Lurasidone-induced Parkinsonism and Hyperprolactinemia

Sir,

Drug-induced parkinsonism (DIP) usually manifests within a few days to up to 3 months of neuroleptic therapy and remits if the offending drug is discontinued.[1] Older age, being a woman, genetic variants, preexisting movement disorders, and cigarette smoking have been identified as risk factors for DIP.[2] Hyperprolactinemia is another common, but neglected, adverse effect of conventional and some atypical antipsychotics that may lead to decrease in libido, amenorrhea and infertility, breast engorgement and lactation.[3] Such adverse effects of medication may be very troublesome for a female in her reproductive period and interfere in the assessment of etiology of infertility too. We encountered a female patient with psychotic depression who developed DIP and had very high levels of serum prolactin following the use of lurasidone.

CASE DETAILS

Ms A, 26-year-old, was brought by the family for sudden onset behavioral abnormalities, reduced sleep, restlessness, anxious and irritable mood, beliefs of being pregnant despite a negative urinary pregnancy test, and delusions of persecution. She refused to take her meals, was aggressive, and had a labile mood. We diagnosed her with acute polymorphic psychotic disorder without symptoms of schizophrenia (an International Classification of Diseases tenth revision/ICD-10 diagnosis). Her complete hemogram, serum biochemistries, and thyroid function were normal. In view of recent-onset amenorrhea, we ruled out pregnancy by the urine pregnancy test and pelvic ultrasonography. She was treated as an inpatient with olanzapine 10 mg/day and clonazepam 0.5 mg twice a day and had about 50% relief in 2 days and was discharged. However, she did not achieve remission, and her symptoms changed during the next 2–3 weeks. She started remaining sad, stopped participating in household activities, and repeatedly voiced her concern about conception. She would prefer to stay alone and had depressive cognitions in the form of bleak views of future, hopelessness, and suicidal ideations. She also had delusions which were mood congruent and revolved around her conception. However, her appetite was increased, and she gained nearly 3 kg of weight during this period. In view of the change of symptomatology, the diagnosis was revised to major depressive disorder current episode of severe depression with psychotic symptoms (F32.3) and she was re-admitted due to suicidal ideations. The rating of her psychopathology on the Brief Psychiatric Rating Scale (BPRS) revealed a

score of 55, suggestive of a severe illness. After informed consent, she was administered modified bi-temporal electroconvulsive therapy (ECT) at a frequency of three treatments/week. In view of weight gain, olanzapine was replaced with lurasidone which was increased to up to 40 mg twice a day. The treatment and associated details are mentioned in Table 1. Olanzapine was cross-tapered with lurasidone over a period of 2 weeks to avoid a rebound of psychotic symptoms. Consultation with an obstetrician was done for amenorrhea. The levels of luteinizing hormone (11.78 mIU/mL), follicle stimulating hormone (7.76 mIU/mL), and estradiol (21.56 pg/mL) were normal; prolactin (41.20 ng/ml) was slightly raised and endometrial thickness was 3 mm. In view of the slightly raised prolactin levels, an endocrinology consultation was also sought, and additional investigations were suggested. These included serum cortisol levels and a brain magnetic resonance imaging (MRI), both of which turned out to be normal, and so no medications were advised. Her depressive symptoms improved significantly within 2 weeks of treatment, but she developed an expressionless mask-like face and had slow gait and reduced span of arm swing. The ratings on the Extrapyramidal Symptom Rating Scale (ESRS)[4] were moderate (score on questionnaire – 3, bradykinesia – 4, gait and posture – 2, and expressive movements – 4). On clinical global impression (CGI), the severity of parkinsonism was rated as 4, i.e., moderate. A repeat serum prolactin showed very high levels (252.4 ng/ml) but she tested negative for urine alpha-fetoprotein. We attributed the extrapyramidal symptoms and hyperprolactinemia to lurasidone. It was tapered and replaced with low dose aripiprazole (5 mg/day) along with trihexyphenidyl 2 mg thrice a day. There was a significant decline in the DIP within the next week, and she was discharged. After 4 weeks of discharge, repeat serum prolactin level was 11.07 ng/ml and her menstruation had resumed.

DISCUSSION

Lurasidone has a potent-binding affinity for D2-dopaminergic and serotonin (5-HT2A) receptors, which is even higher than that of the older atypical and typical antipsychotics.[5] It has moderate-to-high affinity for D3-dopaminergic, 5-HT7, and α-2 adrenergic receptors.[5,6] The high affinity for D2 receptors makes lurasidone liable to cause DIP, and the D2-antagonism in the nigrostriatal/tuberoinfundibular pathways may lead to DIP and hyperprolactinemia. These side effects occur due to the interplay of dopaminergic and serotonergic pathways. The former exerts a tonic inhibition of prolactin secretion via tuberoinfundibular and tuberohypophyseal pathways, while serotonin, via GABA-ergic interneurons, inhibits the tuberoinfundibular pathway. However, the antagonism of 5-HT2A receptors and low-binding affinity for the α 1-adrenergic and histaminergic H1 and M1 muscarinic receptors lowers the risk of DIP, orthostatic hypotension, sedation, and cholinergic side effects like dry mouth and constipation.

When compared to other antipsychotics, its side effect profile is similar to aripiprazole, asenapine, and amisulpride for weight gain; while in the case of DIP and hyperprolactinemia, it is similar to asenapine, chlorpromazine, ziprasidone, and olanzapine. Recently, two case reports mentioned the development of restless leg syndrome[7] and rabbit syndrome[8] in female patients treated with 40–120 mg of lurasidone. A recent meta-analysis of efficacy and tolerability of various antipsychotics in schizophrenia concluded that lurasidone more frequently leads to extrapyramidal side effects (odds ratio = 2.46; confidence interval = 1.55–3.72) as well as hyperprolactinemia (standard mean difference/SMD = 0.34; confidence interval = 0.11–0.57) when compared to placebo.[9] Besides, the product labeling for lurasidone mentions a lower potential for hyperprolactinemia, and it is uncommon to see a rise of more than five times the upper levels of normal

Table 1: Details of treatment, psychopathology, and medication adverse effects

Week of treatment	Rating on BPRS	No. of ECTs administered	Medication details	Adverse effects
1st	55	3	Olanzapine 20 mg reduced to 10 mg Lurasidone 20 mg increased to 40 mg Escitalopram 10 mg	
2nd	41	3	Olanzapine stopped Lurasidone 40 mg increased to 80 mg Escitalopram 10 mg	ESRS - moderate parkinsonism, hyperprolactinemia (serum prolactin=252.4 ng/ml)
3rd	33	3	Lurasidone 80 mg reduced to 40 mg Escitalopram 10 mg	
4th	27	3	Lurasidone stopped Aripiprazole 5 mg started Trihexyphenidyl 2 mg thrice a day Escitalopram 20 mg	ESRS - mild parkinsonism

ESRS=Extrapyramidal Symptom Rating Scale; BPRS=Brief Psychiatric Rating Scale; ECT=Electro Convulsive Therapy

serum prolactin level.[10] Most of the earlier short-term studies of lurasidone had reported a minimal or modest rise in the levels of serum prolactin levels and in one of the studies, more than five times increase was noted in only 2 out of 219 participants.[10] Additionally, all of these studies showed a greater rise in the serum prolactin levels in females. In the index case, gender was the only predisposing factor for both of the aforementioned adverse effects. She was not taking any other medications and had a normal hormonal profile and neuroimaging, which excluded most of the other causes of raised prolactin levels. Therefore, treatment with lurasidone was believed to be the underlying cause of DIP and hyperprolactinemia in her.

To conclude, though, unlike many other atypical antipsychotics, lurasidone may be associated with a lower potential for weight gain and orthostatic hypotension, the adverse effects of DIP, and hyperprolactinemia, especially in young childbearing women, though infrequent, may be disquieting. Thus, we suggest clinicians to use lurasidone in their female clients carefully.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Lopez-Sendon J, Mena MA, de Yebenes JG. Drug-induced Parkinsonism. Expert Opin Drug Saf 2013;12:487-96.
2. Shin HW, Chung SJ. Drug-induced Parkinsonism. J Clin Neurol 2012;8:15-21.
3. Torre DL, Falorni A. Pharmacological causes of hyperprolactinemia. Ther Clin Risk Manag 2007;3:929-51.
4. Chouinard G, Margolese HC. Manual for the extrapyramidal symptom rating scale (ESRS). Schizophr Res 2005;76:247-65.
5. Jaeschke RR, Sowa-Kucma M, Pańczyszyn-Trzewik P, Misztak P, Styczen K, Datka W. Lurasidone: The 2016 update on the pharmacology, efficacy and safety profile. Pharmacol Rep 2016;68:748-55.
6. Ishibashi T, Horisawa T, Tokuda K, Ishiyama T, Ogasa M, Tagashira R, *et al*. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther 2010;334:171-81.
7. Ghori AK, Sajatovic M, Tampi RR. A case of emergent restless legs syndrome with lurasidone therapy. J Clin Psychopharmacol 2016;36:293-4.
8. Reichenberg JL, Ridout KK, Rickler KC. Lurasidone-induced rabbit syndrome: A case report. J Clin Psychiatry 2017;78:e553.
9. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, *et al*. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatment meta-analysis. Lancet 2013;383:951-62.
10. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: A comprehensive review. CNS Drugs 2014;28:421-53.

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