European Review for Medical and Pharmacological Sciences 2013; 17: 1552-1554

Treatment-resistant insomnia treated with pregabalin

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Abstract. – We report a case with refractory insomnia. We diagnosed her case as depression with high levels of anxiety, weakness, with diminished ability to think or concentrate and with a sensory-motor disorder. Although this last symptom was very distressing, it did not satisfy the criteria for RLS (Restless Legs Syndrome). After treatment with paroxetine (20 mg) and zolpidem (10 mg), anxiety and mood deflection were attenuated. Nevertheless, a mild depression, an intermittent awakening (fragmentation of the sleep-wake rhythm) and subsyndromal RLS persisted. Her resistant insomnia was treated with benzodiazepine sleeping drugs (triazolam 0.25 mg, lorazepam 2.5 mg, fluorazepam 30 mg) with only partial insomnia remission, antidepressants (trazodone 150 mg RP, mirtazapine 15-30 mg, agomelatine 50 mg) and antipsychotics (levomepromazine 25 mg, zuclopentixol 25 mg) without results. Her intractable insomnia was markedly responsive to pregabalin without side effects. Our hypothesis is that the therapy with pregabalin may be indicated for resistant insomnia associated with subsyndromal RLS, even when the latter does not satisfy fully all the criteria for diagnosis.

Key Words:
Insomnia, Mild depression, Restless legs syndrome, Pregabalin.

Introduction

Insomnia disorders are characterized by insomnia symptoms accompanied by significant distress or impairment. In DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text revision) the specific diagnosis of primary insomnia is further defined by a duration of at least 1 month and by symptoms that do not occur exclusively during the course of another sleep disorder, mental disorder, or medical disorder or result from use of substances or medications. Furthermore, DSM-IV-TR includes the definition of "secondary" insomnia disorders, in which the insomnia still causes significant distress or impairment or warrants independent clinical attention, but is believed to be directly related to a coexisting mental disorder or medical disorder or to the effects of substances or medications. An insomnia unsuccessfully treated with three different treatment options can be defined as resistant. Traditional treatment of insomnia based on the use of benzodiazepines and non benzodiazepine hypnotics can cause residual effects (hangover), anterograde amnesia, with symptoms of abrupt cessation, rebound effects, paradoxical effects, and cognitive decline[1]. In addition, prolonged treatment carries the risk of developing dependence, abuse and tolerance. These considerations led to the search for new drugs with a different mechanism of action and a different pharmacological profile. These include the new modulators of neural transmission, gaboxadolo, gabapentin, pregabalin, which act as ligands of voltage-gated calcium channels in the central nervous system (CNS). Pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid] is a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Pregabalin (PGB) is in a class of medications called anticonvulsants. The predominant mechanism of action is thought to be through its presynaptic binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels which in turns leads to reduced release of neurotransmitters, eg, glutamate, substance P, and calcitonin gene-related peptide[2]. It is used to relieve diabetic neuropathic pain or pain derived from rash of shingles. Pregabalin shows promising results in the treatment of alcohol dependence[3,4]. Interesting studies concerning the efficacy and safety of pregabalin in current alcoholics show that pregabalin was effective and well tolerated in these patients and it acts within the same range of efficacy as naltrexone which are amongst the most frequently used drugs for such diseases[5].

A study from Kubota et al[6] evaluated the potential somnogenic actions of pregabalin in comparison to triazolam, a drug widely used as hypnotic, in rats. Pregabalin increased the duration of nonrapid eye movement sleep (NREMS) and decreased rapid eye movement sleep (REMS). Triazolam increased duration of NREMS and had no effect on duration of REMS. Power spectrum analysis revealed pregabalin-induced dose-dependent increases in relative

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delta power after administration. Results suggest that pregabalin is a potential sleep modulating agent. These observations were confirmed in 2005 by Hindmarch et al[7], who has also verified the effectiveness of PGB, compared with alprazolam and placebo in reducing sleep latency and improving the continuity of sleep in healthy volunteers. This study indicates that both pregabalin and alprazolam significantly increased total sleep time and sleep efficiency, compared with placebo, whereas the proportion of slow-wave (restorative) sleep was significantly increased with pregabalin, but reduced with alprazolam.

Case Report

The patient is a 52 year-old caucasian woman, 1.65 meters tall, about 75 kg weight. She came to our attention at the Mental Health Center of our urban teaching Hospital complaining insomnia, (fragmentation of the sleep-wake rhythm), weakness, with diminished ability to think or concentrate, and a sensory-motor disorder not well characterized. Some years before she suffered from an episode of major depression with high levels of anxiety, insomnia, weakness, with diminished ability to think or concentrate and with a sensory-motor disorder of her legs. She was treated with paroxetine (20 mg) and zolpidem (10 mg). Anxiety and mood deflection were partially resolved [Hamilton depression (HAM-D) rating scale 28 to 10]. Nevertheless, her intermittent awakening accompanied by uncomfortable and unpleasant sensations that diminish with motor activity, persisted. Her resistant insomnia was treated with benzodiazepine sleeping drugs (triazolam 0.25 mg, lorazepam 2.5 mg, fluorazepam 30 mg) with partial insomnia remission but increased weakness, and antidepressants (trazodone 150 mg RP, mirtazapine 15-30 mg and agomelatine 50 mg/die), according to recent studies that demonstrated the action against subthreshold depressive symptoms[8], with side effects like orthostatic hypotension, hyperactivity and improved impulsivity, and with antipsychotics (levomepromazine 25 mg, zuclopentixol 25 mg) which caused ataxia and hypotension. At the time of presentation to our mental health center she was alert, well oriented in all spheres, time, space and sense of selfhood. There were no false belief and abnormalities of thought content, no abnormal perceptions, abnormal convictions, abnormal impulses, nor abnormalities in the sense of self. We did not detect impulse control disorders nor personality disease. She had no suicidal ideations, her insight and judgment were good. Despite the different treatments she still presented mild-depressive symptoms. These symptoms, that in the past had been characterized as neurotic, included mild but continous anxiety, some phobias and discontinuous sleep. At the moment of our observation the patient suffered from a diminished interest in things which she usually found interesting or enjoyable (HAM-D 10). She carried on her normal life, only appearing low in spirits and possibly less sharp in her thinkings or in her interests. She continued only with the essentials, such as going to work or caring for the family. However, she was not conscientious about these things as previously but became upset because she felt she was not coping as well as she should have because she was too tired. Despite the different treatments she still presented insomnia resentment and a mild sensorimotor disorder too. This sensorimotor disease was sporadically characterized by an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations, characterised by any dysaesthesias of the legs, typically occurring in the evening. However, this syndrome represents only a small fraction of the diagnostic criteria for restless legs syndrome (RLS). She was given a diagnosis of suspected mild depression with sub-syndromal restless legs syndrome and placed on pregabalin progressively increased up to 300 mg die (monoterapy). Finally her intractable insomnia was markedly responsive to our treatment, without side effects even with the increase in dosage, with a remarkably rapid and effective response.

Discussion

Sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning[9] and its recognition and distinction between comorbid and non comorbid (primary) forms is crucial. Common comorbidities include psychiatric disorders: mood disorders[10], anxiety disorders[11], psychotic disorders such as schizophrenia[10], mono and polysubstance dependences[13,14], and eating behaviour disorders[15].

Insomnia can also be a side effect of different drugs like andidepressants, beta agonists and theophyllin derived broncodilators, beta antagonists, decongestionants, corticosteroids, stimulants, statins, dopamine agonists or different medical conditions[16], as in the case described above, where some symptoms of restless leg syndrome were detected. The majority of patients with drug resistant insomnia does not actually complain of daytime sleepiness, that is, the tendency to fall

asleep in inappropriate situations. Rather, insomnia appears to be associated with difficulty sleeping at any time during the 24 hour day.

The first step in the evaluation of the patient is the clinical history[17]. The second one should be focusing on the description of current symptoms, including not only the type of sleep disturbance at night but also sleep habits and patterns. In particular, the clinician should inquire about bed- and wake-up times, variability in sleep timing from day to day, and emotional, cognitive, and physical states surrounding sleep. Symptoms of other specific sleep disorders should also be considered. These include loud snoring and witnessed breathing pauses, which might suggest sleep apnea, and motor restlessness and involuntary leg movements, which might suggest RLS. The clinical history can be usefully supplemented with the collection of a 2 week sleep-wake diary. The assessment of the individual circadian rhythm is another issue that need to be evaluated[18].

Conclusions

Our case is of a 52 year-old woman who came to our attention at the our Mental Health Center exhibiting different treatments resistant insomnia, clinical features of a mild depression and symptoms that may be defined like a subthreshold RLS. In the past the patient developed an episode of major depression, partially controlled. At the moment of our observation she reported a resistant insomnia with partial functional impairment, that could be ascribable either to her mild depression or to a not overt RLS. We assume that the brilliant result with pregabalin may suggest that the drug is useful to treat symptoms like urge to move the legs, uncomfortable and unpleasant sensations of the legs, even if these symptoms are not sufficient for a overt RLS diagnosis.

Conflict of Interest

None to declare.

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