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Restless Legs Syndrome Due to the Use of Trazodone: A Case Report

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SUMMARY

Many case reports have demonstrated that using antidepressants and especially the selective serotonin reuptake inhibitors (SSRIs), and the noradrenergic and specific serotonergic antidepresants mirtazapine and mianserin can lead to restless legs syndrome (RLS). However, there are disagreements in the results of the limited number of investigations on the relationship of RLS with antidepressants. Trazodone is a frequently used antidepressant with complex agonistic/antagonistic effects on the serotonergic system and moderate blockage on the histamine receptor. This report dicusses the case of a 39-year old female patient who developed RLS after using trazodone (100mg/day) prescribed by her pscyhiatrist for treating her insomnia complaints. We have learned from the patient's statement that she felt burning, tingling and restlessness in her legs, that started from the first night of the treatment and caused an urge to move her legs. The effects were attributed to trazodone and the treatment was discontinued. The patient reported at her control examination the disappearance of RLS symptoms one day after discontinuing trazodone use and the complete improvement of her insomnia complaints.

Keywords: Trazodone, restless legs syndrome, histamine receptor

INTRODUCTION

Restless legs syndrome (RLS) is a common sensory-motor circadian disorder with unpleasant sensations, including pain and an irresistable urge to move to alleviate the symptoms, experienced in sleep or the state of rest. RLS mostly causes sleep disorders (Benbir et al. 2004, Ondo 2005, Zintzaras et al. 2010). All four criteria specified by the International RLS Study Group (IRLSSG) have to be met for the disnosis of RLS (Allen et al. 2003) (Table 1). Many case reports have demonstrated that using antidepressants and especially the selective serotonin reuptake inhibitors (SSRIs), and the noradrenergic and specific serotonergic antidepresants mirtazapine and mianserin can lead to restless legs syndrome (RLS) (Paik et al. 1989, Bakshi 1996, Hargrave and Beckley 1998, Sanz-Fuentenebro et al. 1996, Markkula and Lauerma 1997, Bonin et al. 2000, Ağargün et al. 2002, Perroud et al. 2007, Makiguchi et al. 2015). However, there are disagreements in the results of the limited number of investigations on the relationship of RLS with antidepressants (Brown et al. 2005, Rottach et al. 2008, Baughman et al. 2009). In this report the case of a 39-year old female patient who developed RLS after starting trazodone treatment will be presented.

CASE

N.R., the 39-year old lyceé graduate, married female patient, without a history of psychiatric consultation, explained that she had attended, 10 days previously, the psychiatry outpatient clinic of a hospital with complaints of sleep problems that occurred 3-4 days of the week and had persisted for 1 month. After going to bed she could not fall asleep for 2-3 hours but thereafter slept continuously until her usual waking up time. Apart from feeling fatigue and sleeping for 1 hour during daytime, she did not have any other problems. It was understood that sleep problems resulted from having to assist her husband on the computer and drinking 2-3 mugs of caffeinated beverages at night time.

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Table 1. The Diagnostic Criteria Specified by the International Restless Legs Syndrome (RSL) Study Group (IRLSSG)

1.	Generally the presence of disturbing and unpleasant sensations in the legs and the resultant impulse to move the legs (Sometimes this impulse can arise without the disturbing sensations, affecting the arms and other parts of the body).
2.	Starting and worsening of the impulse for movement or the disturbing sensations at times of inactivity such as during resting, sitting or lying down.
3.	Partial or complete improvement of the symptoms during sustained acitivty with movements such as walking or stretching.
4.	Symptoms worsening in the evening or at night as compared to the daytime or starting only in the evening or at night.

The patient had been prescribed trazodone (100 mg/day) for insomnia, immediately after which she started experiencing, especially after going to bed at night, burning and tingling sensations, and restlessness in her legs causing the desire to move them when the sensations subsided. The patient had not previously experienced similar symptoms which had begun on the night she took the first dose, and gradually increased within a span of 10 days. Clinical evaluation indicated that the patient's symptoms met all four criteria for the diagnosis of RLS as specified by the IRLSSG (Table 1). During her mental status examination the patient was conscious, cooperative and fully orientated. She had good self-care, normal pace of speech, and correct associations. She did not describe delusions or hallucinations. Her mood was euthymic. She did not have a history of know diseases; and had only used trazodone during the previous 1 month. The patient scored 1 on the Beck Anxiety Inventory, 4 on the Beck Depression Inventory, and 15 on the Pittsburgh Sleep Quality Index (PSQI). The results of her haemogram, and the laboratory tests on the electrolyte, vitamin B12, folate and ferritin levels and the hepatic, renal and thyroid function tests were within normal limits. On the basis of these data the patients's symptoms were ascribed to trazodone use and the treatment was terminated. The patient was informed that her sleep complaint resulted from not paying attention to sleep hygiene and was given advice on the subject, explained that she did not need any medication and was given a follow up control appointment. At her control examination the patient reported that the RLS symptoms ceased the day after discontinuing trazodone use. She did not have any sleep disorder and had a score of 3 on the PSQI.

DISCUSSION

There are many case reports demonstrating that using antidepressants and especially the selective serotonin reuptake inhibitors (SSRIs), and the noradrenergic and specific serotonergic antidepresants mirtazapine and mianserin can lead to restless legs syndrome (RLS) (Sanz-Fuentenebro et al. 1996, Markkula and Lauerma 1997, Bonin et al. 2000, Ağargün et al. 2002, Perroud et al. 2007, Makiguchi et al. 2015). However, conflicting results have been reported by the limited number of investigations in the literature on the relationship of RLS with antidepressants (Brown et al. 2005, Rottach et al. 2008, Baughman et al. 2009). While some data indicated that antidepressant use may lead to RLS (Ohayon and Roth 2002, Rottach et al. 2008, Baughman et al. 2009), others did not (Brown et al. 2005). One study reported data evincing the subsidence of RLS symptoms by SSRIs (Dimmitt and Riley 2000).

In a group of patients receiving, for the first time, antidepressant treatment with SSRIs, mirtazapine, venlafaxine, duloxetine, and reboxetine, 9% developed RLS on the starting days of therapy. Whereas reboxetine did not have any effect, mirtazapine caused the highest RLS incidence of 28% and the rest of the agents were associated with incidences of 5-10% (Rottach et al. 2008). Attention was drawn to the gender basis of RLS development by antidepressants, with a higher severity of symptoms occurring among male patients (Baughman et al. 2009). Investigation of the incidence of RLS development in our country indicated that prevalence was higher among antidepressant users although using SSRIs or tricyclic antidepressants (TCAs) was not a significant risk factor for the development of RLS. The same study also demonstrated that combined therapy with trazodone and another antidepressant agent resulted in a higher incidence of RLS among female patients (Çalıkuşu et al. 2012). Although slightly less incidence was reported with monotherapy, a statistically significant difference was not determined in the occurrence of RLS with combined or monotherapy with antidepressants. With the exception of escitalopram, RLS development did not significantly correlate with any other antidepressant agent (Odabaş ve Uca 2019). There is one report on the case of a 69-year old male RLS patient, resistant to all medical therapies but clinically responding to combined therapy with clonazepam and trazodone, which was attributed to the delay in sleep latency, enabling sleep continuity and increasing the slow wave sleep by trazodone (Hasegawa et al. 2004).

The dopaminergic system is believed to have the dominant part in the development of RLS. Low dose dopamine agonists improve RLS symptoms. Antidepressants are thought to cause RLS symptoms by increasing serotonergic and noradrenergic activity and decreasing dopaminergic activity (Ağargün et al. 2002, Zhou et al. 2002, Zhou et al. 2005).

The exact mechanism of action of trazodone has not been elucidated. The complex agonist/antagonist action profile on serotonin has been of interest (Golden et al. 2004). Trazodone is a relatively weak SSRI compared to fluoxetine and sertraline (Hytell 1982). This low SSRI effect may contribute to the development of RLS by increasing the serotonin levels and decreasing the amount of dopamine

as seen with other antidepressants. On the other hand, trazodone has some serotonin receptor antagonist activity on the 5-HT1A, 5-HT1C and 5-HT2 receptor subtypes (Haria et al. 1994). The active metabolite of trazodone, meta-chlorophenylpiperazine (m-CPP), has a strong agonistic effect on 5-HT receptors (Golden et al. 2004) which may cause the stimulation of 5-HT2A receptors in the basal ganglia and dopaminergic hypofunction leading to RLS (Çalıkuşu et al. 2012*)*. Furthermore, unlike the SSRIs, trazodone moderately mimics anti-histamines (Golden et al. 2004) which are known to cause RLS (Allen et al. 2005). On the other hand, mirtazapine, associated with RLS in numerous case reports, also causes histaminergic (H1) receptor blockade (Flores and Schatzberg 2004). In the case presented here, occurence of RLS symptoms shortly after starting trazodone treatment suggests that H1 receptor blockage may be the main cause.

This case report is the first in the literature on RLS development after trazodone use. Clinicians should take into account that trazodone, which is frequently used together with other antidepressant drugs, especially in the treatment of insomnia, may cause RLS. Further research is needed on the relationship between antidepressant use and RLS development.

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