

CASE REPORT

Acute Psychosis Associated with Dissociated Sleep-Wakefulness State After Mirtazapine Treatment

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Tricyclic antidepressants decrease rapid eye movement (REM) sleep and may suppress sleep atonia. Reports indicate that these agents can induce visual hallucinations, sometimes characterized as hypnopompic or associated with a dissociated sleep-wakefulness state. In addition, disturbing dreams and confusional states were reported during clinical trials and in subsequent studies. To our knowledge, only two cases of nightmares associated with mirtazapine, a tetracyclic antidepressant, have been previously reported. We describe a 43-year-old Caucasian man with major depressive disorder who started mirtazapine 15 mg at bedtime because he had poor symptom control with other antidepressant drugs. Three days later, vivid dream activity was noted, evolving into realistic nightmares that the patient was not able to distinguish from reality on awakening. Acute paranoia was suspected, and haloperidol was started. The dream activity then ended, and within 3 days the patient was able to identify the dreams as unreality. Haloperidol was discontinued, but mirtazapine was continued, and the vivid dream activity persisted; however, reality testing when awake was intact. A short course of haloperidol restored the patient's reality testing, and mirtazapine was eventually replaced with bupropion. The unusual nocturnal activity resolved as a result. Clinicians should be aware of the possible transition from exceptionally vivid dreams to REM sleep behavior disorder and psychosis based on dream content as an adverse effect of mirtazapine.

Key Words: mirtazapine, acute psychosis, dissociated sleep-wakefulness state, case report, adverse drug reaction.

(*Pharmacotherapy* 2010;30(4):145e–150e)

The phenomenon of believing the content of one's nocturnal dreams to the extreme of acting on the resultant delusions has been previously described. Both in the context of already psychotic psychopathology such as schizophrenia¹ and in a

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premorbid context without such disturbance,² individuals have been driven to violent behavior in wakefulness after a threatening nocturnal dream. Sleep studies and clinical reports over the past 2 decades have defined various dissociated states of wakefulness and sleep, including rapid eye movement (REM) behavior disorder, in which violent behavior can occur during nocturnal dreams and the REM phase of sleep, as well as incompletely declared or mixed states.³ Psychotropic drugs are used to treat these mental disorders and restore normal sleeping patterns, but occasionally they have paradoxical effects.

Tricyclic antidepressants, sometimes used to dampen disturbing nightmares through REM and dream suppression, reportedly have induced

visual hallucinations,⁴ interpreted as dissociation from the prevailing mental state of wakefulness.³ Dissociated sleep-wakefulness state refers to the occurrence of some phenomena that are normally associated with sleep, such as the visual imagery of dreams, with other phenomena that normally occur during wakefulness and not during sleep, such as complex bodily activities involving voluntary muscles. In a clinical case report, a woman with depression was treated effectively with imipramine.⁴ Concomitant with the dramatic improvement in her depression, she developed hypnopompic hallucinations in the middle of the night. A careful reading of the described phenomenon suggests the possibility of REM sleep disorder. Of interest, her depression was inversely associated and her "hallucinations" were positively associated with her dose of imipramine. In one case series, 12 patients developed visual hallucinations while taking imipramine that were dose related, patterned, and geometric "chemogenic"; the hallucinations began 25–60 days after beginning the agent.⁵ Tricyclic antidepressants have also been reported to suppress sleep atonia in humans,⁶ which could in theory promote REM behavior disorder in which the muscle tone of wakefulness is preserved during otherwise REM sleep and dream mentation. Desipramine in particular can suppress both phasic (e.g., dream activity) and tonic (e.g., neuromuscular atonia) elements of REM sleep.⁷ Tricyclic antidepressants, including desipramine, imipramine, clomipramine, and amitriptyline, but not iprindole and trimipramine, have been shown to immediately suppress REM sleep and after several days to promote dissociated REM sleep.⁶ Later, REM sleep can return; once the tricyclic is withdrawn after having been administered for a long period at a high dose, rebound REM sleep can occur.⁶ Although tricyclic antidepressants have had paradoxical unexpected effects on sleep architecture and have triggered psychotic and manic symptoms in bipolar subjects, to our knowledge, an acute paranoid state based on nocturnal dream and dissociated REM sleep has not been described.

In a meta-analysis of placebo-controlled trials, adverse effects of mirtazapine were dry mouth, sedation, increased appetite, and increased weight.⁸ Studies that we reviewed^{9, 10} were consistent with the conclusions of that meta-analysis, and none reported abnormal dream phenomena, dissociated sleep, or psychotic symptoms. On the contrary, studies indicate that

mirtazapine can improve disturbed sleep in depressed individuals by improving sleep efficiency.⁸ Depression is commonly accompanied by increased nighttime awakenings, reduced REM latency, and reduced slow-wave sleep (i.e., deep sleep when dreaming does not take place). In other words, depression is associated with a more rapid onset and longer duration of the phase of sleep that is associated with dream activity. Electrophysiologic studies of patients and volunteers demonstrate reversal of these changes when treated with a tricyclic antidepressant or mirtazapine, resulting in diminished nighttime awakenings, increased REM latency, and increased (i.e., normalized) slow-wave sleep.^{11, 12} In contrast to most antidepressant drugs that suppress REM sleep, a polysomnographic study of five patients demonstrated that mirtazapine left REM sleep essentially unaltered.¹² Polysomnography produces precise data about the quality and duration of sleep, including the phases of sleep, by measuring simultaneously electrical activity of the brain with a somatic variable such as electrical heart activity, breathing pattern, and muscle activity. Using this procedure, one group demonstrated that mirtazapine, in contrast to tricyclic antidepressants, promotes sleep by increasing sleep efficiency and slow-wave sleep.¹³ Results of a more recent study confirmed that mirtazapine usually causes substantial improvement in the quality of sleep, reduces sleep disturbances that are symptomatic of depression, and reduces symptoms of depression in subjects with major depressive disorder.¹⁴

Disturbing dreams and confusional states have been reported with mirtazapine, a tetracyclic antidepressant.¹⁵ These disturbances were reported during clinical trials but not described in detail. In a prescription event-monitoring study with 13,554 patients treated with mirtazapine, 13 patients reported hallucinations and 31 had abnormal dreams thought to be due to mirtazapine.¹⁶ Other published studies of the effects and adverse effects of mirtazapine did not report disturbances in dream activity or dissociated REM or dream states.⁹ Two separate cases of nightmares induced by mirtazapine have been reported in the literature.^{17, 18} In the one case report, nightmares began about 2 weeks after the patient started taking mirtazapine 30 mg before bedtime.¹⁷ The patient awoke from the nightmares, experiencing confusion, fear, palpitations, and perspiration. Within a few days of stopping mirtazapine, the nightmares

disappeared completely. In the other report, vivid nightmares began only 1 day after mirtazapine 15 mg at bedtime was prescribed.¹⁸ The patient awoke frightened and upset after dreaming of being murdered and dismembered. In each of these separately published reports, each patient had once previously experienced nightmares associated with mirtazapine. Discontinuation of the mirtazapine was invariably followed by disappearance of the nightmares. To our knowledge, mirtazapine has not been associated with dissociated sleep-wakefulness state and dissociated reality testing of the dream content. The following case report illustrates this potential antidepressant-induced phenomenon.

Case Report

A 43-year-old Caucasian man (height 70 in., weight 105.9 kg) was jailed for a nonviolent offense. Before incarceration, he had been taking citalopram 40 mg/day for 1 year for major depressive disorder, without improvement. He had been taking fluoxetine (dosage unknown) for 1 year before starting citalopram, again without resolution of his depression. He denied any other previous medical problems or alcohol, tobacco, or illicit drug use. When the patient was first seen in the correctional facility (day 1), citalopram was changed to mirtazapine 15 mg at bedtime. According to the written medication administration record, the patient had been adherent to his drug therapy and did not miss any doses until the drug was withheld (discussed below). Within the first 2 days of starting mirtazapine, he was sleeping better and feeling less depressed.

After taking his third evening dose of mirtazapine, the patient fell asleep and then, according to his recollection the next day, he performed a skit in a comedy show. In a second visual experience, during which he thought that he was awake, a king and a queen were present, then two television stars appeared, Leah Remini and Kevin James. In addition, he heard the voices of two well-known personalities in football, who had apparently entered his jail cell and told him they had come to help him, and he heard a group of people singing "Happy Birthday." When he opened his eyes, he did not visualize anyone, but this did not disabuse him of the conviction that all of these people had just been in his presence. The next time he "woke up," two sheriffs were present to meet with him. In each sequence, he fully believed he was awake,

although he did not recall waking up.

The patient then recalled hearing a person, recognized as an acquaintance of the patient before he went to jail, announce on the television news that he, the patient, was being charged with multiple serious criminal offenses. Various phone calls and other contacts occurred, bolstering his worry about legal repercussions. The patient visualized the acquaintance entering his jail cell, where the acquaintance first hid himself in the wash basin and then brandished a pistol that had a syringe in it. Nurses and backup staff soon arrived, and the acquaintance pulled out a semi-automatic gun. The acquaintance later appeared in the nursing station before disappearing.

The following day (day 3), the patient appeared extremely anxious, tremulous, restless, flushed, and diaphoretic. He was interviewed by the psychologist (R.H.) and related much of this account, and especially the menacing behavior of the acquaintance, as though it had just happened and with absolute conviction in its veridical actuality. On the recommendation of the psychologist, the psychiatrist (A.R.F.) was called and briefed. The initial impression was acute psychotic state, and haloperidol 5 mg was prescribed as a one-time dose.

The following morning (day 4), the patient reported that he had slept soundly and without dreams that he could recall. He related the above account as though he still believed it actually happened, and he remained terrified of the acquaintance's intentions against him. When asked for a chronologic account of his sleep and wakeful activities 2 nights earlier, he allowed for the possibility that these beliefs might have started as upsetting nocturnal dreams. Haloperidol 5 mg at bedtime was prescribed as daily therapy, and the patient slept well and without any dreams he could remember over the next few days. He showed no further signs of paranoid thoughts or fright during the day. By the third day after his brief psychosis (day 6), he began to convince himself of the unreality of those psychotic perceptions and beliefs through a series of reasoning exercises. For example, he thought to himself that it was unrealistic to expect Terry Bradshaw and Jimmy Johnson, the football personalities, to come to his cell to help him because they did not even know him.

Over the following week, the dose of haloperidol was tapered down and then stopped on day 8. Although his reality testing fully returned, and he had no further difficulty distinguishing nocturnal

dream content from conscious thoughts and perceptions, his visual dreams returned and continued to be extraordinarily vivid and intense. The following week (day 16), mirtazapine was withheld for 1 night and resumed on day 17, but during this 24-hour mirtazapine-free interval, the vividness of his dreams persisted without abatement. At the same time, haloperidol was resumed at a lower dose of 2 mg at bedtime. During the third week (day 22), mirtazapine was replaced with bupropion 100 mg twice/day, and 5 days later (day 27) haloperidol was continued at a lower dose of 1 mg at bedtime. He also received bntropine 1 mg at bedtime to prevent extrapyramidal symptoms. After 3 days of taking bupropion and not taking mirtazapine, the vividness, intensity, and frequency of his dreams subsided, although each morning he continued to recall one dream from the night before. The haloperidol was discontinued completely on day 30 without any change in his dreams or mental state. With only bupropion, his depression and anxiety improved, his recollected dreams ceased, and he showed no further disturbance in reality testing. Because of the nature of the patient's reaction and the symptoms subsiding after switching to bupropion, the decision was made by the patient and psychiatrist to avoid a rechallenge with mirtazapine.

The patient's dream history indicated that he had nightmares as a child at around age 13 years. These were vivid, frightful dreams of people chasing after him. These dreams would continue for 2 or 3 successive nights, and he would end up on the floor screaming for help. Then they passed, and he had no further disturbing dreams for several years. He also experienced several episodes of somnambulism in his youth. Various other recurrences of vivid dream activity occurred in his past, usually after a major event (e.g., the respective deaths of his father and mother). The dreams often involved his father chasing him, and he recalled the dreams being "as clear as day." His earlier dreams and other sleep phenomena were not associated with any drug consumption, and he did not take any psychotropic drugs until he entered outpatient treatment for depression 2 years before incarceration. He reported no changes in his sleep pattern or dream activity when he was taking fluoxetine or citalopram. He denied ever having narcolepsy.

Discussion

This patient's detailed sleep and dream history,

completed after his psychotic episode, might have in retrospect suggested a diathesis for vivid visual dreams and auditory dreams that were not dissociated from consciousness. His history of awakening from dreams on the floor may have hinted at some REM sleep behavioral diathesis. Concerns in wakefulness that he could become "paranoid" about debtors coming after him, may have planted the mental seed that led to the disturbing content of his dreams. Presumably the mirtazapine altered the neurochemistry of his sleep, exacerbating his diathesis for vivid visual and auditory dreams with such intensity that he lost reality testing on awakening and continued to believe the content of his dreams. Part, if not much, of his experiences the night of his psychotic episode might have represented REM sleep disordered behavior.

The patient had been taking citalopram before incarceration. Because of his stated lack of benefit from citalopram (a selective serotonin reuptake inhibitor [SSRI]), the drug was discontinued. He was then prescribed mirtazapine, an antidepressant that he had not yet tried, as monotherapy. The question arises then whether his acute disturbance was due to SSRI discontinuation syndrome or REM rebound after discontinuing an SSRI. Discontinuation symptoms typically occur 1–3 days after stopping an SSRI and consist of dizziness, nausea, vomiting, fatigue, lethargy, aches, chills, and disturbances in perception and sleep.¹⁹ The patient's reaction was a disturbance of perception and sleep, occurring 3 days after mirtazapine was started and 4–5 days after his last dose of citalopram. Other symptoms of the usual SSRI discontinuation syndrome were missing.¹⁹ Paroxetine²⁰ and sertraline¹⁹ have been more commonly implicated in the SSRI discontinuation syndrome. Several cases of SSRI discontinuation syndrome associated with sertraline are reported in the literature.²¹ Although the primary symptom is insomnia, disturbances in dream activity are not registered. Whereas citalopram is a mild REM sleep suppressant, it is less suppressing of REM sleep than are paroxetine and sertraline²² and should be less likely to result in REM rebound after cessation. Not surprising then, neither SSRI discontinuation syndrome nor REM rebound are mentioned among adverse events associated with citalopram.²³

Our patient's adverse event did not correspond with symptoms of SSRI discontinuation syndrome and was quite severe for simple REM rebound. Although his acute psychosis responded

to an antipsychotic drug, the disturbing vividness of his dream mentation did not subside until mirtazapine was discontinued. His history of vivid dreams and other types of sleep disturbances in his distant past indicated a proneness to such phenomena, independent of drug therapy. The adverse event described in this case report, however, was qualitatively different from anything he had experienced before (or since). Although withdrawal from citalopram cannot with certainty be ruled out as a potentially confounding factor, when all findings are taken into account, the association with initiation of mirtazapine is most convincing.

Mirtazapine, a piperazinoazepine tetracyclic, is chemically unrelated to any other class of psychotropic drug.²⁴ A potent serotonin (5-HT₂ and 5-HT₃) and central α -adrenergic autoreceptor antagonist, mirtazapine is designated as a noradrenergic and specific serotonergic antidepressant.²⁵ Through antagonism of 5-HT₂ and 5-HT₃ receptors, 5-HT_{1A} receptor-mediated transmission is increased. Moreover, mirtazapine increases the release of both serotonin and norepinephrine by blocking central α -adrenergic autoreceptors and α -serotonergic heteroreceptors, which would otherwise inhibit release of both neurotransmitters.²⁵

The most common adverse effects of mirtazapine are somnolence, increased appetite, and weight gain.²⁵ In terms of its effect on sleep, mirtazapine is described as moderately sedative, with sedation generally inversely proportional to dose and decreasing with continued therapy.⁸ It substantially increases continuity of sleep, moderately increases slow-wave sleep, and has no effect on REM sleep,²² or it increases the latency to the first REM sleep epoch and decreases time in REM sleep.¹¹ Although most antidepressants decrease REM sleep,²⁶ bupropion and nefazodone increase REM sleep.

One group of authors has proposed that the activation-synthesis model of dream generation predicts that dream hyperactivity is a result of diminished motor drive from the brainstem.²⁷ They reported four cases in which dreaming associated with sleep behaviors was described as hyperalert and highly vivid, in terms of visual imagery. According to the activation-synthesis model, structures in the brainstem send memory, cognitive, affective, perceptual, and motor impulses to the forebrain, which integrates the information into the dream phenomenon. The REM sleep behavior results from the strength of activation in the brainstem overriding the

pontine tegmentum in the roof of the midbrain, which normally suppresses all striated muscle activity during REM sleep except that of the extraocular muscles and the diaphragm. Thus, REM behaviors and hypervivid hyperactive dream activity can be associated with each other and can respond similarly to a drug. From this perspective, mirtazapine could have both exacerbated the patient's tendency toward dream hyperactivity and triggered REM sleep behavior. This would be a paradoxical phenomenon given mirtazapine's previously reported absence of effect on REM sleep.

Haloperidol restored our patient's reality testing, ability to distinguish nocturnal dream content from conscious thought, and his ability to sleep restfully, even as he continued to take mirtazapine. When the haloperidol dose was lowered, he maintained reality testing but the vividness of his dreams returned and persisted for several days after mirtazapine was discontinued. Thus, beyond its antipsychotic effect, haloperidol also may have dampened the brainstem activity that contributed to dream hyperactivity. Although the literature suggests that a low dose of a benzodiazepine can sometimes restore normal sleep-wakefulness states in a REM sleep behavior disorder,^{28, 29} if an acute psychotic state has developed, an antipsychotic can be expected to restore reality testing. Once haloperidol was discontinued, dream hyperactivity returned for as long as the patient continued to take mirtazapine.

Our patient experienced vivid dreams, dissociated sleep-wakefulness state, and disturbed reality testing with consequent belief in and extreme emotional disturbance over the content of his dreaming mentation. Haloperidol restored reality testing and normal sleep-wakefulness states and suppressed vivid dreams. After it was tapered and discontinued, as it was no longer needed to treat psychosis, the disturbing vivid dreams returned, but without apparent dissociated sleep-wakefulness state or compromised reality testing. After mirtazapine was changed to bupropion, the dreams at first persisted but with much less intensity, vividness, and frequency, and eventually the recollected dreams subsided altogether. The continuation of vivid dreams initially after discontinuation of mirtazapine is explained by the drug's long half-life of 20–24 hours.¹⁴

The disturbed and dissociated sleep-wakefulness state that occurred on 1 night did not recur and was therefore not studied with

standardized polysomnographic monitoring, electroencephalography, neuroimaging, or even continuous observation; although in the nights that followed, the patient was observed to be sleeping restfully.

Conclusion

This case report raises the possibility of an antidepressant—in this case, mirtazapine—inducing intense, vivid nocturnal dreams, both visual and auditory; dissociated sleep-wakefulness states; and subsequent acute psychosis with persecutory delusions based on the content of dream mentation. In retrospect, our patient's history of somnambulism, vivid nightmares, and auditory dreams might have suggested a vulnerability to such a reaction. An antipsychotic is a logical and effective means of eliminating psychotic thoughts and perceptions. Then, if an antidepressant drug is still indicated, an agent with low risk of promoting such sleep disturbance must be selected.

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