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Case Report

Possible association of severe major depression with acute cessation of long-term excessive triptan use

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SUMMARY

What is known and Objective: **Triptans are approved medications introduced for the acute treatment of migraine, classified as high-affinity serotonin 5-$HT_{1B/D}$ receptor agonists with lower affinity for 5-HT_{1A} receptors. Both migraine and treatment of migraine with triptans have been associated with the development of major depression. However, little is known about the adverse effects of acute cessation of long-term overdose triptan use.**

Case summary: **We report a case of a 49-year-old male patient with first onset of severe major depression following cessation of daily excessive triptan use for 8 years. The depressive disorder was resistant to prior serotonergic antidepressant therapy. Antidepressant treatment with a non-serotonergic agent was successful in resolving depressive symptoms.**

What is new and Conclusion: **The present case report demonstrates for the first time that acute cessation of long-term excessive triptan use has the potential to induce severe major depression, presumably due to persistent alterations in the serotonergic system including downregulation and desensitization of 5-HT_1 receptors. In this case, treatment with a non-serotonergic agent could be a promising therapeutic strategy.**

WHAT IS KNOWN AND OBJECTIVE

It is widely accepted that there is a bidirectional association between migraine and major depression, with each disorder increasing the risk for the subsequent first onset of the other.[1] Therefore, it is suggested that both disorders might share common pathophysiological mechanisms, including dysfunction in serotonergic neurotransmitter systems.[2] Triptans, such as sumatriptan, zolmitriptan or frovatriptan, are approved medications introduced for the acute treatment of migraine, but not for prophylaxis, and are classified as high-affinity serotonin 5-$HT_{1B/D}$ receptor agonists with lower affinity for 5-HT_{1A} receptors.[3] They should not be applied in other types of severe headache except for cluster headache. The use of triptans is restricted to a maximum of 9 days per month according to the International Headache Society (IHS) criteria.[4] High-frequency intake of triptans (≥12 days per month) has the potential to provoke migraine progression to chronic migraine.[5]

Although triptans are not thought to penetrate the blood–brain barrier and to have only modest effects on 5-HT_2 receptors, sumatriptan has been linked to the onset of recurrent major depression in a patient with no pre-existing depressive disorder.[6] Similarly, increased consulting rates for depression have been observed for triptans with enhanced lipophilicity, such as zolmitriptan and frovatriptan, thereby having more potential for central nervous system activity than sumatriptan.[7] This report presents a case of severe major depression following acute cessation of combined long-term excessive triptan use and its implications for possible antidepressant treatment strategies.

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DETAILS OF THE CASE

A 49-year-old married, Caucasian man was admitted to our inpatient psychiatric unit for the treatment of severe major depression resistant to prior therapy. On admission, he presented with very low mood, decreased motivation and inability to experience pleasure in activities that he formerly enjoyed and, furthermore, thoughts and feelings of worthlessness and hopelessness. He suffered from poor concentration and memory, reduced sexual drive, insomnia and suicidal ideations. His illness met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for major depressive disorder.[8] There was no personal or family history of other psychiatric disorders. Repeated physical and neurological examinations, laboratory tests, electrocardiograms and electroencephalograms showed normal results.

The first onset of the depressive disorder was in 2008 immediately after acute cessation of long-term migraine therapy with excessive doses of different triptans. No other trigger for the exacerbation of the depressive episode could be identified. Since 2000, the patient suffered from migraine as diagnosed by the IHS-ICHD-II criteria, described as alternating, unilateral, stabbing headaches that occurred with a frequency of two to three times per week. Migraine attacks were accompanied by vertigo, nausea, vomiting, diarrhoea, phonophobia and photophobia. He received migraine medication by his neurologist and general practitioner with three different types of triptans (zolmitriptan, frovatriptan and sumatriptan) for oral or subcutaneous use. In the beginning of the therapy, the patient used triptans only in acute migraine attacks, as medically prescribed, and responded

rapidly to this treatment. However, in the last 8 years, he self-administered triptans 'prophylactically' in high doses on a daily basis to avoid migraine attacks.

The patient had been hospitalized for two major depressive episodes in the past, the first in 2009 and the second in 2010, both for several weeks in psychiatric hospitals. Since the first onset of the depressive disorder in 2008, there was no clinically relevant improvement of depressive symptomatology, although he received different antidepressants mainly acting on the serotonergic system (amitriptylin, mirtazapine and duloxetine) and augmentation with the atypical antipsychotic quetiapine. During the current inpatient treatment, antidepressant medication was switched to the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion in a dosage of up to 300 mg/day. Amitriptyline, mirtazapine and duloxetine were tapered off. In the following weeks, the patient reported a full relief of his depressive symptoms. Moreover, he presented no recurrence of his migraine symptoms during the whole inpatient treatment period.

DISCUSSION

A variety of clinical studies point to an association between migraine and major depression, presumably due to a partial overlap in abnormal central serotonergic activity.[1] In this context, patients with major depression showed reduced sensitivity of central 5-HT_{1D} receptors that form one of the main pharmacological targets of triptans,[9] as well as reduced density and binding affinity of 5-HT_{1D} receptors in post-mortem samples from suicide victims.[10] Accordingly, triptans used for the acute treatment of migraine are discussed as a contributory factor for the development of depressive disorders as indicated by higher consulting rates.[7] Triptans are high-affinity agonists at 5-HT_{1B}/5-HT_{1D} subtype receptors with lower affinity for 5-HT_{1A} receptors.[3] They have been found to lower extracellular prefrontal serotonin levels in rodents, presumably via interaction with presynaptic 5-HT_1 autoreceptors and subsequent inhibition of serotonin synthesis and release.[11] On the other hand, antagonism at 5-HT_{1B}/5-HT_{1D} receptors increased extracellular serotonin levels in the frontal cortex.[12]

In our case, acute cessation of long-term excessive triptan use (zolmitriptan, frovatriptan and sumatriptan) was associated with the first onset of severe major depression. Based on the observed interaction between triptans and central serotonergic activity, and due to the fact that the patient was resistant to serotonergic antidepressant medication, it is possible to assume that chronic excessive triptan use might have the potential to induce persistent changes in the central serotonergic system including downregulation and desensitization of 5-HT_1 receptors.[13] It is important to note that long-term heavy triptan use is not associated with the development of major depression *per se*, as other case series reported no adverse events during treatment with excessive overdoses of triptans for up to 15 years.[14,15] However, it can be speculated whether acute cessation of use might represent a clinically significant stress factor for the exacerbation of depressive disorders, possibly in patients with an underlying predisposition for the disease. Interestingly, a switch of the antidepressant treatment from serotonergic medication to an NDRI significantly improved depressive symptomatology. This observation would confirm the assumption of persistent downregulation and desensitization of the serotonergic system by long-term overdose triptan use as the underlying pathophysiological mechanism for depressive exacerbation after cessation of use.

WHAT IS NEW AND CONCLUSION

In conclusion, the present case report demonstrates for the first time that acute cessation of long-term excessive triptan use has the potential to induce severe major depression. If discontinuation of long-term treatment with triptans should be medically required, it is recommended to slowly taper the medication off. In case of the occurrence of a depressive disorder as a result of cessation of long-term triptan use resistant to serotonergic antidepressant medication, treatment with a non-serotonergic agent could be a promising therapeutic strategy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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