Journal of Neurology & Experimental Neuroscience

https://doi.org/10.17756/jnen.2018-042

Case Report

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Severe Gastrointestinal Complications Induced by Multiple Psychotropic Agents: A Case Report

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Received: August 18, 2018
Accepted: December 17, 2018
Published: December 19, 2018

Citation: Offerdahl T, Zhou L, Siegel R, Durante SR, Lu P, et al. 2018. Severe Gastrointestinal Complications Induced by Multiple Psychotropic Agents: A Case Report. *J Neurol Exp Neurosci* 4(2): 42-44.

Published by United Scientific Group

Abstract

Psychotropic medications are often prescribed in combination for co-morbid conditions including depression, anxiety, bipolar disorder, insomnia and chronic pain. The combinations of these medications can lead to side effects including severe gastrointestinal (GI) symptoms such as abdominal cramping, nausea, vomiting, and loose bowel movements.

Setting: Emergency Department, Acute Care Hospital.

Case Description: A 45-year-old female with a history of bipolar disorder and chronic abdominal pain presented to the emergency department with abdominal discomfort and inability to take her medications.

Assessment/Results: The patient's GI symptoms resolved after she was safely taken off of lithium, amitriptyline and trazodone.

Discussion: Psychotropic medications are often prescribed in combination for co-morbid conditions including depression, anxiety, bipolar disorder, insomnia and chronic pain. The combinations of these medications can lead to side effects including severe GI symptoms such as abdominal cramping, nausea, vomiting, and loose bowel movements.

Keywords

Psychotropic medications, Gastrointestinal pain

Introduction

The common side effects of antidepressants are nausea, headache, sexual dysfunction, anxiety, weight gain, sleepiness, dry mouth, blurred vision, and constipation [1, 2]. The symptoms of antidepressant overdose include extreme drowsiness, nausea/vomiting, inability to urinate, tremors, seizures, delirium, cardiac arrhythmia, respiratory arrest and death [1]. Using a combination of anti-depressants may cause severe serotonin crisis [3]. There is limited information available regarding severe GI manifestations when taking multiple antidepressants. Here we report a case of severe GI complications induced by using multiple psychotropic agents in a patient.

Case report

A 45-year-old female with a past medical history of bipolar disorder, depression, anxiety disorder and sleep disorder presented to the emergency

department (ED) with eight days of severe abdominal pain, nausea and vomiting. Her past medical history was also notable for a medication overdose resulting in a coma for which she was hospitalized eight years prior to this presentation. Over the past several years, in addition to taking lithium for her bipolar disorder, she had taken antidepressants for her depression, as well as benzodiazepines and zolpidem tartrate for anxiety and insomnia. She experienced recurrent episodes of severe abdominal pain associated with nausea and vomiting when she increased the dosages of these medications or compulsively took these medications. This prompted frequent visits to different EDs and admissions to different hospitals for symptom control and treatment of resulting dehydration. She had extensive GI work-ups in each hospital, including several upper endoscopies, computed tomography, magnetic resonance imaging, upper GI series and ultrasound. All studies were unremarkable. In addition, she underwent two upper GI botulinum toxin injections for symptom management, which initially provided some relief. During her episodes of abdominal discomfort and vomiting she was often unable to take her prescribed oral medications, which led her to develop withdrawal symptoms including diaphoresis and palpitations. After decreasing her medications, her GI symptoms resolved. Before this admission, her medications included lithium 1200 mg daily, amitriptyline 75 mg daily, trazodone 300 mg daily, lorazepam 4 mg daily and zolpidem tartrate 12.5 mg nightly. Physical examination demonstrated that she was mentally stable, but agitated. She presented with a soft abdominal wall with generalized abdominal tenderness, but without focal tenderness. Toxicology study revealed: blood lithium level 0.8 milliequivalents per liter (mEq/L) (safe blood level 0.6 and 1.2 mEg/L); Opioid test: negative.

The patient was hospitalized for close monitoring and adequate fluid resuscitation with intravenous fluids but was still unable to take her oral medications. During a 5-day period, she was safely tapered off of lithium, amitriptyline and trazodone, while being treated with hydromorphone, lorazepam and prednisone to prevent withdrawal symptoms. Following the taper, her GI symptoms completely resolved. Her medication lists were reviewed by psychiatry. The patient was followed by psychiatry and a pain physician. She also was educated regarding the importance of medication compliance. At 6-month follow-up, she had no further episodes.

Discussion

Psychotropic medications are often prescribed in combination for co-morbid conditions including depression, anxiety, bipolar disorder, insomnia and chronic pain. Some of these agents have the potential for severe adverse GI effects when taken concurrently [2]. Most classes of medications used in these diagnoses affect serotonin, epinephrine and norepinephrine in the central nervous system (CNS). For instance, tricyclic antidepressants like amitriptyline are believed to work by blocking the reuptake of both norepinephrine and serotonin at the presynaptic nerve terminal [3]. More specifically, tricyclic antidepressants have potent muscarinic, anti-cholinergic effects, with some minor alpha-1 and histamine-1 (H-1) antagonist activity, with antagonism of both the 5HT and NE transporter [4, 7]. Trazodone, an atypical antidepressant relies heavily on 5HT2 and alpha-1 adrenergic inhibition, and is a weak inhibitor of the 5HT transporter [4, 7]. Lithium, used to treat mania in patients with bipolar disorder, has a mechanism that is largely unknown. It was the first agent used to treat mania that was not an anti-psychotic drug, so comparisons have historically been difficult [8]. A study in animal brain tissue showed some inhibition of the release of NE and DA from nerve terminals, however this did not hold true for 5HT. These same authors suggest a potential small increase in the release of 5HT in the limbic system, which may impact the response of 5HT receptors to some 5HT agonists [9]. Some degree of therapeutic efficacy with lithium may also include inhibition of inositol monophosphatase, as well as in increase in glutamate due to an inhibition of glutamate reuptake at presynaptic nerve terminals [7]. Additionally, lithium is well known to have modulating effects on hormonal responses to vasopressin and thyroid-stimulating hormone [7].

As indicated, these medications have the potential to affect the CNS, peripheral tissue, and smooth muscle by a variety of mechanisms. For instance, these medications act peripherally as smooth muscle relaxants [1]. This combination of central and peripheral effects can result in severe GI symptoms such as abdominal cramping, nausea, vomiting and loose bowel movements [1]. There are a few potential hypotheses that may explain gastrointestinal complaints from a patient on multiple psychotropic medications, and this patient's complaints could be the result of more than one issue. The wide use of selective-serotonin reuptake inhibitors (SSRIs) has strongly indicated that, depending upon the specific serotonergic specificity of the drug, this class of agents has a fairly high incidence of gastrointestinal disturbances [11]. This has prompted several authors to revisit the potential gastrointestinal side effects associated with older psychotropic agents, and to take a closer look at the use of more than one psychotropic agent at a time in patients [8-9, 13-14]. While not all combinations of agents showed an increased likelihood of adverse effects, the authors did conclude that more data on the side effects of multiple psychotropic agents is surely needed [13, 14].

Constipation may be another cause of gastrointestinal pain or complaints and may be due to anticholinergic effects that are a well-known side effect of tricyclic antidepressants like amitriptyline [7]. As seen previously, this group of drugs decreases the cholinergic activity in the gut, resulting in a decrease in tone, which may result in constipation that may be mild to serious [4, 7]. Additional causes of constipation may be due to H-1 antagonism, 5HT increases, as well as a decrease in physical activity [10, 12].

Lastly, while lithium is eliminated renally [5, 11], trazodone and amitriptyline do undergo some biotransformation [7]. While trazodone is not known to participate to any great extent in cytochrome P450-2D6 biotransformation, amitriptyline is a substrate for this isoenzyme, so drugs that inhibit the 2D6 enzyme may increase plasma concentrations of amitriptyline. Additionally, drugs that have H-1, alpha-1, and/or anticholinergic mechanisms may also potentiate blood levels of drugs like amitriptyline [7].

While individual patient cases and some research indicate that a patient may present with gastrointestinal pain from one or more psychotropic medications, what may confuse this presentation is the increasing interest in research and clinical scenarios where patients may benefit from the use of certain psychotropic medications for gastrointestinal pain. The Rome Foundation Working Team report has recently evaluated available information regarding the "gut-brain" interaction [19]. The most well described and researched functional gastrointestinal disorder (FGID) where some of these medications are used is in the treatment of irritable bowel syndrome (IBS), particularly IBS with diarrhea (IBS-D) [15]. Grover and Drossman describe how the enhanced perception of peripheral signals in the gut ("visceral hypersensitivity"), psychological diagnoses or disorders, and likely inflammation or infection all have some impact on the function and regulation of the brain-gut axis [13-16]. Additional research for the use of psychotropic agents in FGIDs like IBS-D indicates that 5-HT and NE impact not just motility, but also sensation in the gut [17]. With psychological diagnoses like anxiety and/or depression plus brain-gut axis dysfunction, it fundamentally makes sense why so many patients with IBS-D are prescribed agents like anti-depressants to treat their symptoms, with many describing benefits and a reduction in GI symptomatology [15-17]. Indicators of poor outcomes regarding the use of anti-depressants for the treatment of IBS include constipation, poor compliance, moderate to severe FGIDs and more complicated psychological diagnoses [15-19].

Conclusion

With the introduction of new and many times better tolerated agents to manage bipolar disorder, lithium continues to remain a valuable drug in the management of mania in some patients, particularly when they have failed other drug classes (eg. anticonvulsants and antipsychotics) [8]. Co-administration of multiple psychotropic medications can result in well-known adverse effects such as serotonin syndrome, which is a potentially fatal complication when combining serotonergic agents [3, 18]. Unfortunately, less well known side effects like severe GI complications may be misunderstood and misdiagnosed. With persistent GI symptomatology of unclear etiology, it is important to consider potential iatrogenic causes as demonstrated in this case. Additionally, this patient was truly in a disastrous circle of multiple practitioners, prescribers, and likely multiple pharmacies. With no true "captain of the ship", patients like this frequently end up with predictable and unpredictable medical issues and adverse effects. What makes the patient described in this case study unique, is her lengthy list of complicated psychological diagnoses and medications, as well as her current and past history of very poor compliance. In the end, the subsequent challenge for these patients is finding the fewest number of practitioners to help put together a reasonable treatment regimen to safely manage their underlying psychiatric disorders and pain syndromes.

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