Topiramate-induced depression in cases using topiramate for migraine prophylaxis

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Topiramate seems effective for migraine prophylaxis, as shown in several multicentre placebo-controlled trials (1–3). Topiramate’s most common adverse side-effects are paraesthesia, fatigue, decreased appetite, nausea, diarrhoea, weight loss, test perversion, hypoesthesia and abdominal pain. The most common adverse effects on the central nervous system are somnolence, insomnia, difficulty with memory, language problems, difficulty with concentration, mood problems and anxiety. The use of topiramate can also be complicated by depression in patients with epilepsy (4) or bipolar disorder (5). To the best of our knowledge, topiramate-induced depression in patients being treated for migraine has not been reported in the English language literature. Here, we describe two patients who experienced depression while using topiramate as a migraine prophylaxis.

Cases reports

Case 1

The patient was a 35-year-old female pharmacist with a 3-year history of migraine without aura. The headaches were described as unilateral, sometimes bilateral, pulsatile and with an intensity of 7/10. Nausea, vomiting, photophobia, phonophobia, and yawning were associated with her headaches. The frequency of attacks varied, but over the last few months had exceeded four times per month without medication overuse. The patient presented with no previous history of depression, mania, anxiety or other psychiatric, mood or any other medical disorders. Her body weight and body mass index were 45 kg and 17.6, respectively. She was started on a low dose of 25 mg topiramate for the first 2 weeks, which was increased to 50 mg in the third week. During the third week, the patient appeared profoundly depressed and tearful. She expressed feelings of worthlessness and despair. She also had loss of appetite and loss of energy. She also had suicidal thoughts. Her depressive symptoms fulfilled the criteria of major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV) (6), except the duration, which was just 1 week. At this time, she did not have a headache.

The topiramate was discontinued and no antidepressant was given because we believed the depression was associated with topiramate and wanted to see if the depression improved after it was discontinued. Within 1 week after the drug was discontinued, the patient reported that her depressive symptoms were much better. She declined rechallenge of topiramate for migraine prophylaxis, but agreed to take gabapentin and nortriptyline as a migraine prophylaxis. At the time of writing, 2 years after the short depressive episode, she has had no further depressive symptoms.

Case 2

A 36-year-old female paramedic had been diagnosed with migraine without aura for 1 year. She experienced dizziness, yawning, nausea without vomiting, photophobia and phonophobia before the onset of a headache. She presented with no history of any psychiatric disorders. The migraines were quite frequent, and had worsened in both duration and intensity in the last few months, and she was self-treating symptomatically with non-steroidal anti-inflammatory drugs without medication prophylaxis. She came to the neurological clinic for...
medical treatment of her migraine. Her body weight and body mass index were 47 kg and 17.1, respectively. Topiramate was started at a dose of 25 mg for the first 2 weeks and increased to 50 mg in the third week. In the fourth week, she began to experience a depressed mood, was easily tearful, with feelings of worthlessness, decreased appetite, psychomotor agitation, and suicidal thoughts. Her depressive symptoms met the DSM-IV diagnostic criteria for a major depressive episode (6). At that time, her headache symptom was improved. She had taken leave from her job for 1 week and then came back for follow-up at the neurological clinic. The topiramate was discontinued, without any antidepressant. Within 3 weeks after discontinuation of the topiramate, she was completely recovered from her depressive symptoms, and there has been no recurrence to date in the 1-year follow-up.

Discussion
To the best of our knowledge, these are the first two cases reports in the literature of topiramate prescribed for migraine prophylaxis apparently inducing depression. Various drugs have been used for migraine prophylaxis such as β-adrenergic antagonists, serotonin antagonists, tricyclic antidepressants, calcium channel antagonists and antiepileptic drugs, with variable efficacy and tolerability (7). An interesting new theory of migraine pathophysiology proposes that these headaches are the result of neuronal hyperexcitability, which is an imbalance between GABAergic inhibition and glutamatergic excitation (8). One mode of treatment for migraine in the current practice involved the use of a variety of antiepileptic drugs that have demonstrated efficacy in migraine prevention. These are broad-spectrum drugs with multiple mechanisms of action, such as valproate and topiramate. Topiramate has several proposed mechanisms of action. It is likely that one or more of these mechanisms may act additively or synergistically to modify the abnormal neuronal activity. Possible mechanisms include modulated GABAergic activity, modified voltage-gated calcium channels, or modulated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated excitatory neurotransmission.

Over the past two decades, there has been mounting evidence that GABAergic neurotransmission may also be involved in mood disorders, based on such lines of evidence as (i) effects of antidepressants on GABAergic transmission; (ii) genetic correlation of GABA receptor subunits with depression; (iii) neuro-interaction between GABAergic and monoaminergic systems; and (iv) treatment of depression using GABA receptor ligands. Antiepileptic drugs may also be involved in the pathophysiology of mood disorders in epileptic patients. GABAergic drugs exhibit negative effects on mood, whereas carbamazepine and lamotrigine appear to influence moods positively (9). Phenytoin, ethosuximide, carbamazepine, oxcarbazepine, gabapentin, valproate, pregabalin and lamotrigine are all associated with a low risk for depression (<1%). Depression has been described in normal volunteers and non-epileptic patients who received topiramate (5, 10). Kellett et al. described a patient with psychotic depression whose symptoms were resolved within 2–3 weeks of stopping topiramate (11). Risk factors seem to include the use of topiramate in the context of polytherapy (12) and a prior psychiatric history (13). The mechanism of topiramate-induced depression was not clear, although several hypotheses have been put forward (5). The first proposes involvement of GABA modulation. Depending on conditions, topiramate might either enhance or inhibit or directly activate GABAA receptors (14). The neutral GABA molecule itself has a self-blocking action at high concentrations that increases with depolarization due to an increase in the rate of desensitization (15). Thus, high concentrations of topiramate introduced over a short period of time may increase the desensitization rate, resulting in rebound currents and voltage sensitivity. A recent study by Mula et al. found a critical role in the topiramate titration rate on the occurrence of depression, showing a fivefold increased risk of developing depressive symptoms when topiramate is rapidly titrated, which may indirectly cause high concentrations (16). However, our patients started topiramate on a low dose and slow titration and still developed depressive symptoms. A second hypothesis to explain topiramate-induced depression involved genetic-related susceptibility. The effect of topiramate on GABA receptor function depends on the expression of specific subunits that can be regionally and temporally distributed, and altered by neurological disorder, and it is thought that the GABA receptors (17) and plasma GABA level might be under single-gene control (18).

In conclusion, topiramate-induced depression in migraine prophylaxis is not uncommon. Based on our observations, practitioners treating migraine patients with topiramate need to be aware of the potential for depressive symptoms.
References