Molecular Pharmacodynamics, Clinical Therapeutics, and Pharmacokinetics of Topiramate

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Topiramate (TPM; TOPAMAX[®]) is a broad-spectrum antiepileptic drug (AED) that is approved in many world markets for preventing or reducing the frequency of epileptic seizures (as monotherapy or adjunctive therapy), and for the prophylaxis of migraine. TPM, a sulfamate derivative of the naturally occurring sugar D-fructose, possesses several pharmacodynamic properties that may contribute to its clinically useful attributes, and to its observed adverse effects. The sulfamate moiety is essential, but not sufficient, for its pharmacodynamic properties. In this review, we discuss the known pharmacodynamic and pharmacokinetic properties of TPM, as well as its various clinically beneficial and adverse effects.

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Abbreviations: AED, antiepileptic drug; ALS, amyotrophic lateral sclerosis; AMPA, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid; AMPK, adenosine 5'-monophosphate-activated protein kinase; ATP, adenosine 5'-triphosphate; AZM, acetazolamide; BED, binge-eating disorder; CA, carbonic anhydrase; CaM, calmodulin; cAPK, cAMP-dependent protein kinase; CNS, central nervous system; GABA, γ -aminobutyric acid; MES, maximal electroshock seizure; NMDA, *N*-methyl-D-aspartic acid; 4-NPA, 4-nitrophenylacetate; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; TPM, topiramate.

Introduction

Topiramate (TPM; TOPAMAX[®]) was first synthesized in 1979 by researchers in the pharmaceutical division of Johnson & Johnson as part of an effort to discover structural analogues of fructose-1,6-diphosphate that could inhibit the enzyme fructose 1,6-bisphosphatase. Compounds with this activity would inhibit gluconeogenesis and thereby have potential as antidiabetic agents. In late 1979, TPM was tested for possible anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice and found to be highly active. Sub-

sequent studies indicated that TPM possesses a long duration of action in mice and rats, with a wide separation between the effective anticonvulsant doses and doses that cause motor impairment. The development of TPM as an antiepileptic drug (AED) was then pursued on the basis of its potency, duration of action, and high neuroprotective index (Maryanoff et al. 1987; Shank et al. 1994).

One of the constituents used in the synthesis of TPM is the natural sugar D-fructose (Fig. 1) (Maryanoff et al. 1987). However, the polar hydroxyl groups of the monosaccharide are masked by two acetonide groups (O-CMe₂-O). Because of this structural feature, the sugar subunit in TPM adopts a certain three-dimensional structure ("twist-boat" conformation) that is conducive to the observed pharmacology (Maryanoff et al. 1987). Nevertheless, the sulfamate moiety (OSO₂NH₂) is an essential component for the anticonvulsant activity. Given that the sulfamate resembles the sulfonamide that is present in some carbonic anhydrase (CA) inhibitors, TPM was examined for possible CA inhibitory activity. Various studies revealed that TPM exhibits CA-inhibitor activity, but it is much less potent compared to the benchmark inhibitor acetazolamide (AZM) (Shank et al. 1994, 2005, 2006; Dodgson et al. 2000). Over time, several other well-substantiated pharmacodynamic properties of

Figure 1 Topiramate and its synthesis.

TPM have been identified, including inhibitory effects on the kainate and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtypes of glutamate activated ionotropic receptors (Gibbs et al. 2000; Skradski and White 2000; Gryder and Rogawski 2003; Qian and Noebels 2003; Angehagen et al. 2004, 2005; Poulsen et al. 2004); inhibitory effects on some types of voltage-gated Na^+ channels (Zona et al. 1997; Taverna et al. 1999; Wu et al. 1999; DeLorenzo et al. 2000; McLean et al. 2000; Curia et al. 2004; Sun et al. 2007) and Ca^{++} channels (Zhang et al. 2000; Russo and Constanti 2004; McNaughton et al. 2004; Kuzmiski et al. 2005); and modulation of some types of GABA_A receptors, which can be either positive or negative depending on the receptor subtype (White et al. 1995, 1997, 2000; Gordey et al. 2000; Herrero et al. 2002; Leppik et al. 2006; Simeone et al. 2006). Some less established biochemical actions have also been noted, such as modulation of some types of K^+ channels (Herrero et al. 2002; Russo and Constanti 2004) and effects on proteins involved in neurotransmitter release from synaptic terminals (Okada et al. 2005a, 2005b). Despite the multiple, diverse pharmacodynamic properties of TPM, there may be a common underlying molecular mechanism. Specifically, it has been suggested that TPM may impede adenosine 5'-triphosphate (ATP)-based phosphorylation of sites on some receptor/channel complexes and/or on auxiliary proteins (Shank et al. 2000; Angehagen et al. 2004).

TPM was originally developed and marketed as an AED, but later was approved for marketing for prophylactic treatment of migraine. In addition, there have been numerous human clinical studies, and preclinical studies in animals, related to the utility of TPM in other clinically important conditions, including neuroprotection against ischemia and other traumatic insults to the brain, body weight loss in obese subjects, antidiabetic ef-

fects, mitigation of alcohol consumption and drug addiction, post-traumatic stress disorder (PTSD), and binge-eating disorders (BEDs). Certain adverse clinical effects have also been noted, such as paresthesia, metabolic acidosis, nephrolithiasis, acute reversible cognitive impairment and other behavioral disorders, oligohydrosis, acute myopia, and secondary bilateral angle-closure glaucoma. Most, if not all, of the pharmacodynamic properties of TPM appear to be dose-related within the clinically relevant dosing range of 15–400 mg/day. Tolerance develops to several of the adverse effects of TPM, which has fostered the practice of initiating therapy at a low dose (15 or 25 mg/day) followed by a gradual increase over a period of weeks to a dose level that is effective and well tolerated.

Pharmacodynamics Related to Anticonvulsant Activity

The anticonvulsant properties of TPM were discovered by employing well-established preclinical animal models of seizures. This drug was originally developed for its potential in the treatment of epilepsy, but other therapeutic indications emerged, mainly as a result of clinical observations in humans. A comprehensive review on the use of TPM in epilepsy has been published recently (Lyseng-Williamson and Yang 2007).

There are at least four established pharmacodynamic properties of TPM that are likely to contribute to its anticonvulsant activity. These include inhibitory effects on voltage-gated Na⁺ and Ca²⁺ channels, inhibitory effects on glutamate-activated ion channels, and variable modulatory effects on γ -aminobutyric acid (GABA)-activated ion channels. At least four more possible pharmacodynamic properties may also be involved, including a positive modulation of some types of voltage-gated K⁺

channels, inhibition of some isozymes of CA, modulation of the presynaptic neurotransmitter release process, and effects on the intracellular concentration of GABA in GABA-ergic neurons.

Modulation of Voltage-Gated Ion Channels

In common with several other anticonvulsant drugs, TPM possesses the ability to block several types of voltage-gated Na^+ and Ca^{2+} channels. Inhibitory effects of TPM on voltage-gated Na^+ channel activity have been reported by at least five research groups. One group found that the activity of TPM was influenced by the phosphorylation state of the channel complex (Curia et al. 2004) and another determined that TPM slows the rate at which Na^+ channels open during the depolarizing phase of the action potential (McLean et al. 2000). These observations suggest that TPM acts differently from other Na^+ channel blockers, and are also consistent with the hypothesis that the action of TPM involves direct or indirect effects on the phosphorylation state of one or more proteins associated with these channels (Shank et al. 2000). Modulatory effects of TPM on voltage-gated Ca^{2+} channel activity have been reported by four research groups (Zhang et al. 2000; McNaughton et al. 2004; Russo and Constanti 2004; Kuzmiski et al. 2005). Each group studied a type of channel different from the other three. Two research groups have reported that TPM modulates the activity of some types of voltage-gated K^+ channels (Herrero et al. 2002; Russo and Constanti 2004).

Most marketed anticonvulsant drugs inhibit either voltage-gated Na^+ or Ca^{2+} channels, or both (Leppik et al. 2006), and it is generally accepted that these properties contribute to their efficacy. McNaughton et al. (2004) reported that seven anticonvulsant agents known to inhibit CA also inhibit the $\alpha(1\text{E})$ subtype of voltage-gated Ca^{2+} channels. The inhibitory effect of TPM on Na^+ channels appears to be less pronounced than other anticonvulsants known to possess this property (McLean et al. 2000), and therefore may serve only a minor role in the anticonvulsant activity of TPM. Information on the Ca^{2+} channel blocking activity of TPM is not sufficient to make a judgment regarding its role in anticonvulsant activity.

Modulation of Ligand-Gated Ion Channels

Inhibitory effects of TPM on the AMPA and kainate subtypes of glutamate receptors have been reported by six groups of researchers. In an early study, Gibbs et al. (2000) observed that TPM had a variable inhibitory effect on AMPA receptors, whereas it had no direct effect on the function of *N*-methyl-D-aspartic acid (NMDA) receptors. Subsequently, other investigators reported that

TPM had no direct effect on NMDA receptors (Qian and Noebels 2003; Angehagen et al. 2004). However, AMPA receptor activity can indirectly influence the activity of NMDA receptors (Kim et al. 2007; Du et al. 2008). Consequently, TPM may indirectly affect NMDA receptor activity through its effect on AMPA receptors. Gryder and Rogawski (2003) reported that TPM was more effective as an inhibitor of GluR5 kainate receptors than AMPA receptors. Studies by Angehagen et al. (2004, 2005) were designed to test the hypothesis that the action of TPM is mediated through a direct or indirect effect on the phosphorylation state of one or more proteins (primary or auxiliary) that comprise these receptor-channel complexes. The results of both studies are consistent with the hypothesis that TPM binds to some vacant phosphorylation sites within one or more proteins that comprise the AMPA or kainate receptor complexes, and thereby prevents phosphorylation, and may exert allosteric modulatory effects on channel activity.

TPM and phenobarbital are the only marketed anticonvulsants that are known to inhibit the activity of AMPA and/or kainate receptors (Leppik et al. 2006); however, there is some evidence that zonisamide may also inhibit AMPA receptors (Huang et al. 2005). Given the neuro-excitatory function of glutamate receptors and the marked inhibitory effects of TPM on these receptors, especially the GluR5 type of kainate receptor (Gryder and Rogawski 2003), this property could contribute to anticonvulsant efficacy.

Modulatory effects of TPM on GABA_A receptors have been reported by White et al. (1995, 1997, 2000), Gordey et al. (2000), and Herrero et al. (2002). These studies revealed that the effect of TPM varies from either enhancing or inhibiting the activity of GABA_A , to having no action at all, depending on the receptor subtype studied and the functional state of the receptor. Current knowledge about the effects of TPM on GABA_A receptors (which is far from complete) suggests that TPM usually enhances activity or has no effect. The effects of TPM on GABA_A receptors are consistent with the concept that the action of TPM may involve phosphorylation sites on one or more proteins associated with the channel.

GABA_A receptors in pyramidal neurons in the CA1 region of the hippocampus mediate normal (hyperpolarizing) inhibitory postsynaptic potentials; however, when neurons are activated at high frequencies some populations of GABA_A receptors mediate depolarizing potentials (Staley et al. 1995, 2001; Kaila and Chesler 1998; Sun et al. 2000; Herrero et al. 2002; Uusisaari et al. 2002). These depolarizing synaptic potentials are usually attributed to an accumulation of intracellular HCO_3^- . The rationale for this derives from the observation that the CA inhibitor AZM partially blocks the emergence of these

depolarizing potentials. The validity of this concept requires a rapid accumulation of intracellular HCO_3^- that is sufficient to shift the equilibrium potential of the synaptic current from -60 to -45 mV in less than 1 second. For this 15-mV shift to occur, the intracellular concentration of HCO_3^- must increase by nearly 10 mM within 1 second. As intracellular HCO_3^- is formed from H_2O and CO_2 , there must be a corresponding increase in CO_2 to drive the increase in HCO_3^- . The rate at which CO_2 is formed depends on the rate of oxidative metabolism, which normally generates CO_2 several hundred-fold slower than the shift in the equilibrium potential of the synaptic current. This is a strong argument against this hypothesis. This hypothesis also is not consistent with experimental observations of Stringer et al. (Stringer 2000; Aribi and Stringer 2002). An alternative hypothesis is that the shift in the equilibrium potential results from a shift in the channel permeabilities of Cl^- and HCO_3^- caused by a change in the phosphorylation state of one or more of the proteins in the receptor/channel complex (Lu et al. 2000; Wang et al. 2003). Accordingly, AZM would be preventing one or more of these proteins from being phosphorylated. TPM exhibited an effect similar to that of AZM, as it had no influence on the normal inhibitory postsynaptic potentials, but partially inhibited the depolarizing potentials (Herero et al. 2002).

The effects of TPM on GABA_A receptors are complex, as suggested by a statement taken from the abstract of the paper by Simeone et al. (2006): "These results suggest that the effects of TPM on GABA_A receptor function will depend on the expression of specific subunits that can be regionally and temporally distributed, and altered by neurological disorders." The current state of knowledge regarding TPM and various subtypes of GABA_A receptors is insufficient to make reliable inferences about their impact on the clinical pharmacology of TPM.

Modulation of Pre-Synaptic Neurotransmitter Release

Evidence that TPM may have direct effects on neurotransmitter release is derived from four types of experimental studies. *In vivo* microdialysis studies revealed that TPM administered intraperitoneally at doses of 25 or 50 mg/kg attenuated nicotine-induced elevation of extracellular dopamine in the nucleus accumbens of freely moving rats by 50–70% (Schiffer et al. 2001). At the same doses, TPM attenuated cocaine-induced elevation of dopamine by ~15%. Notably, TPM did not affect basal extracellular levels of dopamine. Okada et al. (2005a, 2005b) utilized *in vivo* microdialysis to study the effects of TPM on the synaptic release of monoamines in the prefrontal cortex of freely moving rats. These investigators

reported that TPM increased or decreased the release of monoamines in a manner that depended on the concentration of TPM and the procedure used to evoke neurotransmitter release. The results of this study suggest that TPM has direct effects on the activity of two or more proteins involved in exocytosis.

In another study with the double mutant, spontaneous epileptic rats (SER), in which basal extracellular levels of glutamate and aspartate in the hippocampus are 2-fold to 3-fold higher than in normal Wistar rats (Kanda et al. 1996), TPM at doses of 20–40 mg/kg (i.p.) gradually reduced the extracellular levels of glutamate and aspartate ($p < 0.05$) in a dose-related manner over a time course similar to that at which tonic seizures were suppressed (Nakamura et al. 1994). TPM had no effect on extracellular glutamate or aspartate levels in normal Wistar rats. In another study, TPM was reported to enhance synaptic release of GABA in the dentate gyrus of gerbils, possibly by down-regulating the expression of the GABA_B autoreceptor (Kim et al. 2005).

Possible Effects on GABA Presynaptic Levels

Kuzniecky et al. (1998) and Petroff et al. (1999) utilized *in vivo* proton nuclear magnetic resonance spectroscopy to study the effect of TPM on the concentration of GABA in the occipital lobe of humans. The results indicate that TPM significantly increases the concentration of GABA in this region of the brain within a few hours after oral administration of therapeutic doses (100–400 mg). Gabapentin and vigabatrin were also reported to cause a similar increase in GABA (Errante et al. 2002; Errante and Petroff 2003). Vigabatrin would be expected to increase the level of GABA because it inhibits GABA transaminase. These data suggest that TPM induces an increase in the concentration of GABA in GABA-ergic synaptic terminals. Notably, TPM had no effect on the concentration of GABA when measured directly in extracts of the brain of mice or rats that received doses of TPM ranging from 10 to 1000 mg/kg (Sills et al. 2000; Errante and Petroff 2003).

Inhibition of CA and Possible Role in Anticonvulsant Activity

The observation that potent inhibitors of CA, such as AZM, exhibit anticonvulsant activity prompted speculation that inhibition of CA is a mechanism for inhibiting the initiation or the spread of seizures (Millichap et al. 1955; Maren 1967). Anderson et al. (1989) postulated that an intracellular acidifying effect of CA-II inhibition in neurons might account for this mitigating effect. No compelling evidence substantiating or refuting this hypothesis

has been published to date. Thus, the inhibition of CA as an anticonvulsant mechanism remains an open question.

The similarity of the sulfamate moiety of TPM to the sulfonamide moiety of AZM prompted an evaluation of TPM for CA inhibitory activity. The initial studies were performed using intact and lysed erythrocytes (Maryanoff et al. 1987; Shank et al. 1994), which constituted the state of the art when the work was originally done. The apparent K_i values of 240 and 120 μM with the intact and lysed cells, respectively, indicated that TPM has a relatively low affinity for CA. However, as erythrocytes contain CA-I and CA-II, these calculated K_i 's represent a composite of the inhibition of total CA activity in erythrocytes. Subsequently, Dodgson et al. (2000) reported K_i values of 90 μM for hCA-I and 5–9 μM for hCA-II by using purified isozymes from erythrocytes. In sharp contrast, Supuran et al. reported K_i values of 0.25 μM for hCA-I and 0.005–0.01 μM for hCA-II (Casini et al. 2003; Winum et al. 2005a). Because of this disparity, our research group undertook a series of studies (Maryanoff et al. 2005; Shank et al. 2005, 2006, 2008; Klinger et al. 2006) entailing four distinct assay procedures, which produced data comprising both K_i or K_d values. A Michaelis–Menten analysis of the inhibition of purified human CA-I or CA-II by TPM, with either the hydration of CO_2 (natural substrate) or hydrolysis of 4-nitrophenyl acetate (artificial substrate), consistently yielded K_i values of 90–140 μM for hCA-I and 0.3–0.6 μM for hCA-II. Thermodynamically based K_d values were consistent with our enzyme kinetic results. In a separate *in vivo* study, the binding of TPM to human erythrocytes yielded K_d values for CA-I and CA-II within the range established by the other assay procedures (Shank et al. 2005). Thus, we contend that TPM is a moderately potent ($\sim 500\text{-nM}$) inhibitor of human CA-II.

Only a few reports have appeared with respect to K_i values for other CA isozymes. Dodgson et al. (2000) reported K_i 's for human CA-IV (6 μM) and CA-VI ($>100\text{ }\mu\text{M}$), and for rat CA-III ($>100\text{ }\mu\text{M}$), CA-IV (0.2–10 μM), and CA-V (18 μM). More recently, Supuran et al. have reported K_i values for recombinant human CA-VA (0.063 μM), CA-VB (0.030 μM) (Winum et al. 2003), CA-IX (1.6 μM), CA-XII (3.8 μM), and CA-XIV (1.5 μM) (Nishimori et al. 2006a, 2006b).

The free concentration of TPM in the blood plasma of patients receiving TPM therapy is usually in the range of 2–40 μM (Johannessen et al. 2003; Waugh and Goa 2003; Almeida et al. 2007). Assuming the K_i for CA-II is $\sim 0.5\text{ }\mu\text{M}$ and the K_i for CA-I is $\sim 100\text{ }\mu\text{M}$, the estimated inhibition for CA-II and CA-I, respectively, is 75–97% and 4–25%. However, it is important to note that these estimates do not take into account possible effects of compensatory mechanisms, such as induction of CA isozymes and $\text{HCO}_3^-/\text{Cl}^-$ exchange transporters. Two studies have

Figure 2 Log–log plot of the anticonvulsant potency (inverse of ED_{50} obtained with mouse MES test) versus the inhibition of CA-II (which is the most prevalent CA isozyme). The data are the results obtained for TPM and 26 structural analogues. Note that the slope of 0.25 indicates that for every 10-fold difference in anticonvulsant potency, there is a 10,000-fold difference in CA-inhibition potency. Details of the assay procedures are described elsewhere (Shank et al. 1994, 2006; Dodgson et al. 2000).

furnished information relevant to the possible role of CA inhibition as an anticonvulsant mechanism for TPM. In one study, a correlation analysis of the CA inhibition potency and the anticonvulsant potency of TPM and 26 structural analogues was performed (Fig. 2). The results of this analysis revealed a weak correlation with a very low slope. Specifically, for a 10,000-fold increase in the potency of CA inhibition there was a 10-fold increase in anticonvulsant potency.

Leniger et al. (2004) demonstrated that TPM can decrease intracellular pH in rat brain slices, which is consistent with the hypothesis proposed by Millichap et al. (1955). However, the relevance of this effect must be interpreted cautiously because TPM would be expected to decrease pH only if there is a pre-existing state of lactic acidosis, which may not occur when most spontaneous seizures are initiated. Seven potent CA inhibitors with anticonvulsant activity also inhibit the $\alpha(1\text{E})$ subtype of voltage-gated Ca^{2+} channels (McNaughton et al. 2004), and some inhibit water flux through subtypes of aquaporins (Ma et al. 2004; Huber et al. 2007; Ma et al. 2007). These mechanistic observations offer possible alternative explanations for the anticonvulsant activity of such compounds.

Pharmacodynamics Related to Antimigraine Activity

Interest in the utility of TPM for treating migraine arose during epilepsy clinical trials. Some subjects who coincidentally suffered from migraine experienced a reduction in the frequency of symptoms. Subsequently, TPM was found to be effective in animal models of migraine

(Akerman and Goadsby 2005a, 2005b) and in exploratory human clinical studies, as well. Efficacy as a prophylactic treatment has been established in randomized double-blind clinical trials (Silberstein et al. 2006, 2007; Diener et al. 2007), and TPM is now approved for prophylactic treatment of migraine in the U.S.A and many other world markets. An in-depth review article on TPM in migraine prophylaxis has recently appeared (Fontebasso 2007).

Pathophysiology of Migraine

The pathophysiology of migraine is complex and not fully understood. According to Goadsby et al. (2002) and Shields et al. (2005), three key factors include the cranial blood vessels, the trigeminal innervation of the vessels, and the reflex connection of trigeminal neurons with cranial parasympathetic outflow. The pathology appears to include a dysfunction of brainstem or diencephalic nuclei and likely involves nociceptive sensory modulation of craniovascular afferents. The aura associated with some forms of migraine appears to be the human counterpart of the experimental phenomenon termed spreading depression, and is likely initiated by a short phase of hyperemia followed by a wave of oligemia moving across the cerebral cortex at a slow rate of 2–6 mm/min (Goadsby et al. 2002). In some cases, the pathology at the molecular level involves mutations in genes associated with the P/Q subtype of voltage-gated Ca^{2+} channels (Shields et al. 2005).

At the molecular level, there is substantial evidence that excessive activation of AMPA and/or kainate receptors, and several types of voltage-gated Ca^{2+} channels are major contributing factors in the pathology of migraine (Goadsby et al. 2002; Shields et al. 2005; Calabresi et al. 2007; D'Amico et al. 2007; Sanchez-Del-Rio et al. 2007; Vikelis and Mitsikostas 2007).

Pharmacodynamic Basis for the Prophylactic Efficacy of TPM in Treating Migraine

On the basis of the current knowledge of the pharmacodynamic properties of TPM and the pathophysiology of migraine, it appears that the most prominent factors likely to contribute to its antimigraine efficacy are the inhibitory effects on the AMPA and kainate subtypes of glutamate receptors (Vikelis and Mitsikostas 2007), and to a lesser extent voltage-gated Ca^{2+} channels. In double-blind clinical trials, TPM was initiated at 25 mg/day (single dose), then elevated weekly in increments of 25 mg/day to a total maintenance daily dose of 50, 100, or 200 mg/day (Silberstein et al. 2006, 2007; Diener et al. 2007) in two divided doses. These studies re-

vealed that the maximum benefit achieved in most patients occurred at 100 mg/day. Although the frequency of migraine episodes decreased in some subjects at the 50-mg/kg dose, there was not a statistically significant difference from placebo in the population studied. The observation that the range from minimum to maximum efficacy is small (between 50 and 100 mg) is consistent with the notion that only a few of the known pharmacodynamic properties of TPM contribute significantly to the antimigraine efficacy. Based on the known potency of TPM as an inhibitor of the AMPA and kainate receptors, these results suggest that inhibition of the excitatory synaptic effects of glutamate is a prominent factor in the antimigraine efficacy of TPM.

Pharmacodynamics Related to Adverse Clinical Effects

TPM therapy is associated with several recognized adverse effects. The CA inhibitory activity may contribute to paresthesia, metabolic acidosis, and nephrolithiasis, whereas the inhibitory effects on the neurotransmitter function of glutamate may contribute to adverse central nervous system (CNS)-related effects, such as acute cognitive impairment. Recent reports indicate that TPM inhibits the activity of some aquaporins, which raises the possibility that this pharmacodynamic property may contribute to adverse effects, including oligohydrosis, acute myopia, and bilateral secondary angle-closure glaucoma (Ma et al. 2004, 2007). Several anticonvulsants have been reported to inhibit some types of aquaporins (Huber et al. 2007). The possible pharmacodynamic basis for the most common and serious adverse effects are discussed below.

Paresthesia

Paresthesia is an unpleasant tingling sensation that arises from ectopic activation of sensory neurons. These sensations occur in the limbs, especially the fingers and toes. They also can occur on the face, especially around the mouth. They occur naturally when nerves in the limbs become acidotic as a result of ischemia. Some classes of drugs can elicit paresthesia, including CA inhibitors, particularly inhibitors of CA-II. Notably, in peripheral nerves CA-II is much more prevalent in sensory nerves than motor nerves (Fujii et al. 1993), and may function to rapidly dissipate small "pockets" of lactic acid-driven acidosis within the neurons by catalyzing the conversion of H^+ and HCO_3^- to CO_2 and H_2O (Spitzer et al. 2002; Swietach et al. 2003). By inhibiting this process, CA-II inhibitors impede the dissipation of H^+ , which can activate acid-sensing receptors in the nerve cell membrane

(Olah et al. 2001), thereby depolarizing the membrane and initiating the activation of ectopic action potentials. Although this scenario has not been experimentally established, it offers a plausible explanation for the paresthesia associated with CA inhibitors. The action of TPM on aquaporins (vide infra) may also contribute to the development of paresthesia. From the results of one clinical study, supplemental potassium may be effective in reducing TPM-induced paresthesia (Silberstein 2002).

Metabolic Acidosis

Several CA isozymes contribute to the regulation of acid-base balance, especially CA-II and CA-IV (Swenson 2000). The kidney serves a key role in regulating acid-base balance largely by regulating the amount of HCO_3^- excreted in the urine. CA-II and CA-IV contribute to the reabsorption of HCO_3^- from the glomerular filtrate into renal venous circulation. Specifically, CA-IV catalyzes the conversion of HCO_3^- and H^+ to CO_2 and H_2O . Subsequently, CO_2 is driven into the tubule cells by a concentration gradient, whereupon CA-II catalyzes the conversion of CO_2 back to HCO_3^- , again driven by a concentration gradient. This process is impeded by inhibitors of CA-IV or CA-II, resulting in an increase in the amount of HCO_3^- excreted in the urine. Compensatory mechanisms mitigate the loss of HCO_3^- , and in the case of TPM therapy the level of metabolic acidosis is seldom severe in adults ($<18 \text{ mM HCO}_3^-$ in plasma), but blood serum HCO_3^- levels as low as of 13 mM have been reported (Garris and Oles 2005). Recent research indicated that TPM can cause type 3 renal tubular acidosis (Sacre et al. 2006). Appropriate procedures for mitigating metabolic acidosis include administering sodium bicarbonate and reducing the dose of TPM (Ko and Kong 2001).

Nephrolithiasis (Kidney Stones)

The incidence of kidney stones associated with TPM therapy is 2-fold to 4-fold higher than that in the general population (Welch et al. 2006). This outcome can be attributed to an increase in pH in the tubular fluid and a reduction in citrate secretion into the tubular fluid, to promote the precipitation of calcium salts, especially calcium phosphate (Welch et al. 2006). Oral potassium citrate was effective in restoring normal urinary citrate in children with idiopathic hypocitruria and calcium stones (Tekin et al. 2002), and potassium citrate markedly reduced the incidence of kidney stones in children on a ketogenic diet (Sampath et al. 2007). Consequently, children or adult patients who develop kidney stones during TPM therapy may also benefit from oral potassium citrate.

Cognitive Impairment

Some degree of cognitive impairment is associated with most AEDs. Several studies have suggested that cognitive impairment associated with TPM differs from that of other AEDs (Aldenkamp et al. 2003; Kockelmann et al. 2004; Jansen et al. 2006; Smith et al. 2006; Gomer et al. 2007). This effect is dose-related, varies considerably among individuals, and is a factor in defining the limiting tolerable dose. Several of the known pharmacodynamic properties of TPM may contribute to cognitive impairment, including the inhibitory effects of TPM on AMPA and kainate subtypes of glutamate receptors.

There is one report on a clinical study designed to ameliorate TPM-related cognitive and language dysfunction. Addition of DONEPEZIL[®] (rivastigmine), a cholinesterase inhibitor, to the regimen of six migraine patients enabled all of them to remain on TPM therapy (Wheeler 2006).

Oligohydrosis (Hypohydrosis)

Oligohydrosis is a condition in which sweating induced by heat or exercise is insufficient for maintaining body temperature at normal levels. Several clinical reports have presented cases of oligohydrosis with TPM, primarily in children (Ben-Zeev et al. 2003; de Carolis et al. 2003; Galicia et al. 2005; Yilmaz et al. 2005; Cerminara et al. 2006). Some authors have suggested that oligohydrosis may be attributable to the CA inhibitory action of TPM (Ben-Zeev et al. 2003; Cerminara et al. 2006). Another possible cause is inhibition of the expression or functional activity of aquaporin 5 in sweat glands (Ma et al. 2007). The involvement of aquaporin 5 is supported by clinical case reports that TPM inhibits the production of active aquaporin 5 in subjects who suffer from excessive sweating (hyperhydrosis) (Hoehn-Saric 2006; Owen and Meffert 2003).

Acute Myopia and Bilateral Secondary Angle-Closure Glaucoma

Some patients treated with TPM report visual disturbances that are sometimes referred to by the general term "vision abnormal," which include such things as diplopia, blurred vision and myopia. A rare but more serious visual disturbance is termed acute myopia and secondary angle-closure glaucoma (Levy et al. 2006; Rhee et al. 2006; Lachkar and Bouassida 2007; Santaella and Fraunfelder 2007). This condition usually arises within the first month of treatment with TPM, and often within a few days after the dose is increased from 25 to 50 mg/day. Symptoms include acute onset of blurred vision, which is

often severe, and pain associated with ocular hyperemia. Ophthalmic examination typically reveals increased intraocular pressure, myopia, supraciliary effusion, and anterior displacement of the lens and iris associated with a narrowing of the angle between the iris and cornea. Inhibition of CA-II or other CA isozymes is not a likely factor because this enzymic activity within the ciliary body contributes to the formation of ocular fluid. A possible causal factor is inhibition of the function or expression of aquaporin 1 and/or aquaporin 4 in the pigmented epithelial cell layer (Levin and Verkman 2006; Frigeri et al. 2007; Lin et al. 2007). Several sulfonamides have been reported to inhibit aquaporin 4, in addition to inhibiting CA-II (Huber et al. 2007), and some of these are associated with bilateral secondary angle-closure glaucoma (Geanon and Perkins 1995; Lee et al. 2007; Spadoni et al. 2007). It is well established that inhibitors of CA-II and CA-IV can reduce intraocular pressure. At least two CA inhibitors, dorzolamide and brinzolamide, are marketed to treat some forms of glaucoma by topical administration.

It is unlikely that inhibition of CA isozymes is a causal factor in the development of acute myopia and secondary angle-closure glaucoma. However, the roles of aquaporin 1 and aquaporin 4 in forming intraocular fluid and regulating intraocular pressure are not fully understood. Current information suggests that sulfonamides, sulfamates, and other classes of drugs have the potential to inhibit aquaporins (Monzani et al. 2007). However, the relative affinities and intrinsic activity of compounds within these classes may vary widely. Additional research is needed to elucidate the source of this drug-induced condition.

Other Adverse Effects

Information in the TOPAMAX[®] U.S. Product Insert indicates that dizziness, ataxia, and tremor are additional adverse effects related to the nervous system that occur at rates higher than placebo. Other effects that occur at higher frequencies than placebo include nausea, abdominal pain, constipation, adverse taste, and dry mouth. Psychiatric-related adverse effects that have been reported and not specifically included under the term cognitive impairment include nervousness, depression, anorexia, agitation, and mood problems (Kalinin 2007). Most, if not all, of these effects are dose-related and minimized by initiating therapy at low doses (15 or 25 mg/day) and gradually increasing the daily dose until a maximal benefit or a well tolerated effective dose is reached.

Causal factors associated with the nervous system and psychiatric-related adverse effects are likely to be the same biological activities that are associated with TPM's

broad spectrum of clinical efficacy. These may include inhibitory effects of TPM on the AMPA and kainate subtypes of glutamate receptors, the modulatory effects on GABA_A receptors and voltage-gated Ca²⁺ and Na⁺ channels. Inhibition of aquaporins is a pharmacodynamic property that may contribute to adverse CNS effects and to gastrointestinal effects (e.g., constipation).

Considerations for Children, the Elderly, and Pregnant Women

TPM has been very effective in treating childhood forms of epilepsy, including Lennox–Gastaut syndrome, juvenile myoclonic epilepsy (Mikaeloff et al. 2003; Glauser et al. 2007; Malphrus and Wilfong 2007), infantile spasms (Valencia et al. 2005; Zou et al. 2006), and West syndrome (Korinthenberg and Schreiner 2007). Generally, it has been well tolerated in children, and doses on a mg-per-kg body weight basis have often exceeded those of adults (Valencia et al. 2005; Zou et al. 2006; Glouser et al. 2007), possibly because of a more rapid elimination rate in children than in adults (Adin et al. 2004). TPM is approved for therapy in children as young as 2 years of age, but some clinical studies in younger children have been described (Valencia et al. 2005; Zou et al. 2006). A recommended regimen entails the initiation of TPM therapy at low doses, with gradual escalation to the most effective, tolerable dose. Clinical studies and case reports suggest that children are more likely than adults to develop severe metabolic acidosis (Ko and Kong 2001; Takeoka et al. 2001; Philippi et al. 2002; Groeper and McCann 2005). As noted above, oligohydrosis (hypohydrosis) is more prevalent in children than in adults (Ben-Zeev et al. 2003; de Carolis et al. 2003; Galicia et al. 2005; Yilmaz et al. 2005; Cerminara et al. 2006).

Elderly patients tolerate TPM like other adults; however, cognitive impairment may be more frequent, and careful attention should be given to mental status, especially during the titration period (Groseli et al. 2005; Sommer et al. 2007).

As with most AEDs, TPM has the potential to cause defects *in utero*. In rodents, the deformation is limited to a single digit on one paw. There is one case report about a woman treated with TPM at 300 mg/day throughout her pregnancy, who delivered an infant with deformities to the limbs (Vila Cerén et al. 2005).

Pharmacodynamics of Some Other Clinically Identified Properties of Topiramate

In addition to the approved clinical indications, TPM has been reported to possess other pharmacological

Figure 3 Effect of long-term dosing (102 weeks) of TPM on body weight of male and female Wistar rats. Topiramate was mixed into pulverized "lab chow," which was provided *ad libitum*. To ensure that each rat received the intended dose (20, 45, or 120 mg/kg), the amount of TPM added to the chow was adjusted weekly based on the amount of chow each rat consumed during the previous week ($n = 50$ per group). Body weight was

recorded every two weeks. The tendency for the relative decrease in the body weight of TPM-treated rats to reverse reflects, in part, a plateau in the body weight of the control rats, and eventually actual weight loss in the control rats. Topiramate did not have an effect on food consumption in male rats; however, in females there was a dose-related decrease that reached statistical significance at the highest dose ($p < 0.05$).

properties connected with potential clinical utility. These include weight-loss, antidiabetic action, mitigation of the consumption of alcohol and some other addictive drugs, reversal of PTSD, and reduction of eating in BEDs. Relevant information derived from preclinical research and clinical studies is summarized below.

Weight-Loss Effect

In long-term safety studies in animals, TPM was found to cause a gradual, dose-related decrease in body weight gain in rats, and body weight loss in dogs (unpublished). These effects were not associated with any apparent pathology. In rat studies in which TPM was administered daily for a 2-year period at doses of 20, 45, or 120 mg/kg, the mortality rate was higher in the control group than in the groups receiving TPM, which is consistent with experimental evidence that food restriction and reduction of body weight prolongs the life of rats (Goto et al. 2007). The effect of TPM on the body weight of normal rats was greater in females (Fig. 3).

Subsequent animal studies indicated that TPM was even more effective in causing a relative weight loss in rodent models of obesity. Significant dose-related reductions in caloric intake were observed in obese (*fa/fa*) Zucker rats and female Wistar rats (Picard et al. 2000). In female Sprague–Dawley, lean (*Fa/?*) Zucker rats, and Osborne–Mendel rats fed a high-fat diet, TPM increased energy expenditure and reduced energy effi-

ciency (Richard et al. 2000; York et al. 2000). In the hypothalamus of Osborne–Mendel rats, TPM exhibited complex, but significant effects on neuropeptide-Y and its Y1 and Y5 receptors, and corticotrophin-releasing hormone and type-II glucocorticoid receptors. The weight loss in rats was independent of the diet (high fat vs. high carbohydrate) and greater in females. In females, estrogen had a marked positive influence on the weight-loss effect (Richard et al. 2002). The results of these and other studies indicate a complex pharmacodynamic basis for the effect of TPM on body weight (Lalonde et al. 2004).

Lynch et al. (1995) demonstrated that potent CA inhibitors can inhibit lipogenesis. Thus, there is a proposal that the weight-loss effect of TPM is associated with the inhibition of CA-V, a mitochondrial enzyme (Winum et al. 2005b). This hypothesis predicts that TPM should be more effective in low-fat, high-carbohydrate diets; however, the weight-loss effect of TPM appears to be independent of the type of diet (Richard et al. 2000; York et al. 2000; Lalonde et al. 2004). Nevertheless, the results of rat studies indicate that TPM can directly affect the deposition and metabolism of lipid in a manner consistent with TPM-induced weight loss (Richard et al. 2000; Wilkes et al. 2005b; Frigerio et al. 2006).

In human clinical trials conducted to determine the efficacy and safety of TPM as an AED, gradual, dose-related weight loss was observed in some subjects (Van Ameringen et al. 2002; Ben-Menachem et al. 2003). Subsequently, double-blind clinical trials confirmed the weight-loss effect of TPM (Bray et al. 2003; Astrup and

Toubro 2004; Wilding et al. 2004; Ioannides-Demos et al. 2005; Tonstad et al. 2005).

Antidiabetic Effect

In obese individuals with type 2 diabetes, TPM ameliorated several characteristic signs of diabetes (Rice et al. 2007; Rosenstock et al. 2007; Stenlof et al. 2007; Toplak et al. 2007). While it is reasonable to consider that such beneficial effects could derive from weight loss alone, the results of several rat studies indicate otherwise. Studies in diabetic rodents have provided strong evidence that TPM inhibits lipid deposition in adipose tissues (Lalonde et al. 2004) and reverses insulin desensitization in adipose tissue (Wilkes et al. 2005a), skeletal muscle (Wilkes et al. 2005b; Ha et al. 2006), and pancreatic β cells (Liang et al. 2005). A partial mechanistic explanation is that, in adipocytes, TPM promotes the formation of the high molecular weight form of adiponectin (Acrp30) and its release into the blood circulation (Wilkes et al. 2005b). After it is transported to target tissues, including adipocytes, Acrp30 initiates a sequence of events, including the phosphorylation of adenosine 5'-monophosphate-activated protein kinase (AMPK), which in turn promotes the activation of glucose transporters (Ha et al. 2006).

TPM can reverse the detrimental effects of oleic acid on insulin release from cultured β cells and improve mitochondrial function in these cells (Frigerio et al. 2006), which is noteworthy because dislipidemia and lipotoxicity are causal factors in the pathology of β cells associated with diabetes (DeFronzo 2004). These observations offer compelling evidence that TPM possesses pharmacodynamic properties that can reverse some diabetes-associated pathologies.

Effect on Binge Eating

BED is often associated with obesity and differs from bulimia nervosa, in that it does not involve purging. In some respects, BED is an addictive disorder, in that there is a craving for food. Because animal and human clinical studies suggested that part of the weight-loss effect of TPM is attributable to a decrease in caloric intake, clinical studies were initiated in appropriate subjects to investigate the effect of TPM on the frequency of binges (Carter et al. 2003; De Bernardi et al. 2005; Guerdjikova et al. 2005; McElroy et al. 2004, 2007). Subsequently, placebo-controlled double-blind studies were conducted (McElroy et al. 2007). These clinical studies were consistent with the view that TPM is effective in this disorder; however, more definitive clinical trials need to be conducted. In a related double-blind, placebo-controlled trial of TPM for

treatment of bulimia nervosa, a condition similar to BED, TPM exhibited a significant reduction in the frequency of binge and purge episodes (Hoopes et al. 2003).

The basis for the decrease in the frequency of binge eating by TPM may be related, at least in part, to inhibitory effects on AMPA and kainate receptors, because glutamatergic neural pathways are important in promoting caloric intake (Zheng et al. 2002). The complex modulatory effects of TPM on GABA_A receptors may also contribute to the effects of TPM on eating behavior (Cooper 2005). Although BED, and other eating disorders, are generally not included in the classification of "anxiety-related disorders" (*vide infra*), their underlying pathology and mode of treatment may be similar (Lavender et al. 2006).

Alcohol and Drug Addiction

Animal studies have suggested that TPM can reduce alcohol, nicotine, and cocaine craving (Schiffer et al. 2001; Cagetti et al. 2004). Subsequent human clinical studies provided support for an antiaddictive effect for TPM (Johnson 2004a, 2004b; Kampman et al. 2004; Book and Myrick 2005; Sofuoglu and Kosten 2006; Ma et al. 2006; Johnson et al. 2007; Krupitsky et al. 2007). As noted previously for BED, the inhibitory effects of TPM on AMPA and kainate subtypes of glutamate receptors, and modulatory effects on GABA_A receptors, may be prominent factors in the reduction of alcohol and drug craving.

Anxiety-Related Disorders

Anxiety-related disorders typically include panic disorder, agoraphobia, PTSD, obsessive-compulsive disorder (OCD), generalized anxiety disorder, and social phobia. Of these, PTSD has received the most attention with respect to TPM therapy. Berlant (2001) observed that the symptoms of patients with a severe form of PTSD often improved dramatically when treated with TPM. Subsequently, the results of an animal model of PTSD (Khan and Liberzon 2004), and several additional clinical studies (Berlant and van Kammen 2002; Berlant 2004; Aalbersberg and Mulder 2006), including a randomized, double-blind, placebo-controlled study (Tucker et al. 2007), provided further support for efficacy in treating PTSD. However, the results of another double-blind, placebo-controlled study of recent male war veterans with chronic PTSD did not yield evidence of efficacy, although there was an exceptionally high dropout rate (Lindley et al. 2007).

Some reports have suggested that TPM may be effective as an adjuvant to serotonergic agents in the treatment of OCD (Hollander and Dell'Osso 2006; Van Ameringen

et al. 2006; Rubio et al. 2006). However, two case reports suggest that TPM may promote OCD in some patients (Ozkara et al. 2005; Thuile et al. 2006). In an open-label study of 23 patients with DSM-IV social phobia, 9 of 12 patients who completed a 16-week study were positive responders (Van Ameringen et al. 2004). Inhibitory effects on kainate and AMPA receptors in the amygdala and related limbic structures may be connected with the putative efficacy of TPM in some anxiety-related disorders (Gryder and Rogawski 2003; Zullino et al. 2003). The results from Gryder and Rogawski (2003) suggest that the inhibition of GluR5 kainate receptor may be instrumental in "normalizing" the hyperexcitability of the amygdala in PTSD, and possibly other anxiety-related disorders. A comprehensive review on the efficacy of TPM and other anticonvulsants in treating anxiety-related disorders has recently appeared (Mula et al. 2007).

Essential Tremor

Essential tremor is a common movement disorder, often involving trembling hands, but also head, voice, or arms. This disorder may not require treatment unless it becomes debilitating or interferes with normal function. Clinical evidence for the effectiveness of TPM in treating essential tremor was first reported by Connor (2002), which prompted a multicenter, placebo-controlled, double-blind study ($n = 208$ subjects, with $n = 108$ in the TPM group) (Ondo et al. 2006). On the basis of the Tremor Rating Scale, there was a significant benefit in the TPM group at 4 weeks ($p < 0.001$; mean dose of 62 mg/day) and at the end of the study (24 weeks; $p < 0.001$; mean final dose of 292 mg/day). The mean improvement in overall scores was 29% for the TPM group and 16% for the placebo group. Two smaller double-blind studies have been reported, one of which was positive (Connor 2002) and the other negative (Frima and Grunewald 2006). In case reports, Gatto et al. (2003) indicated that three patients with essential tremor, who were otherwise unresponsive to pharmacological treatment, greatly benefited from low doses of TPM (50 mg/day). These studies indicate that TPM possesses some ability to ameliorate essential tremors; however, for most patients, the improvement appeared to be modest (Zesiewicz 2007).

Bipolar Disorder

TPM has been classified as a "broad-spectrum AED" because of its efficacy in blocking seizures in several types of epileptic disorders, including partial onset and generalized epileptic seizures, Lennox–Gastaut seizures, and status epilepticus. Given that other broad-spectrum AEDs

are efficacious in treating bipolar disorder, some psychiatrists specializing in this disorder prescribed TPM for patients whose symptoms were not effectively abated by other drugs. The results of some open-label clinical studies suggested that TPM might be effective in treating some aspects of bipolar disorder (Janowsky 1999; Normann et al. 1999; Erfurth and Kuhn 2000; McElroy et al. 2000; Chengappa et al. 2001). However, in large, randomized, double-blind, placebo-controlled clinical studies, TPM was not efficacious in treating the manic phase of bipolar disorder (Chengappa et al. 2006; Kushner et al. 2006).

Neuroprotection

Interest in neuroprotective effects was first stimulated by the observation that TPM inhibited the AMPA and kainate subtypes of glutamate receptors. Now, there are more than 20 reported studies involving cell cultures or *in vivo* animal models. Basically, neurons were subjected to severe metabolic stress sufficient to cause neuronal cell death, which was induced by hypoxia, ischemia, status seizures, or neurotoxic chemicals. These studies indicated that TPM exhibits a variable neuroprotective effect, depending on the model used. Several studies suggested that TPM was particularly effective in protecting neurons in certain regions of the hippocampus (CA1, CA3, subiculum) (Kawasaki et al. 1998; Niebauer and Gruenthal 1999; Lee et al. 2000; Palmieri et al. 2000). In studies conducted with immature animals (e.g., 4-day-old to 14-day-old rat pups or piglets) in which the brain was subjected to hypoxic/ischemic conditions, TPM consistently mitigated neural damage and behavioral deficits (Koh and Jensen 2001; Cha et al. 2002; Follett et al. 2004; Koh et al. 2004; Liu et al. 2004; Pappalardo et al. 2004; Schubert et al. 2005; Zhao et al. 2005; Suchomelova et al. 2006; Mazarati et al. 2007). Similar beneficial effects were observed when rat pups were exposed to neuroexcitotoxic compounds (Sfaello et al. 2005). These results suggest that TPM may be able to reduce the severity of cerebral palsy or neurological damage caused by severe ischemia/hypoxia in human newborns.

Neonates and infants subjected to hypoxic ischemia can experience seizures that are often treated with AEDs. In recent years, compelling evidence has accrued that AEDs can promote neuronal apoptosis during this period of brain development. In studies conducted in rat pups with five AEDs, phenobarbital, phenytoin, valproate, clonazepam, and TPM, TPM was much less prone to cause apoptosis at therapeutically relevant doses; whereas, phenobarbital was most prone to cause apoptosis (Glier et al. 2004; Zhu et al. 2007). With rats 6 weeks of age or older, TPM has been tested for neuroprotective effects in

models of stroke (Yang et al. 1998; 2000; Niebauer and Gruenthal 1999; Edmonds et al. 2001), status epilepticus (Kudin et al. 2004; Rigoulot et al. 2004; Francois et al. 2006; Suchomelova et al. 2006; Andre et al. 2007; Frisch et al. 2007), and brain trauma (Hoover et al. 2004).

The neurodegenerative disorder amyotrophic lateral sclerosis (ALS) may involve glutamate-mediated neural hyperexcitability, and TPM displayed efficacy in a rat model of ALS (Maragakis et al. 2003). On this basis, a double-blind clinical trial was conducted to evaluate TPM for possible efficacy in the treatment of ALS patients; however, it was not efficacious (Cudkovic et al. 2003).

Neuropathic Pain

Interest in the possible utility of TPM in treating neuropathic pain arose from observations that it was highly effective in blocking allodynia in the Chung rat model of neuropathic pain (Shadiack et al. 1999) and promoted neurite outgrowth in cultures of neurons from rat brain tissue taken from pups on gestation day 18 (Smith-Swintosky et al. 2001). In clinical case reports, TPM mitigated pain in humans suffering from diabetic peripheral neuropathy (Kline et al. 2003; Carroll et al. 2004), oxaliplatin-induced disabling permanent neuropathy (Durand et al. 2005), post-traumatic trigeminal neuropathy (Benoliel et al. 2007), or glossodynia (Siniscalchi et al. 2007), which supports the potential of TPM in treating neuropathic pain (Bischofs et al. 2004). Of particular note, a case report indicated that diabetes-related phrenic nerve palsy was reversed after administration of TPM (Rice et al. 2007). However, three similarly designed placebo-controlled, randomized, double-blind clinical studies in patients with diabetic neuropathy indicated that TPM is not effective in this pain subcategory (Thienel et al. 2004). In contrast, a placebo-controlled, double-blind clinical study with a different study design did provide evidence of efficacy in diabetic neuropathy (Raskin et al. 2004). A possible explanation for the inconsistent efficacy may lie in TPM's neurotrophic property, which could have partially restored the functional activity of sensory neurons, thereby making them more sensitive to normal stimuli.

Pharmacokinetics and Clinical Significance

The pharmacokinetic (PK) characteristics of TPM are exceptionally good in humans. Specifically:

- Nearly complete absorption from the gastrointestinal (GI) tract (bioavailability >80%). Food slows absorption without decreasing absorption. Absolute bioavailability is not known (Nayak et al. 1994).

- Linear and predictable kinetics over the recommended dosing range (15–400 mg/day).
- Long half-life (~24 h) in blood plasma at the most prevalent daily doses (100–200 mg/day).
- Low level of binding to plasma proteins (~10–20%).
- Excreted primarily in urine as the parent compound (~80%).
- Six known metabolites that collectively account for less than 20% of the total drug excreted.
- Metabolites exhibit little or no pharmacological activity.
- Little tendency to inhibit drug metabolizing enzymes or induce their activity.
- At daily doses of 50–200 mg TPM did not interact with oral contraceptives containing norethindrone and ethinyl estradiol.

TPM was first developed as add-on therapy for patients with epilepsy whose seizures were not adequately controlled. Consequently, the early human PK studies were designed with that patient population in mind, and the daily doses reflected the optimal dose for efficacy in blocking seizures of 200, 400, or 800 mg/day. These early studies indicated that TPM has little or no effect on the PK of other AEDs that TPM was paired with; however, phenytoin, carbamazepine, and valproic acid significantly decreased the blood levels of TPM (Gisclon et al. 1994; Sachdeo et al. 1996; Rosenfeld et al. 1997; Perucca 1999, 2006; Garnett 2000). At these dose levels, TPM caused a dose-related decrease in the blood levels of the estrogenic component of oral contraceptives comprised of norethindrone and ethinyl estradiol (Doose et al. 1996; Doose and Streeter 2002). After TPM was approved for marketing, and clinicians prescribing TPM became more familiar with it, an optimal dosing regimen emerged. Over time, it became apparent that a better dosing regimen would be to initiate therapy at a low dose (e.g., 25 mg/day) and gradually escalate the dose over a few weeks to achieve good efficacy with improved tolerability. Thus, the average daily dose declined to less than 200 mg/day. When the migraine clinical trials revealed that the maximum benefit for most patients occurred at 100 mg/day, the subsequent approval of TPM for prophylactic treatment of migraine prompted a further reduction in the average daily dose.

The marked reduction in the average daily dose of TPM prompted additional PK studies in a daily dosing range of 50–200 mg. In this range, TPM did not have a significant effect on the blood levels of the estrogenic component of oral contraceptives comprised of norethindrone and ethinyl estradiol (Doose et al. 2003). Similarly, the effect of metabolism-inducing AEDs on TPM blood levels is less when TPM is administered at less than 200 mg/day (Bialer et al. 2004; Bialer 2005). A possible factor for this

effect is that the relative amount of TPM bound to CA-I and CA-II in erythrocytes increases as whole blood levels decrease, thereby reducing the relative amount available for metabolism. The higher relative binding of TPM to erythrocytes at low blood levels also contributes to the longer half-life of TPM in whole blood and plasma (Shank et al. 2005).

Drug–drug interactions can often be complex. For example, there is a variable influence of carbamazepine or phenytoin on the metabolism and clearance of TPM as a function of the dose of TPM (Bialer et al. 2004; Bialer 2005). In an attempt to determine a set of rational drug combinations for commonly used AEDs, Armijo and Herranz (2007) used available information on the pharmacodynamics, pharmacokinetics, adverse effects, and other criteria to create a suitability list for combinations of AEDs. This list has the following order: levetiracetam/pregabalin > gabapentin > lamotrigine > oxcarbazepine/TPM/zonisamide > tiagabine > valproic acid > carbamazepine > phenytoin > phenobarbital/primidone > benzodiazepines.

As TPM prescriptions for migraine and off-label uses have exceeded those for epilepsy, some drug–drug interaction studies have been conducted with other drugs that might be frequently paired with TPM in clinical practice. These other drugs include lithium, haloperidol, amitriptyline, risperidone, sumatriptan, propranolol, and dihydroergotamine. The results of these drug–drug interaction studies have been reviewed in detail (Bialer et al. 2004; Bialer 2005).

Topiramate and Protein Phosphorylation

Some of the pharmacological effects of TPM appear to arise from interactions with protein complexes that are comprised of several membrane-bound subunits and regulatory (auxiliary) proteins (Kato et al. 2007). Physiologically, the activity of these protein complexes is regulated largely by protein phosphorylation and dephosphorylation. The protein complexes include, but are not limited to, various types of voltage-activated Na^+ and Ca^{2+} channels, GABA_A receptors, and various types of AMPA and kainate receptors. The effects of TPM on the activity of protein complexes can be variable, occurring immediately, or being delayed, or developing gradually. Sometimes, TPM is inexplicably ineffective and sometimes the effect does not readily reverse when TPM is removed. Results from several studies are consistent with the concept that TPM directly or indirectly shifts the level of protein phosphorylation to the dephosphorylated state (Shank et al. 2000; Angehagen et al. 2004). Thus, some hypotheses surrounding the molecular pharmacology of TPM have been posited. First, TPM would interact with a tar-

get protein at one or more sites of phosphorylation, but only when the sites are in the dephosphorylated state. By virtue of binding to these sites, TPM would impede the access of ATP to the site, and thereby inhibit phosphorylation. This situation could account for the variable effects of TPM. Alternatively, TPM would reduce the phosphorylation state of target proteins indirectly by inhibiting certain protein kinases (e.g., cAMP-dependent protein kinase [cAPK], protein kinase C [PKC], calmodulin [CaM]-activated kinase) or directly by activating certain protein phosphatases, such as calcineurin.

The consensus peptide sequence at cAPK-mediated phosphorylation sites exhibits homology; for example, the GluR6 subunit of the AMPA/kainate receptor contains the tetrapeptide motif RRQS, the β subunit of the GABA_A receptor contains RRAS, and some subtypes of the primary subunit of Na^+ and Ca^{2+} channels contain RRNS and RRPT, respectively. The auxiliary proteins that contribute to the regulation of these receptor/channel proteins also contain similar peptide sequences that serve as sites for phosphorylation. Each of these tetrapeptide sequences contains several proton-donor groups that might form H-bonds with the proton accepting oxygen atoms in TPM. If TPM were to bind selectively to these sites only in the dephosphorylated state, such an interaction could explain the immediate and delayed effects and the variable nature of TPM's activity. The reasoning is as follows. Immediately on binding to the site, TPM could exert either a positive or negative allosteric modulatory effect, and simultaneously prevent the protein kinase (e.g., cAPK) from accessing the serine hydroxyl site, thereby preventing phosphorylation. Within a population of target proteins, this would gradually shift the proteins to a dephosphorylated state, which could account for the gradual and delayed effects. The variable activity of TPM could arise from the variable states of phosphorylation of the target proteins. Assuming that TPM does not bind when the protein is the phosphorylated state, its activity would be inversely related to the degree of phosphorylation.

Although several studies have afforded results that generally support this hypothesis, no studies have provided definitive evidence one way or the other. One study that yielded a negative result was designed to test the ability of TPM to inhibit the conductance of depolarizing current through "glutamate" receptor/channels comprised solely of iGluR6 subunits expressed in baby hamster kidney cells (Smith et al. 2000). The receptor/channel complexes were functional because kainate and domoate each promoted a flux of [^{14}C]guanidium ions into the cells. However, TPM (0.1 or 100 μM) did not have any effect on these currents when experimental conditions favored a minimally phosphorylated state or a highly phosphorylated state. Although these results

appear to be inconsistent with the hypothesis that TPM inhibits AMPA or kainate receptor activation by binding to phosphorylation sites, they should be interpreted cautiously because the iGluR6 subunit may not possess a phosphorylation site targeted by TPM. TPM may be more likely to target auxiliary proteins (e.g., PSD-95), over channel subunits, because there are more of the former (Kato et al. 2007).

Conclusion

Topiramate (TOPAMAX[®]) is a broad-spectrum AED that is approved in most world markets for preventing or reducing the frequency of epileptic seizures (as monotherapy or adjunctive therapy), and for the prophylaxis of migraine. TPM, a sulfamate derivative of the naturally occurring sugar D-fructose, is the first of a series of sugar sulfamates (Maryanoff et al. 1987, 1998, 2005, 2008) and related analogues (Shank et al. 2006), to be approved for marketing as a therapeutic agent. The sulfamate moiety is necessary, but not sufficient, for its pharmacodynamic properties.

This drug possesses several pharmacodynamic properties that may contribute to its clinically useful attributes, as well as to its potential adverse effects. The molecular pharmacodynamics profile for TPM is rather complex. It inhibits or enhances the activity of a variety of voltage-gated or ligand-gated Na⁺, Ca²⁺, and Cl⁻ ion channels in neurons and some glial cells, thereby reducing the excitability of some neural circuits. Also, TPM has moderate potency in inhibiting certain CA isozymes and the activity of certain aquaporins. The nearly ideal pharmacokinetics of this drug contributes considerably to its therapeutic utility.

In the therapeutic realm, the complex pharmacodynamics of TPM translates into a complex clinical profile. Although this drug is approved for only two serious medical conditions, epilepsy and migraine, a large body of information in the literature points to other potentially useful clinical effects. Given that TPM's complex clinical profile includes various adverse effects, its ultimate range of therapeutic applications will be determined by the cogent assessment of benefits versus risks.

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Conflict of Interest

The authors have no conflict of interest.

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