

SLEEPWALKING IN FOUR PATIENTS TREATED WITH QUETIAPINE

Michele Raja & Silvia Raja

Centro "Gaetano Perusini", Rome, Italy

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INTRODUCTION

Sleepwalking (SW), also known as somnambulism, is characterized by episodes of complex motor behavior initiated during sleep, including rising from bed and walking about. It tends to occur between the ages of 4 and 8 and is likely to dissipate in adolescence. It occurs in 2-14% of children and 1.6-2.4% of adults (Remulla & Guillemainault 2004). SW occurs during the first third of the night, during non REM stages 3 and 4 of sleep. Throughout the various episodes, the individual has reduced alertness and responsiveness, a blank stare, and unresponsiveness to communication with others or to efforts to be awakened by others. On awakening, the individual has limited recall for those events of the episode and may be confused for a short period of time (American Psychiatric Association 2000). Most behaviors during SW are routine and of low complexity. However, also complex and dangerous behaviors, including screaming, running, and physical aggression, may occur (Bassetti et al. 2000). The disorder runs in families and does have a strong genetic basis, although the mode of inheritance is still unknown (American Psychiatric Association 2000).

SW induced by medication has been reported for hypnotics (zolpidem, (Mendelson 1994, Harazin & Berigan 1999, Yanes Baonza et al. 2003, Sharma & Dewan 2005, Yang et al. 2005), zolpidem in combination with valproic acid (Sattar et al. 2003)), antipsychotics (perphenazine (Huapaya 1979), olanzapine (Kolivakis et al. 2001, Chiu et al. 2008), quetiapine (Hafeez & Kalinowski 2007, Seeman, 2010)), lithium (Landry & Montplaisir 1998), lithium in combination with neuroleptics (Charney et al. 1979, Glassman et al. 1986), antidepressants (amitriptyline (Huapaya 1979), bupropion (Khazaal et al. 2003, Oulis et al. 2010), mirtazapine (Yeh et al. 2009), paroxetine (Kawashima & Yamada 2003), reboxetine (Künzel et al. 2004)), benzodiazepines (Lauerma 1991), diphenhydramine (Huapaya 1979), methaqualone (Huapaya 1979) and topiramate (Varkey & Varkey 2003).

Since SW occurs out of slow wave sleep, the increase in slow wave sleep induced by lithium and certain neuroleptics, e.g. clozapine and olanzapine (Salin-Pascual et al. 1999, Sharpley et al. 2000, Cohrs

2008), may represent a favoring neurophysiological mechanism (Charney et al. 1979).

As far as we know, (PUBMED, June 2012), SW associated with quetiapine treatment has solely been reported by Hafeez & Kalinowski (2007) in 2 patients, one affected by schizoaffective disorder and one by pervasive developmental disorder (both patients were also affected by attention-deficit/hyperactivity disorder (ADHD)) as well as by Seeman (2011) in 1 patient, affected by schizophrenia.

Hereafter, you will be told of four patients who presented SW during treatment with quetiapine, for the first time in their life.

CASE REPORT

Case 1

A 59-year old lady, affected by bipolar II disorder, sought consultation for severe insomnia. Her sleep was characterized by countless awakenings and resulted in diurnal somnolence, fatigue, and mood instability. In the past, we treated her with valproate for bipolar depression with good results. Afterwards, we withdrew valproate for elevated plasma levels of amylase and lipase. She was prescribed quetiapine 25 mg, at bed time. On the first night of treatment, she slept well indeed, for the first time in months. The following night, she presented akathisia of moderate intensity. The same symptom was present in the following two weeks, at night. Then, akathisia vanished spontaneously. The dose of quetiapine was increased to 50 mg, at bed time. Her sleep normalized (total sleep time during the night: 7 hours). Fatigue and mood instability disappeared.

A few months after starting quetiapine, she presented an episode of SW. Three hours after falling asleep, she woke up to go to the bathroom. She was confused. Her recall of what had happened was quite vague. She remembered a dissociative experience. One part of her was going to the bathroom, the other one was running through a field. Her husband woke up for the tumult and saw her running into a closed door. She hurt her face and knees seriously and awoke with a bleeding mouth. In the past, she had never presented SW nor any other parasomnia. Quetiapine dose was thus reduced to 25

mg. Her sleep became irregular, but she did not present SW in the following 9 months. Episodically, she presented akathisia at night. Her brother had presented SW when he was young. His 20 year-old daughter does suffer from SW, too.

Case 2

A 37-year-old man was visited for mood instability and insomnia. He was affected by bipolar II disorder. On being visited, he presented symptoms of depression, with insomnia. He had always been a poor sleeper. We prescribed him ox-carbazepine 300 mg, in the morning, and 600 mg at bed time as well as quetiapine 12.5 mg at bed time. In the following weeks, he got better, his conditions improved, but his sleep remained poor. Quetiapine dose was first increased to 25 mg and then to 50 mg, at bed time. He slept better. However, on awakening, he found objects and furniture in different places from where they originally were the previous evening. He found residual foods, dirty glasses and plates in the kitchen as if somebody had had dinner some time during the night. On several occasions, his roommate observed the patient walking around the house or eating in the kitchen, apparently confused and unresponsive. In the past, the patient had presented episodes of SW while he was assuming zolpidem 10 mg, at bed time. He noted the reappearance of long-lasting and complex episodes of SW when he assumed 25 mg or 50 mg of quetiapine at bed time. On the contrary, the dose of 12.5 mg was not associated with SW but was ineffective and unsuccessful in improving sleep. He substituted quetiapine with promethazine 25 mg at bed time, showing moderate improvement of sleep (total sleep time during the night: 5 hours) and without any further episodes of SW.

Case 3

A 53-year-old man, affected by bipolar II disorder, presented an episode of agitated depression, in October 2009. He was treated with quetiapine (up to 300 mg) and valproate (750 mg), at bed time. His clinical conditions improved, until remission of the episode. In October 2011, one night, about 3 a.m., he got up at once, but was not fully awake. He vaguely remembers that he was dreaming of being an explorer who had to investigate in a strange area. In his dream, he knew he was in a taboo area where one should never ever go. Actually, he was in the bathroom and looked at the toilet pot that he did not single out as such. In order to avoid violating the prohibited area, he went into another room, in which he urinated, on the floor. Finally, he woke up completely, realizing what had happened. In the past, he had never presented SW or any other parasomnia. To his knowledge, none of his relatives had suffered from parasomnias. In the following six months, he did not present any further episode of SW, although he adhered to the same therapy.

Case 4

A 75-year-old woman, affected by unipolar recurrent depression presented a new episode of depression with insomnia and was treated with escitalopram (10 mg/day), quetiapine (25 mg at bed time), and lormetazepam (1-2 mg at bed time). She was also treated with amitriptyline (10 mg at bed time) for migraine prevention, manidipine (20 mg/day) and nebivolol (5 mg/day) for hypertension, metformin (500 mg at dinner) for hyper-glycemia, and fenofibrate (200 mg/day) for hyper-triglyceridemia.

Six months later, one night (time unknown), she felt she was being touched, stood up at once, but was not fully awake. She vagabonded in the room and saw that the room was not her bedroom. Her recall of what had happened was imprecise and indistinct. Everything had changed, there were gilded chairs, the sofa had become a throne, and her bag had become gold. She thought that her friends wanted to make fun of her. She started talking to herself thinking that she was talking with her friends and said: "Now the joke is over. Do you want me to be a Queen? If you do not answer me, I shall get angry." Then her husband, on hearing she was talking alone, aloud in the middle of the night, rushed to her, shook her, and said: "you're dreaming, wake up!" At that point, she woke up completely, recognized her room and said "I was dreaming". In the past, neither she nor any of her relatives had ever had episodes of SW or any other parasomnia.

DISCUSSION

Besides its official indications in psychotic disorders and bipolar disorder, quetiapine is more and more frequently used in the treatment of many other psychiatric disorders, especially where insomnia is a prominent sign. The drug is highly effective in inducing and maintaining sleep, without inducing tolerance nor dependence, even at small doses, devoid of serious side effects in most cases.

Hereafter, we report on SW induced by low doses of quetiapine, a side effect of this drug which could be met at times, especially in relatively young subjects.

The physical hurt associated with episodes of SW was mild in case 1 and absent in the other three cases. However, patients' concern and embarrassment for their aberrant, unexpected, nocturnal behavior was not negligible.

The causal relationship between quetiapine and SW is almost certain in case 2 since the patient, by himself, set up an open n(A-B-A-B) study design, in which the patient served as his own control, and always associated the doses of 25 and 50 mg of quetiapine with SW. He never presented episodes of SW except for treatment with zolpidem or quetiapine. Although the patient was also assuming ox-carbazepine, the role of this drug in inducing SW seems absent or negligible because of the clear-cut association between quetiapine doses and SW.

In case 1, the causal relationship is less certain since the patient presented just one episode of SW. However, the suspect of a causal relationship is grounded. The patient had never presented SW in the past and has not presented further episodes after quetiapine dose reduction. She was not assuming any other drug at the time of SW. Her familial history of SW strongly suggests the diagnosis of SW.

In cases 3 and 4, the causal relationship is uncertain since the patients presented just one episode of SW, although they continued quetiapine treatment with the same dose.

In all cases, SW did not occur immediately after starting quetiapine treatment. In cases 3 and 4, SW occurred only once, although patients continued quetiapine treatment at the same dosage. This suggests that the etiological link between quetiapine and SW is neither simple nor absolute and that other unknown factors are likely to be necessary in order to elicit the clinical manifestation of such disorder.

In cases 1 and 2, as well in the two cases described by Hafeez & Kalinowski (2007), a dose effect was evident. Cases 1, 2 and 4 suggest that even very low daily doses of quetiapine (25-50 mg) can induce SW.

In one of the 2 patients described by Hafeez & Kalinowski (2007), SW appeared when quetiapine dose at bed time was increased to 200 mg. In the other patient, SW appeared at an unspecified dosage of quetiapine. SW resolved at the dose of 25 mg in the first patient and below a dose of 150 mg nightly in the second.

SW etiology and pathophysiology are not clearly understood. A key role of the serotonergic neurons has been hypothesized because these latter are activated by hypercapnia, a precipitating factor of sleepwalking, provide a tonic excitatory drive that gates afferent inputs to motoneurons, and the activity of serotonergic neurons can be dissociated from the level of arousal (Juszczak & Swiergiel 2005).

As some authors have suggested (Juszczak & Swiergiel 2005, Hafeez & Kalinowski 2007, Juszczak 2011), quetiapine may induce SW because of its effects upon 5-HT activity.

Other possibilities should also be considered, however. A hypo-dopaminergic tone in some neural circuits could facilitate SW.

The influence of dopaminergic circuits in modulating sleep and arousal is too complex to be tackled here. Undoubtedly, dopamine plays a pivotal role in influencing sleep-wake cycle and level of arousal, as suggested by the following.

- As reported above, several antidopaminergic drugs have been associated with SW.
- Behavioral and imaging studies suggest that dopamine is a strong arousal signal (Shang et al. 2011).
- While clearly conscious, from a general anesthetic point of view, dopamine-deficient mice have

marginal arousal and appear to be virtually unconscious from a behavioral point of view. Restoration of dopamine signaling within the striatum by viral gene therapy restores most behaviors, suggesting that dopamine signaling is a critical component necessary for the expression of consciousness (Palmiter 2011).

- Dopamine produces arousal by acting on neurons in the shell of the accumbens nucleus. Amphetamine and cocaine stimulate the same nucleus inducing alertness, while caffeine promotes alertness by indirectly modulating these neural substrates (Lazarus et al. 2011).
- Excessive daytime sleepiness is a common non-motor symptom in Parkinson's disease (PD), affecting up to 50% of patients (Knie et al. 2011).
- Adult-onset SW is frequent in patients with PD (Poryazova et al. 2007).

It is indeed interesting to see how one patient described by Hafeez & Kalinowski (2007) presented a long history of restless leg syndrome, possibly indicative, as ADHD itself, of a low dopaminergic tone. Consistently, the reported case 1 presented symptoms of akathisia with 25 mg of quetiapine at night. Quetiapine is characterized by weak antidopaminergic potency. Therefore, the appearance of akathisia in such a low dose suggests extreme sensitivity to even minimal antidopaminergic action.

CONCLUSIONS

Many elderly patients treated with quetiapine for their insomnia present episodes of nocturnal confusion and agitation, "hallucinations", and purposeless behavior that they do not remember or remember vaguely and indistinctly, on awakening. In these cases, the most frequent diagnosis is delirium, possibly attributed to the anticholinergic action of the drug itself.

The reported cases do compel us to look into the monitoring of nocturnal behavioral disorders in a closer way, in quetiapine treated patients, thus considering SW in the differential diagnosis.

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Correspondence:

Michele Raja, MD
Centro "Gaetano Perusini"
Via Prisciano 26, 00136 Rome, Italy
E-mail: michele.raja@libero.it; michele.raja@fastwebnet.it