



Case Report

SNI case of the week: Initial concomitant use of gabapentin, clonidine, and prednisone may enhance suicidal ideation: A case report

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ABSTRACT

Background: Suicide cases are the end product of a combination of biological, clinical, psychological, social, and cultural risk/protective factors, and attempts to remain unpredictable.

Case Description: A 43-year-old male presented to the hospital with jaundiced skin/eyes of 7 days' duration. He had a history of a major depressive disorder and chronic alcohol consumption (e.g., 3–5 alcoholic drinks/day for the past 15 years). Studies documented acute hepatic disease (e.g., biopsy-documented hepatocellular alcoholic hepatitis), accompanied by a cholestatic disease. The patient was discharged on clonidine, iron multivitamin, folic acid, gabapentin, and prednisone. Eight days postdischarge from the hospital, he committed suicide (e.g., self-inflicted gunshot wound to the head).

Conclusion: Concomitant administration of gabapentin, prednisone, and clonidine, especially if used for the first time, may play a synergistic effect in increasing a patient's suicide risk.

Keywords: Alcohol withdrawal syndrome, Clonidine, Gabapentin, Glucocorticoids, Suicide risk

INTRODUCTION

The World Health Organization states that suicide is a global phenomenon, with close to 800,000 people dying from suicide every year.^[24] Global suicide figures might potentially reach 1.5 million deaths by the year 2020.^[2] In the US, suicide is the 10th leading cause of death, and in 2017, firearms accounted for more than 50% of all suicide deaths.^[25]

The pathways to suicide are complex, with suicide being the outcome of a combination of biological, clinical, psychological, social, cultural risk, and protective factors. Therefore, despite the presence of risk factors, or lack thereof, the suicide cases are often unpredictable.

In this case report, we are coming back to the issue of prescribing gabapentin off label, this time being for alcohol withdrawal syndrome (AWS). This is also the first case report discussing a potential synergistic effect of concomitant use of gabapentin, prednisone, and clonidine leading to suicidal ideation, especially if these medications are used for the first time.

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One could argue that any of the aforementioned medications could possibly aggravate the suicidal ideation considering the complex medical history of the patient; nevertheless, they should be considered as risk factors.

CASE REPORT

Clinical history

A 43-year-old male presented to the emergency room with the chief complaint of jaundiced skin and eyes, for 7 days. Vital signs were within normal limits except for a heart rate of 98 beats/min and high blood pressure of 166/98 mmHg; pain score was 0. At the time of admission, he had not taken any medications. During admission, he stated that he was feeling fatigued and noticed a slight distention of his abdomen. He had been using alcohol on a regular basis, and homeopathic pills 3 times per week; he was unable to recall the name and content of pills.

Medical history was significant for obesity: body mass index 43.54 kg/m², hyperlipidemia, and prediabetes. In addition, he was suffering from prolonged major depressive disorder and alcohol abuse problems. He admitted to consuming 3–5 alcoholic drinks per day for the past 15 years. Over the course of several years, he was treated with psychotherapy, electroconvulsive therapy, and venlafaxine 37.5 mg, one capsule daily, with only temporary relief. The patient had a history of soliciting help for his alcohol use disorder from AA group meetings.

Five years ago, he was admitted to the emergency department complaining of a self-inflicted stab wound to the right thigh. He denied any suicidal thoughts and/or past thoughts of self-harm and reports that he impulsively stabbed his thigh while playing with a knife in his car. Laboratory workup was within normal limits, except for ethanol blood level of 214 mg/dL.

During the current encounter, ultrasound investigation revealed no bile duct dilation, no gallstones, gallbladder with wall thickening, enlarged liver without focal mass, and likely thrombosed portal vein. Although the liver injury presented as a cholestatic picture, considering the significant direct hyperbilirubinemia possibly from portal vein thrombosis, he also had a hepatocellular pattern of liver dysfunction typical for alcoholic hepatitis due to >2:1 aspartate aminotransferase/alanine transaminase elevation. Other differential diagnoses were drug-induced: the use of unclear homeopathic supplements, and nonalcoholic steatohepatitis due to severe obesity. Deranged synthetic liver function as evidenced by thrombocytopenia and mild coagulopathy suggestive of hepatic insufficiency, likely due to acute alcoholic hepatitis. During the hospitalization, the patient showed signs of mild alcohol withdrawal with tremor, tachycardia (119 beats/min), and high blood pressure. The symptoms

were managed by administering lorazepam 1 mg, once. Clonidine and gabapentin for ethanol withdrawal were also started, which helped in symptom resolution. The patient was also started on prednisone, per gastroenterologist indication. The recommendations at discharge were strict alcohol cessation, no acetaminophen intake, and hepatitis A and B vaccine when the patient was stable, outpatient gastrointestinal (GI) follow-up, liver function tests, and international normalized ratio follow-up, monitoring for alcohol withdrawal, and psychiatry referral. The medication list at discharge was as follows:

1. Clonidine 0.1 mg/24 h; he had two patches in place, one was supposed to be removed in 3 days and then removal of the last remaining patch on the 4th day
2. Multivitamin – iron one tablet by mouth daily
3. Folic acid – 1 mg tablet take one by mouth daily
4. Gabapentin 300 mg: take one capsule by mouth 3 times a day, then one capsule by mouth twice a day, then two capsules by mouth daily at bedtime and discontinue
5. Prednisone 20 mg: take 3 tablets orally every morning for 28 days, then taper off per instructions by GI doctor.

History of the incident

Eight days later, the patient was brought by the ambulance to the emergency room with a gunshot wound to the head. The event occurred approximately 40 min before presentation, and resuscitation efforts continued. The patient was transferred to a trauma gurney, and cervical neck spinal precautions were maintained. Manual blood pressure was not obtained due to continuous, uninterrupted chest compressions. Prehospital vital signs were: Glasgow coma scale 3, PEA 20s than 70s in the field. The patient shot himself 1 time with a large caliber handgun. Cardiopulmonary resuscitation has been ongoing for approximately 38 min per emergency medical services. The patient had received a total of 5 mg epinephrine and total resuscitation time 40 min. Cardiac monitoring leads and pulse oximeter were placed. FAST exam showed cardiac standstill. The patient's spouse stated that the patient had been dealing with health issues and mental health issues for quite some time. However, the spouse expressed shock and surprise as she did not think he was capable of self-harm [Table 1].

Table 1: Potential risk factors for suicide.

History of depression
History of alcohol abuse
Liver failure
Prednisone
Clonidine
Gabapentin

DISCUSSION

Gabapentin and AWS

After reviewing the previous case report published regarding the dangerous side effects of gabapentin,^[11] we noticed a few similarities between the cases such as: the patient was stable before initiating gabapentin, young adults in 30–40 s, symptoms started within 2 weeks of initiating the medication, and the same dose was administered – 300 mg TID, their partners noticed a change in behavior the night before the incident: they became more depressed, withdrawn, and looked confused.

Gabapentin use in AWS stems from the convulsive and anxiety-relieving benefits that were reported in preclinical studies. Rebound insomnia, anxiety, and cravings often accompany the discontinuation of benzodiazepines and following the acute management of AWS, leading to an increased risk of relapse. Gabapentin is believed to provide a unique bridge therapy from AWS through early sobriety, to sustained alcohol remission. Gabapentin has also been shown to reduce withdrawal excitability in hippocampal slices.^[7]

In a study conducted by Malcolm *et al.*, lorazepam and gabapentin were compared in the treatment of AWS. It was found that gabapentin effectively diminished the symptoms of alcohol withdrawal, the most effective dose being 1200mg, and reduced the probability of drinking during withdrawal and in the immediate weeks following postwithdrawal.^[21]

In his study, Bonnet *et al.* concluded that the initial dose of oral gabapentin 800 mg followed by 600 mg QID for 2 days – loaded up to a total of 3200 mg was helpful only in reducing less severe and less complicated acute AWS. The benefits occur in a dose-dependent manner.^[3] Gabapentin is considered to be safe in an outpatient setting where benzodiazepine use cannot be safely monitored. However, it also requires monitoring, as it is not safe for all patients, and the suicide risk associated with gabapentin should not be taken lightly.^[18]

A study conducted in Sweden on 191,973 people that had been prescribed pregabalin or gabapentin in the 2006–2013 interval found that, compared to people that were not taking a gabapentinoid drug, their risk was 26% higher for suicidal behavior or suicide and 24% higher for accidental overdose.^[20] Gabapentin prescription concomitant with opioids was associated with a 49% higher risk of dying from an opioid overdose.^[12]

The side effect of depression and the associated suicidal ideation that accompanies anti-epileptic drugs have been attributed to a GABAergic-mediated decrease in serotonin secretion at the raphe nuclei.^[22] The limitation of these studies is that gabapentin is often tested along with the standard of care or behavioral support versus placebo. Conclusions have also been limited due to confounding by indication.

Glucocorticoid side effects

Glucocorticoids are the most commonly prescribed anti-inflammatory/ immunosuppressant medication worldwide.

In a study performed on 372,696 patients who were prescribed glucocorticoids, it was found that the incidence of suicide, suicide attempt, or severe neuropsychiatric disorders was 22.2/100 person-years at risk for first-course treatments. The hazard ratio for suicide or suicide attempt in exposed patients was 6.89 (95% confidence interval [CI] = 4.52–10.50), compared to people with the same underlying medical disease who were not treated with glucocorticoids, and 1.83 (95% CI = 1.72–1.94) for depression.^[10] It should be also noted that many patients experience none of the side effects described here.

Risks associated with clonidine

Alcohol withdrawal symptoms are extremely variable, but certain symptoms such as tachycardia, hypertension, and tremor may well be interpreted as reflective sympathetic nervous system hyperactivity, for which clonidine is considered a reasonable symptomatic treatment option.

The alpha 2-adrenoreceptor agonist clonidine may induce a variety of psychological side effects ranging from depression to acute hallucination and delirium.^[8] Fatigue and sedation are the most common side effects, with sedation occurring in one-third of patients, and clonidine may also markedly reduce the duration of rapid eye movement sleep.^[14]

There is a case reported of a 54-year-old man who developed acute hallucinosis while being treated for hypertension with clonidine. The symptoms developed on two separate occasions, and they subsided after discontinuation of the drug.^[9] A similar side effect profile manifested as hallucinations were noted in an elderly patient's treatment of hypertension with clonidine.^[4,5]

Currently, there are no clearly identifiable risk factors for the development of severe psychological side effects, including dose of medication, duration of treatment, or predisposing mental illness.

Alcohol and suicide risk

Alcohol use and suicide are intimately linked, but they are both complex phenomena, originating from several factors, to depression being considered a common significant risk factor.

Depression and/or alcoholism were comorbid in 85% of 100 cases of completed suicide. The risk of a suicide attempt was found to be increased with increasing psychiatric morbidity: subjects with two or more disorders had odds of serious suicide attempts that were 89.7 times higher than the odds of those with no psychiatric disorder.^[11]

Throughout the course of his illness, the patient admitted to depressed mood on many occasions, but always denied any suicidal ideation. The absence of suicidal ideation, however, does not exclude the risk of suicide, and researchers believe

that depression, hopelessness, most mental disorders, and even impulsivity predict ideation, but these factors struggle to distinguish those who have attempted suicide from those who have only considered suicide [Table 2].^[1,5,6,8,10,13-23,26]

Table 2: Differential diagnosis for depression and suicidal ideation.

	No risk predisposition	Increased risk	Potential risk factors	Recommendations
Prednisone	Many patients experience no side effects	Glucocorticoid treatment was associated with a sevenfold higher risk of suicide or serious suicide attempt and with markedly higher risks of the other severe neuropsychiatric conditions examined ^[10] Another study suggests that psychiatric symptoms and conflicts resulting from long-term use of AAS may contribute to completed suicide in certain predisposed individuals ^[26]	Prednisone dosage >40 mg/day, particularly weight-based dosage A history of psychiatric disorders Age: patients age of 18–50 years had the highest risk of suicidal behavior, and those from 18 to 30 had the highest risk of panic disorder Gender: men more likely than women develop mania or delirium, confusion, or disorientation Risk varies with timing: early during the course patients experience manic or hypomanic symptoms ^[23]	Patients' education about possible side effects and the need to report them is essential All patients should be considered to be at risk and should be closely monitored during glucocorticoid treatment and withdrawal ^[15]
Clonidine		Clonidine may induce a variety of psychological side effects ranging from depression to acute hallucination and delirium ^[8] Fatigue and sedation ^[14] Hallucinations ^[5]	History of depression	Avoid concomitant use of alcohol, barbiturates of other sedating drugs
Gabapentin	Antiepileptic drugs do not carry the risk of suicide ^[13]	Gabapentinoid drugs might increase suicidal behavior or suicide risk ^[6,19,20] Increased risk of depression ^[22]	History of depressed mood History of substance abuse	Use caution in patients with a history of psychiatric disorder or aggressive behavior Inform patients and their families of potential side effects Early psychiatric involvement ^[21] Psychiatry referral Alcohol abuse treatment programs
Alcohol use disorder		Alcohol abuse and depression are intimately linked with suicide ^[1]	History of depression Previous suicide attempt	Psychiatry referral Alcohol abuse treatment programs
Liver failure		Liver diseases are associated with major depression and suicide attempts among adults. Adjustment for the amount of alcohol used or sociodemographical factors did not explain the observed association of liver disease with both major depression and suicide attempts ^[17]	Alcohol use disorder Presence of other chronic diseases Depressed mood	

AAS: Anabolic-androgenic steroid

CONCLUSION

The additive effect of gabapentin and clonidine in causing depression may be due to their common effect on reducing the secretion of the stimulating hormones in the central nervous system: dopamine, serotonin, and norepinephrine. It is thought that antiepileptic drugs lead to disinhibition and impulsiveness, which can subsequently influence and promote suicidal acts instead of having a direct effect on behavior. Regarding glucocorticoid administration, preclinical studies showed that elevated levels are associated with functional impairments in the depressed brain, especially in the hippocampus, where it results in reduced neurogenesis and impaired neuroplasticity [Table 3].

Table 3: Recommendations for patients taking gabapentin.

Recommendations

1. Avoid prescribing gabapentin for patients with underlying depression and suicidal ideation
2. Psychological evaluation prior to initiation of gabapentin
3. Rule out organic causes of pain
4. Use caution in patients with a history of psychiatric disorder or aggressive behavior
5. Inform patients and their families of potential side effects
6. Monitor for response to treatment
7. Early psychiatric involvement
8. Consider early hospitalization if any acute mood or behavior changes occur in patients on gabapentin
9. Screening for abuse potential^[11]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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