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Topiramate (Topamax®) in Bipolar Disorder

Topiramate (Topamax®) is an antiepileptic agent approved for use in Canada since 1997 for adjunctive therapy in patients with refractory partial seizures. Preliminary observations indicate that topiramate may have antimanic or anticycling effects in some patients with bipolar disorder, and may be associated with appetite suppression and weight loss. This newsletter reviews topiramate's pharmacology, pharmacokinetics, and adverse effects as well as summarizes published clinical studies with topiramate in bipolar disorder.

Pharmacology

Topiramate is a structurally unique anticonvulsant, derived from d-fructose. Although topiramate's antiepileptic mechanism of action is not yet fully understood, several mechanisms have been proposed. These mechanisms of action are similar to those of established antiepileptic drugs, especially the mood stabilizers carbamazepine, valproic acid, and lamotrigine. These include:

1. GABA receptor agonism at non-benzodiazepine receptor sites,
2. Sodium channel antagonism, resulting in decreased sodium conductance and frequency of action potentials
3. Calcium channel antagonism, modulating L- and N-type calcium channel activity, and
4. Glutamate receptor antagonism at non-NDMA receptors.

In addition, topiramate possesses weak carbonic anhydrase inhibiting properties.

Pharmacokinetics

Topiramate is well absorbed, with an oral bioavailability of >80%, and readily crosses the blood brain barrier. The rate of absorption is slightly decreased in the presence of food, but the extent of absorption remains unchanged. As such, topiramate can be administered without regard to food. Volume of distribution ranges from 0.6-0.8L/kg and it is excreted unchanged in the urine. Elimination half-life is approximately 21 hours, with a twice-daily dosage recommendation. Furthermore, topiramate exhibits predictable linear pharmacokinetics with minimal plasma protein binding (~15%) and has a high therapeutic index.

Drug Interactions

Only a small fraction of topiramate is metabolized in the liver (~20%). Topiramate plasma concentrations are reduced by 40 to 50% when co-administered with carbamazepine and phenytoin. Addition of topiramate in patients with plasma phenytoin concentrations above the therapeutic range may increase phenytoin concentrations by approximately 25%. Concomitant use of digoxin has resulted in reduced serum digoxin concentrations (~15%). Close monitoring for worsening of clinical symptoms is warranted when topiramate is started in a patient already stabilized on digoxin therapy. Topiramate decreases serum concentrations of ethinyl estradiol by ~30%, therefore oral contraceptives containing at least 50mcg of estrogen should be used. To

minimize the risk of nephrolithiasis, avoid concomitant use with other carbonic anhydrase inhibitors such as acetazolamide.

Adverse Effects

The more common adverse effects associated with topiramate therapy are central nervous system-related, such as ataxia, nervousness, speech disturbances, and psychomotor slowing and are more likely to occur when topiramate is co-administered with other antiepileptic drugs. Adverse effects reported at a frequency of $\geq 5\%$ include fatigue, dizziness, somnolence, paraesthesias, confusion, impaired concentration, ataxia, and abnormal thinking. The majority of these reported side effects were rated as mild to moderate, transient, and reversed by the fourth month of therapy. Adverse effects can be minimized by gradual upward dosage titration.

A study assessing the cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults found that topiramate was more likely to cause serious cognitive side effects than either lamotrigine or gabapentin. However, the initial topiramate dose was rather large (200mg/day), and dose titration was at least four times as rapid as clinical practice. Unlike other mood stabilizers, such as lithium and valproic acid, and atypical antipsychotics, topiramate has been associated with a lack of weight gain, and in many overweight patients, even weight loss. Mild weight loss, ranging from 1.1kg with 200 mg/day to 5.9kg with ≥ 800 mg/day, has been associated with long-term topiramate therapy. Weight loss can be seen within the first 3 months of therapy and peaks at 12-15 months of therapy.

Nephrolithiasis is reported to occur in 1.5% of patients studied, all of whom were males between the ages of 21 and 54. None of the kidney stones required surgical removal, with stones passing spontaneously in $\frac{3}{4}$ of patients, and requiring lithotripsy in the remaining $\frac{1}{4}$ patients. In 5 double-blind studies assessing the antiepileptic efficacy of topiramate, 14% of

topiramate-treated patients and 3% of placebo-treated patients withdrew from the study due to an adverse event. Topiramate has teratogenic effects in animals and should be avoided, if possible, during pregnancy. Adverse events can be minimized by gradual upward dosage titration.

Efficacy in Bipolar Disorder

No randomized, double blind, placebo-controlled studies assessing the mood-stabilizing efficacy of topiramate in bipolar disorder are published to date. The efficacy of topiramate as a mood stabilizer in bipolar disorder has been suggested in case reports, retrospective and several open studies.

I. Acute Mania

The findings of several small studies suggest that topiramate is effective in the treatment of acute mania. A small pilot study (Calabrese et al 2001) of 10 hospitalized patients with severe bipolar type I disorder during a severe acute manic episode that was not responsive to lithium, valproic acid, or a combination of both agents, used topiramate monotherapy for up to 28 days. The mean Young Mania Rating Scale (YMRS) score decreased from 32 at baseline to 22 at the end of the study. Five patients exhibited evidence of moderate to marked improvement. (Three subjects had at least a 50% reduction in YMRS scores, and the other two patients experienced an improvement of 25% to 49% on the YMRS.) The mean dose was 313 mg/day (range 50 - 612mg/day)

In another study (Grunze et al 2001), the response of eleven hospitalized, treatment refractory manic patients to treatment with topiramate was analyzed using the YMRS scale. The study found that 3/11 patients showed marked improvement ($\geq 50\%$ decline) in YMRS, and two patients improved moderately (25-49%). Mean topiramate dose on day 22 was 172 ± 137 mg/day.

A prospective report (Chengappa et al 1999) found antimanic efficacy using the CGI scale in 60% of eighteen patients with a diagnosis of Bipolar I disorder when they received adjunctive topiramate with standard mood stabilizers. The YMRS scores improved from 30 (severe mania) to 12 (sub-threshold manic symptoms) at 5 weeks in all patients. The mean topiramate dose was 135 mg/day (range 25-300 mg/day), with an average treatment duration of 142 days.

II. Maintenance

A retrospective chart review study (Marcotte 1998) assessed add-on topiramate therapy in 58 patients with mood disorders (bipolar I, bipolar II, mixed bipolar, cyclothymic disorder, bipolar not otherwise specified, schizoaffective disorder, dementia, and psychosis) refractory to previous therapies. Mean topiramate dosage was approximately 200mg/day (range 25-400mg/day), with a mean treatment duration of 16 weeks. According to the Likert global assessment scale (appetite, sleep, mood and concentration), a marked or moderate improvement was shown in 52% of patients. Responders improved within 72 hours after initiating treatment.

Another retrospective chart review (Ghaemi et al 2001) assessed 76 bipolar spectrum disorder outpatients treated with topiramate for a minimum of 2 weeks. Adjunctive topiramate was found to be mildly effective, based on the CGI scale in 47% of patients, and 13% showed moderate-to-marked improvement. Treatment response was significantly correlated with dose. The mean dose of topiramate was 96 ± 94 mg/day (range 12.5-400mg/day) for a mean duration of 17.5 ± 16.7 weeks. The majority of patients were treated with concomitant mood stabilizers or antidepressants.

An open label study (McElroy et al 2000) evaluated the response to topiramate in 56 patients with various bipolar disorders either inadequately responsive to or poorly tolerant of at least one standard mood stabilizer or

antidepressant. Nineteen out of 30 (62%) of the patients with manic symptoms at study initiation demonstrated significant decreases in CGI and YMRS scores after both four and ten weeks of treatment, and at their last evaluation. Only three of the eleven patients (29%) who were initially depressed were much or very much improved by week 10. A relatively high percentage of patients (33%) discontinued the drug during the first 10 weeks of treatment, due to increased depressive symptoms, side effects and an increase in manic symptoms. Mean duration of topiramate treatment was 214 days, with a mean dose of 191mg/day (range 25-1000mg/day).

Despite the differences in study designs, diagnoses, and concomitant medication some preliminary conclusions can be drawn. It appears that topiramate is effective in 50 to 60% of patients in acute mania and that it is less useful in the depressed phase of bipolar disorder. When used as add-on treatment in patients with bipolar disorder considered refractory to other mood stabilizers, approximately 50% of patients have responded.

Dosage

For acute treatment of mania, the doses used were 200 to 400 mg/day titrated over 4 to 10 days, while the typical maintenance or add-on doses are 50 to 400 mg/day with a titration of approximately 25mg/week. Dosing and titration should be performed on an individual basis dependent on clinical efficacy and tolerability. There is conflicting evidence regarding the relationship between dose and treatment response, with one trial demonstrating higher doses of topiramate in treatment responders than non-responders, and one trial finding no dose-response relationship.

Cost

DOSAGE FORMS AVAILABLE	COST (PER TABLET)
25 mg	\$1.12
100 mg	\$2.13
200 mg	\$3.37

Summary

Topiramate appears to be effective in the treatment of acute mania and as add-on treatment in some patients refractory to other mood stabilizers. Its use as monotherapy in maintenance treatment of patients with bipolar disorder still needs to be studied. Topiramate's advantage over other agents is that it causes weight loss rather than weight gain, however intolerance due to other adverse effects is not uncommon. Slower upward dose titration is recommended to improve tolerance and prevent non-compliance.

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