Topiramate: Its Pharmacological Properties and Therapeutic Efficacy in Epilepsy

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Abstract: Since 1990 eight new antiepileptic drugs (AEDs) have been developed. Among these new drugs, Topiramate (TPM) is one of the latest AEDs available for treating drug resistant partial epilepsy both in adults and in children. The mechanisms underlying TPM antiepileptic activity are still incompletely understood. However, TPM, a sulfamate-substituted derivative of the naturally occurring monosaccharide D-fructose, has a different structure from other known AEDs. The antiepileptic activity of TPM in animal models of partial and generalized tonic-clonic seizures has been shown to be more effective as compared to other AEDs. Proposed mechanisms of action include reduction of epileptiform discharges through a voltage-dependent block of Na^+ channels, enhancement of the activity of γ-aminobutyrate at some subtypes of γ-aminobutyrate receptors, and antagonism of non- N-methyl-D-aspartate (NMDA) glutamate receptors. The pharmacokinetic profile of TPM, which is characterized by its rapid and almost complete absorption after oral administration, linear pharmacokinetics, minimal protein binding and predominantly renal excretion, makes the drug a good option for the treatment.

TPM was found to be effective and well tolerated in many studies conducted in adults and pediatric patients suffering from epilepsy.

This review, summarising the main studies in this field, provides an overview of the current knowledge about the relevant pharmacological and clinical information on the efficacy and tolerability of TPM.

INTRODUCTION

Epilepsy is one of the most common neurological disorders. Even though existing antiepileptic drugs (AEDs) can render 80% of newly diagnosed patients seizure free, a significant number of patients have chronic intractable epilepsy causing disability with considerable socioeconomic implications [1].

With significant advances in our understanding of neuropathology, neuropharmacology and neurophysiology of epilepsy, several new AEDs have been developed in recent years. Among these new AEDs, Topiramate (TPM), a sulfamate-substituted monosaccharide, is one of the most important new tool for the treatment of partial and generalized epilepsies [1, 2].

The aim of this review is to provide an overview of the current knowledge about this new AED and attempt to bridge experimental and clinical evidence to discuss the correct use of TPM.

CHEMISTRY

TPM, a structurally novel AED, is a derivative of D-fructose in the pyranose configuration, and it has the molecular formula $C_{12}H_{21}NO_8S$ (Fig. **1**) and a molecular weight of 339,4 [2-4]. TPM drug substance is a white crystalline powder with a bitter taste and is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. In addition, it is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/ml at room temperature. A saturated aqueous solution has a pH of 6.3. Aqueous solubility is increased by the addition of cosolvents, such as propylene glycol or polyethylene glycol 400, 1500, 4000 or 6000 [5].

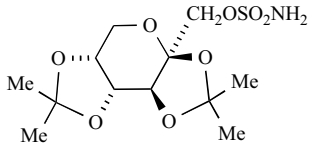

Fig. (1).

PHARMACOKINETIC PROPERTIES

After oral administration TPM is rapidly absorbed, with peak plasma concentration occurring at approximately 2 to 4 hours [6], with oral bioavailability of at least 81% [7].

TPM is poorly bound to plasma proteins, generally between 9-17% of TPM over a concentration range of 1 to 250 μg/ml [Unpublished data]. Although TPM has a chemical structure similar to that of carbohydrates, no carrier-mediated transporter appears to be significantly involved in drug absorption; similarly, tissue distribution is rapid, with no

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1389-5575/08 $55.00+.00

evidence of transporter-dependent exposure. The primary route of elimination of unchanged TPM and its metabolites is renal excretion. A significant percentage of the dose (40% in 10 days) is excreted in urine as intact TPM.

MECHANISMS OF ACTION

Several pharmacologic properties have been identified and may account for the broad anticonvulsant preclinical profile of TPM in animal models. In the last years TPM has been evaluated in numerous *in vitro* assays in order to identify the molecular mechanisms of action underlying its broad preclinical and clinical spectrum of activity. These data suggest that TPM acts at various voltage- and receptor-gated ion channels and may account for its *in vivo* activity. In particular, in rat pyramidal neurones and slices in culture, which displayed spontaneous epileptiform discharges, TPM dose-dependently reduced the duration and frequency of action potentials associated with repetitive firing [8-10].

There are several mechanisms that might explain the antiepileptic effect of TPM, including blockade of voltage-dependent sodium channels, enhancement of the current response elicited by gamma-aminobutyric acid (GABA), blockade of kainate-evoked currents, effects on voltage-activated Ca^{2+} channels, inhibition of carbonic anhydrase isoenzymes, and interaction with protein kinase phosphorylation sites [11-15].

Blockade of Voltage-Sensitive Sodium Channels

In 1996 TPM was shown to be able to reduce the duration and frequency of action potentials and the amplitude of inward voltage-gated Na^+ currents cerebellar granule cells of the rats [16]. Subsequent studies investigated the effect of TPM on voltage-dependent Na^+ channels using an *in vitro* seizure model of cultured hippocampal neurons where at concentrations of 10 microM TPM decreased or abolished recurrent seizures, with a marked voltage-dependent Na^+ and Ca^{2+} conductances responsible for the generation and propagation of action potentials [17]. However, this mechanism seems to differ from that of classic Na^+ channel blocking AEDs such as phenytoin, Carbamazepine (CBZ) and lamotrigine (LTG). Therefore, it has been suggested that Na^+ channel blockade may not be the primary mechanism by which TPM exerts its anticonvulsant activity [18].

Enhancement of GABA-evoked Chloride Currents

GABA belongs to main inhibitory neurotransmitter in the Central Nervous System (CNS) through three types of specific receptors ($GABA_A$, $GABA_B$, $GABA_C$) [19]. TPM has been demonstrated to potentiate GABA-ergic transmission, rapidly and reversibly increasing GABA-mediated chloride channels in mouse cortical neurons at concentration of 1-30 microM [20]. Although, similarly to benzodiazepine, TPM has effects on $GABA_A$ channel kinetics, flumazenil, a benzodiazepine antagonist, does not block TPM's ability to enhance $GABA_A$-mediated chloride currents [20]. These findings suggest that TPM may exert its positive modulatory effects by binding to a different site on the GABA receptor or to a novel site on the $GABA_A$ receptor complex.

To investigate the modulatory effects of TPM on various $GABA_A$ receptor subtypes, specific subunits of the $GABA_A$ receptor in Xenopus oocytes were expressed. TPM reversibly inhibited GABA-evoked chloride currents in oocytes expressing the $GABA_A$ receptor subunits $\alpha1\beta2\gamma2S$ and $\alpha2\beta2\gamma2S$, potentiating currents in oocytes expressing the $\alpha2\beta2\gamma2S$ subunit combination, but having no effects on oocytes containing $\alpha2\beta2\gamma2S$ $GABA_A$ receptors. In addition, using the Xenopus oocytes expression system, it has been shown that effects of TPM on the $GABA_A$ receptor system are subunit selective [21]. $GABA_A$ receptors containing $\alpha4$, $\beta3$, and $\gamma2S$ subunits are particularly sensitive to direct activation with TPM at concentrations as low as 10 microM [22].

Effects on Glutamate-mediated Excitatory Neurotransmission

The excitatory neurotransmitter glutamate exerts its excitatory actions by binding to both ionotropic [NMDA, alpha-amino-3-hydroxy-5-methil-4-isoxazolepropionic acid (AMPA) and kainite] and metabotropic glutamate receptors ($mGluR_{1-8}$). TPM exerts a negative modulatory effect on kainate-elicited excitatory currents. A series of electrophysiologic studies using rat hippocampal neurons in culture first described this activity, reporting that TPM blocked membrane currents evoked by kainate but had no activity at the NMDA-mediated glutamate receptor subtype [9, 23, 24]. In addition, TPM exerts a biophasic effect on kainate-evoked currents [13]. In particular, TPM produced a concentration- and time-dependent inhibition of cobalt (Co^{2+}) uptake into cultured cerebellar granule cells. Specifically, inhibition was evident at 10 microM, and complete inhibition was observed at 30 microM. Maximal inhibition of Co^{2+} uptake required pretreatment with TPM for $\geq$ 30 minutes before stimulation by kainate [25].

The ability of TPM to reduce neuronal excitability has been also evaluated. In particular, the effect of TPM on excitatory amino acid-evoked currents was studied. Kainate and NMDA were applied to cultured rat hippocampal neurons by using a concentration-clamp apparatus to selectively activate the AMPA/kainate and NMDA receptor subtypes, respectively. The evoked membrane currents were recorded by using perforated-patch whole-cell voltage-clamp techniques. TPM partially blocked kainate-evoked currents with an early-onset reversible phase (phase I) and a late-onset phase (phase II) that occurred after a 10- to 20-min delay and did not reverse during a 2-h washout period. TPM at the concentration of 100 microM blocked kainate-evoked currents by 90% during phase II, but had no effect on NMDA-evoked currents. The median inhibitory concentration values for phase I and II block of kainate currents were 1.6 and 4.8 microM respectively, which are within the range of free serum levels of TPM in patients [13].

Furthermore, the ability of TPM to inhibit a kainate-induced accumulation of free Ca^{2+} in cultured neurons from rat cerebral cortex is inversely related to the level of cAMP-dependent protein kinase mediated phosphorylation of kainate-activated receptors/channels. TPM binds to phosphorylation sites on AMPA and kainate receptors, but only in the dephosphorylated state, thus exerting an allosteric modulatory effect on channel conductance [26].

The effect of TPM on AMPA-induced intracellular calcium responses in cultured rat cortical astrocytes, with special interest in intracellular mechanisms has been recently investigated. The ability of TPM (1-100 microM) to inhibit AMPA-induced accumulation of Ca^{2+} in astrocytes was reported to be inversely related to the level of protein kinase A-mediated phosphorylation of channels activated by AMPA. Even in cultured cortical astrocytes, TPM significantly reduced the phophorylation level of Glutamate receptor 1 (GluR1) subunits [27].

Effects on Voltage-activated Ca^{2+} Channels

The effects of TPM on both N- and L- type high-voltage-activated calcium channel (HVACC) currents has been demonstrated in vitro. HVACC currents were recorded from rat dentate gyrus granule cells by using whole-cell patch-clamp techniques. TPM activity was tested at concentrations of 1, 10 and 50 microM. TPM inhibited L-type currents and was more effective at 10 microM than at 50 microM, suggesting that there may be an optimal concentration at which TPM decreases L-type currents. The inhibitory effect of TPM on L-type HVACCs was evident 10 min after initiating the application of TPM, and partially reversed after a washout period of 5 min. An inhibitory effect on L-type HVACCs could be another potential anticonvulsant mechanism [14, 28]. Additionally, TPM reduces ictal-like activity in CA1 hippocampal neurons through a novel inhibitory action of R-type calcium channels. The actions of TPM on the generation of plateau potentials (PPs) has been investigated. Whole-cell patch-clamp recordings from CA1 pyramidal neurons in rat hippocampal slices were used. In current-clamp mode, action potentials evoked PPs after cholinergic receptor stimulation. Therapeutically relevant concentrations of TPM (50 microM) depressed the PPs evoked by action potentials. Unexpectedly, in voltage-clamp mode, the cyclic nucleotide-gated current that underlies PPs generation was not depressed, probably due to the calcium entry trigger for evoking PPs depressed by TPM. TPM had no effect on calcium spikes after cholinergic-receptor stimulation. R-type calcium spikes are enhanced by cholinergic-receptor stimulation and these spikes were significantly depressed by TPM [29].

Inhibition of Carbonic Anhydrase Isoenzymes

Carbonic anhydrase is an enzyme that regulates intracellular chloride content through a cellular pump, exchanging extracellular chloride for intracellular HCO_3. Therefore, its inhibition can decrease HCO_3^- levels and increase pH, enhancing intraneuronal CO_2 concentration [30].

At concentrations of 1-10 microM, TPM weakly inhibits the CA isoenzymes CAII and CAIV [15]. TPM contains a sulfamate moiety that is likely to be responsible for its CA-inhibiting properties. Although inhibition of CA is generally not considered to represent a significant anticonvulsant mechanism of TPM, the possibility remains that this inhibition may contribute to its anticonvulsant action by modulation of pH-dependent voltage- and receptor-gated ion channels. The described metabolic changes in turn reduce pH and K^+ in the interstitial fluid; neuronal excitability can finally be described because of an extracellular reduction of K^+ or an increase of H^+, which can either block NMDA receptors or enhance $GABA_A$ activity [31, 32].

Interaction with Protein Kinase Phosphorylation Sites

TPM activity can influence the phosphorylation state of the receptor/channel complexes [13]; the ability of TPM to inhibit kainate-induced calcium currents on cultured rat neurons is inversely related to channel phosphorylation level [26, 33]. TPM seems to bind to phosphorylation sites on AMPA and kainate receptors only in the dephosphorylated state, supporting an allosteric modulatory effect on channel conductance [33].

CLINICAL EFFICACY AND USE IN EPILEPSY

The antiepileptic efficacy of TPM has been extensively evaluated in placebo-controlled, double-blind, add-on trials conducted in the US and in Europe. Major information regards the use in patients with partial and secondarily generalized seizures refractory, generalized tonic-clonic seizures (GTCS), drop attacks in patients with Lennox-Gastaut syndrome (LGS) and West syndrome. The efficacy of TPM monotherapy in adults and children with newly diagnosed or therapy-resistant epilepsy has been recently evaluated. The following sections review the clinical use of TPM in patients with different types of seizures.

Refractory Partial-Onset Seizures, with or Without Secondarily Generalized Seizures, in Adults

Single target or a range of target doses of TPM have been investigated.

Single Target Dosage of TPM

Single target dosage of TPM as adjunctive therapy in patients with partial-onset seizures has been evaluated. 167 of 209 patients received TPM at doses up to 1,000 mg/day or maximum tolerated dose. The mean dosage achieved was 799 mg/day. The median reduction in seizure frequency versus baseline was 51% after TPM treatment compared with 1% reduction after placebo ($p<0.001$). 6% of TPM-treated patients *vs* none of placebo group were seizure free [34]. These results were confirmed by subsequent single-dosage trials, studying different target dosages of 300, 400, 600 or 800 mg/day. In particular 46 patients were randomized to receive TPM (300 mg/day) or placebo. Mean reduction in seizure frequency was 44% in the TPM group and 7% in the placebo group ($p<0.01$) [35]. In addition, TPM (400 mg/day) resulted in a median percentage reduction in seizure rate of 40.7% versus 1.1% in those receiving placebo. There were significantly more responders (<50% reduction in seizure rate relative to baseline) in the TPM-treated group than in placebo group (35% versus 8%, $p<0.05$). 9% of those receiving TPM were seizure free vs none of those receiving placebo [36].

In patients titrated up to a target dose of 600 mg/day, and after 519 mg/day as mean dosage of TPM was achieved, the median percentage reduction in seizure rate was 46.4% in TPM-treated patients and 12.2% among placebo group ($p<0.005$). There were more treatment responders (≥50% reduction) in the TPM group (47%) than in placebo group (10%) ($p<0.001$) [37].

A trial of Korean Topiramate Study Group compared 600 mg TPM (or highest tolerated dose) with placebo in 177 pa-

tients. The mean achieved dose was 449 mg/day; with only 51 of 91 patients randomized to TPM achieved the target dose. Median reduction in seizure frequency was 51% in patients receiving TPM (versus 13% receiving placebo, $p< 0.01$) [38]. A TPM target dose of 800 mg/day (n=8) versus placebo (n=28) has been also considered. The mean daily dose of TPM was 568 mg/day. There was a significant reduction in average monthly seizure rate in the TPM group compared with placebo group (35.8% *vs* 17.8%, respectively) ($p< 0.001$) [39].

Multiple Target Dosage of TPM

Faught and collaborators considered 200, 400 and 600 mg/day with 4-week titration. Mean doses were 200, 391, and 556 mg/day, respectively. The median percentage reduction in seizure rate was significantly higher in the 400 and 600 mg/day TPM groups than in placebo group [40]. Similarly patients receiving 600, 800 and 1,000 mg/day and the mean daily doses achieved were 544, 739 and 799 mg, respectively, have been studied. A significant higher percentage of patients in the TPM group *vs* placebo group responded to treatment: 44%, 40% and 38% for the 600, 800, and 1,000 mg/day groups, respectively, compared with 9% in placebo recipients ($p<0.001$). Doses >600 mg/day did not appear to be associated with any significant advantage [41].

Additional information on the efficacy of TPM has been provided by pooled analyses of the data generated in various trials conducted in USA and in Europe. A rapid dose escalation schedule used in the initial trials starting dose 100 mg/day TPM, increased weekly in 100-200 mg/day increments has been reported. Median percentage reduction in TPM-treated patients was 44% compared with 2% in placebo-treated patients ($p\leq0.001$). TPM-treated patients achieved ≥50% (43% vs. 12%, $p\leq0.001$), ≥75% (21% vs. 3%, $p\leq0.001$) and 100% (5% vs. 0%,$p\leq0.001$) seizure reduction. Median percentage of seizure reduction between TPM and placebo achieved statistical significance at dosage ≥400 mg/day. These findings suggested that optimal dose ranges is 400-600 mg [42].

Patients receiving stabilized dosage of CBZ were randomized to placebo to 200 mg/day TPM or to 200 mg/day TPM. After 12 weeks of treatment, median percent reduction was 44% in TPM-treated patients versus 20% in those treated with placebo ($p\leq0.005$). After 2 weeks of treatment median percentage reduction was 60% versus 17% in those treated with placebo ($p\leq0.001$). Thus, TPM dosages of 100-200 mg/day appear to be appropriate target dosages to initially evaluate therapeutic response in adults receiving enzyme-inducing AEDs [43, 44].

All these data were confirmed by Bootsma and collaborators who analyzed all patients treated with TPM in the Epilepsy Centre Kempenhaeghe [45].

In an open, prospective, observational study TPM efficacy in 211 patients with treatment resistant partial-onset seizures has been explored. After baseline evaluation TPM was administrated at a target dosage of 200 mg/day over a 1-month period, followed by a maintenance period in which TPM dose varied according to the clinical results. After 6 months seizure frequency decreased to 35-40% of baseline values. Patients with at least 50% reduction in seizure frequency increased during the first 3 months until a final 80-85% [46]. Likewise, thirty patients suffering from refractory partial seizures with secondarily GTCS were randomized into a low dosage (100 mg/day) and a parallel medium dosage (200 mg/day) groups of TPM add-on medication (15 patients for each group). A major number of patients in the medium dosage group rather than in the low dosage group were free from GTCS during the dose maintenance phase ($p<0.05$). Moreover, TPM dosage of 300 mg/day was effective for seizure reduction in refractory partial epilepsy of adults [47, 48]. In a large, open-label, multicentre study conducted to explore dosing needed for patients typically found in clinical practice, TPM was initiated at 50 mg/day with weekly dosage increase of 25-50 mg/day accordingly to patient response. With a mean TPM dosage of 323 mg/day, median seizure reduction was 73%, with 68% of patients achieving ≥ 50% seizure reduction. In patients with less than four baseline seizures per month, the mean TPM dosage was 303 mg/day compared with 341 mg/day in patients with four or more baseline seizures per month ($p=0.005$) [49].

Efficacy of levetiracetam (LEV) and TPM during the first 15 days of add-on treatment of refractory partial epilepsy in adults has been compared in an open-label, non-controlled study. Two groups of patients with ≥ 3 simple or complex partial seizures per month over a 8-week baseline period received LEV or TPM in two distinct phases, in addition to standard antiepileptic treatment. During the first 15 days of the therapy, LEV was added at the dosage of 250 mg or TPM at 25 mg. Total number of seizure-free days during 15 days before treatment was 637 with LEV and 621 with TPM; in the 15-days evaluation period the seizure-free days increased to 748 (17.4%) and 668 (7.6%), respectively ($p<0.05$). Twenty-six patients (42.6%) taking LEV were seizure free compared to 10 (16.4%) receiving TPM ($p=0.003$). These results showed early efficacy of LEV as add-on therapy in patients with refractory partial epilepsy [50]. LEV is an AED with a novel mechanism of action and simple pharmacokinetic; LEV binds selectively and with high affinity to synaptic vesicle protein 2A (SV2A), a protein involved in the coordination of synaptic vesicle exocytosis and neurotransmitter release. LEV seems to partially inhibit N-type high-voltage-activated Ca+2 currents and reduces the Ca2+ release from intraneuronal stores. Therefore, the mechanisms of action of LEV seem to be completely different from those of TPM.

Refractory Partial-Onset Seizures, with or Without Secondarily Generalized Seizures, in Children

TPM was evaluated in children with partial-onset seizures during a 16-week randomized, double-blind, placebo-controlled trial. Median seizure reduction was 33% in TPM-treated compared with 11% in placebo-treated children ($p=0.03$). The proportion of TPM treated children achieving ≥50% seizure reduction was higher than in the placebo group (39% versus 20%, $p=0.008$). From baseline seizure rate of 20 seizures/month, 5% of children TPM treated were seizure free, no placebo-treated children were seizure free [51].

Children treated with one or two standard AEDs at optimal dosages during a 8-week baseline period had at least six partial-onset seizures, with or without secondary generaliza-

tion. Afterwards, children were randomized to placebo or TPM. Seizure control in this open–label extension was greater than that observed during double-blind treatment with TPM mean dose of 4.8 mg/kg/day. The increase in seizure control appeared to reflect the dosage adjustment [52]. In adults, however, maximum control of seizure was obtained with mean dose of 400 mg/day [36, 40].

Moreover twenty-two children with a diagnosis of refractory epilepsy have been considered. TPM (dose 0.5-2 mg/kg/day) was titrated at 2-week intervals up to the recommended dose of 6-12 mg/kg/day. Seizure frequency rate reduction was found significant, declining from 23 ± 5.1 seizure/week at baseline phase to 3.5 ± 1.2 seizure/week at the end of the 16-week stabilization phase ($p< 0.001$). After 16 week of stabilization, 86% of patients had more than 50% seizure reduction, 31% was 100% seizure-free, 9% manifested no improvement [53].

Veggiotti and colleagues reported the case of a 3 month-old female affected by refractory partial seizures, despite standard AEDs administration, treated with an initial TPM dose of 2.5 mg/kg/day and with a final dosage of 4 mg/kg/day. After 1 year of TPM monotherapy, the patients was still seizure free, even after the other drugs were discontinued [54].

Several studies evaluated TPM efficacy in patients with various types of seizures considered separately. Efficacy of TPM has been also evaluated in children with partial seizures (n=5), with generalized tonic-clonic seizures (n=3), myoclonic seizures (n=1) and infantile spasms (n=4). Mean age was 9.7 months. TPM was started at mean age of 11.4 months (4-23 months). Mean follow-up was 14 months. Mean dose of TPM was 8.8 mg/kg/day (2.5-18 mg/kg/day). Degree of seizure reduction was >75% in 5 children (38.5%), 50% to 75% in 3 children (23%), and 0 to 25% in 5 children (38.5%). 75% of patients with infantile spasms had a >75% reduction in seizure [55].

TPM was effective as monotherapy in children with partial onset epilepsy also in other studies considering not separately several types of seizures [56].

Refractory Primary Generalized Tonic-Clonic Seizures in Adults and Children

In several studies TPM was evaluated in patients with primary GTCS, with or without other generalized seizure types. Twenty-weeks placebo-controlled, double-blind, add-on trials with identical protocols and similar patient populations were conducted in patients ≥ 4 years of age. Patients had at least 3 primary GTCS a month during an 8-week baseline and an EEG consistent with a diagnosis of generalized epilepsy. In these studies there was a significant reduction in primary GTCS [57-60]. Twelve patients who participated in the double-blind study by Biton [57] were selected by Sachdeo to continue TPM treatment in a 20-week open extension. Compared with baseline, the frequency of GTCS was reduced by ≥ 50% in 11 of 12 patients (91%). Absence of seizures was achieved by 7 of 12 patients (58.3%) [61].

Additionally, an open-label study was conducted to investigate the effects of long-term add-on TPM in children with primary GTCS. Adjunctive TPM was given to 33 patients for ≥3 months. Compared with baseline of the double-blind trial, 67% of patients showed a reduction in seizure frequency of ≥ 50%, whereas 6% were seizure free during the 3-month period [62].

Chadwick and collaborators pooled the results from both studies [61, 62]. Median per cent reduction in primary GTCS was 57% in TPM-treated patients and 27% in the placebo group ($p=0.003$). 55% of TPM-treated patients had ≥ 50% seizure reduction compared to 28% in the placebo group ($p=0.001$). TPM was equally effective in children (≤ 16 year of age) and adults (> 16 years of age) [63].

TPM has been also evaluated in a long-term, open-label study, and the dosages of TPM and other AEDs have been individually adjusted. Mean duration of treatment was 387 days. During the study, 16% of patients receiving TPM ≥ 6 months had no GTCS for at least 6 months (mean TPM dose, 500 mg/day or 7 mg/kg/day for children) [64].

Some studies considered both patients with refractory partial and with generalized epilepsy. 134 adults with refractory localization-related epilepsy and 36 patients with idiopathic generalized epilepsy have been studied. TPM dosages substantially lower than those used in randomized controlled trials provided effective seizure control. With a mean dose of 250 mg/day, 23% of patients became seizure free. Among 119 patients who achieved ≥ 50% seizure reduction, including 13 of 31 patients (42%) who became seizure free, 29 patients (24%) were receiving ≤ 100 mg/day TPM [65].

Arroyo and colleagues evaluated TPM as first-line therapy in children (≥ 6 years of age) and adults with epilepsy that was not being treated when randomized to 400 or 50 mg/day topiramate as target maintenance dosages. In addition to ≥ 2 lifetime unprovoked seizures, patients had to have one or two partial-onset seizures or generalized-onset tonic-clonic seizures in the 3-month retrospective baseline. Double-blind treatment was discontinued after 6 months the last patients was randomized. Seizure-free at 6 months was 83% in patients randomized to 400 mg/day and 71% in those randomized to 50 mg/day ($p=0.005$). Seizure-free rates at 12 months were 76% and 59% respectively ($p=0.001$). Differences favouring the highest dose were significant in patients with partial onset seizure ($p=0.009$) and in those with GTCS ($p=0.005$) [56].

Several types of seizures were also considered individually in order to evaluate the efficacy of TPM in children with several types of seizures: partial (n=5), generalized tonic-clonic (n=3), myoclonic (n=1) and infantile spasm (n=4). Mean age was 9.7 months. TPM was started at a mean age of 11.4 months (4-23 months). Mean follow-up was 14 months. Mean dose of TPM was 8.8 mg/kg/day (2.5-18 mg/kg/day). Degree of seizure reduction was >75% in 5 children (38.5%), 50% to 75% in 3 children (23%), and 0 to 25% in 5 children (38.5%). Three of four (75%) patients with infantile spasms had a >75% reduction in seizure [55]. Thus, TPM showed favourable effects in these types of seizures. Another study compared different AEDs with TPM estimating remission rates on valproate (VPA), LTG, TPM, and combinations of these AEDs in patients with idiopathic generalized epi-

lepsy. Results showed that 54.3% of 962 patients had achieved a one year period of remission; this was most likely with VPA monotherapy (52.1%), with lower rates for LTG and TPM (16.7% and 34.6%, respectively). The combination of VPA and LTG achieved a remission rate of 15.3% [66].

Regarding the other AEDs it is important to underline that VPA combines several mechanisms of action: reduction of sustained, repetitive, high frequency firing by inhibiting voltage sensitive sodium channels, activating calcium dependent potassium conductance and possibly by direct action on other ion channels. VPA has a GABAergic effect through elevation of brain GABA by various mechanisms, such as inhibiting GABA transaminase, enhacing GABA synthesising enzymes, increasing GABA release and inhibiting GABA uptake. In addition, the effect of VPA on neuronal excitation mediated by the NMDA subtype of glutamate receptors, might be important for its anticonvulsant effects.

LTG is an effective broad-spectrum AED. LTG is a phenyltriazine derivative, that prevents the release of excitatory aminoacids, particularly glutamate and stabilising neuronal membranes through the inhibition of voltage-activated sodium channels and possibly calcium channels. LTG is rapidly and completely absorbed from the gastrointestinal tract with not significant first-pass metabolism. Oral absorption of LTG is rapid and complete and food coingestion only produces a slight delay, but not the extent, of absorption. Steady-state of LTG concentrations increase linearly with dose. Several studies evaluated efficacy of TPM in several types of epilepsy not considering singularly the types of seizures.

Sixty-five patients with more than 8 seizures during an 8-week baseline were randomized to 3 specified TPM plasma levels (low: 2 mg/L, medium: 10.5 mg/L and high: 19 mg/L). In the individual groups median reduction during 12-week observation period compared with baseline was as follows: low 39%, medium 85%, high 39%. Comparisons between the 3 groups showed significant differences between low and median group (p=0.03), medium *vs* high group (p=0.05) and low *vs* high group (p=0.81). Patients with medium TPM plasma level had the best seizure outcome [67].

TPM efficacy has been evaluated in 277 children (mean age 8.4 years) with drug-resistant epilepsy in a multicentric, retrospective, open-label, add-on study. After a mean period of 27.5 months of treatment (range 24-61 months), 11 patients (4%) were seizure-free and 56 (20%) had more than 50% reduction in seizure frequency. The efficacy of TPM treatment was noted in localization-related epilepsy and in generalized epilepsy [68]. In addition, in a group of 114 patients, the initial efficacy (evaluated after 9 months of follow-up) and the retention at a mean of 30 months of TPM with regard to loss efficacy (defined as the return to the baseline seizure frequency) were compared. 48% of patients were initial responders. The retention at a mean of 30 months was 20%, 3.5% of whom were still seizure-free. Loss efficacy occurred in 58% of the initial responders. It was prominent in patients with generalized epilepsy, symptomatic infantile spasms, LGS and Dravet syndrome. Well-sustained TPM efficacy was noted among patients with localization-related epilepsy. TPM seemed to be beneficial in a wide range of seizures, particularly in localization-related epilepsy. Similar results were obtained in patients who had taken or were still taking LTG, LEV and TPM [69]. A subsequent open, prospective, and pragmatic study considered 59 children aged less than 2 years and affected by localization-related epilepsy (n=22), generalized epilepsy (n=23), Dravet syndrome (n=6) and unclassifiable epilepsy (n=8). TPM was more effective in localization-related epilepsy (48% of responders) than in generalized epilepsy (32% of responders). TPM resulted less effective in infantile spasms (only five of 19 patients were seizure-free) [70].

Adults and children aged ≥ 2 years who were diagnosed with epilepsy (focal epilepsy, n=421; generalized epilepsy, n=148) within the last 5 years, resistant to other AEDs, received individually adjusted doses of TPM, after escalation to 100 mg/day over 4 weeks (maximum 400 mg/day) or 3 mg/kg/day over 6 weeks (maximum 9 mg/kg/day), respectively. Median TPM dose used was 125 mg/day in adults and 3.3 mg/kg/day in children (≤12 years). After 7 months, 44.3% of patients were seizure-free and 76.3% achieved ≥50% reduction in mean monthly seizure frequency ($p<0.001$). 39.4% of patients with focal epilepsy and 61.5% of patients with generalized epilepsy were seizure free [71].

Zanotta and collaborators considered TPM as add-on therapy in 26 patients, only in one as monotherapy de novo, one case changed from TPM as add-on to TPM monotherapy. Mean follow-up was 11 months. Mean TPM dose was 3.9 mg/kg. Four patients became seizure-free, all with TPM dosages lower than the mean. Eleven patients had at least 50% seizure reduction [72].

Newly and Recently Diagnosed Epilepsy

A conversion-to-monotherapy trial in adults with refractory partial onset seizures receiving one or more traditional AEDs was recently published [73]. Patients were randomized to one of two TPM dosages, 100 mg/day or 1000 mg/day TPM. The baseline AEDs was gradually withdrawn as the TPM dose was increased. With the highest TPM dose, fewer patients exited the study. In one of two open label extension phase, 19 of 20 patients experienced a reduction in seizures of ≥ 50% at an average dose of 555 mg/day (range 100 to 800 mg/day). Freedom from seizure was achieved in 14 patients for periods ranging from 3 months to > 2 years [61].

The second six-month open-label study evaluated the efficacy and safety of TPM monotherapy for partial-onset or primarily generalized seizures in 22 adults with newly diagnosed epilepsy. The initial TPM dose of 25 mg could be titrated to a maximum effective or maximum tolerated dose of 200 mg/day. The mean TPM dose was 200 mg/day (range, 75-200 mg/day). Compared with baseline, monthly seizure frequency decreased 89%, with 94% of patients achieving complete control. In this small study, TPM in doses ranging from 75 to 200 mg/day was effective and well tolerated as monotherapy [74].

In a double-blind study limited to patients with newly diagnosed epilepsy, a strongly significant dose-response effect was observed with TPM monotherapy [56]. In this study, the difference in time-to-first seizure was statistically

significant (p= 0.0002) in favour of 400 mg/day TPM (n=236) versus 50 mg/day (n=234) TPM. Statistically significant differences in favour of 400 mg/day were also observed in 6-month (83% versus 71% with 50 mg/day, p=0.005) and 1 year (76% versus 59% with 50 mg/day, p=0.001) seizure free rates. During double- blind treatment, 6% of patients receiving 50 mg/day and 17% of patients receiving 400 mg/day discontinued therapy due to adverse events. The seizure-free rates with 400 mg/day TPM exceed those reported with other AEDs (6 months, 35-48%; 1 year, 54-61%) [75-77].

A subsequent dose-comparison study evaluated the effectiveness of TPM as initial/early therapy in patients with less severe epilepsy. In this study, 252 patients (≥3 years of age) with an epilepsy diagnosis within 3 years before study entry and one to six partial onset seizures during a 3-month retrospective baseline were randomized to double-blind treatment with 50 mg/day (n=125) or 500 mg/day (n=127) [78]. Patients weighing ≤50 kg were randomized to 25 or 200 mg/day, respectively. Although time-to-exit was longer in the 200/500 mg/day group (422 days versus 293 days with 25/50 mg/day TPM) the difference was not statistically significant. However a post-hoc analysis showed a statistically significant difference (p=0.01) between treatment groups in favour of patients receiving 200/500 mg/day TPM (p=0.02). Some studies compared efficacy of TPM and of other AEDs. A randomized controlled trial evaluated initial target dosages in patients with newly diagnosed epilepsy. TPM monotherapy (100 and 200 mg/day) was compared with CBZ, at 600 mg/day, and VPA at 1,250 mg/day. TPM resulted as effective as CBZ and VPA in broad spectrum of patients with newly diagnosed epilepsy. The 6-month seizure free rate with 100 mg/day TPM was 49%; with 200 mg/day TPM, CBZ and VPA, the 6-month seizure free rate was 44% in each group. With treatment duration up to 2 years, discontinuation rates due adverse events for 100 mg/day TPM, 200 mg/day TPM, CBZ and VPA were 19%, 28%, 25% and 23% respectively. Although 100 mg/day and 200 mg/day dosages of TPM were similarly effective, 100 mg/day was better tolerated, with fewer discontinuations due to adverse effects [79]. CBZ is an iminodibenzyl derivative designated chemically as iminodibenzyl and it is structurally related to the trycyclic antidepressants. CBZ inhibits sustained, repetitive high-frequency firing of cortical neurons via use and frequency dependent blockade of voltage gated sodium channels. Other mechanisms of action include inhibition of L-type calcium channels and modulations of neurotransmission. It has a moderate anticholinergic action. Oral bioavailability is 75-85 % and unaffected by food intake. Bioavailability may be reduced by up to 50% when stored in hot humid conditions. After oral administration, absorption is relatively slow and often erratic reaching peak plasma concentrations within 4-24 hours.

In addition, patients with epilepsy diagnosed in the preceding 5 years, aged ≥65 years were enrolled in a larger open-label trial. After titration to TPM 100 mg/day over 4 weeks, the dose was adjusted according to individual response (maximum 400 mg/day). Patients were followed up for at least 7 months. After this period 79% of patients remained in this study. Seizure frequency decreased significantly versus baseline (p<0.001); ≥50% reduction in seizure frequency was achieved in 875 patients, 64% remained seizure-free. Both previously treated and naïve patients responded [80].

On the other hand TPM monotherapy 100 or 200 mg/day was reported to be effective as CBZ 600 mg/day or VPA 1,250 mg/day in children (aged ≥ 6 years) and adults with epilepsy. TPM monotherapy dose dependently reduced the number of patients who had experienced partial or generalized seizures. Six-month and 1-year seizure-free rates were dose-dependently reduced [81]. Also first- and second-line monotherapy with TPM was demonstrated to be more effective than VPA or LTG [82].

Wheless and collaborators in a novel double-blind trial compared TPM with CBZ or VPA as first-line therapy. Among 613 patients enrolled in the trial, 119 (19%) were children or adolescents (6-16 years of age). No differences between fixed doses of TPM (100 and 200 mg/day) and CBZ (600 mg/day) or VPA (1,250 mg/day) were observed in efficacy measures: time to exit, time to first seizure, and the proportion of patients who were seizure free during the last 6 months of treatment. TPM 100 mg/day (2.0 mg/kg/day in this study population) was associated with the fewest discontinuations owing to side effects. The recommended target dose for TPM as first-line therapy in children and adolescents is 100 mg/day [83].

In patients with newly diagnosed epilepsy according to the epileptic syndrome and to the patient's gender and age VPA and LTG are the two drugs of choice for generalized epilepsies. In cases of failure and/or intolerance to one of these AEDs, the principal alternatives are oxcarbazepine, VPA and TPM [84]. Target dose for first line therapy in children and adolescents is 100 mg/day, range 100 to 800 mg/day. Oxcarbazepine is 10,11-dihydro10-oxo-carbamazepine. It is different from carabamazepine because has a 10,11 double bond that is converted to an active epoxide. At the 10 position of the central 7-membered ring, OXC has a keto group that is rapidly converted to an active monohydroxy derivative in humans. This AED has a variety of actions: sodium channel blockade, open K channels, blockade of NMDA receptor-mediated activity.

Status Epilepticus

A small number of studies evaluated efficacy of TPM therapy in patients with status epilepticus. The Three patients with status epilepticus were treated with TPM 500 mg twice daily for 2-5 days, with the dose gradually tapered thereafter to 200 mg twice daily. One patient with subacute encephalopathy complicated by secondarily generalized status epilepticus resistant to other drugs. TPM was added and, 2 days later, pentobarbital was tapered with no recurrence of ictal discharges as the patient improved clinically. Second patient had end-stage liver disease and was hospitalized for peritonitis, and his course was complicated by partial status epilepticus. TPM was started, and 2 days later, his mental status improved as repeat EEGs showed no further ictal discharges although periodic epileptiform discharges were seen in the left centroparietal area. Third patient experienced a cardiopulmonary arrest, and developed postanoxic seizures, which

did not respond to other drugs and showed recurrent generalized slow wave activity and no ictal discharges [85].

Three children with refractory status epilepticus were treated with TPM, after failure to respond to treatment with Benzodiazepines, Phenytoin, Phenobarbital, Midazolam, or Pentobarbital. Age of the three children were 4.5 month, 34 months, and 11 years. TPM was initiated at 2 mg/kg/day in two children and at 3 mg/kg/day in the third. The status was terminated in all three children within 24 h of maintenance therapy with TPM at 5-6 mg/kg/day [86].

Perry and colleagues reported three children with status epilepticus who were refractory to therapeutic doses of at least two AEDs, treated with TPM, 10 mg/kg/day, followed by maintenance doses of 5 mg/kg/day. In each case status epilepticus was aborted within 21 hours of the initial dose of TPM [87].

Starting TPM therapy at higher doses, in this and in other studies, produced the reduction of time necessary to achieve seizure control.

Juvenile Myoclonic Epilepsy

Several studies evaluating efficacy of TPM in treatment of juvenile myoclonic epilepsy (JME) showed no statistically significant results [57-59]. Primary GTCS were reduced in 73% of TPM-treated patients and in 18% of placebo-treated patients. Weeks seizures free increase of 171% in TPM-treated patients and of 130% in placebo-treated patients. More recently Biton and collaborators have done a post-hoc analysis of a patient subset from two multicenter, double-blind, randomized, placebo-controlled, parallel-group trials. A total of 22 patients with JME participating in placebo-controlled trials assessing TPM efficacy (target dose, 400 mg/day in adults) in inadequately controlled primary GTCS were considered. ≥50% reduction of primary GTCS in 8 of 11 TPM-treated patients (73%) and 2 of 11 placebo-treated patients (18%) ($p=0.03$) were observed. Reductions in myoclonic, absence, and total generalized seizures were also reported, despite TPM *vs* placebo differences did not achieve statistical significance [88]. The efficacy of TPM in 18 patients (mean age 9 years) with severe myoclonic epilepsy and refractory seizures of different types has been also evaluated. TPM was added to other drugs at initial dose of 0.5-1 mg/kg/day, followed by a 2-weeks titration at increments of 1-3 mg/kg/day up to a maximum daily dose of 12 mg/kg. After a mean period of 11.9 months, 16.7% of patients had 100% seizure reduction and 55.5% patients had more than 50% seizure decrease [89]. TPM resulted particularly effective against GTCS [90].

Similarly, TPM has been shown to be an effective and well-tolerated drug in the treatment of JME. In 22 patients aged 13 to 53 years, target TPM dosage was up to 200 mg/day. GTCS were completely controlled in 62.5% of patients, and a reduction of ≥50% in 25.0%, and ≤50% in 12.5% were observed. Myoclonias were controlled in 68.8% and persisted in 31.2% of patients [91].

The use of TPM in children with severe myoclonic epilepsy of infancy has been also reported. TPM was added to current therapy in 18 children who had been treated with a mean of 6.7 drugs, at a starting dose of 1 mg/kg/day and titrated to a maximum 6-8 mg/kg/day, with a mean observation time of 10.5 months (6-18 months). 55.6% of patients reached ≥ 50% reduction in seizure rate, 22.2% achieved a reduction greater than 75% and 16.6 % became seizure free [92].

A retrospective cohort study compared in 72 consecutive JME patients efficacy of treatment with VPA, LTG, TPM, phenytoin, or CBZ, suggesting that LTG and TPM may be effective alternative options to VPA in the treatment of JME. TPM is an effective option as polytherapy in JME, but more data are needed to determine if it is an effective option as monotherapy [93].

Lennox-Gastaut Syndrome

TPM has been also evaluated as an adjunctive therapy in patients with LGS. A multicenter, double-blind, placebo-controlled trial enrolled patients with multiple seizure types (tonic or atonic drop attacks) and atypical absence seizures plus an EEG pattern typical of LGS and a history of ≥ 60 seizures in the month before baseline. In particular, 98 patients were enrolled in the trial (48 randomized to TPM and 50 to placebo). Mean age was of 11 years in each group. The average TPM dose was 4.8 mg/kg/day. Topiramate adjunctive therapy was effective in reducing the number of drop attacks and major motor seizures and in improving seizure severity as determined by parental global evaluation [94]. In an open-label extension of the study, 97 patients (mean age 11 years) received open-label TPM for a mean treatment duration of 539 days at a mean dose of 10 mg/day, starting at 1 mg/kg/day and increasing at weekly intervals to 3 mg/kg/day and then 6 mg/kg/day. Of those patients who received TPM for ≥ 6 months and who experienced drop attacks, 55% had reduction in drop attacks ≥ 50%. A reduction ≥ 75% was experienced by 355 of these patients, and 155 were free of drop attacks for at least 6 months; 71% of the patients who started open–label TPM treatment continued therapy for at least 3.4 years [95].

Eighty-seven children were treated with TPM and analyzed retrospectively. Grater than 90% seizure reduction was achieved in 9% of patients, 50%-90% in 24% of patients, < 50% in 62% of patients. Four patients (5%) had a deterioration in seizure control [96]. An Italian multicentric study evaluated the efficacy of TPM added to one or two other baseline drugs in 45 patients (mean age 15.9 years). Initial dose of TPM was 0.5-1 mg/kg/day, followed by a 2-week titration at increments of 1-3 mg/kg/day, until to a maximum daily dose of 12 mg/kg. After a mean period of 15.8 months at a mean dose of 4.1 mg/kg/day, 40% of patients had seizure reduction ≥ 50% [97].

TPM resulted effective in LGS similarly to LTG as reported in a controlled trial. The placebo-adjusted responder rate for drop attacks was 14% for TPM and 15% for LTG; the median percent reduction in drop attacks was 15 % (in major motor seizures was 26%) in TPM group compared to a 5% increase in drop attacks. Patient achieving ≥ 50% reduction in drop attacks was 28% in TPM group versus 14% in placebo group [98]. Similar results were reported by Guerriero and collaborators in an open-label, 36 months add-on

study, in which 75% of TPM treated had seizure reduction ≥ 50% [99]. In conclusion, TPM has been reported to be effective and well tolerated in patients with LGS [70, 100-108].

West's Syndrome (Infantile Spasms)

The efficacy of TPM has been evaluated in children with West's syndrome, characterized by infantile spasms, mental retardation and hypsarythmia. Spasm frequency was significantly reduced ($p<0.003$): spasms were reduced ≥ 50% in nine patients (82%), and five patients (45%) became spasm free. Seven patients were successfully converted to TPM monotherapy. During long-term treatment, four of the five spasm-free children remained spasm free for an average of 18 months (mean TPM dose, 29 mg/kg/day) [109, 110].

Twenty-eight infants younger than 24 months of age with refractory epilepsy (infantile spasms were the most common epilepsy syndrome) were evaluated in an open-label, multicenter chart review study. Mean age of seizure onset was 3.8 months (range 0-10 months). TPM was prescribed as add-on therapy in 25 cases and as monotherapy in 3 cases. The average treatment duration among TPM responders was 11 months. TPM was effective and well tolerated in these infants [111].

Valencia and collaborators evaluated efficacy of TPM in children with infantile spasms (n=4), partial seizures (n=5), GTCS (n=3) and myoclonic seizures (n=1). Mean age was 9.7 months. TPM was used as monotherapy in seven children and as politherapy in six children. Mean dose of TPM was 8.8 mg/kg/day (2.5-18 mg/kg/day). After 14 months follow-up 75% of patients with infantile spasms had a >75% reduction in seizure. Degree of seizure reduction was >75% in 38.5% of children, 50% to 75% in 23 %, and 0 to 25% in 38.5% [55].

Nine children with infantile spasms (19%), 25 with LGS (53%) and 13 with other epilepsies (28%) were treated with TPM as add-on therapy in a daily dose of 1 mg/kg/day for 2 weeks, followed by increases of 1-3 mg/kg/day at 2-week intervals, up to a maximum of 10 mg/kg/day. After a minimum treatment of 6 months, 60% of children had satisfactory response (completely seizure free, or more than a 50% seizure reduction). The remaining 40% had unsatisfactory response (50% or less reduction in seizure frequency, no change or increased seizure frequency). TPM appeared to be equally effective in infantile spasms, LGS and children with other types of epilepsies, with no significant difference between those with a satisfactory and an unsatisfactory response ($p=0.089$) [108].

Among 15 children with infantile spasms treated with TPM, 12 patients had symptomatic infantile spasms, and two patients had cryptogenic infantile spasms. The primary efficacy measure was comparison of the seizure rate during the 2-week baseline with the median seizure rate during the first 2 months of treatment. The median seizure rate reduction during the first 2 months of treatment was 41% ($P = .002$). Three patients became spasm free (20%), five had > 50% reduction, and three had at least 25% reduction. TPM resulted effective in 50-70% of patients with West syndrome at dosages ranging from 10 mg/kg/day to 29 mg/kg/day [112].

Other Patients Populations with Seizures

Clinical reports suggest that TPM may be effective in other seizure disorders, including tuberous sclerosis [113], and patients with Amyotrophic lateral sclerosis [114].

Kelly and colleagues evaluated efficacy of add-on TPM therapy in patients with learning difficulties and refractory epilepsy. After 6 months 25% patients became seizure free and 45% patients had seizure reduction ≥ 50%. Finally, TPM doses and plasma levels varied widely among patients [115]. In 20 patients with intractable epilepsy (mixed seizures), mental retardation and developmental disabilities who were treated with TPM adjunctive therapy, 69% of patients had ≥ 50% seizure reduction and 13% were seizure free [116]. Fifty-seven patients with refractory epilepsy and intellectual disability showed after 6 months TPM therapy significant seizure reduction: 17% of patients was seizure-free, 46% had seizure-reduction ≥50%, 29% had less 50% seizure reduction. 50% seizure-reduction was found in 100% of patients with temporal lobe epilepsy, in 75% of patients with spike-waves during sleep syndrome, 52% of patients with LGS and 25% of patients with infantile spasms [117].

Also five children with Angelman's syndrome showed a good response. After a mean 8.8 months on the medication 4 children were on monotherapy with TPM, 2 of whom were seizure free, and one discontinued the drug. The mean dosage was 12 mg/kg/day[118]. It has been also shown that TPM is effective in patients with neuropsychiatric disorders that can occur in patients with epilepsy [119-123].

Moreover, seven of eight patients with Rett syndrome had improvement in seizure control and/or respiratory abnormalities on TPM [124].

Recently TPM was evaluated as therapy for patients affected by nocturnal frontal lobe epilepsy. Twenty-four patients (mean age 29.3 ± 10.4 years) received TPM as single or add-on therapy from 50 to 300 mg daily at bedtime. The follow-up duration ranged from 6 months to 6 years. Patients seizure-free were 25%; patients with reduction of at least ≥50% of seizures were 62.5%; and patients non-responders were 12.5% [125].

INDICATION AND DOSAGES: CLINICAL THERAPEUTICS

TPM has been shown to be an effective broad-spectrum agent in the treatment of epilepsy. Efficacy has been demonstrated against all seizure types in placebo-controlled and open-label trials, with little evidence of aggravation of seizures.

After clinical studies conducted with TPM, it was approved as add-on therapy in focal seizures in children, adolescents and adults, in primary GTCS and in the LGS, and in patients with partial seizures as monotherapy. In children (≥2 years) starting dose is 1-3 mg/kg/day for the first week and subsequently has to be increased at 1- or 2- week intervals by increments of 1-3 mg/kg/day. In general, administration in adolescents should be started with an initial dose in the first week of 25-50 mg/day. Thereafter, every 1-2 weeks, the dose should be increased by 25-50 mg/day in two divided doses. The recommended initial target dose for adults on monother-

apy is 100 mg/day. As add-on treatment, the normal maintenance dose for adults is between 200 and 400 mg/day. When terminating treatment, tapering off the dose by 50-100 mg/week is recommended [126].

SIDE EFFECTS

Effects on Central Nervous System

Data from the five early randomized controlled trials suggested that CNS effects are the most troublesome. They consisted mainly of somnolence, fatigue, headache, psychomotor slowing, confusion, difficulty with memory, impaired concentration, attention, and speech language problems [127]. CNS-related side effects were reported by ≤40% of patients specifically under investigation for this aspect [128]. In some trials TPM withdrew prematurely because of an adverse event. The most common of these events were CNS adverse effects, depending on the increasing of TPM dosage [129].

In a multicenter, randomized, double-blind study of patients with partial epilepsy cognitive and behavioural effects of add-on TPM (400 mg/day) and VPA (2250 mg/day) were analyzed. Attention/vigilance, psychomotor speed, memory, word fluency and mood were assessed at baseline and during maintenance. No significant differences were found in CNS side effects between TPM and VPA group, except for verbal fluency and complex visuomotor ability and speed, for which TPM produced slightly greater cognitive effects in comparison to VPA [130]. Another study randomized 17 young, healthy subjects to LTG, Gabapentin or TPM. Gabapentin is a novel amino acid derived by addition of a cyclohexyl group to the chemical backbone of GABA; this AED interacts with a specific high-affinity binding site in mammalian brain membranes that is an auxiliary protein subunit of voltage-gated calcium channels; in addition, gabapentin reduces the release of several monoamine neurotransmitters. These subjects firstly received single dose of the drugs (LTG 3.5 mg/kg; gabapentin 17 mg/kg; TPM 2.8 mg/kg) and after 3 hours underwent neuropsychological test that revealed a significant decline in attention and word fluency only in patients TPM treated. After acute phase patients started titration (LTG ≤7.1 mg/kg/day, gabapentin ≤35 mg/kg/day and TPM ≤5.7 mg/kg/day) over 30 days. During the second and the fourth week of treatment subjects were administered neuropsychological test that showed the same results and reported more symptoms of depressed mood and of anger/hostility. The verbal fluency rate of TPM group dropped an average of 50 % per subject compared with a negligible change for the other 2 groups, and a three-fold error occurred for the visual attention task. The other two groups had no performance changes. At the 2- and 4-week test period only TPM-subjects continued to display neurocognitive effects [131, 132].

Aldenkamp and collaborators have subsequently reported on a study comparing the cognitive effects of TPM to those of VPA given as first-line add-on therapy to steady state treatment with CBZ. TPM was introduced at 25 mg and increased with weekly 25 mg/day increments to a minimum dosage of 200 mg/day. The target dosage ranged from 200 to 400 mg/day for TPM and was 1800 mg/day for VPA. This multicenter randomized, observer-blinded, parallel group clinical trial evaluated changes in cognitive function from baseline (2 week before start medication) to endpoint (after 20 weeks treatment) and during titration (after 8 weeks of treatment). Test measuring short-term verbal memory showed a statistically significant difference between the treatments with worsening for TPM, comparing baseline and endpoint results. Similar difference was found comparing baseline and titration results. No statistically differences were found between treatments [133].

Deterioration in verbal intelligence quotient (IQ), verbal fluency and verbal learning, decline in attention and concentration, processing speed, language skills and perception were demonstrated in adults with epilepsy treated with TPM [134, 135]. Profound language regression has been reported as a reversible side effect of TPM in neurologically impaired children [136].

Psychotic episodes have rarely been reported in TPM treated patients. Initial reports showing that ≤12 % of patients experienced psychotic symptoms [137]. Therefore, a dedicated study was conducted in 431 adults with epilepsy, 23.95% of patients experienced psychiatric adverse events, 10.7% affective disorders, 5.6% aggressive behaviour, 3.9% other behavioural abnormalities and 3.7% psychotic disorders [138].

Hyperammonaemic encephalopathy has been also described in a few patients on polytherapy including VPA and TPM. These patients presented stupor, focal neurological signs, slowing of background electroencephalography activity and seizure worsening [139,140]. Additionally, reversible haemiparesis during add-on TPM treatment in 2 adults with brain damage has been described [141]. Ataxia and haemiparesis, atypical absences and worsening spike-and-wave activity and focal seizures appeared in a child with focal symptomatic epilepsy after add-on TPM treatment was started [142]. Seizure control was achieved on VPA-ethosuximide bitherapy, likewise previous observations in children with rolandic epilepsy who experienced seizure worsening on CBZ [143].

Post-hoc analyses were performed by Majkowski using data from a large multicenter, double-blind, placebo-controlled trial in which 200 mg/day was added to CBZ in adults with resistant partial-onset seizures. The daily incidence of somnolence, headache, loss of appetite, nervousness, fatigue, dizziness, upper respiratory tract infection, and vertigo peaked during titration and declined to rates similar to that of placebo after the target TPM dose has been reached. Cognitive symptoms ranged from 9% to 44% of TPM-treated patients [144, 145].

Bootsma and colleagues reported that a number of drug discontinuations and high frequency of neurocognitive complaints in the first period of TPM were significantly different from LEV ($p=0.042$). Although efficacy in seizure reduction, TPM had significant negative effects on the digit span and verbal fluency tests. These cognitive effects were dose-related and significantly improved after withdrawal from TPM [146].

Weight Loss

In early trials weight reduction appeared to be dose related, with mean decreases ranging from 1.1 kg in patients

receiving 200 mg/day to 5.9 kg in patients receiving ≥800 mg/day [129]. These decreases tended to plateau during long term therapy. Weight loss also appears to be greatest in heavier patients; 8% weight loss was seen in TPM treated patients who had baseline weight of more than 100 kg compared to 3% in those who initially weighed less than 60 kg [42]. The mean body decrease was 2-7% [147]. Anorexia appeared to be a common complaint amongst patients taking TPM in clinical trials but rarely led to discontinuation. This side effect remains scarcely understood and might include reduction of appetite and inhibition of fat deposition as observed in animal models [148].

Kidney Stone Formation

The incidence of nephrolithiasis observed with TPM in clinical trials was 1.5%, approximatively 2 of 4 times higher than expected in a similar untreated population. Stones passed spontaneously in two-thirds of those affected, and 75% of patients decided to continue TPM therapy despite this occurrence [147, 149]. It has been suggested that other risk factors, such as increased urinary sodium, calcium and oxalate excretion, may play an important role [150]. TPM seems **to** reduce urinary citrate excretion because its carbonic anhydrase inhibitory effect, producing an increase in the urinary pH [151]. TPM treated children with ketogenic diet are at higher risk [152].

Thirty-two TPM treated subjects have been compared with 50 healthy volunteers for stone risk. TPM treatment caused metabolic acidosis, increased urinary pH, urinary bicarbonate excretion and fractional excretion of bicarbonate and lower urinary citrate excretion, higher relative saturation ratio for brushite and lower urinary saturation of undissociated uric acid. These changes commonly increase the susceptibility to form calcium phosphate stones [153].

Effect on Oral Contraceptives

TPM has been found to increase the clearance of the estrogenic component of oral contraceptives in a dose-related manner. The efficacy of low-dose oral contraceptive may be reduced in the presence of TPM. Opposite results were found in a randomized, open-label study that examined five groups of healthy obese and non obese women who received oral dose of a contraceptive. Coadministration of TPM at daily dose of 50, 100 and 200 mg (non obese patients) and 200 mg (obese patients) did not significantly ($p>0.05$) change the mean area under the curve (AUC) of ethinyl estradiol by -12%, + 5%, -11%, and 9% respectively, compared with oral contraceptive monotherapy. Similarly, no significant difference was observed with the plasma levels and AUC values of norethindrone ($p>0.05$). TPM at daily dose of 50-200 mg, did not interact with an oral contraceptive containing norethindrone and ethinyl estradiol [154].

Pregnancy

The current data on pregnancies in women receiving TPM are insufficient to assess accurately this topic.

Other Effects

Hypohydrosis associated with TPM administration has been reported in children and adults, although children seem to be more prone to develop this side effect [155]. In a study of 13 children and young adults, 9 reduced sweating on the pilocarpine iontophoresis sweat test. Occasionally was made necessary drug withdrawal in children with fever due to environmental high temperature [156]. Drug discontinuation was followed by resolution of this side effect. In adults a reduction in sweating area has been reported [157].

Main ocular side effects of TPM were acute glaucoma, acute myopia, suprachoroidal effusion, periorbital oedema and scleritis. Acute onset, progressive blurred vision, bilateral eye pain and retrobulbar headache have been reported [158]. These symptoms have been described within a few days after starting treatment (mean 7 days), and at daily mean TPM dosage of 25-50 mg/day [159]. Moreover, anterior chamber shallowing, closed angles and increase in intraocular pressure have been found, although reversible with drug withdrawal [160].

CONCLUSION

TPM is an effective drug for the treatment of difficult-to-treat focal seizures, primary GTCS and the LGS. It has also been recently approved for monotherapy. TPM is a relatively well-tolerated and safe AED, because of the absence of significant effects on cardiovascular function, bone density, bone marrow cells and thyroid function. Efficacy has been demonstrated with TPM at a wide range of doses. The most common adverse effects are CNS-related and include dizziness, fatigue, ophthalmological problems, ataxia and, sometimes, impaired concentration and depression. Also weight loss and nephrolithiasis have been reported. The large majority of these side effects are dose-related. The place of TPM in the treatment of epilepsy will be more clearly defined over the next years, as experience from clinical use continue to increase.

ABBREVIATIONS

AEDs	=	Antiepileptic drugs
AMPA	=	Alpha-amino-3-hydroxy-5-methil-4-isoxazolepropionic acid
AUC	=	Area under the curve
CBZ	=	Carbamazepine
CNS	=	Central Nervous System
GABA	=	Gamma-aminobutyric acid
GluR1	=	Glutamate receptor 1
GTCS	=	Generalized tonic-clonic seizures
HVACCs	=	High voltage activated calcium channels
IQ	=	Intelligence quotient
JME	=	Juvenile Myoclonic Epilepsy
LEV	=	Levetiracetam
LTG	=	Lamotrigine
LGS	=	Lennox-Gastaut syndrome
NMDA	=	N-methyl-D-aspartate

PPs = Plateau potentials

SV2A = Synaptic vesicle protein 2A

TPM = Topiramate

VPA = Valproate

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Received: 05 January, 2007 **Revised: 13 July, 2007** **Accepted: 13 July, 2007**