

# DEBILITATING INSOMNIA AND DULOXETINE-ASSOCIATED PERIODIC LIMBS MOVEMENT SUCCESSFULLY IMPROVED WITH BUPROPION—A CASE REPORT

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O wandering graves! O restless sleep!  
O silence of the sunless day!  
O still ravine! O stormy deep!  
Give up your prey! Give up your prey!

Ave Imperatrix, Oscar Wilde (1854-1900)

## Introduction:

Insomnia is one of the diagnostic criteria of major depressive disorder (MDD) and is a multi-factorial problem. In this report, the authors present a case with major depressive disorder initially exhibited with prominent insomnia. During the treatment, although the depressive symptoms were significantly improved with duloxetine, an antidepressant with serotonergic-norepinephrine reuptake inhibitor (SNRI) effects, the insomnia persisted and restless legs syndrome (RLS) and periodic limbs movements during sleep (PLMS) were diagnosed. After shifting to bupropion, a norepinephrine – dopaminergic reuptake inhibitor (NDRI), the insomnia disappeared along with the limbs movement problem.

## Case Report:

In July 2012, a 56-year-old woman was referred to us due to persistent insomnia, low mood and repeated suicide attempts in the past 2 months. Except for hypertension, the patient has no systemic or mental illness. She was extroverted and love outdoor activities. However, she injured her right leg in a traffic accident in March 2012; although X-ray proved no prominent fracture, she canceled the following scheduled trekking. She gradually had sleep disturbances. In May, daytime drowsiness and anergia developed subsequent to insomnia; she quitted her job in late May, and sought for help in 2 clinics before visiting our clinic in early July, where estazolam and lorazepam were prescribed under the impression of non-organic insomnia; diagnosis such as major depressive disorder or post-traumatic stress disorder couldn't be made that time. She responded poorly to the hypnotics, and turned to a neurology clinic but still in vain. She attempted suicide by swallowing detergent (pH = 1.0) then and was sent to our emergency department and further admitted to our thoracic surgery ward due to corrosive injury of esophagus and stomach without perforation. She attempted suicide again in the ward by hanging herself due to persistent insomnia, depression, anergia, anxiousness, worthlessness and hopelessness. The psychiatrists were consulted, and the DSM-IV diagnostic criteria for major depressive disorder were fulfilled. Mirtazepine, lorazepam, and alprazolam were prescribed, but the patient remained depressive and seriously insomniac one week later, and was referred to us.

At the referral, the total score of the 17-item Hamilton Depression Rating Scale (HDRS-17) was 36, and a 10 points subjective visual analogue score for sleep (VAS-10) was rated 2 points, indicating almost the worst sleep one could imagine. Normocytic anemia (Hb: 12.5 gm/dl, MCV: 90.5 fl) and hypokalemia (K<sup>+</sup>: 3.0 mmol/L) were also disclosed; nutritional supplement was encouraged. We shifted to escitalopram for depression, and added propranolol for anxiety in addition to adding zolpidem for insomnia for another 10 days, but the outcome was not favorable. We then shifted to duloxetine and replaced alprazolam with clonazepam for insomnia. Her depression, hypoactivity and anxiety gradually improved in 2 weeks, and no further suicidal ideation were noted; daytime lorazepam was discontinued, and propranolol was titrated down. She started to walk or even jog in the outdoor corridor everyday; she stated that she "just can't sit for too long, it's not comfortable, and needs to walk or jog;" while she used to sit in a corner reading her book all day long previously. Notably, she exercised more in the evening and before bedtime since "some exercise before bed is good for my sleep." However, such behaviors and pharmacotherapy did not yield a good sleep in return; the HDRS-17 improved to 12, but the VAS improved only from 2 to 3.

She still complained of very shallow sleep. In addition to pharmacotherapy, relaxation skills and warm water footbath at bedtime were also introduced before we arranged a polysomnography (PSG) in mid August. Interestingly, although mild obstructive apneas (6 obstructive apneas, and 28 hypopneas) along with frequent snores were noted in PSG, the patient also has severe periodic limbs movement during sleep (PLMS, a total of 167 events per night; 34.4 events per hour), along with reduced REM sleep (10%) and severely reduced slow wave sleep (SWS, 0%). Repeated medical workup disclosed decreased serum ferritin level (104.1 ng/ml (normal range for female: 192-382) and normocytic anemia (Hb: 12.2gm/dl; MVC: 91.1fl). We cross-titrated from duloxetine to bupropion. Her depression and anxiety did not relapse, and dramatically, she reported 7 points in VAS one week later, and felt "fell into asleep." She was discharged after 2 weeks of bupropion therapy at the beginning of September with medication including bupropion 300mg daily, propranolol 5mg twice daily and clonazepam 2.0mg at bedtime. She returned to OPD one week later, and the HDRS-17 further improved to 5, SSS-10 remained 7. We kept bupropion and further titrated down clonazepam to 1.5mg at bedtime and discontinued propranolol. A PSG was arranged in mid September; although her sleep latency did not improve, the amount of PLMS significantly improved to 24.1 events per hour, and the amount of REM normalized to 31.4%. In October, there was no depressive symptom (the HDRS-17 further improved to 5 and 3); and no diurnal difference of exercise or other symptom/sign suggestive of RLS anymore. A PSG was repeated in mid October, and all the examined parameters, including sleep latency (17 minutes), REM sleep (35.5 %), REM latency (51 minutes) and PLM (62 events per night, 10.8 events per hour) significantly improved; and the VAS further improved to 8.

## Discussion:

Antidepressants, especially but not limit to serotonin-specific reuptake inhibitors (SSRIs) are known to cause or enhance restless legs syndrome (RLS) and periodic limbs movement during sleep (PLMS); either one alone could deteriorate sleep quality, and our patient had both. Screen for iron status is recommended for patient with RLS; our patient has mildly lower serum ferritin level, but was not significant for medical treatment. Also, although a few recent studies suggest that RLS may arise from peripheral limb lesions, our patient's RLS became prominent after duloxetine usage, and was significantly relieved after shifting to bupropion, suggesting its iatrogenicity. Dopamine agonists are the standard treatments for RLS or PLMS, but are rather costly and may induce other psychiatric disorders. Bupropion is an antidepressant with noradrenalin and dopamine reuptake inhibition (NDRI) activity, has been shown to treat MDD patient without exacerbating the symptoms of RLS. Our case report suggests that, although insomnia is one of the diagnostic criteria of MDD, it could also be an isolated event not related to MDD, or even an adverse effect after antidepressants treatment for MDD. For depressive patients, when insomnia was not ameliorated with other depressive symptoms, RLS and PLMS should be screened and treated carefully when proved.

## Reference

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