Topiramate: Effects on cognition in patients with epilepsy, migraine headache and obesity

Ther Adv Neurol Disord
(2013) 6(4) 211–227
DOI: 10.1177/1756285613481257

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Abstract: This paper reviews the clinical implications of topiramate (TPM)-induced cognitive deficits in patients with epilepsy, migraine headache, obesity, and in normal populations, followed by reviews of the literature describing the reversal of such deficits upon medication discontinuation. It also discusses animal investigations of TPM's role of neuroprotection in brain injury. TPM's most intolerable adverse effects (AEs) are on verbal fluency and reaction time, resulting in high discontinuation rates in patients taking it for epilepsy and migraine headache. However, because TPM is so effective in the treatment of epilepsy and migraine headache, its use is expected to continue. There appears to be greater tolerance of TPM's cognitive AEs when it is used in the treatment of obesity, perhaps because of the lower doses required. Research attempting to predict the populations most vulnerable to the cognitive effects caused by TPM is ongoing. Studies suggest that one such population may include patients with a past psychiatric history. Slow titration and administration of the lowest possible doses may decrease risk of cognitive deficits.

Keywords: cognition, epilepsy, migraine, obesity, psychiatric, topiramate

Introduction

Topiramate (TPM), a second-generation antiepileptic drug (AED), is highly effective in the treatment of seizure disorders and migraine headaches, and has promise for use in psychiatric disorders and obesity. Its unique biochemical profile may underlie both its clinical utility and its unique side effects, which include negative effects on cognition, spontaneous glaucoma, weight loss, renal stones, and acidemia [Faught, 2007; Van Passel *et al.* 2006].

TPM has multiple mechanisms of action, including inhibition of voltage-dependent sodium and calcium ion channels, potentiation of gamma-aminobutyric acid (GABA) inhibition, blocking of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainate receptors, enhancement of potassium currents, and inhibition of several carbonic anhydrase isozymes [Czapinski *et al.* 2005; Shank *et al.* 2000]. TPM has a simultaneous effect on these channels that is unique among the AEDs, and may help to explain its unique effects on cognition [Shank *et al.* 2000]. In general, AEDs with predominantly sodium channel actions are associated with fewer cognitive side effects while drugs with GABAergic profiles appear to negatively impact vigilance and attention. Antiglutamatergic drugs on the other hand, appear to have negative effects on memory and learning [Lagae, 2006].

Many studies have corroborated that despite good seizure control TPM induces specific negative effects on cognition, both in patient populations and in normal volunteers, thus causing a higher dropout rate than other second-generation AEDs.

TPM is approved for the treatment of epilepsy in over 60 countries, for migraine headache in over 20 countries, and as add-on therapy for Lennox–Gastaut syndrome for children over 2 years of age [Van Passel *et al.* 2006].

When used in combination with phentermine, TPM is prescribed for the additional indication of obesity, one of seven known potentially controllable risk factors for Alzheimer's disease [Barnes and Yaffe, 2011]. The adverse cognitive effects of TPM will need to be assessed against the potential cognitive risks posed by obesity itself. This is

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especially important in young populations in whom obesity and type 2 diabetes are rising.

Patients with epilepsy, particularly temporal lobe epilepsy (TLE), may be at risk for cognitive decline over time [Jokeit and Ebner, 1999; Motamedi and Meador, 2003; Sommer and Fenn, 2010], and the adverse side effects of TPM may compound these cognitive problems. Nonetheless, patients with such complex disorders represent another cognitively at-risk group who may benefit from TPM treatment.

Subjective cognitive complaints may exaggerate the magnitude of patients' presentations. One study that examined healthy volunteers, patients with seizure disorders, and patients with Parkinson's disease, treated either with TPM or lamotrigine (LTG), found that quality of life and cognitive complaints were more related to mood than to medication [Marino *et al.* 2009]. Arif and colleagues found the highest level of subjective cognitive complaints in patients who took TPM compared with several other AEDs [Arif *et al.* 2009]. This suggests that in addition to objective cognitive adverse effects (AEs), subjective complaints may further reduce a patient's ability to tolerate and continue with TPM treatment.

Interestingly, animal data show that TPM counterintuitively may be neuroprotective under certain circumstances. For example, TPM may play an important role in protection and regeneration of the nervous system after brain injury [Noh *et al.* 2006; Kouzounias *et al.* 2011]. Furthermore, one preliminary study of humans, using microdialysis, has shown that after crossing the blood–brain barrier, TPM is able to decrease elevated glutamate levels after traumatic brain injury (TBI) [Alves *et al.* 2003].

This paper presents a review of studies investigating TPM-induced negative cognitive effects, and clinical implications in epilepsy, migraine, psychiatric, obese, and normal populations. We review the literature describing the reversal of such negative effects upon medication discontinuation, and the use of TPM in special populations such as the elderly and developmentally delayed. Finally, we discuss a possible role of TPM as a protector in neuronal injury, and potential areas for future investigation.

Effects of TPM on cognition in patients with epilepsy

The cognitive effects of TPM compared with other AEDs in patients with partial epilepsy generally show that when taken in doses over 300 mg/day, the discontinuation rate is high [Bootsma *et al.* 2004]. Despite adequate seizure control, discontinuation rates of up to 70% were found in one longitudinal study that followed 470 patients over 4 years, with 28% of patients reporting 'mental slowing' [Bootsma *et al.* 2004].

Even in lower doses, the negative effects on cognition may be intolerable for some patients [Kim *et al.* 2006]. However, several studies have shown that when TPM is taken in low doses and is titrated slowly, it is better tolerated, either as monotherapy or when used to augment other AEDs, for complex partial seizures in both young adults and the elderly [Arroyo *et al.* 2005; Ben-Menachem, 2008; Faught, 2007; Groselj *et al.* 2005; Salinas-Estabane, 2002; Stefan *et al.* 2008].

When comparing patients on low *versus* high doses, Arroyo and colleagues found cognitive AEs in 15% and 24% of patients, respectively [Arroyo *et al.* 2005]. Besides dose, study design appears to impact the level of both subjective and objective cognitive AEs. Many open-label studies seem to show fewer adverse cognitive effects than double-blind random prospective trials [Korean Topiramate Study Group, 2002]. This suggests that when TPM administration is individualized, rather than standardized, as required by clinical trials, the patients experience fewer AEs [Giannakodimos *et al.* 2005].

TPM has been found to have a negative impact on working memory, processing speed, psychomotor speed, and verbal fluency [Fritz *et al.* 2005; Kim *et al.* 2006; Kockelmann *et al.* 2003; Lee *et al.* 2006]. It also has been speculated that patients with epileptic activity involving the left temporal areas may be at specific risk for word-finding deficits from TPM treatment [Mula *et al.* 2003]. Table 1 shows the effects on cognition in adults from several studies when TPM is given either as monotherapy or in conjunction with other AEDs. In general, the results show that TPM affects cognition in a significant minority of patients, especially in higher doses. In many patients, the practical result of such AEs is medication discontinuation despite adequate seizure control.

In studies comparing TPM to other AEDs, similar discontinuation rates were found. One study comparing TPM with levetiracetam (LEV) found

Table 1. Topiramate and cognitive tests in patients with epilepsy.

Study	Medication	Dose (mg)	*n*	Cognitive measures	Cognitive declines	Dropout from cognitive AEs
Aldenkamp *et al.* [2000]	TPM *versus* VPA (adjuvant to CBZ)	200–400	TPM = 24 VPA = 29	FePSY, finger tapping test, simple reaction time, binary choice reaction, computerized visual search, recognition of words and figures, RAVLT	Information processing, speed, memory	TPM = 5 VPA = 1
Meador *et al.* [2003]	TPM *versus* VPA + CBZ	400	TPM = 34 VPA = 29 Placebo = 13	CPT, digit cancellation, choice reaction time, grooved pegboard, Medical College of Georgia complex figures, WAIS-R (LM), SDMT, COWA, Stroop Test	Graphomotor coding, verbal fluency	TPM = 6 VPA = 2
Lee *et al.* [2003]	TPM off and on	100–700	22 on–off 16 off–on	WAIS-R (digit span, digit symbol) serial digit learning, VIGIL, COWA, animal naming, grooved pegboard	Attention/ concentration, processing speed, verbal fluency	Not discussed
Kim *et al.* [2006]	TPM *versus* OXC monotherapy	50–200	TPM = 30 OXC = 30	MAS, WMS-R (digit span), TMT, BDAE-3 semantic fluency	Working memory, verbal fluency, memory	None
Blum *et al.* [2006]	TPM *versus* LTG (adjuvant to CBZ or PHT)	300	TPM = 96 LTG = 96	COWA, Stroop Test, digit cancellation, grooved pegboard, RAVLT, SDMT	Processing speed, phonemic fluency, disinhibition	TPM = 24 LTG = 20
Lee *et al.* [2006]	TPM monotherapy	50, 75, or 100	36	MAS, WMS-R digit span, TMT, BDAE-3	Attention/ concentration, verbal fluency	7
Gomer *et al.* [2007]	TPM *versus* LEV	TPM = 50–400	TPM = 21	TMT, LPS 6, WMS-R (digit span, spatial span), VLMT, DCS, block	Cognitive speed, attention, verbal and spatial working memory, mental flexibility,	None

AE, adverse event; BDAE-3, Boston Diagnostic Aphasia Examination-Third Edition; CBZ, carbamazepine; COWA, controlled oral word association; CPT, Continuous Performance Test; DCS, Diagnosticum fur Cerebralschadigung; LEV, levetiracetam; LM, logical memory; LPS 6, Leistungspruf-system; LTG, lamotrigine; MAS, Memory Assessment Scale; OXC, oxcarbazepine; PTH, phenytoin; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; TPM, topiramate; VLMT, Verbal Learning and Memory Test; VPA, valproate; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS, Wechsler Memory Scale.

that AEs led to discontinuation in 22% of TPM patients compared with 6% of LEV patients after 24 months. Although there was no difference in seizure response, 28% of TPM patients reported 'mental slowing' compared with 14% of LEV patients. Other significant AEs included dysphasia, mood changes, paresthesias, appetite loss, skin complaints, weight loss, headache, and dizziness [Bootsma *et al.* 2008]. Another prospective study evaluated the effect of TPM as an add-on AED for intractable epilepsy in patients aged 18–65 years, comparing slowly titrated TPM (maximum dose of 200 mg/day) to tiagabine (TGB) (maximum dose of 32 mg/day). The overall dropout rate was similar in the two groups, but significant declines in performance were seen in measures of verbal and nonverbal working memory, semantic and phonemic fluency, and verbal comprehension in the TPM group. While the TGB group also showed declines in verbal memory, declines in overall verbal fluency appeared unique to the TPM group. These effects continued even after a 3-month maintenance phase [Fritz *et al.* 2005].

Bootsma and colleagues, however, found that after a period of 12 months, the rate of cognitive complaints in a TPM group approached that of a

LEV group [Bootsma *et al.* 2006]. It appeared that in the patients who were able to tolerate and remain on TPM for 6 months, cognitive AE differences between medications were minimal. Compared with zonisamide, gabapentin, and LTG, studies have found that TPM consistently impacted verbal fluency (both semantic and phonemic) as well as other areas of cognition, taking weeks to normalize upon medication discontinuation [Martin *et al.* 1999; Ojemann *et al.* 2001]. Verbal fluency steadily declines as TPM is given with increasing numbers of concomitant drugs to patients with epilepsy. Even TPM monotherapy has been found to give rise to verbal fluency declines, which may be attenuated by a later onset of seizure disorder and higher education [Witt *et al.* 2012].

An example of a practical effect of TPM on daily life has been shown using motor-vehicle performance as an outcome measure. At least two studies found TPM-related changes in driving ability [Gordon and Logan 2006; Mills *et al.* 2008]. One randomized, placebo-controlled double-blind study compared the cognitive effects of TPM and LTG in a subsample of patients with partial seizures, using a computerized task measuring visual scanning, divided attention, and effective field of view. The TPM-treated group experienced restricted field of view after 8 weeks, and was unable to overcome this deficit over the 16 weeks of the study. This was not thought to be due to angle-closure glaucoma, a rare AE from TPM. There were also declines in simple target identification and divided attention performance in the TPM group compared with the LTG-treated group. These negative changes were similar to the effects of a low dose of alcohol (0.002 mmol/l) or alprazolam (0.5 mg) [Mills *et al.* 2008].

Gordon and Logan retroactively evaluated TPM-positive cases in motor-vehicle accidents resulting in fatalities [Gordon and Logan 2006]. They were able to associate cognitive slowing in some drivers with blood levels of TPM as low as 50 mg/l. This retrospective, correlational study was inconclusive, but compelling in its suggestion that the negative cognitive effects induced by TPM may profoundly affect driving skills.

The above studies on the effects of TPM given to patients with epilepsy when taken together show that the negative effects seem greatest in patients with left temporal damage, in patients who take multiple medications, and perhaps in those with lower educational attainment. When doses are slowly titrated, the cognitive effects are better tolerated. The areas most affected are verbal fluency and memory, and may persist as long as the medication is taken.

Cognitive effects of TPM discontinuation in patients with epilepsy

Studies have assessed the effects of TPM discontinuation on cognition to determine whether these negative effects are temporary. An early retrospective study found that the despite decreases in verbal fluency, list learning, and verbal IQ in TPM-treated patients when compared with controls, significant improvements were seen upon medication discontinuation [Thompson *et al.* 2000]. Rorsman and Källen noted that after discontinuing TPM in two patients with intractable seizures, neuropsychological testing results improved considerably [Rorsman and Källen 2001]. A prospective study evaluated 20 consecutively admitted presurgical patients with intractable partial seizures and found that compared with controls, a dramatic amelioration in five out of six measures of frontal lobe function after TPM was discontinued [Kockelmann *et al.* 2003]. In particular, verbal fluency, verbal and spatial working memory, and cognitive flexibility improved. Only five of the 20 patients reported TPM-induced cognitive complaints prior to withdrawal, and no patients complained about AEs after withdrawal. This suggests that in some patients, the effects on cognition may be subtle and go unnoticed. Another study aimed to assess the effects of low-dose chronically administered TPM given as monotherapy finding that after 1 year, impairments in attention/concentration and verbal fluency disappeared within 1 month of medication withdrawal [Lee *et al.* 2006].

These studies suggest that the cognitive effects of TPM are reversible, disappearing upon discontinuation of the medication.

Effects of TPM on cognition in patients with migraine headache

The doses of TPM required to treat migraine headache are lower than those needed for epilepsy control, resulting in a lower prevalence of observed and/or reported cognitive AEs [Brandes, 2005]. Brandes and colleagues studied 483 migraine patients in a pivotal trial, demonstrating adequate tolerability on 50 mg, 100 mg, or 200 mg doses

[Brandes *et al.* 2004]. Reported AEs included paresthesia 50%, fatigue 14%, anorexia 13%, memory complaints (12 %), nausea (10%), and weight loss (11%) [Brandes *et al.* 2004]. A second efficacy study using 100 mg and 200 mg doses found the most common AEs related to the central nervous system, included paresthesia (11% and 15%, respectively), concentration difficulties (4% and 12%), fatigue (4% and 10%), and insomnia 3% and 7%) [Diener *et al.* 2004].

A third pivotal trial evaluated 469 subjects taking 50 mg, 100 mg or 200 mg, finding few spontaneous cognitive complaints (< 10%), and similar types of AEs as in other studies [Silberstein *et al.* 2004]. The doses required to treat migraine headache were lower than those needed for epilepsy control, possibly explaining the lower incidence of cognitive complaints in this population [Brandes, 2005].

A recent open-label, naturalistic study compared the clinical and adverse effects of valproate (VPA) and TPM on migraine headaches [Krymchantowski and Jevoux, 2011]. TPM was begun at an initial dose of 25 mg/day, and increased by 25 mg every 10 days until a target dose of 150 mg was reached. Of the 69 patients in the TPM group, six withdrew by the end of the study due to cognitive AEs while none of the 51 patients in the VPA group withdrew. The most common AEs reported in the TPM group were weight loss (50%), paresthesia (48%), and cognitive disturbance (20%).

One recent study of migraine patients evaluated the effects of TPM specifically on cognitive function. Using a maximum dosage of 50 mg twice per day, 35 patients (mean age of 34.9 years) were evaluated over the course of 3 months. Cognitive testing was conducted at baseline and at 3 months, using the Wechsler Memory Scale. Reported cognitive AEs decreased from 41% in the first month, 24% in the second month, and 23% in the third month. Patients' reported cognitive AEs were attenuated over time in part because dose titration was stopped in patients with complaints. Decline in attentional ability was the only significant cognitive change found on objective test measures [Kececi and Atakay, 2009]. A similar open-label trial assessed cognition in 20 migraine patients (mean age 37.7 years) over 16 weeks with TPM (starting dose of 25 mg/day and increased weekly by 25 mg until a target dose of 50–100 mg/day) [Romigi *et al.* 2008]. By the end of the study, a decline in phonemic fluency was seen, similar to findings in studies of patients with epilepsy taking higher doses.

In a recent placebo-controlled, double-blind study evaluating cognitive effects of TPM on migraine patients aged 12–17 years, three treatment groups were administered placebo, 50 mg/day, or 100 mg/day for 16 weeks. Cognition was evaluated using the Cambridge Neuropsychological Test Automated Battery at baseline and at the completion of the drug trial. There was a significant decline in semantic fluency even on the 50 mg/day dose. In the 100 mg/day dose group, significant declines were seen in psychomotor reaction time, pattern recognition latency, and visual processing latency. Interestingly, no changes were found in semantic fluency in this higher dose group [Pandina *et al.* 2010].

A recent study aimed to address whether there were differential cognitive AEs with TPM in patients with migraine headache compared with patients with epilepsy. Luykx and colleagues performed a systematic review of all randomized controlled trials comparing TPM monotherapy in epilepsy and migraine, finding that the AE profile differed in the two groups given the same doses of drug [Luykx *et al.* 2009]. Patients with migraine were found to be more likely to drop out of trials due to AEs. Cognitive complaints (memory and concentration), alteration of taste, and complaints of paresthesia were found in the migraine group. The epilepsy group complained more often of headache, depression, and/or confusion. Possible confounds to these findings may have been: (a) epilepsy studies predated the migraine studies, and may have alerted investigators to the possibility of the AE; (b) migraine cohorts were slightly older than the epilepsy cohorts; (c) the epilepsy cohorts may have perceived their disorder as more serious and thus may have been more tolerant of AEs; (d) titration schedules differed among the two patient populations; (e) assessment of cognition was inconsistent among the studies [Luykx *et al.* 2009].

In summary, patients with migraine headache, as opposed to epilepsy, in general appear to have fewer cognitive complaints from TPM, perhaps reflecting the lower doses needed, younger age, and differences in titration schedules. When migraine patients drop out of TPM trials, the complaints seem to be concerned with memory and concentration.

Effects of TPM on cognition in patients with psychiatric disorders

While there is objective evidence that AEDs such as TPM negatively affect cognition in both bipolar and epilepsy patients [Gualtieri and Johnson, 2006], a past psychiatric history itself also predicts TPM-induced cognitive AEs [Kanner *et al.* 2003]. As TPM may play a valuable, second-line role in the treatment of psychiatric disorders, additional studies are warranted to assess for adverse cognitive events in psychiatric populations.

Although TPM is not approved by the Food and Drug Administration (FDA) for any psychiatric disorders, it has been seen as efficacious in many conditions. A recent review of the mechanisms and efficacy of AEDs used in the treatment of psychiatric disorders concluded that TPM shows promise in the treatment of social phobia and as an adjuvant medication in drug-resistant schizophrenia [Johannessen, 2008]. In combination with other medications, TPM has been shown to reduce mixed and manic mood symptoms, cycling in bipolar I disorder [McElroy *et al.* 2000], provide mood benefits in refractory bipolar I and II disorders, and cyclothymia [Marcotte, 1998], and to reduce depressive symptoms in acute bipolar depression [McIntyre *et al.* 2002]. However, more rigorous studies are needed to evaluate the efficacy of TPM as monotherapy in acute affective episodes [Vasudev *et al.* 2006]. TPM shows promise in patients with bipolar disorder and comorbid conditions such as eating disorders and alcohol dependence [Ketter, 2010], and there is evidence that TPM treatment may reduce both depression and anger in depressed women [Nickel *et al.* 2005]. Certain symptoms of borderline personality disorder, including aggression and anxiety, may be reduced with TPM therapy [Loew *et al.* 2006]. Studies show benefits to behavioral disturbances such as aggressive behavior in dementia patients [Fhager *et al.* 2003], and in individuals with severe intellectual disability with co-occurring mood disorders [Janowsky *et al.* 2003]. Finally, TPM may be an effective treatment for alcohol dependence [Johnson *et al.* 2007].

Studies assessing cognitive effects of TPM in psychiatric patients most often have focused on the bipolar spectrum disorders. A review of four studies of TPM in the treatment of bipolar I disorder (combined $n = 142$) reported relatively few AEs. 'Slowed thinking/cognitive impairment' was reported in 9% of patients taking an average daily dose of 200–300 mg/day. However, daily doses amongst studies ranged from 25 mg/day to 1200 mg/day [Chengappa *et al.* 1999; Marcotte, 1998; McElroy *et al.* 2000; Suppes, 2002]. Another prospective chart review of 14 patients with bipolar I and II disorder, using a mean dose of TPM at last observation of 100 mg/day (range 25–300 mg/day), showed only one patient discontinuing treatment because of cognitive complaints [Guille and Sachs, 2002]. Another study of TPM in treatment-resistant bipolar spectrum disorders (mean dose at endpoint 202 mg/day; range 100–400/day) again found only one out of 34 patients dropped out of the trial because of reported concentration problems [Vieta *et al.* 2002]. Treatment of acute mania with TPM in 14 hospitalized patients yielded no cognitive AEs with a mean dose of 310 mg/day TPM (range 150–700 mg/day) [Bozikas *et al.* 2002]. A more recent study evaluating TPM for management of acute mania with target doses of 200 mg, 400 mg, or 600 mg/day, found dose-related AEs, including reports of memory difficulty ranging from 1% to 7%, language problems ranging from 1% to 6%; the higher rates were reported by patients at the highest (600 mg/day) dose [Kushner *et al.* 2006]. Although taken together these studies suggest a TPM dose-dependent relationship to AEs, dose ranges across patients were too large for this to be concluded with certainty.

Aside from the bipolar spectrum disorders, there are few reports on incident cognitive AEs related to TPM use in other psychiatric conditions. One preliminary study of recently sober patients with alcoholism demonstrated positive cognitive effects of TPM [Likhitsathian *et al.* 2012]. However, this study lacked a placebo group. Therefore, differentiation between positive effects of TPM *versus* alcohol discontinuation remains inconclusive. In post-traumatic stress disorder and borderline personality disorder, TPM was proposed to facilitate traumatic memory extinction. It is interesting to note that traumatic memory extinction is not thought to be due to the memory-impairing properties of TPM, since memory retrieval is necessary fear memory extinction [Do Prado-Lima *et al.* 2011].

Taken together, while TPM is increasingly used for many psychiatric symptoms, its cognitive effects have been studied primarily in bipolar disorders. These studies have been observational, with large dose ranges. The types of cognitive impairments are similar to those seen in the epilepsy population,

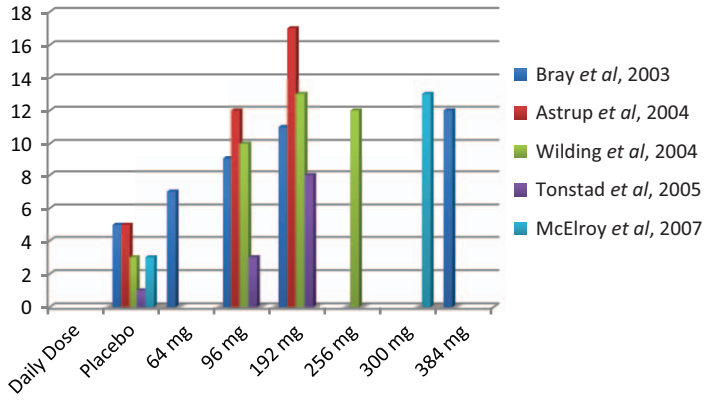

Figure 1. Topiramate monotherapy for weight loss: percentage of subjects reporting 'difficulty with concentration or attention'.

with verbal learning and concentration the most prominent deficits, occurring only at the highest dose. TPM has had empirical use in many other psychiatric populations, but its effects on cognition in such patients, for example those with alcoholism, eating disorders, personality disorders, and depression, who often take other centrally active medications, have not been studied.

TPM for weight loss

Not only is obesity a known risk factor for medical conditions such as metabolic syndrome, type 2 diabetes, hypertension, coronary artery disease, stroke, obstructive sleep apnea, and some cancers [Kopelman, 2007], obesity has been found to be one of seven potentially modifiable risk factors for the development of Alzheimer's disease [Barnes and Yaffe, 2011]. The prevalence of obesity (body mass index > 30) is increasing dramatically in the USA [Baskin *et al.* 2005; Sturm and Hattori, 2012], and this will predict a commensurate increase in these conditions in the future. Until recently, only a few medications have been available for the treatment of overweight or obesity, such as orlistat, lorcaserin, and phentermine monotherapy. FDA approval of weight-reduction medications has been limited by potentially dangerous side effect profiles, including, but not limited to, cardiac or cerebrovascular complications [Yen and Ewald, 2012]. Predicting the likelihood of AEs prior to the approval of any weight-loss medication is crucial, but this needs to be weighed against the cost of inadequate treatment of the serious condition of obesity.

The number of people prescribed TPM will likely increase significantly in the near future due to the recent FDA approval of a new combination medication containing TPM. Qsymia, phentermine and TPM extended-release capsules, has been approved for chronic weight management in both obese patients and overweight patients with weight-related comorbidities [VIVUS Inc., 2012]. Qsymia has been shown to cause both moderate rates of sustained weight loss and other health benefits related to obesity and overweight. In fact, Garveyand colleagues found that over 50% of patients receiving this combination drug achieved a 10% weight loss by the end of 108 weeks [Garvey *et al.* 2012]. Secondary positive results included improvements in blood pressure, lipid and glycemic profiles, as well as a reduction in the number of medications needed for treatment of obesity comorbidities.

The following is a review of the incidence of cognitive AEs of TPM treatment for weight loss and maintenance of weight. As use of this medication is likely to increase for obesity treatment, examination of any effects on cognition in this particular population is warranted.

Cognitive effects of TPM monotherapy for weight loss

Subjective cognitive complaints from TPM monotherapy for weight reduction and maintenance have been assessed in several studies. Studies of patients reported 'difficulty with concentration or attention' using immediate-release TPM monotherapy for obese subjects for (a) weight loss or maintenance, (b) weight loss and blood pressure reduction, and (c) control of binge eating are displayed as percentages in Figure 1. Duration of studies ranged from 16 weeks to 83 weeks, the

number of subjects ranged from 385 to 1282, and mean age ranged from 43.8 years to 50 years of age. Most of the patients were women (72–85%). With the exception of the McElroy and colleagues' study [McElroy *et al.* 2007], all subjects were required to adhere to additional lifestyle or dietary modification plans. Three studies were terminated early after a controlled-release formulation of TPM was introduced [Astrup *et al.* 2004; Tonstad *et al.* 2005; Wilding *et al.* 2004]. Three of these studies had additional subject-selection criteria, including previous weight loss through diet [Astrup *et al.* 2004], essential hypertension [Tonstad *et al.* 2005], and binge-eating disorder [McElroy *et al.* 2007].

In general the studies listed in Figure 1 found higher reports of cognitive complaints in patients receiving TPM for weight loss compared with placebo-treated patients. Although weight-loss efficacy of TPM monotherapy across doses was not shown to differ between 64 mg and 96 mg [Bray *et al.* 2003], there did appear to be greater than 1% additional weight loss with doses between 96 mg and 192 mg [Bray *et al.* 2003; Wilding *et al.* 2004]. Additional weight loss greater than 1% was not found with even higher doses (≥192 mg) [Bray *et al.* 2003; Wilding *et al.* 2004]. Differences in cognitive complaints, particularly attention/concentration difficulties, also appeared to be dose related; increases of approximately 2% were associated with each increase in dose. In studies of TPM monotherapy for weight loss that included quantitative neuropsychological assessments [Aarsen *et al.* 2006; Loring *et al.* 2011], dose-related cognitive effects were similarly found. One study using the Computerized Neuropsychological Test Battery (CNTB) found a dose-dependent decline in cognitive abilities [Loring *et al.* 2011]. No significant declines in objective measures were found at the 64 mg dose. At the 96 mg dose, significant declines in visual memory were seen. At the 192 mg doses, additional significant declines were found in simple reaction time, associative delayed memory, and total CNTB summary score. With a further increase to 384 mg, there were additional significant declines in delayed verbal memory (word list), paired associative learning, choice reaction time, and naming. Declines seen at 6 weeks were predictive of declines after 24 weeks of treatment.

To review, TPM monotherapy is used in a long-acting form, and the cognitive effects are most apparent as the doses increase beyond 96 mg. Specific deficits are noted in reaction time and verbal memory, as is the case in patients with epilepsy and migraine headache.

Cognitive effects of TPM plus phentermine combination for weight loss

Qsymia, controlled-release TPM plus phentermine, was developed for chronic weight management in obese patients. This combination medication is meant to limit the AEs anticipated if either medication were to be given alone, requiring higher doses. The additive weight-loss benefit of the combined medications also provides effectiveness at lower doses [Gadde *et al.* 2011]. Several phase III clinical trials (CONQUER, SEQUEL, and EQUIP) included an evaluation of the cognitive AEs of Qsymia in obese and overweight subjects. CONQUER [Gadde *et al.* 2011] was a 56-week trial using once-daily controlled-release TPM plus phentermine for weight reduction and associated comorbidities in obese and overweight patients. SEQUEL was a 52-week extension study of the CONQUER study [Garvey *et al.* 2012], which assessed sustained weight loss and metabolic benefits. The mean age of participants was 51 years and 70% were women. Doses of trial drug were phentermine 7.5 mg + TPM controlled release 46 mg, or phentermine 15 mg + TPM controlled release 92 mg. In the CONQUER phase, 'disturbance in attention', was reported in 1% of the placebo group, 2% in the lower dose group, and 4% in the higher dose group. The other cognitive AE reported was 'memory impairment' but only at the highest dose and at less than a 1% frequency. In contrast, the primary outcome measure of weight loss and the secondary outcome measure of improved cardio-metabolic risk were more effective at the higher doses. In SEQUEL, no cognitive AEs were noted; the authors reported other AEs of < 5% frequency.

EQUIP [Allison *et al.* 2012], the third 56-week trial of phentermine and controlled-release TPM for weight loss and metabolic improvements, used medication doses of phentermine 3.75 mg + TPM 23 mg and phentermine 15 mg + TPM 92 mg. The mean age of subjects was 42.7 years and again most subjects were female (83%). The only cognitive AE reported, 'disturbance in attention', was significantly greater than placebo in the high dose group. Around 4% of subjects in the higher dose group, and less than 1% of subjects in the lower dose and placebo groups experienced AEs.

These data indicate that when TPM is combined with phentermine and administered at a low dose with slow titration as a controlled-release formulation, there is a low incidence of cognitive AEs, and few study dropouts. The manufacturer's recommendation is to start the medication at a low dose (3.75/23 mg), and to increase it over many weeks following specific parameters determined by weight-loss assessment [VIVUS Inc., 2012]. Clinicians should expect a significantly lower rate of cognitive complaints in this setting compared with the use of TPM for other conditions in clinical practice.

Altogether, the rates of cognitive AEs in patients given TPM for obesity or overweight are low compared with other patients, reflective of the lower doses, and there have been few dropouts.

Effects of TPM on cognition in special populations: learning disabled and the elderly

Patients with concurrent epilepsy and learning disabilities may comprise a unique population who do not seem to be at increased risk of AEs from TPM. One study evaluating overall tolerability found that patients were less likely to discontinue the medication if they also had learning difficulties [Lhatoo *et al.* 2000]. Another investigation showed that in the treatment of adults with refractory seizures and learning disabilities, TPM was well tolerated and offered good quality of life, with few patients needing withdrawal. The most reported AE was paresthesia and there were no complaints of word finding or recall problems [Kelly *et al.* 2002].

Another small observational study of 20 adults with developmental disabilities and refractory seizures found no discontinuation of drug because of cognitive AEs, although neuropsychological testing was not performed [Singh and White-Scott, 2002]. A German 3-month open, prospective study of patients with epilepsy and intellectual impairment found that six out of 24 patients suffered from 'confusion and severe deceleration of thinking and acting' with doses ranging from 50 mg to 900 mg/day [Huber, 2002]. Lee and colleagues found in an 'on–off' study of epilepsy patients, that intellectual capacity was significantly positively correlated with changes in the Wechsler Adult Intelligence Scale-Revised arithmetic subtest [Lee *et al.* 2003]. In other words, patients with higher intellectual capacity were differentially affected on this measure that assesses concentration, attention, and educational attainment compared with patients with lower global cognitive abilities. The authors suggested that this finding was due to a possible 'floor effect' in patients whose scores were already limited on the arithmetic subtest. No other changes in cognitive scores correlated with IQ scores. Nonetheless TPM was well tolerated in patients with such intellectual disabilities.

Clinical management of epilepsy in the older patient is another unique challenge because of etiological differences of seizure disorders, and because of increased susceptibility to the cognitive effects of concomitant medications and other causes compared with younger adults [Stefan *et al.* 2008; Sommer and Fenn, 2010]. Despite the decreased cognitive reserve at baseline, Stefan and colleagues found that whether TPM was given as monotherapy (mean doses 98 mg/day; range 25–200 mg/day), or as add-on therapy (mean dose 153 mg/day; range 25–400 mg/day), overall quality of life was enhanced and medication tolerability was good [Stefan *et al.* 2008]. Findings from this 1-year open trial showed that of 107 patients with a mean age of 69 years, 11 patients complained of cognitive AEs. In a double-blind randomized study, Ramsay and colleagues assessed the effects of TPM as both monotherapy and adjunctive treatment of older patients with epilepsy [Ramsay *et al.* 2008]. Using doses of either 50 mg or 200 mg, in a total of 77 patients, the authors found that the rate of seizure reduction was similar in the two groups when given as monotherapy. However, the higher dose achieved greater seizure control when used as an augmentation strategy. The most common AEs reported were somnolence, dizziness, and headache. Of the 10 patients (13%) complaining of cognitive AEs, six were in the lower (50 mg) group. The most common complaints were those of memory and language problems. In a more recent study, Chung and colleagues assessed 51 patients over 50 years old with partial epilepsy, before and after 16 weeks of treatment with add-on LTG, or slowly titrated TPM (maximum doses of 500 mg and 300 mg, respectively) [Chung *et al.* 2009]. While some specific cognitive measures (phonemic fluency and processing speed) significantly declined in the TPM group, the combined analysis of all administered tests showed no significant change differences between groups.

Table 2. Effects of topiramate on cognition in normal controls.

Study	Dose of TPM (mg/day)	*n*	Time on TPM (weeks)	Cognitive AEs from TPM
Martin *et al.* [1999]	5.7 mg/kg	TPM = 6 LTG = 5 GBP = 6	4	Psychomotor speed, verbal memory
Meador et al. [2005]	300	TPM = 37 LTG = 38	8	Attention/vigilance, memory, naming and verbal fluency, cognitive/motor speed
Salinsky *et al.* [2005]	200–400	TPM = 15 GBP = 16 Placebo = 8	12	Psychomotor speed, verbal contextual memory, consistency of word recall, letter fluency
Werz *et al.* [2006]	300	TPM = 37 LTG = 37 (cross-over)	12	Attention/vigilance, and verbal memory, naming and verbal fluency, and psychomotor speed
Loring *et al.* [2011]*	64 96 192 384 Placebo	76 75 76 78 75	24	Dose dependent, clinically significant deficits, beginning at the 96 mg/day dose. At highest dose, deficits in visual and verbal memory, naming, and reaction speed

*Cognitively normal obese population. AE, adverse event; GBP, gabapentin; LTG, lamotrigine; TPM, topiramate.

These studies suggest that in subjects who may already be intellectually compromised, the effects of TPM given in modest doses, titrated slowly may be well tolerated. Despite its known AE of cognitive impairment, TPM may be indicated in these populations as a second-line treatment, particularly if the rationale is for the treatment of seizures not adequately treated with other medications.

Effects of TPM on cognition in normal volunteers

Many studies have specifically evaluated the effects of TPM on normal volunteers [Loring *et al.* 2011; Martin *et al.* 1999; Meador *et al.* 2005; Mecarelli *et al.* 2001; Salinsky *et al.* 2005; Werz *et al.* 2006]. Also included in this review is a study by Loring and colleagues that evaluated TPM in obese patients with normal baseline cognitive abilities [Loring *et al.* 2011]. This allows examination of an at-risk population and helps to differentiate between cognitive declines induced by TPM and those associated with obesity itself. Studying a population without baseline central nervous system deficits also aids in understanding the cognitive impact of TPM treatment *versus* the cognitive burden of the underlying disorders (e.g. epilepsy, migraine headache) it is used to treat. Table 2 shows several studies that describe the specific effects of TPM in this population.

Mecarelli and colleagues also found slight changes in electroencephalogram patterns associated with the administration of 100 mg doses of TPM in healthy volunteers [Mecarelli *et al.* 2001]. Changes included increases in delta and theta activity, and reductions in alpha rhythm, which were correlated with both sedation, and adverse cognitive effects. It was suggested that these simultaneous effects were unique among the AEDs.

TPM as a neuroprotective agent following neuronal injury

Although clinically, TPM may give rise to cognitive AEs, it has been shown to confer neuroprotection in animal models of neuronal injury. For example, it increases survival of pyramidal cells in status epilepticus [Kudin *et al.* 2004], protects oligodendrocytes and neurons after spinal cord injury [Gensel *et al.* 2012], and reduces infarct size and risk of cerebral hemorrhage following focal cerebral ischemia [Yang *et al.* 2000].

TPM is not unique in its ability to confer neuroprotection in animal models of neuronal injury [Trojnar *et al.* 2002]. Felbamate, gabapentin, TGB, vigabatrin, and benzodiazepines, also appear to offer neuroprotection in experimental models of ischemia, seizure, and TBI [Niebauer and Gruenthal 1999; Edmonds *et al.* 2001; Lee *et al.* 2000; Noh *et al.* 2006; Schubert *et al.* 2005;

Table 3. Topiramate and cognitive tests in rats exposed to neuronal insult.

	Highest daily dose of topiramate (mg/kg/day)	Model of injury	Cognitive test	Effect on learning or memory compared with injured rats without topiramate administration	Details
Cha *et al.* [2002]	80	Seizure	Water maze	+	Spatial learning improved in weanlings
Zhao *et al.* [2005]	80	Seizure	Water maze, open field	+	Spatial learning improved
Frisch *et al.* [2007]	20 and 100 once	Seizure	Water maze	+	Spatial learning improved only in the 20 mg/kg group
Hoover *et al.* [2004]	30	Traumatic brain injury	Water maze	_	Learning was impaired 1 month post-injury
Shatskikh *et al.* [2009]	40	Seizure	Water maze	+	Spatial learning modestly improved
McDaniel *et al.* [2007]	Not reported	Intracerebral hemorrhage	Water maze	+	Spatial learning improved in early training
Mikati *et al.* [2011]	30	Hypoxia-induced seizure	Water maze	+	Prevented long-term memory impairment

Trojnar *et al.* 2002]. Other AEDs, such as carbamazepine, phenytoin, TGB, and vigabatrin, may have differing effects depending on brain maturity, and conversely, evidence exists showing neurodegenerative effects of valproate and phenytoin in animal models [Trojnar *et al.* 2002].

Several processes may be responsible for the neurodegenerative changes observed in epilepsy, such as glutamate-induced excitotoxicity, apoptotic cell destruction, growth factor withdrawal, and cytokine or toxin accumulation [Vajda, 2002]. TPM has multiple mechanisms of action, including modulation of calcium and chloride channels, reduction of excitatory neurotransmission, and enhancement of GABA-mediated inhibition [Czuczwar and Patsalos, 2001]. Calabresi and colleagues provide an extensive review of the literature on the effects of AEDs on decreasing brain excitability, facilitating neuroprotection in animal models [Calabresi *et al.* 2003].

This evidence that administration of TPM confers protection against neuronal damage and cell death following cerebral injury may have implications for learning and memory following cerebral injury. This has been shown in rat models of cerebral injury, induced through hypoxia, induced seizure, middle cerebral artery lesion (to induce ischemia), and TBI [Cha *et al.* 2002; Frisch *et al.* 2007; Hoover *et al.* 2004; McDaniel *et al.* 2007; Mikati *et al.* 2011; Shatskikh *et al.* 2009; Zhao *et al.* 2005].

While there is consistent evidence that TPM leads to cognitive AEs in healthy humans, the findings are less consistent in rat models. In nonepileptic rats, TPM has been shown to produce modest disruptions in working memory [Shannon and Love, 2004], and spatial memory [McDaniel *et al.* 2007], with sparing of learning [Shannon and Love, 2007], and attention [Shannon and Love, 2005]. A recent study of short- and long-term memory in healthy rats showed low doses (0.01 mg and 0.10 mg/kg) TPM improved, whereas high doses (10.0 mg and 100.0 mg/kg) impaired consolidation and retrieval [Martins de Lima *et al.* 2007].

The studies in Table 3 used rat models to investigate the effect of TPM administration on learning and memory following cerebral injury. Hoover and colleagues found that while there was a beneficial effect on preservation of motor function, learning performance was impaired in brain-injured rats administered TPM 1 month post-injury [Hoover *et al.* 2004]. Other studies found that rats given TPM had preservation of some cognitive abilities following brain injury compared with brain-injured rats not administered TPM. Amelioration of

deficits in learning and memory however, were inconsistent between doses and tests used for assessment making generalization difficult.

These results suggest that there may be a dose-dependent positive effect on cognition after trauma in laboratory animals, and that some of the positive effects of TPM are unique among the effects of other AEDs.

Functional magnetic resonance imaging studies

Recent small functional magnetic resonance imaging (fMRI) studies have attempted to better explain the neural mechanisms that underlie the negative cognitive impact of TPM. Jansen and colleagues compared fMRI findings of five epilepsy patients taking TPM and 10 control subjects with epilepsy not taking TPM [Jansen *et al.* 2006]. Several expressive language tasks were administered during imaging and, relative to the controls, the patients taking TPM demonstrated significant underactivation of the whole brain, particularly in the left prefrontal cortex. This underactivation in the prefrontal language areas was consistent with neuropsychological test performance in the patient group [Jansen *et al.* 2006]. The findings recently were expanded in a sample size of 32 patients with both left and right TLE compared with controls matched for age, sex, and handedness. In general, fMRI results showed that patients with TLE had poorer performance in language (semantics and tone decision) compared with controls. The patients given TPM were noted to have signal changes in cingulate and bilateral superior frontal gyri associated with the differences in semantic decisions and verbal memory [Szaflarski and Allendorger, 2012]. While these studies were small, they may help to better understand the neural mechanisms that underlie TPM-induced cognitive AEs.

Summary

TPM is an effective and commonly used AED with documented importance in the treatment of epilepsy, migraine headache, and some psychiatric disorders. In general, TPM is recommended as a safe medication with notable AEs, particularly on cognition [Faught, 2007; Van Passel *et al.* 2006]. It is anticipated that use of TPM will increase as the prevalence of obesity increases. TPM is best tolerated when doses are titrated slowly and lowest doses possible are used. The negative cognitive effects induced by TPM often are temporary and resolve after medication discontinuance.

Other than the above fMRI studies, few have attempted to better understand specific populations most vulnerable to the cognitive effects of TPM. In one, Cirulli and colleagues found that one 100 mg dose given to healthy volunteers gave rise to a 55-fold variation in blood levels [Cirulli *et al.* 2012]. However, no particular genetic predisposition to cognitive susceptibility to TPM appeared when assessed retrospectively through their genome-wide association study.

Areas for future research may include additional studies of possible genetic predisposition to the cognitive effects of TPM. If clinicians were able to predict those patients most vulnerable to the negative cognitive effects of TPM, they could limit administration to select populations and improve overall tolerability. Other areas of research in vulnerable populations may include more in-depth study of psychiatric patients' increased relative risk to cognitive impairment from TPM. For example, previous studies have been limited to the study of patients with bipolar disorder. As TPM will be prescribed in the future to psychiatric patients with weight gain from the AEs of their medications, it will be important to assess if there are specific vulnerabilities among patients of different diagnoses in this population.

A potentially promising area for research may include the use of TPM as a neuroprotective agent after TBI. While it is known to decrease cognition acutely, its biochemistry in laboratory animals suggests that in the long term it may prophylax against the excitatory effects of brain trauma, delaying or attenuating post-traumatic cognitive deficits.

In summary, TPM as a commonly used AED with additional indications for use in migraine headaches, obesity, and psychiatry has verbal learning, retention, and memory loss as major AEs. While these effects are reversible upon discontinuation of the medication, they preclude a significant minority of individuals from continued use. At this time, it is not possible to predict which patients are most vulnerable to such cognitive effects.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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