



The endocrine impact of long term risperidone therapy in Asian Indian patients

Abstract

Background: Risperidone is a widely used antipsychotic, known to cause secondary hyperprolactinaemia. Related problems include bone mineral density (BMD) and vitamin D deficiency. However, there is insufficient information about the extent, severity, and association between these side effects, particularly in the Asian population. **Objectives:** To estimate the prevalence of osteoporosis, and vitamin D deficiency in patients taking risperidone for more than one year. Also, to investigate whether erectile dysfunction (ED) or menstrual dysfunction (MD) can be used as a proxy indicator of BMD loss in such patients, replacing dual energy X-ray absorptiometry (DEXA) scan. **Method:** Sixty-five patients (mean age 29.6) receiving risperidone as the only prolactin raising medication for minimum period of one year were selected taking into consideration the socio-demographic and clinical variables. History of ED/MD, DEXA measurement of their lumbar and hip bone, and endocrine variables were recorded. **Results:** The prevalence of hyperprolactinaemia in female was found to be 84.4% and in males 78.8%; females being 1.4 times more at risk than males. Abnormal BMD was found in more than 40% of the subjects. Furthermore, 30% had vitamin D deficiency and 60.8% had vitamin D insufficiency. A statistically significant association was observed between ED/MD and BMD (odds ratio [OR] 3.71, confidence interval [CI] 1.23-11.24, $p=0.02$), but this varied according to the gender. **Conclusion:** These results suggest that patients on long term risperidone are at high risk of developing hyperprolactinaemia, reduced BMD and Vitamin D, although multiple contributory factors or mechanisms can be suggested. Clinically, ED was more significantly associated with changes in BMD.

Keywords: Antipsychotic. Hyperprolactinaemia. Bone Mineral Density. Erectile Dysfunction. Menstrual Dysfunction.

JP Russell Ravan¹, Naveen Thomas², Thomas Paul³, Samuel Prasanna⁴, Nihal Thomas⁵, Deepa Ramaswamy⁶

¹Associate Professor and Head of Unit II, Post Graduate of Psychiatry, Kalinga Institute of Medical Science and PBMH, Bhubaneswar, Odisha, India, ²Consultant Psychiatrist, Melbourne Health, Australia, ³Department of Endocrinology, CMC Vellore, Tamil Nadu, India, ⁴Department of Biostatistics and Research, CMC Vellore, Tamil Nadu, India, ⁵Professor of Endocrinology, CMC Vellore, Tamil Nadu, India, ⁶Professor and Unit Head, Department of Psychiatry, CMC Vellore, Tamil Nadu, India

Correspondence:

Dr JP Russell Ravan, MD, DPM (CMC Vellore), Associate Prof and Head of Unit II, Post Graduate of Psychiatry & Behavioral Sciences, Kalinga Institute of Medical Science and PBMH, Bhubaneswar-751024, Odisha, India. jpr_219@yahoo.co.in

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Introduction

Schizophrenia is a chronic and disabling mental disorder associated with abnormalities of brain structure and function.[1] Atypical antipsychotics (excluding clozapine) are the first line therapeutic agents for schizophrenia.[2] While prescribing atypical antipsychotic medication as the first line, clinicians need to be aware of and screen for adverse effects like weight gain, dyslipidaemia, impaired glucose tolerance, and hyperprolactinaemia. There is a need to develop a protocol for early detection and intervention of these disorders. The antipsychotic drugs that have induced hyperprolactinaemia and its related morbidity is a neglected area in clinical practice as well as in research. Secondary hyperprolactinaemia could lead to a menstrual delay in females, disturbed sexual function in males, and may cause a reduction in bone mineral density (BMD).[3]

Clozapine, quetiapine, and olanzapine are generally not associated with persistent hyperprolactinaemia, though there are some reports.[4] In contrast, risperidone and

amisulpiride cause a marked and sustained increase in serum prolactin levels. Risperidone is an atypical antipsychotic, is widely available, relatively inexpensive, and extensively used in India.

Hyperprolactinaemia with antipsychotic medicines may influence BMD. Studies designed to identify reduced BMD in patients treated with antipsychotics are preliminary, and are limited by small sample sizes and other methodological shortcomings.[5] However, these adverse effects are of concern and need to be more objectively in people on psychotropic medication. Hyperprolactinaemia caused by risperidone may adversely affect BMD by inducing hypogonadotrophic hypogonadism. Most of these groups of patients have inadequate sunlight exposure which can predispose them to vitamin D insufficiency or deficiency. This results in secondary hyperparathyroidism which affects the bone remodeling. Vitamin D deficiency is becoming an increasing concern and is being recognised more in various cohorts of subjects like postmenopausal women,[6] and adult

men and women on antiretroviral treatment.[7] However, there are paucity of studies in patients with mental illness with relation to the bone disease.

The current study was undertaken with an objective to assess the prevalence of hyperprolactinaemia, decreased BMD, and hypovitaminosis D in a homogenous group of patients on long term risperidone treatment and to study the correlation between vitamin D insufficiency, hyperprolactinaemia, and BMD in ambulatory, stable chronic mentally ill patients exclusively on risperidone as the only hyperprolactinaemia inducing psychotropic agent.

Methods and methodology

Inclusion and exclusion criteria

The study population was drawn from all patients with mental illness attending the outpatient review services in the Department of Psychiatry, Bagayam, Christian Medical College, Vellore. Following Institutional Review Board (IRB) approval (IRB clearance number and date: 6366/11.09.2007), the Principal Investigator (PI) hand screened all charts issued for outpatient review. A note was put into any likely candidate's chart, requesting the concerned doctor to send the patient to the PI for detailed screening after his/her routine review. Screening was stopped after sample size was achieved. The participants were included in the study after informed consent was administered. The study population included all subjects within the age group of 18 to 45 years on a stable dose of risperidone for at least a period of one year. Other comorbid conditions which lead to hyperprolactinaemia or BMD changes like the alcohol dependence syndrome or anorexia nervosa, non-ambulatory myopathic disorders, pregnancy, other medications which cause hyperprolactinaemia like sodium valproate, carbamazepine, tricyclic antidepressants, specific serotonin reuptake inhibitors (SSRIs), and oral contraceptive pills were screened for and excluded from entry into the study. Patients who were on calcium, vitamin D, and other medications which affect bone metabolism were also excluded.

Evaluation

Following entry into the study, the clinical and demographic profile was reassessed, including the duration of untreated psychosis, past history of exposure to antipsychotic medication, duration of treatment with risperidone, and other coadministered psychotropic drugs, history of bone pains, fractures, and proximal muscle weakness. From the patient case records, details regarding the Axis-I diagnosis and other comorbid conditions were obtained.

Fasting blood samples were collected for the assessment of serum calcium (8 to 10 mg/dl), phosphate (2.5 to 4.5 mg/dl), alkaline phosphatase (20 to 140 IU/L), albumin (3.5 to 5 g/dL), creatinine (0.5 to 1.4 mg/dL) and were measured on the HITACHI 911 model auto analyser (Boehringer Mannheim). 25-hydroxy vitamin D was measured using electrochemiluminescence (Roche Diagnostic, Indianapolis, US). (Coefficient of variation of 6.6 to 9.9% at low and high levels). Vitamin D levels more than 30 ng/ml was considered sufficient.[8] Levels between

10-30 ng/ml were considered insufficient and levels <10 ng/ml were considered vitamin D deficient. Serum prolactin was assessed using chemiluminescent assay in Immulite 2000. Hyperprolactinaemia was defined as the level of serum prolactin of >24.20 ng/ml for females and >18.77 ng/ml for males. This assay had an analytical sensitivity of 0.16%.

BMD was assessed by using the Hologic Machine (QDR 4500; Hologic, Inc., Waltham, MA, USA) at the lumbar spine and the femoral neck. The reference population was normal for Caucasians (manufacturer's database). Precision was two per cent at both the measured sites (spine and neck of femur). The normal range was defined as a T score of -1 or higher, and osteopenia as T score between -1 and -2.5, and osteoporosis as a T score of -2.5 or lower.

Sample size calculation

Sample size of 64 was required to find a prevalence of change in bone mineral density of 20%[9] with a precision of ten per cent and with a 95% confidence interval (CI).

Statistics

All numerical variables were described using mean with standard deviation (SD), and categorical variables were summarised using frequencies and percentages. Continuous variables were compared between the study groups using independent two sample t test if they were normally distributed and nonparametric tests were used if their distribution were not normal (e.g. prolactin). Chi square or Fisher exact test was used for comparison when variables were categorical. Logistic regression analyses were done to assess the independent effect of multiple variables on BMD and osteoporosis. Odds ratios (OR) with 95% CI were obtained and p-values of less than 0.05 were considered statistically significant. Statistical analysis was done using the SPSS 11 software package.

Results

Sixty five patients with a mean (SD) age of 29.4 (6.5) years fulfilling the inclusion criteria were included in the study after obtaining informed consent. An ICD-10 diagnostic criterion for schizophrenia was met by 38 (58.5%). The remainders were diagnosed to have either psychotic bipolar disorder (35.4%) or acute psychosis (3.1%) or schizoaffective disorder (3.1%).

Eighteen (27.7%) of the patients were only on risperidone whereas the others were on combination therapy- risperidone with lithium: 11 (16.9%), risperidone plus trihexyphenidyl: 27 (41.5%), risperidone plus lithium with trihexyphenidyl: five (7.7%), and risperidone with benzodiazepine: four (6.1%).

The consecutive sample consisted of 32 women (49.2%) with mean (SD) age of 28.8 (6.59) years and 33 men (50.8%) with a mean age of 30.06 (6.53) years. There was no significant difference between the male and female groups in terms of occupation, comorbid Axis-I diagnosis, or past history of exposure to other antipsychotic agents (Table 1). There was no significant difference in terms of age of onset of psychotic illness, duration of untreated psychosis, average dose, and mean duration of treatment with risperidone.

Table 1: Baseline variables

Baseline variables	N (%)	Normal BMD (N=39)	Osteoporosis/osteopenia (N=26)	p-value
Gender				
Male	32 (49.2)	20 (51.3)	12 (46.2)	0.801
Female	33 (50.8)	19 (48.7)	14 (53.8)	
Diagnosis of the patient				
Schizophrenia	38 (58.5)	24 (61.5)	14 (53.8)	0.612
Bipolar affective disorder/Schizoaffective disorder	27 (41.6)	15 (38.5)	12 (46.2)	
Comorbid Axis-I diagnosis				
No	55 (84)	33 (84.6)	22 (84.6)	0.631
Yes	10 (15.4)	6 (15.4)	4 (15.4)	
Occupation				
Unemployed	11 (16.9)	7 (17.9)	4 (15.4)	0.99
Employed	54 (83.1)	54 (83.1)	22 (84.6)	
Medication				
Risperidone	18 (27.7)	13 (33.3)	5 (19.2)	0.266
Other	47 (72.3)	26 (66.7)	21 (88.8)	
Biochemical parameters (Mean±SD)*				
Prolactin level	46.73±32.51	43.67±31.13	49.74±33.90	0.460
Serum calcium	8.57±0.315	8.64±0.32	8.51±0.31	0.119
Vitamin D	15.18±8.19	16.83±9.23	13.54±7.15	0.133
Serum alkaline phosphatase	83.06±50.25	81.43±21.08	84.69±29.17	0.603
Serum phosphorous	3.66±0.52	3.86±0.55	3.46±0.48	0.004

*Mann-Whitney U test was used for the comparison, N=Number, BMD=Bone mineral density, SD=Standard deviation

The hyperprolactinaemia was seen in 27 females (84.4%) and 26 males (78.8%). The odds ratio estimation showed that females were 40% at more relative risk of hyperprolactinaemia as compared to males.

Of the 65 subjects included in the study, two females and one male (4.6%) did not have a Vitamin D level assessment. Of the rest, 60 (92.3%) had vitamin D deficiency (n=20, 30.8%) or vitamin D insufficiency (n=40, 61.5%). There was no difference between gender groups in relation to Vitamin D deficiency and sufficiency.

BMD measure in lumbar spine and neck of femur

Twenty nine (44.7%) subjects had BMD abnormalities in the lumbar spine. Nine (13.8%) had osteoporosis, and 20 (30.9%) had osteopenia. Of the nine with osteoporosis, seven were men and two were women.

Forty per cent (n=26) of subjects had BMD abnormalities in neck of femur. Two subjects (3.09%) had osteoporosis and 24 (36.91%) had osteopenia. Both subjects with osteoporosis were male. Overall, 14 (42.5%) of the men and 12 (37.5%) of the women had reduced BMD values at neck of femur.

When looked at the differences between the normal BMD group and the osteopenic/osteoporotic group either in lumbar spine or at neck of femur, in terms of gender, occupation, Axis-I diagnosis, exposure of other antipsychotic

medication in the past, and other comorbid conditions, no statistical difference was seen.

Prevalence of gonadal dysfunction (Table 2)

Of the 65 subjects, 21 (32.8%) had either amenorrhoea or erectile dysfunction (ED). Eight of 33 females (24.2%) reported amenorrhoea and 14 of 32 males (43.8%) had ED.

On comparing report of either ED or amenorrhoea with BMD changes at lumbar spine, a statistically significant difference was seen. The OR was 3.71 with CI of 1.23-11.24.

In Table 2, a sub group analysis across gender groups in relation to BMD changes at spine was carried out. Lowered BMD did not correlate with amenorrhoea in women (p=0.399) and OR 2.0 (CI: 0.39-10.16).

Among men, ED is significantly related to BMD changes at lumbar spine (p=0.026) and OR 5.71 (1.16-28.07).

As shown in Table 3, of the 65 subjects, 90.8% had abnormal serum vitamin D levels. In accordance with the Holick's criteria, 20 (30%) had Vitamin D deficiency, 40 (60.8%) had vitamin D insufficiency, and 3 (4.1%) had vitamin D sufficiency. For analysis, they were divided into deficient and not deficient groups.

In males the prevalence of vitamin D deficiency was 13 (41.9%) and in females it was seven (22.6%). No statistical difference was seen when vitamin D deficient group and vitamin D non deficient group were

Table 2: Sexual dysfunction compared in both normal and abnormal BMD at lumbar spine

Variable	N (%)	Normal BMD spine	Abnormal BMD spine	p-value	OR (95% CI)
ED/amenorrhoea*					
Yes	21 (32.8)	7 (33.3)	14 (66.6)	0.016	3.71 (1.23-11.24) Reference
No	43 (67.2)	28 (65.1)	15 (34.9)		
Amenorrhoea in female*					
Yes	8 (25.0)	4 (50.0)	4 (50.0)	0.399	2.0 (0.39-10.16) Reference
No	24 (75.0)	16 (66.7)	8 (33.3)		
ED in male					
Yes	13 (40.6)	3 (23.1)	10 (6.9)	0.026	5.71 (1.16-28.07) Reference
No	19 (60.4)	12 (63.2)	7 (36.8)		

*One of the subject data was missing; BMD=bone mineral density, N=number, OR=odds ratio, CI=confidence interval, ED=erectile dysfunction

Table 3: Prevalence vitamin D deficiency* and antipsychotic medication

Variables	N (%)	Normal/insufficiency	Vitamin D deficient	p-value	OR (95% CI)
Gender					
Male	31 (50)	18 (58.1)	13 (41.9)	0.103	2.47 (0.821-7.46) Reference
Female	31 (50)	24 (77.4)	7 (22.6)		
BMI*					
Normal	27 (53.4)	19 (70.4)	8 (29.6)	0.829	1.13 (0.37-3.46) Reference
Obesity	31 (46.6)	21 (67.7)	10 (32.3)		
ED/amenorrhoea					
No	40 (64.5)	29 (72.5)	11 (27.5)	0.280	0.55 (0.18-1.64) Reference
Yes	22 (35.5)	13 (59.1)	9 (40.9)		
Dose of risperidone (mg)					
2-4	33 (53.23)	26 (78.8)	7 (21.2)	0.047	3.01 (0.99-9.157) Reference
4.5-10	29 (46.77)	16 (55.2)	13 (44.8)		
BMD in spine*					
Normal	33	23 (69.7)	10 (30.3)	0.786	0.783 (2.68-2.28) Reference
Abnormal	28	18 (64.3)	10 (35.7)		
BMD in neck					
Normal	26 (41.94)	17 (65.4)	9 (34.6)	0.736	0.83 (0.28-2.43) Reference
Abnormal	36 (58.06)	25 (69.4)	11 (30.6)		

*Four subjects' vitamin D serum value was not in the laboratory follow-up report; N=number, CI=confidence interval, BMI=body mass index, BMD=bone mineral density

compared on the basis of gender, body mass index (BMI), ED/amenorrhoea, and abnormal BMD changes in spine and femur neck.

However, the group on higher dose of risperidone (>4 mg per day) showed higher risk of developing vitamin D deficiency with a p-value of 0.047, OR 3.01 (CI 0.99-9.157) as compared to the group of patients with average dose of risperidone less than 4 mg per day.

Discussion

Antipsychotic induced hyperprolactinaemia

In our study, 84% of women and 78.8% of men, have hyperprolactinaemia. In a study approximately 60% of women and 40% of men treated with a prolactin-raising antipsychotic had a prolactin level above the upper limit of the normal range.[5] Our finding of hyperprolactinaemia

in female is comparable to the findings of the other studies. However, in males the prevalence of hyperprolactinaemia is almost double than that of what has been cited in available literature. Such a high prevalence of hyperprolactinaemia in Indian male psychiatric population needs further study in greater detail.

In our study 81% subjects had hyperprolactinaemia. Eighty one per cent of hyperprolactinaemia is higher when compared to the 62% of hyperprolactinaemia detected in western patients,[10] who found out that patients on risperidone had the highest level of serum prolactin, when compared to those on typical antipsychotic medication.

Hyperprolactinaemia is an adverse effect of antipsychotic medication that has been underinvestigated by clinicians and researchers. Risperidone, in comparison to other atypicals commonly used, is more likely to cause hyperprolactinaemia. This effect needs to be taken seriously and investigated further.

No published data is available so far for the Indian population.

Antipsychotic induced menstrual irregularities and hyperprolactinaemia

Sixty per cent of women subjects, with a mean age of 30 years, had menstrual related abnormalities. Twenty four per cent had amenorrhoea and 38% had delayed menstruation. All women who developed amenorrhoea had hyperprolactinaemia.

Existing data suggests that irregular cycles and galactorrhoea are common, but that clinicians underestimate the prevalence. For example, well conducted studies of women treated with conventional antipsychotics have reported prevalence rates of approximately 45% for oligomenorrhoea/amenorrhoea and 19% for galactorrhoea.

An illness-related under-function of the hypothalamic-pituitary-gonadal axis in female patients with schizophrenia may also contribute to menstrual irregularities. Also, there is evidence in literature to show that baseline menstrual problems get worsened and that galactorrhoea or gynaecomastia manifest only after exposure to antipsychotic medication.[11] However we did not elicit information regarding galactorrhoea. This must be done in future studies.

Biller *et al.*[12] showed that the duration of amenorrhoea was positively associated with severity of BMD loss. They showed that 42% of hyperprolactinaemic women who remained amenorrhic for a period of 1.7 (SD 0.2) years exhibited BMD loss more than two standard deviations below the control mean. Hyperprolactinaemic hypogonadal women with secondary amenorrhoea resulting from low oestrogen production were found to have significantly lower BMD than hyperprolactinaemic women who maintained sufficient oestrogen levels to retain menses.

This suggests that women on risperidone, who develop amenorrhoea, are at high risk for lowered BMD and possibly for fractures. The present study has not assessed the duration of amenorrhoea and its relationship with changes in BMD.

Sexual dysfunction and antipsychotic medication

Forty four per cent of males with mean (SD) age of 28.84 (6.59) years reported ED. In a study by Ghadirian *et al.*,[13] among outpatients with schizophrenia, 54% of men and 30% of women reported sexual dysfunction. Under reporting of sexual dysfunction in our study is possible. Reasons include lack of extensive questionnaire, culture specific factors, and stigma related issues. Studies show that psychiatric patients rated drug-induced sexual dysfunction as more 'bothersome' than most psychiatric symptoms of their illness.[14]

Knegtering *et al.*[15] reported a study to comparing sexual side effects of prolactin rising antipsychotic medication with those on non prolactin rising ones. Results showed that prolactin raising antipsychotic induced sexual side effects were significantly more as compared to prolactin sparing antipsychotic medication.

The presence of ED was significantly associated with impairment in BMD. The report of ED in psychiatric clinic should alert the clinician to evaluate BMD.

Antipsychotic medication and BMD changes

Our data showed that 40% of patients on risperidone had low BMF (osteopenia or osteoporosis). Out of ten people who have osteoporosis, 80% were males and 20% were females. The remaining 23 had osteopenia. This is a high prevalence, given the mean age (29.4 years, SD 6.5) and the fact that these are ambulatory patients, with the majority having some form of productive occupation (76.7%).

The prevalence found by our study is similar to the finding of the other studies, like in non-Indian populations by Meaney *et al.*[10] The inpatients who were on prolactin rising antipsychotic medication for a average period of ten years measures to have reduced BMD as 7 (57%) of the male and 8 (32%) of the female patients.

In a study on psychiatric inpatients, significant numbers of patients had a remarkable decrease in BMD when compared with age- and sex-matched normal data.[16] Wyszogrodzka-Kucharska and Rabe-Jabłońska [16] demonstrated that patients with schizophrenia suffered from a lower mean BMD in comparison to the control group. However, both these studies were conducted on inpatients on a psychiatric ward. There is no data on Indian ambulatory patients in remission and also on regular dose of risperidone as only antipsychotic medication.

It is possible that normative data derived from Caucasian populations is inapplicable in our population, leading to an overestimate of low BMD in our study population. Unfortunately, there are no established norms for BMD in healthy Indians.

Hyperprolactinaemia and BMD changes

88.5% of our subjects who had decreased BMD at either neck of femur or lumbar spine, or both, had hyperprolactinaemia.

Abraham *et al.*[17] reported an inverse relationship between prolactin level and bone mass in patients receiving

antipsychotic medications. Other studies have found a similar relationship. However, these have been looked at as continuous variables, without categorisation into hyper or hypoprolactinaemic states.[9,18]

Thus patients on prolactin raising antipsychotic medication need to be screened for hyperprolactinaemia and other factors which can decrease BMD. Patients with hyperprolactinaemia should be investigated further in order to monitor BMD changes.

Vitamin D and chronic mental illness

Our study on patients with long term risperidone showed that more than 90% had either vitamin deficiency or insufficiency. Thirty per cent were deficient in Vitamin D (<10 ng/mL). It is alarming to note that 30% of ambulatory psychotic outpatients in their maintenance phase of treatment, with a mean age of 30 years had significant vitamin D deficiency. Vitamin D deficient patients received a significantly higher dose of risperidone, and this association has to be studied in larger sample size.

A few studies have evaluated the magnitude of vitamin D deficiency in patients on long term antipsychotic medication. Tiangga *et al.*[19] has studied the prevalence of vitamin D deficiency in a group of male psychiatric inpatients and observed that vitamin D deficiency was mostly associated with black and minority ethnic background suggesting that that the psychiatric patients may be at risk for vitamin D deficiency. Poor nutrition and reduced duration of exposure to sunlight have been postulated as possible mechanisms responsible for a vitamin D3 deficiency in patients with schizophrenia.

Vitamin D therapy is recommended in clinical practice in patients suffering from a decrease of BMD. It is cheap, easily available, and dosing regimen is simple. Our finding of a relationship between low vitamin D levels and reduced BMD resulted from an exploratory analysis and therefore needs to be replicated with prior hypothesis testing. It raises the possibility that prophylactic addition of vitamin D to the treatment of patients with antipsychotics could reduce the risk of loss of BMD.

Conclusion

This hospital-based outpatient study of patients receiving maintenance risperidone for a minimum of one year showed a higher prevalence of BMD abnormalities in the lumbar spine (44.7%) as compared to BMD changes in the neck of the femur (40%). Nine (13.8%) had osteoporosis, and 20 (30.9%) had osteopenia in lumbar spine whereas two subjects (3.09%) had osteoporosis and 24 (36.91%) had osteopenia in neck of femur. The mean (SD) age of these subjects was only 29.4 (6.5) years. The association of BMD changes in around half of subjects could be sedentary life style, sun exposure, comorbid harmful use of substance, and use of prolactin rising antipsychotic medication.

Sixty per cent of women had menstrual irregularities and all women with amenorrhoea were hyperprolactinaemic. Forty four per cent of the men reported ED. ED was more significantly associated with changes in BMD. Thirty per cent of the subjects had severe vitamin D deficiency. The direction

of causality, if any, and its possible therapeutic potential to reverse or delay this process, remains to be explored.

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