CASE REPORT

Adverse reaction with suvorexant for insomnia: acute worsening of depression with emergence of suicidal thoughts

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SUMMARY

A 59-year-old woman on daily peritoneal dialysis for end-stage renal failure received care at an outpatient psychiatric clinic for her diagnoses that include major depressive disorder, generalised anxiety disorder and insomnia disorder. Although there was partial improvement in the patient's mood and anxiety symptoms with antidepressant treatment, insomnia remained a persistent complaint despite adequate trials of different sleep medications. The novel hypnotic, suvorexant (Belsomra, Merck & Co.) was then initiated at the recommended bedtime dose of 10 mg and was followed by a 15 mg dose the following night. Within an hour after taking her second suvorexant dose, the severity of patient's depression symptoms worsened and was accompanied by new onset of suicidal thoughts.

BACKGROUND

This is a case report highlighting an adverse reaction to the novel hypnotic, suvorexant, in a patient with partially treated depression. This case is clinically relevant because suvorexant is a newer insomnia medication and the first marketed orexin antagonist. Although it has not been evaluated in subjects with depression, suvorexant will likely be prescribed to mood disorder patients who have failed preferred insomnia treatments.

CASE PRESENTATION

The patient is a 59-year-old married Caucasian woman on dialysis for renal failure who lives at home with her husband, and is on disability for reflex sympathetic dystrophy. Additional ongoing medical illnesses include hypertension and nephrogenic diabetes insipidus. She endorsed a maternal history of anxiety and she suspects a paternal history of bipolar disorder but family history was otherwise non-remarkable for psychiatric or significant medical history.

She initially presented to an outpatient psychiatric clinic for symptoms of depression, anxiety and insomnia, each lasting greater than 1 year in duration. After treatment with fluoxetine 10 mg for 3.5 weeks, with some improvement in her anxiety and depressive symptoms, and failed trials of zolpidem 5 mg, doxepin 3 mg, temazepam 15 mg and over-the-counter melatonin 3 mg for sleep, she was started on a trial of suvorexant 10 mg for her persistent chronic insomnia. Fluoxetine was initiated at 10 mg because of the patient's hesitancy with starting a medication.

She reported that on the first night of this medication trial, she had not noticed any improvement in her prolonged sleep-onset latency, nighttime awakenings or subjective sleep quality. She said the next day she felt particularly drowsy but otherwise normal. The following day, she was instructed to take suvorexant 15 mg before bedtime, but again continued to have tremendous difficulty with these same sleep parameters. She said it took her 'hours' to fall asleep, only garnishing approximately 3 hours of sleep despite lying in bed for around 10 hours total. She said she experienced between 5 and 10 nighttime awakenings after sleep onset. She said this sleep pattern was very similar to how she slept prior to her suvorexant trial.

She explained that during the night and in the morning, she experienced 'the worst depression of my life.' She said she felt hopeless, frightened and 'scary depressed' with crying spells, decreased motivation, extreme fatigue, low energy, poor concentration and suicidal thoughts. She said she felt the sense of 'overwhelming darkness' unlike anything she has ever felt before with a feeling of mental confusion and a sense of detachment from reality. She said she has had depression in the past but this was 'much worse.' She said by the evening, her brief but severe depression with suicidal thoughts began to lessen in intensity and she noticed significant improvement in her symptoms the following day.

INVESTIGATIONS

The patient did not have any laboratory work until approximately 4 months after her adverse reaction to suvorexant which showed elevated creatinine at 5.22 (0.60–1.20) and elevated blood urea nitrogen at 56 (7-25).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes an acute reaction to severe insomnia, substance-induced reaction (ie, unreported drug/alcohol use) and withdrawal effects from discontinuation of melatonin.

TREATMENT

Following partial improvement of the patient's depression with fluoxetine, and four failed trials of hypnotics for her insomnia, suvorexant was tried. After her 15 mg dose, which was on the second

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night, she began experiencing severe depression with suicidal thoughts just 'hours' after taking the medication. She reported significant improvement in her depression and complete resolution of suicidal ideation (SI) in 24 hours, with return to baseline in 48 hours.

The patient had not reported any adverse events with prior trials of sleep medications with the exception of transient, mild anxiety, with discontinuation of temazepam.

OUTCOME AND FOLLOW-UP

The patient continues to be seen by a psychiatrist on an outpatient basis for anxiety, depression and insomnia.

DISCUSSION

Suvorexant is a newer insomnia medication and belongs to a novel class of hypnotic agents referred to as dual orexin receptor antagonists.[1] Suvorexant suppresses wakefulness by blocking the hypothalamic neuropeptides, orexin A and orexin B, from binding to orexin OX1R and OXR2 receptors.[2] It is a schedule IV controlled substance approved in August 2014 for the treatment of sleep onset and/or sleep maintenance insomnia.[3]

Suvorexant dosages range from 5 mg to 20 mg (recommended starting dose=10 mg) and should be taken within 30 min before bedtime with at least 7 hours remaining before planned awakening.[4] With peak plasma concentrations (Cmax) occurring 2–3 hours after dose administration, suvorexant is primarily metabolised via CYP3A4 and has a relatively long half-life ($T_{½}$) of 12 hours.[3] Renal clearance plays a minor role in suvorexant elimination. Dose-adjusted suvorexant exposure is characterised by an increase in Cmax and decreased clearance is greater in patients who are women, obese (body mass index >30 kg/m^2), elderly (age ≥65 years) and those taking strong CYP3A4 inhibitors (eg, ketoconazole).[4] Downward starting dose adjustments may be indicated for such patients. Suvorexant dosage adjustments are not required in patients with renal impairment.[4]

Suicide risk was prospectively assessed during suvorexant phase II and phase III clinical trials using the Columbia-Suicide Severity Rating Scale (CSSRS).[5–7] Subjects with insomnia and depression or other mood disorders were excluded from participation in suvorexant premarketing clinical trials. Analysis of pooled CSSRS clinical trial data suggested a dose-dependent increase in SI.[8] The incidence of SI reported for patients receiving suvorexant at high doses (30 mg–40mg), low doses (15 mg-20mg) or placebo were 0.7% (n=9/1291), 0.2% (n=1/493) and 0.1% (n=1/1025), respectively.[8] The earliest time of SI onset reported during suvorexant clinical trials was study day 9 and SI events were characterised as mild to moderate in intensity and lasted minutes to hours. No suicidal behaviours were reported.[8]

Dose-dependent or blood level-dependent daytime somnolence with functional impairment was the most common side effect reported in suvorexant clinical trials and occurred in 5% (placebo <1%) of subjects taking the 20 mg bedtime dose.[8] Although suvorexant phase III pivotal trials evaluated doses up to 40 mg, recognition that obesity decreases suvorexant clearance and is prevalent in the general population lead the Food and Drug Administration (FDA) to lower the maximum approved dose to 20 mg and add 5 mg to the approved dosage range.[8]

Prescription medications indicated for insomnia treatment are associated with an increased risk for SI, suicidal behaviour and death by suicide.[9] Evidence from postmarketing surveillance and epidemiological studies suggest a link between increased suicide risk and insomnia treatment using benzodiazepine and the Z-drug hypnotics (ie, zolpidem, zaleplon and eszopiclone), all of which modulate gamma-aminobutyric acid A receptors.[10 11] A recent literature review that also included unpublished FDA data supports an association between suicide risk and hypnotics.[9] Although a causal relationship has not been clearly established, the FDA requires the drug label of currently marketed prescription hypnotics to include a statement that warns of increased risk of worsening depression and SI and behaviour, regardless of the drug's mechanism of action or suicide risk.[12]

Studies indicate that both hypoactivity and hyperactivity of orexin signalling pathways have been found to be associated with depression.[13] The data from suvorexant clinical trials signalled concerns for increased risk of suicide due to reports in normal study volunteers. Questions remain regarding the use of suvorexant in patients with comorbid anxiety or depression. To our knowledge, this is the first published case report of SI associated with suvorexant treatment, outside premarketing clinical trials. While no causal links have been clearly established, an increase in the risk of suicide is independently associated with insomnia, related to both medical and psychiatric conditions, as well as hypnotic medications.

SI from suvorexant clinical trial data suggest at least several days of treatment before onset of mild to moderate severity SI lasting minutes to hours. Our case presentation involves a depressed outpatient partially responsive to antidepressant treatment and treatment resistant insomnia. She experienced rapid onset of severe SI that lasted several hours after a second bedtime dose of suvorexant. This suggests that starting doses of suvorexant in insomnia patients with active depression symptoms may lead to SI that has an earlier onset and greater severity than in non-depressed patients.

Learning points

- Insomnia is considered a symptom of major depression; however, patients with major depression may have comorbid medical conditions (eg, pain, renal failure) that can give rise to insomnia.
- Suvorexant shares a warning for worsening depression and suicidal ideation (SI) and behaviour with other classes of hypnotic medications.
- Suvorexant is the only hypnotic with a warning for a dose-dependent increased risk of SI.[9]
- Suvorexant use in insomnia patients with depression may lead to SI that has an earlier onset and greater severity than in non-depressed patients.
- Further research is needed to adequately assess the relationship between orexin antagonists and depressive disorders.

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Competing interests None declared.

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Unexpected outcome (positive or negative) including adverse drug reactions