Restless legs syndrome due to aripiprazole

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Although the restless legs syndrome (RLS) is a common cause of sleep disruption and the prevalence of this condition in primary care is high (15-25%)[1], most physicians have remained unaware of the disorder. Many patients have remained undiagnosed or misdiagnosed and have not been managed adequately with a subsequently negative impact on sleep and quality of life [2-4]. The RLS diagnostic is clinical and the 4 criteria are: (1) the patient must have an urge to move the legs; (2) symptoms must be aggravated by rest; (3) symptoms must be alleviated by movement, especially by walking; and (4) symptoms must be worse in the evening or night (circadian rhythm) [4,5]. This syndrome may be the result of dopamine and iron system abnormalities and the role on RLS pathophysiology has been supported by demonstrated therapeutic benefit, although these relationships are not fully understood [6-8].

A 45 year old woman, with no past medical history, was diagnosed with major depressive disorder and was prescribed 5mg olanzapine and 5mg aripiprazole daily. After ten months the olanzapine was discontinued and the aripiprazole was increased to 15mg daily. Her depressive symptoms were improved but few days after this dosage increase she presented unpleasant aching sensation on both legs with creeping and crawling feelings during the night constantly interrupting the sleep; these symptoms appeared about 3-4 hours after the medication. She had no sudden involuntary muscles contractions, previous legs trauma or akathisia. The symptoms relieved by moving the legs or by walking and they were mild during the early morning. There was no history of caffeine intake or any other medication that may exacerbate this condition.

Physical examination showed no abnormalities and no clinical signs of anemia; peripheral neuropathy or vascular diseases were not found. A diagnosis RLS was made. Lab test were done looking for secondary causes of RLS (iron, ferritin, creatinine, BUN, thyroid hormones, glucose and rheumatoid factor). All findings were normal. Even though aripiprazole was effective for her depressive symptoms it was gradually discontinued causing the RLS symptoms disappearance.

The dopamine agonists have demonstrated their efficacy in the treatment of the RLS. This class of drugs directly stimulates dopamine receptors and has a longer half-life (four to six hours) than levodopa (90 minutes). They are generally superior to levodopa for the treatment of daily RLS. The mechanism by which these dopamine agonists improve the symptoms of RLS is the stimulation of dopamine D_2 receptors.

Aripiprazole and olanzapine are atypical antipsychotics, acting as partial agonist and antagonist of the dopamine D_2 receptor, respectively. Aripiprazole has not been associated with RLS in other case reports

[6-8], where antidepressants and antipsychotics induced RLS and it is the first singularity distinguished this case. In theory the difference in the mechanism of action may explain why RLS was not seen with aripiprazole. If antidepressants are necessary, the symptoms of secondary RLS can usually be treated in the same way as primary RLS [1-4]. Bupropion is an alternative antidepressant that may be less likely to induce or worsen RLS [4,5].

Dopamine antagonist have been shown to exacerbate RLS and the second particularity is the absence of RLS related with olanzapine like others case reports [6,7] when the symptoms resolved after this drug was discontinued.

The third peculiarity, RLS was not developed during the initial prescription of aripiprazole and it appeared during the increase of the dose. It could suggest a probably dose dependent appearance of the RLS associated to aripiprazole. The classification of RLS is shown in table 1.

We suggest future research should focus the antipsychotic induced RLS.

References

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Table 1
Classification of RLS

Primary	**Secondary**
Idiopathic	Iron deficiency
	Pregnancy especially third trimester
	Uremia
	Peripheral neuropathies
	Thyroid disease
	Diabetes
	Rheumatoid arthritis
	Fibromyalgia
	Venous insufficiency
	Spinocerebellar ataxia
	Drugs
	Metoclopramide
	Phenytoin
	Antipsychotics
	Occasionally tricyclic antidepressants SSRI, lithium