the Drug Induced Extra-Pyramidal Symptoms Scale tended to decrease, (iii) prolactin decreased but gonadal hormones remained unchanged, and (iv) scores on all three subscales (psychosocial, motivation/energy, and symptoms/side effects) in the Japanese version of the Schizophrenia Quality of Life Scale (JSQLS) decreased. However, there were no significant group effects, or time-by-group interactions. In addition, score changes from baseline in psychosocial and motivation/energy subscales in the JSQLS were correlated with those in psychotic symptoms, particularly in the anxiety-depression factor. Moreover, responders had been taking lower doses of typical antipsychotic drugs, and had higher serum estradiol concentrations than non-responders before the switch.

CONCLUSIONS: The study indicated that the switch to atypical antipsychotic drugs was effective in reducing elevated prolactin without affecting the gonadal hormones and in improving quality of life patients who had been treated with typical antipsychotic drugs.

* This article is based on a study first reported in Rinsyo Seisin Yakuri (Japanese Journal of Clinical Psychopharmacology), Vol. 7, pages 483-492, 2004 (in Japanese).

Abbreviations:

QoL:	Quality of life
PRL:	prolactin
HPG:	hypothalamo-pituitary-gonadal
DSM:	Diagnostic and Statistical Manual of the American Psychiatric Association
BPRS:	Brief Psychiatric Rating Scale
DIEPSS:	Drug Induced Extra-Pyramidal Symptoms Scale
AD:	anxiety-depression
AN:	anergia
TD:	thought disturbance
AC:	activation
HS:	hostile-suspiciousness
JSQLS:	Japanese version of the Schizophrenia Quality of Life Scale
LH:	luteinizing hormone
FSH:	follicle-stimulating hormone
IRMA:	immunoradiometric assays
RIA:	radioimmunoassays
ANOVA:	analysis of variance

Introduction

Quality of life (QoL) in people with schizophrenia is one of the important subjects of interest. Since atypical antipsychotic drugs are considered to have favorable risk-benefit profiles, they are expected to improve QoL in people with schizophrenia. However, there are still very few prospective investigations of specific atypical antipsychotic medications and QoL [1–3].

Sexual function is thought to affect the QoL scores [4], and it depends on the interplay of many hormones and neurotransmitters. Among hormones, prolactin (PRL) and hypothalamo-pituitary-gonadal (HPG) axis hormones have important roles in regulating sexual function. So far, the effects of both typical and atypical antipsychotic drugs on PRL have been much investigated. However, the effects of antipsychotic drugs on HPG axis hormones have been less investigated, and there are still very few investigations of atypical antipsychotic medications and HPG axis hormones [1, 5–7].

This study was performed to investigate the effects of a switch from typical to atypical antipsychotic drugs (olanzapine, perospirone and quetiapine) on QoL and HPG axis hormones. The neuroendocrine and clinical assessments were done before and after the switch, and then compared. To our knowledge, this is the first prospective study to evaluate the effects of olanzapine, perospirone and quetiapine on the HPG axis hormones in patients with schizophrenia.

A preliminary report of the results of this study with up to 40% of the sample reported here has been published previously [8–11].

Subjects and methods

In this prospective, open-label study, 30 male inpatients with chronic schizophrenia were recruited. The diagnosis was based on Diagnostic and Statistical Manual of the American Psychiatric Association (DSM)-IV criteria for schizophrenia [12], a detailed clinical interview, and review of the prior records. In the subjects, hepatic and renal functions were normal, and subjects were excluded if they presented with any organic central nervous system disorder, significant substance abuse, and mental retardation. For the

hormonal comparison, 18 normal subjects were also recruited, and they had no ongoing medication. The study was approved by the relevant ethics committee and was performed in accordance with the Declaration of Helsinki II. The patients who gave informed consent to the research participated in this study. We chose to examine only male subjects in order to avoid the problem of menstruation related hormonal fluctuations.

Antipsychotic drugs received by the patients prior to the inclusion in the study were as follows: bromperidol (n=3, mean dose=18 mg), chlorpromazine (11, 101.4 mg), fluphenazine (1, 10 mg), haloperidol (27, 8.1 mg), levomepromazine (8, 28.1 mg), mosapramine (3, 76.7 mg), pipamperone (3, 200 mg), sulpiride (2, 500 mg), timiperone (4, 10.8 mg), and zotepine (4, 337.5 mg). Seventeen out of 30 (56.7%) patients were receiving more than two antipsychotic drugs. Six (20%) patients were receiving depot antipsychotic medications (fluphenazine, n=2, mean dose=25 mg/2wks; haloperidol, 4, 62.5 mg/4wks). Also, 25 (83.3%) patients were receiving anticholinergic medications.

The patients were included because their conditions were considered not to be optimal due to the lack of treatment responses or adverse events to the typical antipsychotic drugs. These patients were then switched to olanzapine, perospirone or quetiapine. Basically, the switch was performed systematically in the following manner: olanzapine, perospirone or quetiapine was added onto their previous antipsychotic drugs and gradually increased over a 6-week period (33.3% of pretreatment equivalent during week 2, 66.6% during week 4, and 100% during week 6). At the same time, their previous medications including anticholinergic medications were gradually tapered (pretreatment decreased 33.3% week 2, 66.6% week 4, and 100% week 6). Each antipsychotic was converted to its haloperidol equivalent using the dosage comparability table [13–16].

The following scales were completed by trained psychiatrists in the morning of the day when blood samples for the hormone estimation were drawn: Brief Psychiatric Rating Scale (BPRS₁₋₇) [17], and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) [18]. Based on previous groupings of BPRS symptoms [19], the following five BPRS factors were derived: anxiety-depression (AD), anergia (AN), thought disturbance (TD), activation (AC), and hostile-suspiciousness (HS). These factors were computed by summing the relevant items of the BPRS. The DIEPSS is composed of eight individual parameters and one global assessment constructed to measure EPS, using 5-point scales, and we considered the ratings of overall severity as the EPS scores.

The Japanese version of the Schizophrenia Quality of Life Scale (JSQLS) [20] was administered to assess the QoL. The JSQLS is a scale developed by Wilkinson et al. [21] for the QoL measure specific to people with schizophrenia. The JSQLS is a 30-item questionnaire, and provides scores on three scales (psychosocial, motivation/energy, and symptoms/side effects). Each item has a 5-point scale. The JSQLS was established

through back-translation into English, which was checked by the author of the scale. The JSQLS has been shown to be reliable, validated and practical [20].

The neuroendocrine and clinical assessments were done on two occasions (1) prior to atypical antipsychotic treatment, and (2) after a mean period of 81.1 days (SD=12.2) atypical antipsychotic treatment, and data were collected from all subjects. At the time of second assessment, 8, 9, and 13 patients were taking a mean dose of 15.6 mg (SD=5.0, range 10–20) olanzapine, 43.1 mg (9.8, 24–48) perospirone, and 559.6 mg (166.9, 300–750) quetiapine daily, respectively. Blood samples for the hormone estimation were drawn from all subjects between 0600 and 0700 h. The sera were prepared and stored at –20 centigrade until the time of analysis. Prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were assayed by immunoradiometric assays (IRMA), and testosterone and estradiol by radioimmunoassays (RIA). The coefficients for intraassay and interassay variation were $\leq 7.1\%$ and $\leq 3.6\%$ for PRL, $\leq 5.3\%$ and $\leq 9.0\%$ for LH, $\leq 4.6\%$ and $\leq 2.8\%$ for FSH, $\leq 11.2\%$ and $\leq 11.4\%$ for testosterone, and $\leq 7.0\%$ and $\leq 8.1\%$ for estradiol.

The data analysis was conducted using StatView-5.0J for Mac software. The differences in hormonal levels and clinical assessment scores between groups were compared by the analysis of variance (ANOVA), followed by post hoc comparisons (Fisher PLSD). Also, the changes of hormonal levels and clinical assessment scores between groups were compared by ANOVA with repeated measures. Pearson's correlation was used to examine the relationships between variables. The level of significance was set at $p < 0.05$.

Results

Demographic Characteristics

Before the switch, no significant differences between the groups for age, duration of illness, dose of typical antipsychotic medications, BPRS and EPS scores were revealed by ANOVA followed by post hoc comparisons (Table 1).

Measures of Psychotic Symptoms

Repeated measure ANOVA revealed significant time effects for the scores of BPRS total [F(1,27)=10.4 $p < 0.01$], AD [F(1,27)=15.8 $p < 0.001$], AN [F(1,27)=6.1 $p = 0.01$], and TD [F(1,27)=5.6 $p = 0.02$] (Table 2). In addition, there was a trend for the AC scores to be better after the switch [F(1,27)=2.9 $p = 0.09$]. However, there were no significant group effects, or time-by-group interactions.

EPS Assessment

For the EPS scores, there was a trend in the group effect [F(1,27)=3.4 $p = 0.07$]. There was no significant group effect, or time-by-group interaction (Table 2). Meanwhile, 25 out of 30 (83%) patients needed anticholinergic medications before the switch, but three (10%) patients needed anticholinergic medications after the switch [$\chi^2 = 6.0$, $df = 1$, $p = 0.01$].

Hormonal Measures

The mean values of the hormones measured are shown in Table 3. For the mean baseline serum PRL concentrations in patients, a repeated measure ANOVA revealed a significant time effect [F(1,27)=45.1 $p < 0.0001$], but there was not a significant group effect, or time-by-group interaction. A significant decrease in the mean PRL concentrations was observed in each group of patients treated with olanzapine [F(1,7)=6.2 $p = 0.04$], perospirone [F(1,8)=12.7 $p < 0.01$], and quetiapine [F(1,12)=47.4 $p < 0.0001$]. As a result, after the switch, the mean PRL concentration in patients was not significantly different from that in the normal controls, though the mean baseline serum PRL concentration in patients was significantly higher than that in the normal controls before the switch [F(1,46)=41.3 $p < 0.0001$].

For the mean baseline serum LH, FSH, testosterone and estradiol concentrations in patients, a repeated measure ANOVA revealed no significant time effects, group effects, or time-by-group interactions (Table 3). The concentrations of these HPG axis hormones were not significantly different from those in the normal controls before or after the switch.

Meanwhile, before the switch, there was a positive correlation between the serum PRL concentrations and doses of antipsychotic drugs [$r = 0.46$, $p = 0.01$, $n = 30$]. However, there was no significant correlation between the serum PRL and testosterone concentrations. After the switch, there were no significant correlations between the serum PRL concentrations and doses or testosterone concentrations.

QoL Assessment

Repeated measure ANOVA revealed significant time effects for the scores of all three JSQLS subscales [psychosocial, F(1,27)=18.2 $p < 0.001$; motivation/energy, F(1,27)=9.1 $p < 0.01$; and symptoms/side effects, F(1,27)=26.2 $p < 0.0001$] (Table 4). However, there were no significant group effects, or time-by-group interactions.

QoL and Variables

Psychosocial subscale score changes from baseline (Δ psychosocial) were correlated positively with the Δ BPRS [$r = 0.48$, $p < 0.01$, $n = 30$], Δ AD [$r = 0.47$, $p < 0.01$], Δ AC [$r = 0.41$, $p = 0.02$], and Δ HHS [$r = 0.39$, $p = 0.03$]. Δ motivation/energy was correlated positively with the Δ BPRS [$r = 0.65$, $p < 0.0001$, $n = 30$], Δ AD [$r = 0.54$, $p < 0.01$], Δ AC [$r = 0.51$, $p < 0.01$], Δ AN [$r = 0.50$, $p < 0.01$], and Δ HHS [$r = 0.45$, $p = 0.01$].

No significant correlations were found between Δ symptoms/side effects and score changes in psychotic symptoms. Also, no significant correlations were found between the changes in QoL scores and hormones.

Responders vs. Non-Responders

When a responder was defined a priori as any patient who achieved at least a 20% reduction in BPRS total scores from baseline, 12 out of 30 patients (40%) showed improvement. Moreover, responders were tak-

Table 1. Demographic Information

	Normal controls	Patients			P Values ^c	
	(n=18)	Total (n=30)	Olanzapine (n=8)	Perospirone (n=9)		Quetiapine (n=13)
Age (yrs)	36.3 (9.3)	35.9 (10.0)	34.4 (10.5)	34.2 (10.9)	38.1 (9.5)	0.77
Duration of illness (yrs)	–	13.4 (7.8)	10.9 (8.4)	13.8 (7.2)	14.8 (8.2)	0.55
Dose before switching (mg/day) ^a	–	16.8 (12.2)	12.0 (10.7)	20.2 (15.1)	17.5 (10.9)	0.37
BPRS (total)	–	43.3 (13.5)	43.6 (10.9)	41.3 (13.3)	44.5 (15.8)	0.87
DIEPSS ^b	–	0.9 (0.9)	0.9 (0.8)	0.8 (0.7)	1.0 (1.2)	0.86

Data are given as mean (SD). BPRS=Brief Psychiatric Rating Scale; DIEPSS=Drug Induced Extra-Pyramidal Symptoms Scale.

^aHaloperidol equivalent [16].

^bThe ratings of overall severity in the DIEPSS were used.

^cComparisons between groups using analysis of variance (ANOVA) followed by post hoc.

Table 2. Scores on BPRS and DIEPSS

	Before Switching	After Switching	Time Effect (P Values) ^b	Time by Group Interaction (P Values) ^b
BPRS (Total)	43.3 (13.5)	36.3 (11.5)	<0.01	0.53
BPRS (AC)	6.4 (3.3)	5.5 (2.5)	0.09	0.76
BPRS (AD)	9.6 (4.7)	6.7 (2.9)	<0.001	0.40
BPRS (AN)	9.7 (3.1)	8.3 (3.3)	0.01	0.77
BPRS (HS)	6.8 (3.6)	5.8 (3.5)	0.10	0.86
BPRS (TD)	10.9 (3.9)	9.3 (4.1)	0.02	0.86
DIEPSS ^a	0.9 (0.9)	0.5 (0.6)	0.07	0.92

Data are given as mean (SD). AC=activation; AD=anxiety-depression; AN=anergia; HS=hostile-suspiciousness; TD=thought disturbance.

^aThe ratings of overall severity in the DIEPSS were used.

^bComparisons between pre- and post-switching using ANOVA with repeated measures.

Table 3. Data of Prolactin (PRL) and Gonadal Axis Hormones

	Normal Controls	Before Switching	After Switching	Normal Range	Time Effect (P Values) ^a	Time by Group Interaction (P Values) ^a
PRL (ng/mL)	5.63 (2.72)	17.27 (9.94)*	5.38 (3.90)	1.5–9.7	<0.0001	0.10
LH (mIU/mL)	4.71 (2.44)	4.63 (2.19)	4.76 (4.11)	1.8–5.2	0.63	0.57
FSH (mIU/mL)	7.05 (4.08)	6.40 (4.37)	7.78 (9.04)	2.9–8.2	0.55	0.19
Testosterone (ng/mL)	5.691 (1.522)	5.079 (1.616)	5.060 (1.839)	3.00–10.50	0.96	0.43
Estradiol (pg/mL)	29.3 (10.9)	42.4 (22.1)	44.5 (25.0)	20–60	0.51	0.97

Data are given as mean (SD). FSH=follicle-stimulating hormone; LH=luteinizing hormone;

^aComparisons between pre- and post-switching using ANOVA with repeated measures.

* $p < 0.0001$ versus normal controls by ANOVA.

Table 4. Scores on Quality of Life (QoL) Scale

	Before Switching	After Switching	Time Effect (P Values) ^a	Time by Group Interaction (P Values) ^a
JSQSL (PS)	60.2 (21.6)	46.4 (19.8)	<0.001	0.32
JSQSL (ME)	62.5 (16.7)	50.2 (17.5)	<0.01	0.86
JSQSL (SS)	44.8 (17.3)	30.8 (18.2)	<0.0001	0.68

Data are given as mean (SD). JSQSL=Japanese version of the Schizophrenia Quality of Life Scale; ME=motivation/energy; PS=psychosocial; SS=symptoms/side effects.

^aComparisons between pre- and post-switching using ANOVA with repeated measures.

Table 5. Differences in Baseline Data between Responders and Non-Responders

	Responders (n=12)	Non-Responders (n=18)	P Values ^c
Age (yrs)	34.7 (9.1)	36.8 (10.8)	0.58
Duration of illness (yrs)	10.8 (7.4)	15.2 (7.8)	0.14
Dose before switching (mg/day) ^a	10.2 (10.7)	21.3 (11.3)	<0.01
BPRS (Total)	47.3 (15.9)	40.6 (11.3)	0.18
DIEPSS ^b	1.0 (1.1)	0.8 (0.8)	0.63
PRL (ng/mL)	15.7 (10.8)	18.3 (9.5)	0.19
LH (mIU/mL)	4.6 (2.5)	4.6 (2.1)	0.93
FSH (mIU/mL)	6.4 (5.1)	6.4 (4.0)	0.87
Testosterone (ng/mL)	5.065 (1.616)	5.088 (1.663)	0.97
Estradiol (pg/mL)	55.9 (26.2)	33.3 (13.1)	<0.01

Data are given as mean (SD).

^aHaloperidol equivalent.

^bThe ratings of overall severity in the DIEPSS were used.

^cComparisons between responders and non-responders.

ing significantly lower doses of typical antipsychotic drugs [$F(1,28)=13.5$ $p<0.01$], and had significantly higher serum estradiol concentrations [$F(1,28)=9.3$ $p<0.01$] than non-responders before the switch (Table 5).

Discussion

Our results showed that switching medications from typical antipsychotic drugs to olanzapine, perospirone or quetiapine was effective in reducing elevated basal serum PRL levels without affecting the HPG axis hormones and in improving all three QoL subscales in male patients with chronic schizophrenia.

In this study, we found significant improvements in the scores of BPRS total, AD, AN and, TD factors, and a trend for the AC scores to be better after switching medications, though there were no significant group effects, or time-by-group interactions. The findings seem to indicate that olanzapine, perospirone and quetiapine had a broader spectrum of efficacy in psychotic symptoms, and they may be useful for the patients especially when their condition were not to be optimal due to the lack of treatment responses or adverse events to typical antipsychotic drugs. We did not find a significant improvement in scores of HS factor, possibly because HS symptoms had been managed effectively with typical antipsychotic drugs.

Decrease, or absence, of the capacity to cause EPS is considered to be one of the criteria to define atypical antipsychotic drugs [22]. In this study, there was a trend for the EPS score to decrease, and the usage of anticholinergic drugs decreased. The reduction in the EPS score did not reach statistical significance, possibly because the mean EPS score in our patients before starting atypical antipsychotic drugs was low due to the presence of anticholinergic drugs.

Typical antipsychotic drugs are known to block D_2 receptors and increase PRL secretion from anterior pituitary mammatropes. In fact, in this study, before switching to atypical antipsychotic drugs, the mean serum PRL concentrations were elevated above normal in patients who were treated with various typical antipsychotic drugs, and, moreover, the serum PRL concentrations were related to doses of typical antipsychotic drugs. Previous reports have been indicated that olanzapine and quetiapine do not induce a persistent PRL increase [23], although they may lead to a transient PRL elevation [24, 25]. Also, perospirone has been reported not to induce a persistent PRL increase [26], though the frequency of hyperprolactinemia in patients treated with perospirone was reported to be comparable to that with haloperidol [27]. Our findings showed that olanzapine, quetiapine, and perospirone did not induce a persistent PRL increase.

In contrast to the effects of antipsychotic drugs on PRL, there are contradictory findings regarding the effects of typical antipsychotic drugs on the HPG axis [28, 29]. In this study, significant differences were not shown between normal controls and patients on typical antipsychotic medications for the HPG axis hor-

mones, regardless of PRL elevations. Since PRL has been reported to act at the hypothalamus to cause a decrease in gonadotropin secretion, and thus to cause a decrease in testosterone secretion [30], the degree of hyperprolactinemia found in this study may have been insufficient to cause hypogonadism in patients in this study. Regarding the effects of atypical antipsychotic drugs on the HPG axis, risperidone [1, 5, 6] has been reported not to affect HPG axis hormones regardless of significant increases in the PRL levels. Markianos et al. [7] also showed that clozapine did not have any substantial effect on the HPG axis hormone levels, although it reduced substantially the PRL levels. A comprehensive search has been conducted by using a MEDLINE search (1966–2003) of the English-language literature, and reveals no reports on effects of olanzapine, perospirone or quetiapine on testosterone. In this prospective study, we found that HPG axis hormones remained unchanged during olanzapine, perospirone and quetiapine treatment regardless of significant decreases in PRL levels. Also, this study didn't show statistically significant differences between normal controls and patients on atypical antipsychotic medications for the HPG axis hormones. Our findings indicated that atypical antipsychotic medications might not affect the HPG axis in male patients with chronic schizophrenia.

Voruganti et al. [3] examined the long-term consequences of switching patients from typical to atypical antipsychotic drugs (olanzapine, quetiapine, or risperidone), and reported that atypical antipsychotic drugs were significantly tolerated better, and had a positive impact on treatment-adherence, psychosocial functioning, and QoL. Our results also showed that switching medications from typical antipsychotic drugs to olanzapine, perospirone or quetiapine produced significant improvements in all three SQLS subscales. Several factors have been indicated to affect QoL, including severity of psychopathology, cognitive functions, and side effects [31]. In this prospective study, score changes from baseline in psychosocial and motivation/energy subscales in the JSQLS were correlated with those in psychotic symptoms, particularly in the AD factor. Priebe et al. [32] also found that changes in subjective QoL and anxiety-depression were correlated in first-admitted patients with schizophrenia. We, therefore, speculate that one of the major factors that contributed to the improvement in the QoL scores may be the change in the psychotic symptoms, particularly in the anxiety-depression. Since the potential value of atypical antipsychotic drugs for improving cognitive impairment in patients with schizophrenia has been indicated [33], atypical antipsychotic drugs might have improved directly the QoL scores by improving cognitive impairment, though no measures of cognitive function were collected in this study. In addition, atypical antipsychotic drugs may have improved indirectly the QoL scores via improving cognitive impairment by making anticholinergic medications needless, since anticholinergic drugs have been reported to induce cognitive dysfunction [34].

Also, atypical antipsychotic drugs may have improved indirectly the QoL scores via improving sexual function by reducing PRL levels, though sexual function was not assessed in this study. Regarding the improvement in the score on the symptoms/side effects, QoL subscale may provide additional support for the view that olanzapine, perospirone and quetiapine have overall favorable comparative side-effect profiles.

So far, biological or clinical predictors of patient responses during antipsychotic drug treatment have not been established, though some factors have been suggested as predictors of antipsychotic responses. In this study, responders were taking lower doses of typical antipsychotic drugs, and had higher serum estradiol concentrations than non-responders before the switch. Patients, who were treated with adequate typical antipsychotic medications but without significant symptom relief, might have been treatment-resistant, and thus clinical improvement may not be expected when switching chronically psychotic patients from typical to atypical antipsychotic drugs. Meanwhile, estradiol is suggested to be involved in schizophrenia, and influence neuronal pathways in negative symptoms, particularly in females [35]. Via its neuroprotective properties, estradiol may affect progression and therapeutic responses of schizophrenia, even in male patients.

A larger sample replication study is necessary to confirm and generalize the observations of this study.

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