

Topiramate in the Treatment of Epilepsy – A Review

a report by

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Introduction

Since 1990 around seven new anti-epileptic drugs (AEDs) have joined the marketplace. Among them, topiramate (TPM), a sulphamate-substituted monosaccharide, which was originally synthesised as an oral hypoglycaemic, has proven to be remarkably effective through a wide series of trials.

Mechanism of Action of Topiramate

Although the exact mechanism of action of TPM remains unknown, multiple mechanisms have been hypothesised based on *in vitro* studies, including voltage-sensitive sodium channel blockade, GABA_A-mediated chloride current increment, glutamate-mediated neurotransmission inhibition, increase of potassium conductance, carbonic anhydrase isoenzyme inhibition, and interaction with protein kinase phosphorylation sites. The proposed mechanism of action for TPM has been extensively reviewed.¹

In comparison to other AEDs, TPM has exhibited a modulatory effect on potassium conductance. TPM-induced hyperpolarisation and decrease in input resistance is due to an increase in potassium conductance.²

Drugs that potentiate potassium-channels, such as TPM, would be expected to have an anti-epileptic effect by decreasing the excitability of neurons. Loss-of-function potassium channel mutations are responsible for benign neonatal convulsions.³

Interactions with Other Drugs

The inhibitory action that TPM exerts on the CYP2C19 isoenzyme may lead to potential interactions with phenytoin and diazepam but known interactions with other drugs are modest and rarely of clinical significance.¹ An interaction between TPM and oral contraceptives may require a moderate increase in the contraceptive dosage to maintain its effects.¹

Anti-epileptic Effects of Topiramate and Clinical Evidence

In Europe, TPM is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial (focal) seizures with or without secondarily generalised seizures.

It is also indicated as adjunctive therapy for epilepsy in children over two years of age and adults with either partial onset or generalised tonic-clonic seizures. Additional indications include the add-on treatment of Lennox-Gastaut syndrome in children and adults.

Topiramate as Monotherapy

TPM as monotherapy in patients with either with drug-resistant or newly diagnosed epilepsies has been studied in three different trials. In a cohort of 48 adults (≥ 14 years of age) with drug-resistant partial epilepsy, TPM was titrated to 1,000mg/day or to the highest tolerated dose ($n = 24$) or to 100mg/day ($n = 24$) over five weeks in a double-blind fashion.⁴

Concomitant AEDs were tapered off over the same period, whereas maintenance lasted 11 weeks. Time to exit due to seizure deterioration was significantly longer for patients in the high dose group ($p = 0.002$). High doses were associated with better seizure control (46% versus 13% of patients with $\geq 50\%$ seizure reduction) and with higher rates of patients being seizure-free.

A multicentre study analysed the efficacy of TPM as monotherapy in recently (≤ 3 years) diagnosed partial epilepsy.⁵ A total of 252 patients (6–85 years of age) were randomised either to low doses (25mg/day if weight ≥ 50 kg, or 50mg/day, if weight ≤ 50 kg) or to high doses (200mg/day if weight ≤ 50 kg, or 500mg/day if weight ≥ 50 kg). Time-to-exit due to the recurrence of a second seizure favoured the high doses (422 versus 293 days) without reaching a statistically significant difference.

However, when time to first seizure (317 versus 108 days) was added as a covariate, the differences between groups reached statistical significance ($p = 0.01$) as it did for the number of seizure-free patients during the six-month study (54% versus 39%; $p = 0.02$).

A multinational, double-blind study in newly (≤ 3 months) diagnosed partial epilepsies involved 613 patients (6 to >65 years of age) from 115 centres.⁶ TPM 100 or 200mg/day was compared with either carbamazepine (CBZ) 600mg/day or valproate (VPA) 1,250mg/day. Patients were allocated to either CBZ or VPA, according to their clinical features, followed by randomisation to receive either the designated comparator drug or TPM 100 or 200mg/day in double-blind fashion.

Efficacy parameters, represented by time to exit, time to first seizure, and proportion of seizure-free patients during the six-month period of the study, did not differ between groups, showing that all used medications possessed equivalent efficacy. However, TPM 100mg/day was associated with fewer side effects. Further analysis of the paediatric subpopulation of the study (6–16 years of age) produced similar results when analysed in more detail.⁷

5% of patients treated with TPM and in none of those on placebo.

A placebo-controlled trial of adults with drug-resistant partial epilepsy supported the clinical efficacy of lower doses of TPM seen in the earlier trials.⁹

In the study, 263 adults (18–67 years of age) receiving carbamazepine CBZ were randomised to either placebo ($n = 92$) or TPM 200mg/day ($n = 171$). The study design was similar to the previous placebo-controlled trials, consisting of a four- to eight-week escalation period and a 12-week maintenance period. The TPM arm reported a median seizure frequency reduction of 44% versus 20% in the placebo arm ($p \leq 0.001$).

TPM has also been studied in children (2–16 years) with focal epilepsy as adjunctive therapy in a randomised placebo-controlled study.¹⁰ Thirty-nine percent of patients treated with TPM ($n = 41$) had a seizure reduction of $>50\%$ compared with only 20% on placebo ($n = 45$). TPM had different target doses according to body weight (125mg/day for 16–24.9kg, 175mg/day for 25–33.9kg, 225mg/day for 34–42.9kg and 400mg/day for ≥ 43 kg). The results were of borderline statistical significance.

TPM was considered to be as effective as standard AEDs in the treatment of newly diagnosed partial epilepsy in adults and children.

Topiramate in Focal Epilepsies

The efficacy of TPM as an add-on AED in refractory partial epilepsy in adults has been studied in eight multicentre, randomised, placebo-controlled trials.¹ In the different trials, either a single dose (200, 400, 600, 800 or 1,000mg/day) or a range of doses (300–600 or 600–1,000mg/day) were used. Because the eight studies all had a similar design: a titration period of 3–11 weeks followed by 8–12 weeks of maintenance, a pooled data analysis was possible.⁸ Of the 527 adults with focal, drug-resistant epilepsy treated with TPM, 43% of the patients experienced a reduction in seizure frequency of $\geq 50\%$, compared with only 12% of 216 patients on placebo ($p < 0.001$). Seizure freedom was reported in

However, 5% of TPM-treated children were seizure-free versus none of those on placebo. An open-label extension of the study showed that 64% of the children treated for six months had a seizure frequency reduction of $\geq 50\%$, and 14% were seizure-free.¹¹

Recently published evidence-based guidelines reviewed efficacy and tolerability of new AEDs in the treatment of new onset and refractory epilepsy.

According to classes of evidence, TPM was considered to be as effective as standard AEDs in the treatment of newly diagnosed partial epilepsy in adults and children. Class I evidence was also obtained for TPM use in refractory focal and generalised epilepsy in adults and children, as monotherapy in refractory focal epilepsy in adults, and in Lennox-Gastaut syndrome.^{12,13}

Topiramate in Generalised Epilepsies

The efficacy of TPM as adjunctive therapy has been studied in 80 patients (3–59 years of age), including 21 children (age 4–16 years) with primary generalised tonic-clonic seizures, with (67.5%) or without (32.5%) other generalised seizures.¹⁴

Patients in the trial had an idiopathic generalised epilepsy that was resistant to medications. Patients with Lennox-Gastaut syndrome were excluded from the study.

The study design included eight-week titration and 12-week maintenance phases. Overall, 39 patients were allocated to TPM (adjusted to patient's weight) and 41 to placebo. Median percentage reduction in generalised tonic-clonic seizures was 56.7% on TPM and 9% on placebo ($p < 0.05$). Considering all generalised seizures, difference between reductions with TPM and placebo was even greater ($p < 0.005$). Response rate (RR) was statistically higher in patients receiving TPM than in those on placebo.

common side effect observed in clinical trials. Controlled clinical trials on TPM showed that discontinuation rate related to adverse events ranged from 8–26% in the TPM arm versus 0–7% in the placebo arm.¹³

Hypohydrosis associated to TPM administration had been reported in children and adults, although children seem to be more prone to develop this side effect.¹ Renal calculi have been observed in about 1.5% of treated patients (82) and have been estimated to be 2–4 times higher than expected in the general population.¹

TPM treatment has been associated to ocular side effects such as acute glaucoma, acute myopia, suprachoroidal effusion, periorbital oedema, and scleritis in isolated case reports, whose actual frequency remains unclear.¹ These ocular manifestations are reversible upon drug withdrawal.

Data about the use of TPM in pregnancy have only been collected from add-on use and are therefore inadequate to assess whether any teratogenic potential is present in monotherapy

In clinical trials TPM has been shown to be a relatively well-tolerated and safe AED.

TPM efficacy as add-on therapy was studied in patients with Lennox-Gastaut syndrome. Patients were assigned to an 11-week, double-blind treatment phase with either TPM ($n = 48$) reaching a maximum dose of 6mg/kg/day or placebo ($n = 50$).¹⁵

In the study, 33% of patients responded to TPM, and 8% to placebo. Considering seizures causing drop attacks as the most disabling seizure type, TPM-treated patients had a mean reduction of 15%, whereas placebo-treated patients had a 5% increase.

Safety of Topiramate

In clinical trials TPM has been shown to be a relatively well-tolerated and safe AED, considering its lack of significant effects on cardiovascular function, bone density, bone marrow cells and thyroid function. The most common side effects responsible for discontinuation of treatment relate to cognitive functions. Weight loss is also a

and comparable of other AEDs.¹

Experimental data suggest that TPM can be teratogenic in mice, rats, and rabbits, producing craniofacial defects, limb and vertebral malformations.¹⁶

CNS-related Side Effects

CNS-related side effects represented the most common adverse reactions in controlled and open-label studies.¹³ They consisted mainly of somnolence, fatigue, headache, psychomotor slowing, confusion, difficulty with memory, impaired concentration, attention, speech and language problems. CNS-related side effects were reported by $\leq 40\%$ of patients who were specifically investigated for this aspect.¹⁷ Profound language regression has been reported as a reversible side effect of TPM in neurologically impaired children (113).¹⁸

A recent study evaluated the cognitive side effects of tiagabine (TGB) and topiramate.¹⁹ The study, a comparative open randomized trial with TPM and TGB as add-on therapy, analysed the influence of treatment on cognition, mood, and health-related quality of life (HRQOL).

Forty-one patients with refractory epilepsy were randomly assigned to either TPM or TGB. Intelligence, attention, working memory, episodic memory, and language were assessed at baseline, after titration and during maintenance. Self-report questionnaires were used to assess mood and HRQOL.

From baseline to after the titration paired sampled tests revealed significant deterioration in verbal fluency, language comprehension, working memory and visual block tapping under TPM. These functions remained stable in the maintenance phase.

Self-report measures initially indicated concerns about AED side effects in both groups and

TPM. The mean body weight decrease is 2–7%, occurring early in the course of treatment and reaching its maximum by 15–18 months.⁸ The reasons behind this side effect is not fully understood. It has been hypothesised that it may include reduction of appetite and inhibition of fat deposition as observed in animal models.²¹

Topiramate Dosing

Data from a large international study with a naturalistic design suggest that TPM should be slowly titrated and used at low-medium dosage with ‘flexible’ dose adjustments in order to enhance tolerability and increase retention rates.²⁰

Good efficacy with an excellent tolerability and safety profile are obtained at doses up to 200mg/day in adults and to around 3.5mg/kg/day in children.

Adults should receive an initial treatment with 25mg/day in the evening, followed by weekly increments of 25mg/day during four weeks until reaching the target dose of 100mg/day, given twice daily as morning and evening doses.

Data from continuing trials and greater clinical experience will help to clarify the specific categories of patients that are most likely to benefit from initial monotherapy with TPM.

concerns about worse cognitive functioning and depression under TPM. In the maintenance phase patients on TPM demonstrated improvement on all QOLIE scales on a descriptive level.

The authors concluded that TPM intake appeared to be associated with persistent negative cognitive side effects on frontal lobe-associated functions.

However, in the TPM group initially negatively affected HRQOL returned to baseline in the long run on a descriptive level. A relatively common neurological side effect observed in ≤60% of treated patients is paresthesia, which is usually mild and can spontaneously disappear.^{4,20} This side effect might be related to the carbonic anhydrase inhibitory activity associated to TPM.

Weight Loss with Topiramate

Weight loss is a frequently reported side effect with

In children, TPM is better started at 0.5mg/kg/day in the evening, and escalated with 0.5mg/kg/day during six weeks to the target dose of 3mg/kg/day.

However, patients with refractory epilepsy may benefit from further up-titration until the optimal balance between seizure control and tolerability is reached.

Summary

TPM, an AED with multiple putative mechanisms of action, has proven to be remarkably effective through a wide series of trials in several types of epilepsy.

Slow titration of TPM to a low-medium dosage will enhance tolerability. Good efficacy with an excellent tolerability and safety profile are obtained at doses (200mg/day in adults and ~3.5mg/kg/day in children. Furthermore, long-

term follow-up studies indicate that the response to TPM is maintained.

diazepam. Thus, TPM offers a valid therapeutic option in a wide spectrum of epileptic disorders.

Known interactions with other drugs are modest and rarely of clinical significance, however, its inhibitory action on the CYP2C19 isoenzyme may lead to potential interactions with PHT and

Data from continuing trials and greater clinical experience will help to clarify the specific categories of patients that are most likely to benefit from initial monotherapy with TPM. ■

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