*Case report*

**Opioid-induced mania in a sickle cell disease patient with major depressive disorder: a case report and literature review**

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ABSTRACT

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| Opioids are well-known potent medications used for moderate to severe pain management. They act mainly through binding to μ-opioid receptors in the brain as well as having an inhibitory effect on serotonin and noradrenalin reuptake centrally, thus, increasing their levels. Considering the fact that Selective Serotonin Reuptake Inhibitors (SSRIs) act similarly, concurrent use of SSRIs along with opioids can induce mania. In this case report, we discuss a patient known to have sickle cell disease (SCD) with frequent painful crises managed with opioid analgesics; namely Tramadol and occasionally Pethidine. In addition, patient has been struggling with unipolar depressive disorder for the past ten years for which she was taking Paroxetine, there was no history of mania till few weeks prior to her current atypical presentation which coincide with an increment in her antidepressant's dose as well as her escalating misuse of the opioid analgesics. She was brought to the emergency department with mixed features of depression and mania with bouts of severe agitation. She was admitted to the psychiatric ward, her basic work up and brain imaging were unremarkable. She was diagnosed to have bipolar disorder type 1 with the possibility of opioid induced mania. Her management was a challenging process especially with her comorbid opioid misuse. She was stabilized on Aripiprazole 30mg, education about the importance of proper and cautious use of opioids was conducted to the patient and her family. The case highlights the importance of careful inquiry of concurrent opioid use in chronic painful conditions as well as adjunct use of SSRIs and other antidepressants. It also emphasizes the need to conduct longitudinal studies of the effects opioid may exert on the mood and behavior especially in individuals with mental disorders with chronic painful disorders. |

*Keywords: Opioids, Tramadol induced mania, sickle cell disease (SCD), bipolar disorder, selective serotonin reuptake inhibitors (SSRIs).*

1. INTRODUCTION

Sickle Cell Disease (SCD) is a chronic, genetic, hematological disease characterized by a wide range of complications throughout the body, mainly due to vascular occlusion by the sickled cells. The most common clinical complication of the disease is acute painful vaso-occlusive crises (VOC); in which patients experience severe pain mandating the frequent use of potent analgesics, mainly opioids (Borhade , Patel & Kondamudi, 2024). In addition to these common acute crises, SCD patients commonly have chronic pain; which may as well lead to the use of opioid analgesics (Carroll, 2020). Psychiatric comorbidities are not uncommon among patients with SCD; these include depression, anxiety, sleep disorders and substance related difficulties (Pecker & Darbari, 2019). Regarding depression in particular, one study found that around a third of SCD patients had depression (Hasan, Hashmi, Alhassen, Lawson, & Castro, 2003). This comorbidity can lead to a bidirectional relationship between psychiatric conditions and SCD pain as well as the utilization of opioids. Additionally, it commonly leads to the concurrent administration of analgesics and antidepressants. It is important to consider the effects of opioids on central neurotransmitters before prescribing them; especially in those receiving antidepressants, such as SSRIs. Examples of these effects include the inhibitory effect of tramadol on serotoninergic and noradrenergic reuptak (Grond & Sablotzki, 2004) as well as the inhibitory effect of pethidine on dopamine and norepinephrine transporters (Yasaei R, Rosani A, Saadabadi, 2023). As some opioids and antidepressants share some biological effects, the concurrent use of both agents may increase the potential risk of serious side effects like mania and serotonin syndrome.

Opioids were known for centuries to have an antidepressant effect, and their potential therapeutic use for depression was examined as well (Kosten, 2016). However, the literature review on opioids and their correlation with mania is scarce, consisting mainly of case reports. Literature included, in addition to mania, hypomania and psychosis; both as a first episode and on top of a pre-existing mood disorder.

In this report, we discuss a complex case since the development of mania was in the context of concurrent administration of an SSRI and opioid analgesics, with the possibility of substance use disorder (opioids) in this case.

2. CAsE PRESENTATION

Patient is a 37 years old female known case of sickle cell disease; with frequent crises, mainly painful vaso-occlusive crises, for which she has received oral and parenteral opioids mainly Tramadol, and occasionally Pethidine and Morphine. She was also diagnosed with major depressive disorder (MDD) 10 years prior to presentation, after a history of recurrent episodes of low mood, tearfulness, anhedonia, death wishes and disturbed sleep. She was stabilized on paroxetine 50mg OD (once daily) since then. She was brought to the emergency department by her family with chief complaint of two weeks history of decreased sleep duration, severe anxiety, and irritability.

An initial impression of a major depressive episode with anxious distress was established and she was admitted to the psychiatric ward for further observation and management. Her physical and neurologic examination was unremarkable. Basic investigations were ordered with no significant finding apart from thrombocytopenia which is explained by splenectomy. Brain CT was normal. At the time of admission, patient was pain-free and had no active SCD complaints. There is no family history of psychiatric disorders. Following admission, collateral detailed history from the patient and her husband reveals recent manic symptoms in the form of talkativeness, restlessness, sexual disinhibition, decreased need for sleep, racing thoughts, verbal and physical aggression toward family members and excessive money spending. Those changes coincide with recent increment of her paroxetine dose. Hence; the impression was changed into a manic episode with mixed features, as a part of Bipolar disorder type 1. Paroxetine was tapered off and Quetiapine was started and optimized to a dose of 800mg gradually over the course of three weeks. Initially, we attributed the manic episode to Paroxetine and there was partial improvement following its discontinuation. Then she started complaining of severe leg pain, mainly in the calf area. She was attributing it to a painful crisis and asking for opioids. However, after hematology consultation was made, the clinical characteristics of pain as per history and physical examination were less likely to be attributed to a painful VOC, and more similar to the presentation of restless leg syndrome, which we attributed to Quetiapine. Thus, she was switched to Aripiprazole, on which she showed partial improvement in about two week. However, shortly after few days of out-on-pass she came back with worsening symptoms; and asking for something to calm her down. The impression of akathisia as a side effect of Aripiprazole was established and Clonazepam was added. Considering the fact of the patient’s frequent use of opioid analgesics, reluctance and minimization of the use of opioids that are obtained from multiple different hospitals, her refusal of non-opioid analgesics offered by her previous physicians, we could know neither the exact dose of tramadol and other opioid analgesics nor the last dose used. Therefore, the possibility of dual-diagnosis of opioid use disorder on top of Bipolar I disorder was suspected. Furthermore, after observing the patient at the hospital, nurses noted some behaviors such us being hyperactive, jumping, and frequently asking for analgesics or agents that can help her to “elevate mood”. Additionally, the patient’s husband and brother were interviewed, they reported some concerning behaviors; such as a recent increased frequency of ED visits (multiple times a week; much more than her usual) seeking for parenteral opioids, using increasing amounts of multiple oral analgesics at home -mainly opioids-, and sneaking her brother’s pain relivers -opioids- that he uses for cancer. After that, opioid induced mania was the most probable cause, and resolution of her symptoms occurred after few days of tight control of her medications. She was discharged in a stable condition on Aripiprazole 30mg and a follow up appointment.

3. discussion

Opioids are a group of analgesics that are often used for moderate to severe pain management. It is the mainstay management of painful vaso-occlusive crises of SCD (Puri , Nottage, Hankins, & Anghelescu, 2018). Apart from their strong analgesic properties, opioids have many adverse effects including dependence, tolerance, and other psychiatric side effects (Benyamin et al., 2008). Considering SCD in particular, in an eleven-patient case series reported by (Kotila, Busari, Makanjuola, & Eyelade, 2015) six patients were classified by the authors as “addicted” to opioids without having any identifiable cause of chronic pain, while the other five cases were referred to as “Pseudoaddiction” by the authors. However, few cases in literature linked opioids usage to the induction of hypomania, mania or psychosis, either as a first episode or on top of bipolar disorder or unipolar depression. Among these, some were prescribed opioids for medical reasons (Arencibia-Arencibia et al. (2015). M.B. Arencibia-Arencibia1 et al. (2015) described a 49 years old female with no history of psychiatric disorders, who developed an acute manic reaction after being started on Tapentadol, an opioid analgesic, to manage the pain of her herniated lumbar disc, and immediately after its discontinuation, the manic symptoms resolved.

 The mechanism of action of Tramadol (which was the main agent consumed by our patient) is mainly through binding to centrally located Mu-type opioid receptor as well as inhibiting the neuronal uptake of serotonin and noradrenalin. This applies to tapentadol as well. Tramadol is metabolized to O-desmethyltramadol which acts as an agonist of μ-opioid receptors that are responsible for alleviation of pain. Furthermore, the inhibition of serotonin and noradrenalin suggests that it has similar molecular structure and effect to antidepressants especially venlafaxine (Sharma, 2016). Thus, the side effects of tramadol could be similar to venlafaxine which include inducing mania in a similar way of how antidepressants do, and serotonin syndrome. Pethidine, which was also used frequently in our case, has a stimulant effect by inhibiting dopamine and norepinephrine transporters (Yasaei et al., 2023).

The likelihood of having any of these side effects, is increased by the concurrent use of opioids with SSRI or SNRI antidepressants. In 2007, a retrospective study by [Schaffer CB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Schaffer%20CB%5BAuthor%5D&cauthor=true&cauthor_uid=18070849) and others (Schaffer, Nordahl, Schaffer, & Howe, 2007), the mood effects of opioids in thirty three patients with bipolar disorder were investigated. It was found that nine patients had significant manic or hypomanic reactions. And two others had antidepressant effect. Another retrospective study was held in a large referral psychiatry hospital over a three year period and published by Shariat, Hosseinifard, Taban, & Shabani, 2013. Out of 765 cases admitted with mania, in 45 cases, the emergence of mania was found to be following opioid withdrawal, including 28 patients with their first manic episode, and 17 patients with a previous history of bipolar disorder. John and Koloth, 2007 described one patient who has been treated for MDD with paroxetine, and was on tramadol as well. Suddenly, the patient had a manic episode, as well as serotonin syndrome. Another case by Gonzalez-Pinto, Imaz, De Heredia, Gutierrez, Micó, 2001 described a patient with unipolar depression treated with fluoxetine for ten years, experienced a manic episode after 18 days of using tramadol. We considered the fact that the patient had a recent increment of paroxetine which may be the trigger of the manic switch, but on the basis of that she has been taking the same medication for the last ten years without experiencing any manic switch and based on previous literature and the chronological order of the events occurred we considered the possibility of the association between opioid usage and her manic episode.

4. Conclusion

In conclusion; bearing in mind the fact that concurrent use of opioids and SSRI can cause different psychiatric complications, a clinician prescribing opioids should consider these effects, especially in patients with mood disorders such as those with depression treated with antidepressants and even those without any psychiatric conditions. As overuse of narcotic analgesics can lead to unwanted adverse effects that include drug interactions and opioid use disorder, it is prudent to urge physicians to use non pharmacological approaches and to follow a step-wise pain management. In a review study by [Hants Williams](https://www.ncbi.nlm.nih.gov/pubmed/?term=Williams%20H%5BAuthor%5D&cauthor=true&cauthor_uid=26596876) and others, 2015, 28 non-pharmacological interventions for pain in patients with SCD were examined. Approximately half of the studies reviewed demonstrated success in alleviating pain (Williams and Tanabe, 2016).

Nonetheless, this should not be understood to be synonymous to depriving those in need for potent analgesics from their treatment. Patients with SCD might be stigmatized because of their frequent need of opioids. However, VOC in SCD is a common, acute and severely painful condition that urges the use of potent analgesics when needed; and these are in fact the classic evidence-based treatment for such episodes. Moreover, when patients with SCD are undertreated, the severe pain can put them at risk of self-medication, alongside with all of its serious and potentially life-threatening complications (Alao, Westmoreland, & Jindal, 2003).

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