

Psychiatric uses of topiramate: What is the current evidence?

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Topiramate enhances gamma-amino-butyric acid effects, has anti-glutamnergic effects, and is a state-dependent sodium channel blocker.¹ It is registered as an adjunctive treatment for epilepsy but is not registered for psychiatric indications. Nevertheless, it may be useful beyond its initial indication, considering the promising literature on which I report below. However, much more research evidence is needed to establish sufficient scientific justification for prescribing it routinely for psychiatric purposes.

Eating disorders

Three randomised, double-blind, placebo-controlled studies on the use of topiramate for bulimia nervosa have been undertaken.²⁻⁴ All reported promising reductions in bingeing and purging behaviour, as well as body mass. One study specifically reported an improvement in body image, eating attitudes, anxiety and self-esteem.³ Treatment was phased in at 25 mg per day, and increased where necessary to up to 400 mg per day. Topiramate appears to have been well tolerated but was discontinued in a small minority of subjects owing to side-effects. These studies were of relatively short duration (10 weeks) on relatively small numbers of subjects (60 - 70). Barbee reported 5 cases of severe bulimia nervosa with co-morbid mood and/or anxiety disorders.⁵ Three of the 5 patients progressed to almost complete remission on topiramate. The effect was maintained during an 18 months' follow-up period. One subject showed a partial response, and the other could not tolerate topiramate. Two single-case reports also describe that bulimia nervosa responded to topiramate.^{6,7}

Appolinario *et al.* described an open-label trial on 6 obese patients with binge eating disorder without neuropsychiatric co-morbidity, whose eating behaviour and weight improved significantly on topiramate.⁸ Kotwal *et al.*, however, reported on a naturalistic case series of 12 obese patients with bipolar disorder and co-morbid binge eating disorder who received topiramate for obesity and binge eating disorder, but needed lithium augmentation for optimal effect.⁹

A retrospective chart review done by Carpenter *et al.* found promising results regarding weight loss in the treatment of obese

patients suffering from major depressive disorder.¹⁰ The results were less convincing regarding depression, and the investigators were concerned about central nervous system (CNS) side-effects.

A case was reported of a woman suffering from anorexia nervosa and epilepsy, whose epilepsy was treated with topiramate. After topiramate was started, the anorexia nervosa flared up again. The authors concluded that it might have been precipitated by topiramate.¹¹

Obesity/weight gain

Several studies indicate either as the main aim of that study or as a serendipitous result that topiramate may be useful to manage weight gain. The potential usefulness of topiramate for this purpose is not clear yet, because many psychotropics used concomitantly have weight gain as a side-effect. For example, a study by McElroy¹² compared sibutramine and topiramate as adjunctive treatment for psychotropic-associated weight gain in adult, obese patients with a diagnosis of bipolar disorder in a randomised, open-label, flexible dose, drug comparison design. The trial lasted 24 weeks and involved 18 subjects on sibutramine (dose 5 - 15 mg per day) and 28 subjects on topiramate (dose 25 - 600 mg per day). Both treatment groups were associated with similar weight loss. However, the drop-out rates for both groups were high (78% for sibutramine and 79% for topiramate), calling into question the real usefulness of these drugs in clinical practice. Roy Chengappa *et al.*¹³ performed a randomised, double-blind, placebo-controlled trial to assess the efficacy of topiramate as an adjunctive treatment in adults with bipolar I disorder. Although topiramate turned out to be an inefficacious adjunctive treatment, significant weight loss was found when compared with placebo. Although the literature clearly indicates that weight loss can occur on topiramate, it is not registered for that purpose; neither did I find any practice guidelines in this regard.

Weight loss on topiramate has also been described in children suffering from bipolar disorder who gained weight due to psychotropic treatment. The study was small (10 subjects), relatively brief (11 weeks) and had an open-label design.¹⁴ Of note are the findings of Canitano.¹⁵ This paper describes children and adolescents with autistic spectrum disorders who gained weight substantially after having received neuroleptics for behavioural control. The study was also small (10 subjects) with an open-label design. Topiramate was slowly titrated up to 1 - 3

mg/kg/day. Six subjects took topiramate on a regular basis; 4 dropped out. Four patients showed variable degrees of weight reduction. Two subjects gained weight. Behavioural adverse effects were observed in 3 patients, necessitating withdrawal of the medication. The author warned that topiramate should be used with caution in autistic spectrum disorders because it may cause behavioural disruption in this group of patients.

Disorders of substance abuse

Alcohol abuse

In a randomised, double-blind, placebo-controlled study that received favourable comments,¹⁶ Johnson *et al.*¹⁷ reported that topiramate had a significant effect on abstaining from alcohol among 150 subjects suffering from alcohol dependence. The daily dose was about 200 mg; the study duration was relatively short (12 weeks).

Rubio *et al.*¹⁸ reported on 24 patients with alcohol dependence with other co-morbid psychiatric disorders '... for which the use of topiramate was indicated'. These patients received topiramate (average dose 262 mg per day) and other psychiatric drugs. They reported that, except for 3 patients who discontinued treatment, topiramate was well tolerated. It seemed that the addition of topiramate decreased the craving for alcohol. The authors concluded that topiramate might be beneficial for alcohol dependence.

Raguraman *et al.*¹⁹ described 22 subjects with alcohol dependence who received topiramate (250 - 300 mg per day) in an open-label study lasting 12 weeks. Six subjects did not complete the study because of problems with compliance. The treatment was discontinued for another subject owing to the development of a severe depressive episode. They found improvement in reported alcohol-related behaviour. Reported side-effects included psychomotor slowing, depression, memory impairment, concentration impairment, drowsiness and excessive sedation, but no weight loss.

Huguelet and Morand-Collomb described 2 patients (one suffering from schizophrenia, the other from bipolar disorder) with severe co-morbid alcohol abuse.²⁰ Komanduri described 2 patients with alcohol abuse.²¹ In both of these case studies, topiramate appeared to improve the alcohol abuse.^{20,21}

Smoking

Johnson *et al.*²² extended their above-mentioned study¹⁷ to investigate the effect of topiramate on cigarette smoking. They

used a double-blind, placebo-controlled design involving 94 subjects over a 12-week period. They concluded that topiramate showed potential for the treatment of cigarette smoking in alcohol-dependent individuals. Khazaal *et al.*²³ reported on a small number (13) of cigarette smokers who were given topiramate in an open-label trial. After 2 months, 6 of them were abstinent, 3 had a temporary reduction in smoking, and 3 could not tolerate topiramate.

Cocaine

Kampman *et al.*²⁴ described a 13-week, double-blind, placebo-controlled trial with topiramate as the active medication for the treatment of 40 subjects diagnosed with cocaine dependence. The results indicated that the topiramate-treated subjects were more likely to abstain from cocaine than the placebo-treated subjects. The authors came to the conclusion that topiramate might be effective for the treatment of cocaine dependence.

Borderline personality disorder

Relatively small and brief randomised, placebo-controlled studies indicate that topiramate may be useful for treating borderline personality disorder (BPD) at dosages of 200 mg per day (that were titrated upwards from 25 mg per day). Loew *et al.*²⁵ studied 56 patients over a 10-week period with promising results. Nickel *et al.*²⁶ studied 29 women with BPD and found significant reductions in anger measurements. Nickel *et al.*²⁷ repeated the study with 42 male subjects suffering from BPD, with similar results. In both the Nickel *et al.* studies, the dosages were 250 mg per day after titration upwards from 50 mg per day.

Do Prado-Lima *et al.*²⁸ reported a case study of a woman with BPD who responded to topiramate. Cassano *et al.*²⁹ described a 24-year-old woman with bipolar II disorder and BPD who was treated with topiramate in the course of trying to find a drug that controlled her depression; self-mutilation ceased after 2 weeks on 200 mg per day, despite no improvement of her depression. After topiramate had been discontinued, self-mutilation recurred, but ceased again after re-introducing the topiramate.

Anger, aggression and self-injury

Gobbi *et al.*³⁰ reported on a retrospective, case-controlled, mirror-image study involving 45 inpatients with marked aggression and agitation who were managed in a maximum-security Canadian psychiatric hospital. The patients were suffering from schizophrenia, schizo-affective disorder and bipolar disorder. The authors compared sodium valproate, topiramate and a combination thereof. Both valproate and topiramate reduced

aggression, but only valproate reduced agitation. They suggested that topiramate might be useful in the treatment of aggression in psychosis, calling for double-blind randomised, placebo-controlled studies.

Nickel *et al.*³¹ studied the effects of topiramate on symptoms of anger in women with recurrent major depressive disorder of a mild to moderate degree of severity. They used a randomised, double-blind, placebo-controlled design involving 64 subjects over a 10-week period. They concluded that topiramate appeared to reduce depressive symptoms and anger. The reduction in anger symptoms was strongly correlated with a reduction in Hamilton Depression Rating Scale scores. The study reported a significant improvement in both depressive symptoms and anger, as well as a correlation between the two. It is however not clear whether the anger improved owing to a selective effect of topiramate on anger or owing to the improvement in the depressive disorder.

Phager *et al.*³² retrospectively evaluated the outcome of topiramate used on 15 patients suffering from dementia who were severely aggressive and failed to respond to neuroleptics. The dementias were of various types. One group of patients received topiramate alone (8 subjects, mean age 75, standard deviation 6.2) and the other group received topiramate adjunctively (7 subjects, mean age 79.9, standard deviation 6.4). Topiramate dosages were 25 - 150 mg daily. The subjects were assessed with the Cohen Mansfield Agitation Inventory at baseline and after 2 weeks of receiving topiramate. Both groups showed significant improvement in aggressive behaviour. Interestingly, a neuroleptic was added to the group that received topiramate alone, but it conveyed no further benefit. The authors did not comment on side-effects but acknowledged the limits of the study and suggested double-blind placebo-controlled trials to investigate the possible usefulness of topiramate in patients suffering from dementia.

Kossoff and Pyzik³³ reported 3 boys, aged 5 - 12 years, with refractory epilepsy who were treated with combination therapy of topiramate and vagus nerve stimulation. All 3 showed a significant reduction in seizures, but what impressed them even more was a dramatic improvement in aggression, social interaction and ambulation. The authors were of the opinion that this was not due solely to seizure reduction, which was observed only differentially at 12 months.

Janowsky *et al.*³⁴ studied the effect of topiramate in an open-label trial on a group of 22 adult, institutionalised, severely to profoundly intellectually disabled individuals. Fifteen had bipolar disorder and 5 had another mood disorder. Other additional disorders

included autism, an anxiety disorder, obsessive-compulsive disorder, and no additional psychiatric diagnosis. Subjects also had diagnoses of various general medical conditions. The mean daily dose of topiramate was 202 mg with a range of 150 - 350 mg. The subjects were treated for '... aggression, self-injurious behaviors, destructive/disruptive behaviors or a combination of these, and/or other challenging and maladaptive behaviors'. They were also receiving concurrent psychotropic and/or anticonvulsant medications. There were promising improvements in the global severity scores, cumulative aggression, and worst behaviour rates at 6 months after starting topiramate. There were no significant weight changes. Other complications were noted: 1 patient developed delirium, 1 hypoglycaemia, 1 sedation, and 2 constipation. The authors concluded that topiramate might have a role in the treatment of challenging/maladaptive behaviours in intellectually disabled individuals.

Disorders of impulse control

In an open-label pilot study involving a small number of patients (14) for a relatively short period (16 weeks), Lochner *et al.* indicated that topiramate showed promise for use in trichotillomania.³⁵ They used a flexible dose of 50 - 250 mg per day.

After a single-blinded 12-week study of 31 male subjects with a DSM-IV diagnosis of pathological gambling, the authors concluded that both topiramate and fluvoxamine may be effective in the treatment of pathological gambling.³⁶ This study was small and of relatively short duration. In a small case series of 3 kleptomaniac patients, it was reported that subjects responded well to topiramate given either alone or in combination with an SSRI.³⁷

Grant³⁸ described an 18-year-old male with pyromania who received a combination of topiramate (75 mg per day) and cognitive behavioural therapy (CBT) for 3 weeks. Apparently, topiramate reached a dose of 75 mg after 3 weeks of CBT and 'After 3 weeks of CBT and 1 week of topiramate 75 mg/day, Mr. A denied urges to set fires'. He was considered free from symptoms on topiramate 20 months later.

Post-traumatic stress disorder

Berlant and Van Kammen³⁹ performed a naturalistic data review of medical records involving 35 adults who were treated for DSM-IV chronic post-traumatic stress disorder (PTSD). Some were treated with topiramate (12.5 - 500 mg/day) as monotherapy (7 patients), but most received topiramate as add-on treatment

(28 patients). The mean duration was 33 weeks (range 1 - 119 weeks). Nightmares, flashbacks and intrusive thoughts decreased significantly after topiramate had been introduced. There were also significant improvements in avoidance and hyperarousal. They reported a relatively rapid onset within 1 - 2 weeks. One instance of narrow-angle glaucoma occurred. Their conclusion was that double-blind studies were indicated. The same conclusion was reached after a small (3 subjects) case series of adults with chronic PTSD.⁴⁰

Mood disorders

Initially, topiramate seemed an encouraging candidate in the treatment of bipolar disorder and its subtypes, especially rapid cycling.⁴¹ However, double-blind placebo-controlled trials failed to support topiramate as monotherapy or as add-on therapy for any of the phases of bipolar disorder.^{13,42-44} A single-blind study comparing topiramate with sustained-release bupropion in the depressive phase of bipolar disorder showed promising results for topiramate.⁴⁵ This study, however, had significant methodological shortcomings.⁴⁴ Furthermore, in a double-blind placebo-controlled study, topiramate was not found efficacious as an add-on treatment for schizo-affective disorder, bipolar type.⁴⁶ Another, more recent, double-blind placebo-controlled trial, however, has reported topiramate to be as efficacious for the treatment of mania in adolescents with bipolar I disorder.⁴⁷ Therefore, although no recommendation can be made regarding the use of topiramate in either adults or adolescents, one can expect further studies in this regard.

In a retrospective study, Carpenter found that only a small percentage of patients suffering from major depressive disorder improved when topiramate had been used as an add-on treatment.¹⁰ At present, however, the use of topiramate in the treatment of major depressive disorder is not supported scientifically, if not in fact dubious. There has been a case report of topiramate-induced depression.⁴⁸

Cautions

As with all medication, topiramate has side-effects, and some are serious. For this reason, the decision to use it in conditions for which it has not been approved must not be taken lightly. Cereza *et al.*⁴⁹ warned about serious adverse events when topiramate had been prescribed for conditions for which it was not approved. These side-effects include glaucoma and abnormal vision. Mula and Trimble⁵⁰ remind clinicians that topiramate can also cause psychopathology as a side-effect. They found mood disorders (mostly a depressive disorder and 1 incidence of mania), aggressive behaviour, psychosis, anxiety, and personality

changes as side-effects of topiramate. These authors observed that psychopathology was related to seizure control in a subgroup of patients. They mentioned that the role of forced normalisation, interlinked with interactions with other anti-epileptic drugs, could be relevant. They suggested slower titration for seizure control as a measure to prevent these side-effects. Furthermore, one must note that, in some of the abovementioned studies, subjects had to be withdrawn owing to side-effects, as well as noting their high drop-out rates.

Conclusions

Topiramate is an anti-epileptic medication that shows promise for psychiatric uses. One disappointing indicator from double-blind placebo-controlled trials is that topiramate appears inefficacious for mood disorders. At present, topiramate's use in psychiatry seems most promising for bulimia nervosa and BPD but, even in these disorders, much more research involving larger numbers of subjects over longer trial periods is necessary before clear evidence-based recommendations can be made. Although promising results in a double-blind placebo-controlled trial were found for alcohol and nicotine dependence, more and longer trials too are needed. Confounding factors make interpretation of studies involving topiramate and other psychiatric disorders difficult. Nevertheless, it seems worthwhile to investigate the use of topiramate in disorders of impulse control, PTSD, angry/aggressive behaviour, self-injury, and perhaps primary depressive disorders. It must be emphasised that no firm evidence-based recommendations can be made regarding any of these conditions.

Topiramate is clearly associated with weight loss. This side-effect could possibly be of use in selected cases, but there are no clinical guidelines as yet for its use in treating obesity or weight gain secondary to psychotropic medication. Some studies indicate that topiramate is well tolerated while others indicate that it is poorly tolerated, with significant and even serious side-effects. Topiramate may worsen anorexia nervosa, cause psychopathology in adults and cause behavioural problems in children with autistic spectrum disorders.

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