

Case Report

Topiramate-Induced Suicidal Ideation and Olfactory Hallucinations: A Case Report

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Abstract: Antiepileptic drugs prescribed in the context of migraine have been reported to be potentially linked with an increased risk of suicidal ideation and behavior. Meta-analyses support the evidence that amongst antiepileptic drugs, Topiramate has the greatest potential for facilitating the occurrence of suicidal ideation and behavior. Studies indicate that this occurs via the increased incidence of mood disorders amongst the population with migraines using Topiramate as a treatment, with a slow and progressive onset of suicidal ideation (if any). We discuss the unique case of a 43-year-old man known to have chronic migraines, who presented with intense rapid-onset suicidal ideation and olfactory hallucinations, three weeks after the introduction of Topiramate for chronic migraines. After a negative extensive investigation panel to rule out common organic diseases, Topiramate was ceased. The suicidal ideation and olfactory hallucinations resolved in less than 24 h without further interventions. This case report highlights that rapid-onset suicidal ideation and olfactory hallucinations could be linked as an unusual side effect to the introduction of Topiramate. The removal of Topiramate from the patient's pharmacological treatments prevented further psychological distress linked to ego-dystonic suicidal ideation and a resolution of olfactory hallucinations. He was discharged 48 h later.

Keywords: case report; suicidal thoughts; psychiatry; topiramate; olfactory hallucinations



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1. Introduction

Antiepileptic drugs (AED) are commonly used to prevent migraine [1]. However, their side effect profile includes psychiatric adverse events [2]. Meta-analysis conducted by the FDA on 43,892 patients with epilepsy, psychiatric disorders and neuropathic pain reported an increased risk in suicidal ideation and behavior in users of AED [3]. However, these studies have been challenged due to various inconsistencies, such as patients with epilepsy and polypharmacy and the various diverging side effect profiles of different AEDs [4]. Amongst AEDs, Topiramate (TPM) has been reported as being the most linked to increase risk of suicidal ideation and behavior [4].

Few studies linking TPM with suicidal ideation and behavior are available. In 1999, Khan and his team conducted a retrospective chart review of 80 patients with refractory epilepsy who began TPM between 50 and 400 mg/day and found that five patients had developed definite psychotic symptoms, one of whom developed suicidal thoughts. Symptoms quickly resolved after discontinuing the medication [5]. Abraham et al., in 2003, reported a case of a 41-year-old woman with an history of bipolar disorder who developed severe suicidality after reaching a dose of 50 mg/TID of TPM used as a mood stabilizer. It was one of the first and only cases of severe suicidality linked to Topiramate ever reported in patients with mood disorders [6]. Later, Faubion and his team reported the case of a 72-year-old male without any past or family history of mental illness who

started TPM as a treatment for partial seizures [7]. He had made a suicide attempt when his medication reached 50 mg/day [7]. Other cases report psychotic symptoms such as auditory hallucinations linked to the initiation of Topiramate in patients with various medical conditions [8–12]. Many articles suggest that patients with migraine have a higher prevalence of mood disorders [13,14]. No study has yet addressed cases of suicidal ideation and olfactory hallucination in patients with chronic migraine receiving Topiramate as a prophylactic agent.

The objective of this case report is to highlight these unusual side effects of TPM and the challenge of rapid-onset suicidal ideation and olfactory hallucinations in a patient with chronic migraine. There is a risk linking AED to the increase of suicidal ideation and behavior that should be considered by clinicians when assessing the suicidal potential of their patients, in the context of the initiation of TPM as a treatment.

2. Case Presentation Section

2.1. Demographic Details, Medical History and Initial Presentation

The patient was a 43-year-old Caucasian man, celibate, with a BMI of 38, known to experience migraines, hypertension, and diabetes mellitus. The personal psychiatric history of this patient was insignificant. He was diagnosed with attention deficit disorder with hyperactivity at the age of 12 for which he was untreated. He was never hospitalized, nor in the past did he consult psychologists, counsellors, or psychiatrists. The patient described himself as in overall good health. He had been monitored by a neurological team since 2018 for chronic migraine treated with Amitriptyline 25 mg daily. Three weeks prior to his admission, Amitriptyline was ceased, and he was started on TPM 50 mg daily which considerably decreased his number of migraines per week. The patient was college-educated, working 40 h a week and had a small but strong social network. The patient's family history of psychiatric illnesses included depression on his mother's side of the family.

He was admitted to the psychiatric emergency ward after he called a suicide hotline for violent, rapid-onset, ego-dystonic suicidal ideation over the course of three days. One week prior to his admission, he described his mood as excellent but mentioned having a mild cognitive impairment at work. He reported having short episodes of memory loss and struggling to concentrate. He woke up three days prior to his admission in sweats, with a strong urge to kill himself with anything he could find in his room. This was a first episode for him, as he never previously experienced any suicidal ideation or suicide attempts and had no history of mood disorders. He mentioned that it was difficult for him to fall asleep as he was ruminating different ways to end his life. He also experienced strong moments of anxiety, without panic symptoms, describing them as including an unbearable sensation that he would lose control over his life. The patient reported this feeling as being torn in two: one side of his mind fighting to stay alive and one actively trying to find a way to die. After 48 h, he was unable to cope any more with the pain linked to this suicidal ideation. He contacted the medical team monitoring him for diabetes mellitus and they provided him with suicide hotline numbers.

2.2. Clinical Findings and Mental State Examination

Vital signs were normal upon arrival at the emergency room. He was first assessed by the primary care physician who did not find any clinical abnormalities. The patient did not report any cardiovascular, pulmonary or gastrointestinal complaints.

The patient appeared distressed and in pain. He was oriented in all three spheres. His hygiene was adequate. Despite his engagement during the medical interviews, he was barely able to maintain eye contact. His psychomotor activity was normal and he did not exhibit any abnormal movement. His speech was fluent and articulated. His mood was rather anxious and congruent to his affect. His thought was concrete and coherent, but invaded by strong suicidal ideation with violent connotations. Numerous times he stated that he did not understand why he felt that way as he is usually a very happy person and

could not identify any specific trigger that could explain the present situation. He was concerned that he would never be able to recover his normal life and was willing to stay in the hospital, if needed, to receive assistance because he did not want to die. He reported olfactory hallucinations, mentioning that his food and drink had recently smelled like gasoline, and he was convinced this was abnormal. He believed that a medical condition probably explained this and wanted to receive appropriate treatment. He did not exhibit any hetero-aggressive behavior and he disagreed with his suicidal ideation. His judgment and insight were adequate.

2.3. Diagnosis Testing

The patient did not meet the criteria for a mood disorder as per DSM-5 and had no psychotic features. The atypical presentation led us to assess organic causes for the suicidal ideation and olfactory hallucinations. A full blood count was conducted to assess for anemia or potential infectious diseases. Hepatic viral infections panel (hepatitis A, B and C), VDRL (Syphilis) and HIV tests were conducted. A C-reactive protein test (CRP) was also ordered to assess for inflammatory diseases. A liver panel, a thyroid function level test, a glycated hemoglobin test, and an extended electrolytes panel were conducted to assess for hepatic and endocrine dysfunction. Extensive laboratory testing results can be found in Table 1. Considering the initial presentation and the olfactory hallucinations, an electroencephalogram and a brain ct-scan were ordered. Urinary drug testing was also conducted to rule out drug-induced causes. All the investigations turned out to be negative.

Table 1. Laboratory testing results.

Test	Normal Value	Patients' Value
Haemoglobin	134–175 g/L	134 g/L
Hematocrit	0.410–0.500	0.388
Platelet count	140–400 × 10 ⁹ /L	237 × 10 ⁹ /L
Neutrophils abs.	1.5–7.7 × 10 ⁹ /L	5.4 × 10 ⁹ /L
Lymphocytes abs.	1.0–4.4 × 10 ⁹ /L	3.2 × 10 ⁹ /L
Eosinophiles abs.	0.0–0.7 × 10 ⁹ /L	0.5 × 10 ⁹ /L
Sodium	135–145 mmol/L	141 mmol/L
Potassium	3.5–5.1 mmol/L	4.0 mmol/L
Chlorus	100–110 mmol/L	108 mmol/L
Magnesium	0.70–1.03 mmol/L	0.70 mmol/L
Calcium	2.17–2.56 mmol/L	2.45 mmol/L
Phosphorus	0.72–1.44 mmol/L	1.22 mmol/L
Creatinine	80–115 µmol/L	69 µmol/L
Urea	2.5–7.8 mmol/L	4.6 mmol/L
Aspartate aminotransferase (AST)	13–39 U/L	23 U/L
Alanine aminotransferase (ALT)	10–39 U/L	39 U/L
Alkaline phosphatase (ALP)	53–128 U/L	61 U/L
Gamma glutamyltransferase (GGT)	0–55 U/L	35 U/L
Lipase	12–62 U/L	36 U/L
C-reactive protein (CRP)	0.00–9.99 mg/L	5.20 mg/L
Hemoglobin A1C	0.040–0.060	0.066
Thyroid-stimulating hormone (TSH)	0.270–4.200 Mu/L	1.510 mU/L
Human immunodeficiency virus (HIV)	Negative	Negative
Venereal disease research laboratory (VDRL)	Negative	Negative
Hepatitis A (anti-HAV IgM)	Negative	Negative
Hepatitis B (HBS Ag)	Negative	Negative
Hepatitis C (antibodies HCV)	Non-reactive	Non-reactive

2.4. Therapeutic Intervention and Outcomes

Upon arrival at the psychiatric emergency ward, observation was the main course of action to objectify the patient's claims. He actively tried to find ways to end his life

in the examination room but had enough self-control to warn the staff about his ego-dystonic suicidal ideation. After 24 h, considering the atypical clinical presentation, a neurologist was consulted regarding the possibility of TPM being involved in suicidal ideation. Considering the negative investigations and the severity of the presentation, he suggested temporarily ceasing TPM.

Less than 24 h after cessation of TPM, suicidal ideation and olfactory hallucinations disappeared altogether, as did the anxiety presented by the patient. The patient was discharged with a follow-up after 24 h additional hours of observation. No other treatment or changes in his medication were conducted during his stay in hospital. The main diagnosis retained was suicidal ideation and olfactory hallucinations induced by TPM.

As per further pharmacological treatment regimen for such presentation, it is important to note the need to address the patient's complaints of suicidal ideations and olfactory hallucinations. Considering the acute presentation, a treatment of serotonin uptake inhibitors for suicidal ideation as seen in major depression or anxiety disorders was not indicated. The appropriate approach, after eliminating organic causes, was to cease TPM and observe. With the cessation of TPM, the patient's migraines needed to be addressed. Propranolol, a non-selective beta-blocker, was introduced as per recommendations for migraine prophylaxis.

3. Discussion

The patient presented above developed severe suicidal ideation and olfactory hallucinations three weeks after the initiation of TPM. This is a rare and poorly documented probable side effect of that medication, and rapidly resolved after discontinuation of the drug. Studies have shown that AEDs are linked to an increased risk of suicidal ideation and behavior [15]. In addition, co-occurrence of migraine increases the risk of suicidality [16].

Patients presenting with suicidal ideation often exhibit risk factors such as personality characteristics, psychiatric disorders, physical disorders, psychosocial crises, traumatic life events, genetic loading, and neurobiological disturbances [17]. In the absence of such risks, rapid-onset suicidality requires a more extended panel of investigations to account for organic causes. The patient presented above was worried about mild cognitive impairments during the week prior to his suicidal ideation. Cognitive adverse events (CAE) linked to TPM are documented in the literature [18]. However, patient profiles that are more prone to CAE remain unclear and this should be further studied. A case report of a 25-year-old woman highlights an extreme case of cognitive impairment where she experienced dissociative amnesia at TPM 100 mg/day for migraine prophylaxis [19]. The explanation brought forward by the authors was that the action of TPM inhibits excitatory glutamate and enhances the inhibitory effects of the gamma-aminobutyric acid (GABA) system due to its impact on neurons' voltage-gated sodium and calcium channels [19]. Considering that TPM can take up two to four weeks to reach its full effect in the prevention of migraine and as an anticonvulsant, it is possible that the presented patient experienced his mild cognitive symptoms as a result of taking TPM [20]. While little data exists on the subject, suicidal ideations and behaviors have also been hypothesized to be linked with GABAergic-mediated decrease in serotonin secretion at the raphe nuclei [21]. Considering the higher prevalence of anxio-depressive psychiatric disorders in patients suffering from migraine, and the effect of TPM on the GABAergic system, the presence of suicidal ideation could be a result of CAE resulting in an increase in impulsivity. The limitation of our case report was the lack of available objective methods to verify the severity of cognitive impairment and therefore the reliance entirely on the recollection of the patient, which is prone to recall bias. Another hypothesis for the patient's presentation could be the growing body of evidence on the impact of TPM on gut microbiota. Different anti-seizure medications, including TPM, can have an impact on the growth of gut bacterial species resulting in consequences in host responses [22]. Also, several studies have demonstrated an association with migraine and gastrointestinal disorders [23]. While this patient did not experience any gastrointestinal symptoms, the use of TPM might have caused gut dysbiosis that could have resulted in the

reported clinical symptoms. In future studies, the impact of TPM on gut microbiota and an account of the patient's food diary should be considered to have a better overview of the patient's clinical presentation.

Very little literature currently provides explanations for the olfactory hallucinations experienced by the patient. A case report on a 3-year-old-boy reports that he lost his ability to detect and distinguish between odors during TPM treatment and entirely recovered it upon discontinuation of TPM [24]. Animal models on rats outline the implication of TPM in the hyperpolarization and modulation of olfactory cortical neurons. However, no such study on human subjects seems to exist [25]. The patient presented above reported olfactory hallucinations that appeared at the same time as the suicidal ideation and ceased after discontinuation of TPM, which hints at a potential correlation. While the association of olfactory hallucinations and TPM is not described in the literature, it might possibly be linked to the anxiety state related to the CAE induced by TPM. Olfactory neuroanatomy has numerous axonal connections with the primary emotion areas of the limbic system [26]. Considering that the olfactory system is impacted by increased anxiety, the anxiety experienced by this patient might have altered his olfactory perception [27]. However, migraines can also present with auras that have a variety of profiles including olfactory hallucinations [28]. It is therefore possible that the patient was experiencing a migrainous aura during this episode. However, considering the timeline of the symptoms, it is more likely that the olfactory hallucinations were psychiatric adverse effects of TPM. This needs to be further investigated.

4. Conclusions

In conclusion, suicidal ideation and olfactory hallucinations linked to TPM seem to be rare but possible side effects of the medication. This should be monitored during the initiation of AED as the side effect profiles tend to vary from mild psychiatric adverse effects to severe suicidality. Clinicians should be aware of this potential side effect and consider it in the event of rapid-onset suicidal ideation and olfactory hallucinations. In the case of the presented patient, discontinuation of the medication resulted in a quick resolution of the suicidal ideation and olfactory hallucinations. He was contacted three months after discontinuation and reported no recurrence of suicidal ideation and olfactory hallucinations.

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