Topiramate and cognitive impairment: evidence and clinical implications

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Abstract: Topiramate is an antiepileptic drug (AED) with multiple mechanisms of action that has been shown to be effective in a number of neuropsychiatric disorders. However, cognitive dysfunction is frequently observed in such patients, often representing a relevant challenge in their management. Moreover, there is a long-held recognition that AEDs may profoundly affect cognitive functions. This paper reviews available data on cognitive adverse events in patients with neurological disorders treated with topiramate, discussing the role of different contributing factors such as the pharmacological properties of the drug, the specific features of the brain disorder, and other variables pertinent to the discussion. All studies agree that up to 10% of patients may complain of treatment-emergent adverse events on cognition. Such problems occur early during treatment (i.e. within 6 weeks) and emerge in a dose-dependent fashion, suggesting that such prevalence may be significantly reduced using the drug in monotherapy and adopting individualized doses and titration schedules. The magnitude of the problem is generally mild to moderate and the subjective perception of the patient needs to be taken into account. In fact, apart from language problems, data are not conclusive. Comparisons with new AEDs are limited to levetiracetam and lamotrigine, in both cases generally disfavoring topiramate, while data regarding first-generation AEDs show clear differences only for verbal fluency.

Keywords: adverse event, antiepileptic drugs, cognition, epilepsy, headache, neuropsychology, topiramate

Introduction

Antiepileptic drugs (AEDs) are central nervous system (CNS) agents that are prescribed in a number of different conditions ranging from epilepsy and pain syndromes (both central and peripheral) to mood and anxiety disorders [Mula *et al.* 2007; Johannessen Landmark, 2008]. Cognitive dysfunction is frequently observed in subjects with CNS disorders and the relative contribution of AEDs in this regard may be of relevance [Mula and Trimble 2006]. Moreover, the fact that a considerable number of patients need AED therapy for many years, or even for a lifetime, emphasizes the need to focus on the long-term adverse effects of these drugs on cognition.

Topiramate is an AED structurally unrelated to previous and subsequent compounds. It had been initially marketed for the add-on treatment of patients with drug-resistant partial epilepsy and,

through the following years, it has shown a broad spectrum of efficacy, which extends to primary generalized tonic-clonic seizures [Biton *et al.* 1999] and tonic-atonic seizures associated with the Lennox-Gastaut syndrome [Sachdeo *et al.* 1999]. Data in special populations such as elderly people [Zhang *et al.* 2011] and mentally handicapped children [Kluger *et al.* 2009] are also available. In addition to its use in epilepsy, topiramate showed therapeutic effects in a number of neurological conditions such as migraine (sporadic, chronic and migraine overuse headache) [Magis and Schoenen, 2011], pain syndromes [Tremont-Lukats *et al.* 2000; Backonja, 2002] and movement disorders (tics, restless leg syndrome, tremor) [Spina and Perugi, 2004]. Currently, topiramate has an approved indication in the treatment of children and adults with epilepsy, treatment of Lennox-Gastaut syndrome and the prevention of migraine.

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The aim of this paper is to review data on cognitive tolerability during treatment with topiramate in neurological disorders, discussing the role of different contributing factors such as the pharmacological properties of the drug, the specific features of the CNS disorder, and other variables pertinent to the discussion. Papers about topiramate in psychiatric disorders or obesity have been excluded because the problem of cognition and treatment-emergent adverse events in this particular population would deserve a separate paper. References were identified by searches of Medline/PubMed using the terms 'topiramate', 'cognition', 'epilepsy', 'headache', 'pain', 'movement disorders'. Only papers published in English in international peer-reviewed journals were considered. The reference list of relevant articles was hand searched for additional publications (e.g. book chapters or review papers) if relevant for the discussion.

Mechanisms of action of topiramate

The variety of proposed clinical applications is consistent with the multiple mechanisms of action, ranging from voltage-gated calcium channel blockade to modulation of synaptic neurotransmission [Shank *et al.* 2000; White, 2003]. Topiramate reduces the frequency of activation of voltage-sensitive sodium channels in a state- or use-dependent manner. It produces a voltage-sensitive, use-dependent and time-dependent suppression of sustained repetitive firing (SRF) in cultured mouse spinal cord and neocortical cells [McLean *et al.* 2000]. However, such activity on sodium channels differs from that of other AEDs (such as phenytoin, carbamazepine and lamotrigine), in which a rapid limitation or complete block of SRF occurs. A second mechanism of action is the potentiation of the inhibitory γ -aminobutyric acid (GABA)-mediated neurotransmission through an interaction with the GABA_A receptors [White *et al.* 1997]. Interestingly, such an effect does not involve an action on the benzodiazepine (BDZ)-binding site, as it is not modulated by flumazenil [Shank *et al.* 1994]. A third mechanism of action is the inhibition of neuronal excitatory pathways through a selective action at the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate subtypes of glutamate receptors [Delorenzo *et al.* 2000]. Some studies demonstrated a biphasic effect of topiramate on kainate-evoked currents [Gibbs *et al.* 2000], as revealed by an initial inhibition of the kainate-evoked currents, followed by a delayed

additional inhibitory effect. A further mechanism of action is the inhibition of high voltage-activated calcium currents on L-type calcium channels, thus reducing neurotransmitter release and inhibiting calcium-dependent second-messenger systems [Zhang *et al.* 2000]. Finally, topiramate seems to be a weak inhibitor of type II and type IV carbonic anhydrase (CA), thus modulating pH-dependent activation of voltage- and receptor-gated ion channels [Leniger *et al.* 2004]. Topiramate, like acetazolamide, contains a sulfamate moiety that is likely to be responsible for its CA-inhibiting properties. However, when compared with acetazolamide, topiramate is approximately 10–100 times less potent as an inhibitor of these isoenzymes [Shank *et al.* 1994]. CA-inhibiting properties are considered not to be relevant to the anticonvulsant activity but they are thought to be of significance in determining some of the adverse effects, such as increased risk of nephrolithiasis and metabolic acidosis, as observed with acetazolamide [Kennedy and Lhatoo, 2008]. Finally, a proposed unifying mechanism that can possibly account for the wide range of pharmacological effects exerted by topiramate is the action on the phosphorylation state of membrane proteins [Shank *et al.* 2000]. Emerging evidence suggests that topiramate may bind to phosphorylation sites within AMPA, kainate, GABA_A and voltage-activated sodium channels. Topiramate binds to such sites on receptor proteins only in the dephosphorylated state, exerting a possible bifold effect. Therefore, topiramate can modulate ion conductance through the channel by an immediate allosteric action, and it could exert a delayed effect by shifting the channel toward the dephosphorylated state [Shank *et al.* 2000].

Data from healthy volunteers

Although studies in healthy volunteers are often criticized for the lack of relevance to the clinical situation, they allow focusing on the effect of the drug on cognitive functions without all confounding variables related to the underlying brain disorder. Available data focus mainly on gabapentin and lamotrigine in comparison to topiramate with all authors agreeing that the latter has negative effects on memory, verbal and executive functions [Martin *et al.* 1999; Aldenkamp, 2000; Lhatoo *et al.* 2000; Meador *et al.* 2005; Salinsky *et al.* 2007]. Interestingly, neuroimaging studies point out that topiramate, especially when rapidly titrated, is associated to GABAergic potentiation [Kuzniecky *et al.* 1998, 2002]. However, neuropsychological effects

of topiramate are slightly different from those reported, for example, with BDZs. In fact, the acute administration of BDZs is associated with sedation, drowsiness, psychomotor slowing and anterograde amnesia [Stewart, 2005], while long-term treatment with impairment in visuospatial and visuo-motor abilities, decreased IQ, motor incoordination, slowing psychomotor speed, decreased speed of information processing, verbal learning and concentration, and delayed response times [Stewart, 2005]. Therefore, the GABAergic potentiation of topiramate during rapid titration may explain only some of the negative effects on cognition. In fact, studies investigating electroencephalogram changes in healthy volunteers suggest a unique profile of topiramate compared with other AEDs such as carbamazepine, phenytoin or gabapentin [Mecarelli *et al.* 2001; Wang *et al.* 2003; Smith *et al.* 2006; Salinsky *et al.* 2007].

Data from different neurological disorders

Epilepsy

First, it has to be stated that a variety of factors, in addition to AEDs, can affect cognitive functions in patients with epilepsy. Thus, it is imperative to realize that, in clinical practice, many cognitive problems have a multifactorial origin and different combined aspects are responsible in the individual patient [Mula and Trimble 2009].

Early clinical studies of topiramate as add-on treatment in patients with drug-refractory partial epilepsy report concentration and memory problems in up to 10% of subjects [Ben-Menachem *et al.* 1996; Privitera *et al.* 1996] with a two- to fivefold increased risk of developing cognitive complaints compared with placebo [Jette *et al.* 2008]. However, as adverse events usually occur during controlled trials, they can be explained by the forcedly rapid titration schedule adopted, the increased vulnerability of the investigated population (difficult-to-treat patients) and the likelihood of developing pharmacodynamic interactions. In fact, cognitive complaints decrease to 3–4% when topiramate is prescribed in monotherapy [Arroyo *et al.* 2005] or flexible, individualized doses are adopted [Krakow *et al.* 2007]. In this regard, Ramsay and collaborators point out that even a very rapid titration schedule (i.e. 100 mg on the first day) can be successfully used in monotherapy with a relatively low discontinuation rate due to adverse events [Ramsay *et al.* 2010].

One of the first studies specifically designed to investigate the impact of topiramate on cognitive functions was conducted in 10 patients with epilepsy evaluated at weekly intervals over a period of 3 months [Burton and Harden, 1997]. The authors suggested that high topiramate doses are associated with a poor performance for attention. A retrospective study evaluated neuropsychological tests in 18 patients before and during at least 3 months of topiramate treatment, comparing them with 18 matched controls [Thompson *et al.* 2000]. The authors reported a progressive decline in verbal functions, especially verbal fluency, and reassessment of eight patients after discontinuation shows improvement in all measures [Thompson *et al.* 2000]. That topiramate may selectively affect language functions has been replicated by a number of studies [Mula *et al.* 2003b; Gross-Tsur and Shalev, 2004, Cappa *et al.* 2007] and seems to be related to a specific under-activation of Broca's area induced by the drug [De Ciantis *et al.* 2008] in a specific subset of more vulnerable patients [Mula *et al.* 2003b]. This is further confirmed by the lack of association with the starting dose or the titration schedule [Mula *et al.* 2003b], being reported also with very low doses (less than 100 mg) or in long-term treatment [Lee *et al.* 2006].

Data about topiramate in comparison to older AEDs come from two multicenter, double-blind, randomized, parallel-group studies comparing topiramate with valproate as add-on therapy to carbamazepine [Aldenkamp *et al.* 2000; Meador *et al.* 2003]. On a number of neuropsychological measures, the two compounds displayed slight differences favoring valproate on measures of speech [Meador *et al.* 2003] and short-term memory [Aldenkamp *et al.* 2000]. Regarding new AEDs, a multicenter, double-blind, randomized, prospective study compared lamotrigine and topiramate as an adjunctive therapy with carbamazepine or phenytoin [Blum *et al.* 2006]. Topiramate again showed a detrimental effect on specific measures of language compared with lamotrigine [Blum *et al.* 2006]. An unblinded observational study explored cognitive functions in 51 patients with focal epilepsy treated with levetiracetam or topiramate as add-on or monotherapy [Gomer *et al.* 2007]. The authors observed detrimental effects of topiramate in attention, short-term memory and verbal fluency.

Neuropsychological studies of patients taking topiramate in monotherapy are very limited, with

a single 12-month follow-up study suggesting some negative effects on memory, information processing and verbal fluency [Baker *et al.* 2011].

Of great clinical relevance are data coming from populations of children with epilepsy. In general terms, clinical studies suggest an acceptable tolerability profile with low dropout rates for cognitive problems [Novotny *et al.* 2010; Pina-Garza *et al.* 2011]. A double-blind, dose-controlled study examined efficacy and tolerability of topiramate monotherapy in newly diagnosed children and adolescents with epilepsy [Glauser *et al.* 2007]. The incidence of treatment-emergent adverse events seems to be clearly dose dependent with concentration/attention difficulties occurring only in a limited number of subjects. A 12-week, open-label study explored cognitive outcomes of 53 children treated with topiramate as monotherapy or add-on therapy, reporting no significant changes in measures of memory [Brandl *et al.* 2010]. A multicenter, randomized, open-label, observer-blinded, parallel-group clinical trial examined cognitive functions and behavioral problems with topiramate compared with carbamazepine in monotherapy for children with benign Rolandic epilepsy [Kang *et al.* 2007]. On a neuropsychological test battery, arithmetic is the only variable with a significant worsening after 28 weeks of treatment. However, looking at children treated at the minimum target dose (from 12.5 to 75 mg according to weight), no significant difference between topiramate and carbamazepine could be observed.

By contrast, data in children with learning difficulties, especially severe ones, suggest poor cognitive and sometimes behavioral tolerability. An observational open study in children with multiple disabilities (aged 1–15), with difficult-to-treat epilepsy, investigated efficacy and tolerability of rapid oral initiation of topiramate (starting dose 1 mg/kg/day) [Kluger *et al.* 2009]. Although no serious adverse events were reported, the rapid dose escalation is associated with a very low tolerability. In fact, 17 out of 19 patients reported adverse events, with behavioral disturbances occurring in 15.8%. An open study examined the behavioral and cognitive effects of topiramate as add-on treatment in children and adolescents with mild to severe mental retardation [Coppola *et al.* 2008]. The authors reported a significant cognitive deterioration in about 70% of patients at 3 months, persisting in about 20% at 12 months.

Data about older patients with epilepsy are mixed. Cognitive complaints are reported in the region of about 10% in a context of dropout rates of about 46% [Groselj *et al.* 2005; Stefan *et al.* 2008]. However, older patients with newly diagnosed epilepsy are often sensitive to their initial drug treatment [Rowan *et al.* 2005]. Moreover, older subjects may be particularly sensitive to the cognitive effects of AEDs and a clearly dose dependency is not always evident [Ramsay *et al.* 2008].

Headache

Data from controlled studies in adult patients with migraine show a prevalence of impaired concentration or memory in around 10% [Silberstein *et al.* 2007, 2009; Lipton *et al.* 2011]. However, an analysis of pooled safety data obtained from over 1500 patients who participated in four randomized, double-blind, placebo-controlled, clinical trials points out that the majority of adverse events are usually mild to moderate in severity and occur during the titration phase rather than during the maintenance period [Adelman *et al.* 2008]. In fact, difficulties with concentration are reported in the region of 1% during the maintenance period at different target doses (50 mg, 100 mg and 200 mg), against prevalence rates of 3%, 6% and 9% during the titration phase. Interestingly, a double-blind, randomized, controlled study of topiramate and amitriptyline, either alone or in combination, reported that the combination of the two drugs is not only more effective than the single treatment but also better tolerated with fewer adverse events [Keskinbora and Aydinli, 2008].

In difficult-to-treat patients, such as chronic migraine or medication overuse headache (MOH), topiramate displays not only a good tolerability but also a positive impact on quality-of-life measures [Diamond *et al.* 2005]. An open-label, prospective study compared topiramate (100 mg) and pregabalin (150 mg) in patients with MOH, showing similarities in terms of efficacy and tolerability [Rizzato *et al.* 2011]. A large randomized, double-blind, placebo-controlled trial of topiramate in chronic migraine demonstrates a significant improvement in migraine-related limitations on daily activities and emotional distress beginning as early as week 4 and continuing up to week 16 after treatment [Dodick *et al.* 2007].

The different pattern of adverse events reported in migraine populations treated with topiramate,

compared with patients with epilepsy, represents another interesting point. A randomized, double-blind, placebo-controlled study of topiramate in chronic migraine reported paraesthesias in 53% of patients treated with topiramate *versus* 6% of attention problems [Diener *et al.* 2007]. An open-label, flexible-dose, clinical trial in patients with episodic migraine showed a premature discontinuation rate (37.6%), mainly due to adverse events (23.6%) [Malessa *et al.* 2010]. Interestingly, all studies suggest that paraesthesias represents the most common and disabling adverse event (sometimes up to 50%), with memory impairment occurring in 10.2% of subjects. Data from noninterventional studies in patients with episodic migraine in a general practice setting have confirmed assumption [Nelles *et al.* 2009, 2010]. A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine shows that patients with migraine have a two- to threefold increased risk of developing paraesthesias [Luykx *et al.* 2009].

As for patients with epilepsy, particular attention needs to be paid to pediatric patients. Randomized, double-blind, placebo-controlled studies of topiramate in children with migraine have reported low rates of somnolence or other cognitive complaints [Winner *et al.* 2005; Lewis *et al.* 2009]. Pandina and colleagues specifically investigated the impact of topiramate 100 mg daily on learning, memory and executive functions and observed a significant decrease in psychomotor reaction times [Pandina *et al.* 2010]. However, a review of five papers on pediatric migraine treated with topiramate (two randomized, controlled trials and three *post hoc* subset analyses of adolescents who were included in three randomized, controlled trials conducted in adults) shows somnolence and concentration problems in rates similar to those reported in adults (around 8%) [Ferraro and Di Trapani, 2008]. In general terms, available data, although limited, seem to suggest that topiramate is well tolerated in pediatric populations of patients with migraine. Adverse events may occur early during treatment and tend to decline over time while a significant improvement in terms of school absenteeism and disability can be seen. Nevertheless, adverse events such as somnolence of subjective concentration problems may be particularly distressing for children and adolescents; therefore, the decision to initiate such a treatment must be carefully considered for the individual patient.

Other neurological disorders

Although topiramate has no indication in other neurological conditions, a number of studies have shown interesting applications, especially in essential tremor and neuropathic pain.

A 24-week, multicenter, double-blind, placebo-controlled, parallel-design study examined the efficacy and safety of topiramate (400 mg) monotherapy in patients with essential tremor reporting concentration and memory difficulties in only 3% of patients [Ondo *et al.* 2006]. An analysis of three randomized, double-blind, placebo-controlled, crossover trials of topiramate in patients with essential tremor describes cognitive complaints in around 10% of patients [Connor *et al.* 2008].

A 10-week, randomized, double-blind, placebo-controlled study of topiramate in patients with low back pain showed very good tolerability, with a significant improvement in terms of mood and quality of life [Muehlbacher *et al.* 2006].

Discussion

Treatment-emergent cognitive adverse events have a multifactorial origin with a number of variables implicated (Table 1). Furthermore, one of the major limitations in reviews of the literature in this area is that neuropsychological tests used in the studies are not uniform [Mula and Trimble 2009]. In fact, many different test batteries have been used, and the administration of tests and reporting of test results differ across all presented studies, which makes it impossible to formulate a qualified comparison of the results. Neuropsychological tests must also meet the criteria of reliability, validity and sensitivity to change. Further, they should have been standardized in the epilepsy population. The results of studies adopting neuropsychological tests that have not been standardized, with respect to epilepsy, may expose clinicians and patients alike to unreliable information regarding specific AEDs.

In general terms, all presented data suggest that up to 10% of patients treated with topiramate may complain of cognitive problems. However, it is important to state that cognitive complaints do not necessarily reflect a negative effect on cognitive functions. A nonrandomized, open-label, parallel-group study comparing the long-term cognitive effects of topiramate and levetiracetam

Table 1. Mechanisms of action of topiramate (TPM) in comparison to selected old and new anticonvulsants.

	CBZ	VPA	TPM	LTG
Blockade of voltage-dependent sodium channels	+	+	+	+
Blockade of calcium channels (channel type)	–	+ (T)	+ (L)	+ (L,N,P)
Antagonism of glutamatergic receptors (receptor type)	(+) (NMDA)	(+) (NMDA)	+ (AMPA/K)	(+) (NMDA)
Potentialiation of GABA transmission	(+)	+	+	–
AMPA/K, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate; CBZ, carbamazepine; GABA, γ -aminobutyric acid; LTG, lamotrigine; NMDA, N-Methyl-D-aspartate; VPA, valproic acid.				

as add-on treatment in patients with intractable epilepsy showed that memory does not represent a concern despite the high incidence of memory complaints and that topiramate may not necessarily have absolute deteriorating effects even in subjects with mesial temporal lobe epilepsy and baseline poor cognitive performance [Huang *et al.* 2008]. Nevertheless, topiramate is perceived by patients (and as a consequence by clinicians) to have a worse tolerability profile than other AEDs [Arif *et al.* 2010] and this is further confirmed by retention rate studies [Marson *et al.* 2007a, 2007b]. Subjective preference for CNS drugs is quite an unexplored topic with very limited data. A double-blind, randomized, crossover study tried to examine the subjective preference for either topiramate or lamotrigine in healthy volunteers [Werz *et al.* 2006]. A large majority of subjects (70%) were shown to prefer lamotrigine and such preference was consistent with a better performance on a number of neuropsychological and behavioral measures, mood state in particular. In this regard, an established finding is that the subjective perception of treatment-emergent cognitive adverse events may be related more to the mood state rather than to the objective performance [Kanner *et al.* 2003; Marino *et al.* 2009]. A number of studies point out that topiramate may have a negative impact on mood [Mula *et al.* 2003a; Mula *et al.* 2009] and such an effect may consequently have an influence on the subjective perception of tolerability, increasing rates of cognitive complaints [Kanner *et al.* 2003; Mula *et al.* 2006].

The contribution of the mechanisms of action of topiramate to the overall cognitive tolerability is difficult to establish (see Table 2 for a comparison with other AEDs). As previously discussed, neuroimaging studies in healthy subjects have demonstrated a significant GABAergic potentiation with topiramate [Kuzniecky *et al.* 1998, 2002], but neurophysiologic data are not along the same

line [Mecarelli *et al.* 2001; Wang *et al.* 2003; Smith *et al.* 2006; Salinsky *et al.* 2007]. What is becoming evident is that topiramate preferably affects frontal lobe functions [Kockelmann *et al.* 2003; Jansen *et al.* 2006; Gomer *et al.* 2007] and such preference is particularly reflected by the effect on verbal fluency. Topiramate is a sulfamate and specific language toxicity has been reported with other compounds containing a sulfa moiety [Ojemann *et al.* 2001], such as zonisamide [Wilensky *et al.* 1985], sulthiame [Dodrill, 1975] or sulfasalazine [Hill *et al.* 1994]. Therefore, it is tempting to speculate that there may be a specific sensitivity of the Broca's area to sulfa-containing compounds [Ojemann *et al.* 2001]. Further studies in this area are needed.

Another relevant issue relates to the timing of the adverse events. All studies agree that cognitive problems with topiramate can be identified early during treatment (i.e. within 6 weeks) and emerge in a dose-dependent fashion [Loring *et al.* 2011]. This is reported with almost all CNS drugs, and after a short period (i.e. a few days or weeks), normalization usually occurs. This phenomenon, also known as tolerance or habituation, needs to be carefully considered to avoid an overestimation of the negative effects of a drug on cognition. As pointed out by Aldenkamp, in clinical assessment, we should conclude that a drug has significant 'cognitive side effects', only if these persist during long-term treatment [Aldenkamp *et al.* 2003].

Finally, the possible association with drug serum levels needs to be discussed. Data on topiramate are more than scanty. A prospective study in poorly controlled patients with epilepsy examines the relationship between adverse events and serum topiramate concentrations [Froscher *et al.* 2005]. The authors suggest a maintenance level below 4 $\mu\text{g/ml}$ to avoid psychomotor slowing or abnormal thinking.

Table 2. Mechanisms for cognitive adverse effects of antiepileptic drugs.

Direct (drug related)
Mechanisms of action
Drug class
GABAergic potentiation
Pharmacokinetics
Toxic plasma levels
Pharmaceutical formulations (i.e. extended release)
Interactions
Pharmacodynamics
Polytherapy
Interactions
Indirect (drug unrelated)
Disorder related
Nature of the brain disorder and pathophysiology
Presence of brain pathology
Age at onset and duration of the disorder
Presence of psychiatric comorbidities
Patient related
Age
Gender
Baseline cognitive performance
GABA, γ -aminobutyric acid.

Conclusions

All presented data suggest that up to 10% of patients treated with topiramate, either for epilepsy or migraine, may complain of cognitive problems but such prevalence may be significantly reduced using topiramate in monotherapy and adopting individualized doses and titration schedules. Although the magnitude of such treatment-emergent adverse events is generally mild to moderate, the subjective perception needs to be considered. In this regard, it has to be taken into account that, in some selected cases, topiramate may negatively impact on mood. In fact, apart from language problems, data are not conclusive. Comparisons with new AEDs are limited to levetiracetam and lamotrigine, in both cases generally disfavoring topiramate, while data regarding first-generation AEDs show clear differences mainly for verbal fluency. The case of topiramate clearly points out that a careful use of the drug is always mandatory to maximize compliance and not to deprive patients of an effective treatment.

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Conflict of interest statement

In the past, the author has received travel grants or consultancy fees from various pharmaceutical companies, including Pfizer, UCB-Pharma, Janssen, that are involved in the manufacture of antiepileptic drugs.

References

- Adelman, J., Freitag, F., Lainez, M., Shi, Y., Ascher, S., Mao, L. *et al.* (2008) Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. *Pain Med* 9: 175–185.
- Aldenkamp, A. (2000) Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 54: 271–272.
- Aldenkamp, A., Baker, G., Mulder, O., Chadwick, D., Cooper, P., Doelman, J. *et al.* (2000) A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia* 41: 1167–1178.
- Aldenkamp, A., De Krom, M. and Reijls, R. (2003) Newer antiepileptic drugs and cognitive issues. *Epilepsia* 44(Suppl. 4): 21–29.

- Arif, H., Buchsbaum, R., Pierro, J., Whalen, M., Sims, J., Resor, S., Jr, *et al.* (2010) Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. *Arch Neurol* 67: 408–415.
- Arroyo, S., Dodson, W., Privitera, M., Glauser, T., Naritoku, D., Dlugos, D. *et al.* (2005) Randomized dose-controlled study of topiramate as first-line therapy in epilepsy. *Acta Neurol Scand* 112: 214–222.
- Backonja, M. (2002) Use of anticonvulsants for treatment of neuropathic pain. *Neurology* 59: S14–S17.
- Baker, G., Taylor, J. and Aldenkamp, A. (2011) Newly diagnosed epilepsy: cognitive outcome after 12 months. *Epilepsia* 52: 1084–1091.
- Ben-Menachem, E., Henriksen, O., Dam, M., Mikkelsen, M., Schmidt, D., Reid, S. *et al.* (1996) Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 37: 539–543.
- Biton, V., Montouris, G., Ritter, F., Riviello, J., Reife, R., Lim, P. *et al.* (1999) A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group. *Neurology* 52: 1330–1337.
- Blum, D., Meador, K., Biton, V., Fakhoury, T., Shneker, B., Chung, S. *et al.* (2006) Cognitive effects of lamotrigine compared with topiramate in patients with epilepsy. *Neurology* 67: 400–406.
- Brandl, U., Kurlmann, G., Neubauer, B., Rettig, K., Schauble, B. and Schreiner, A. (2010) Seizure and cognitive outcomes in children and adolescents with epilepsy treated with topiramate. *Neuropediatrics* 41: 113–120.
- Burton, L. and Harden, C. (1997) Effect of topiramate on attention. *Epilepsy Res* 27: 29–32.
- Cappa, S., Ortelli, P., Garibotto, V. and Zamboni, M. (2007) Reversible nonfluent aphasia and left frontal hypoperfusion during topiramate treatment. *Epilepsy Behav* 10: 192–194.
- Connor, G., Edwards, K. and Tarsy, D. (2008) Topiramate in essential tremor: findings from double-blind, placebo-controlled, crossover trials. *Clin Neuropharmacol* 31: 97–103.
- Coppola, G., Verrotti, A., Resicato, G., Ferrarelli, S., Auricchio, G., Operto, F. *et al.* (2008) Topiramate in children and adolescents with epilepsy and mental retardation: a prospective study on behavior and cognitive effects. *Epilepsy Behav* 12: 253–256.
- De Ciantis, A., Muti, M., Piccolini, C., Principi, M., Di Renzo, A., De Ciantis, R. *et al.* (2008) A functional MRI study of language disturbances in subjects with migraine headache during treatment with topiramate. *Neurol Sci* 29(Suppl. 1): S141–S143.
- Delorenzo, R., Sombati, S. and Coulter, D. (2000) Effects of topiramate on sustained repetitive firing and spontaneous recurrent seizure discharges in cultured hippocampal neurons. *Epilepsia* 41(Suppl. 1): S40–S44.
- Diamond, M., Dahlof, C., Papadopoulos, G., Neto, W. and Wu, S. (2005) Topiramate improves health-related quality of life when used to prevent migraine. *Headache* 45: 1023–1030.
- Diener, H., Bussone, G., Van Oene, J., Lahaye, M., Schwalen, S. and Goadsby, P. (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 27: 814–823.
- Dodick, D., Silberstein, S., Saper, J., Freitag, F., Cady, R., Rapoport, A. *et al.* (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. *Headache* 47: 1398–1408.
- Dodrill, C. (1975) Effects of sulthiame upon intellectual, neuropsychological, and social functioning abilities among adult epileptics: comparison with diphenylhydantoin. *Epilepsia* 16: 617–625.
- Ferraro, D. and Di Trapani, G. (2008) Topiramate in the prevention of pediatric migraine: literature review. *J Headache Pain* 9: 147–150.
- Froscher, W., Schier, K., Hoffmann, M., Meyer, A., May, T., Rambeck, B. *et al.* (2005) Topiramate: a prospective study on the relationship between concentration, dosage and adverse events in epileptic patients on combination therapy. *Epileptic Disord* 7: 237–248.
- Gibbs, J., 3rd, Sombati, S., Delorenzo, R. and Coulter, D. (2000) Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia* 41(Suppl. 1): S10–S16.
- Glauser, T., Dlugos, D., Dodson, W., Grinspan, A., Wang, S. and Wu, S. (2007) Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. *J Child Neurol* 22: 693–699.
- Gomer, B., Wagner, K., Frings, L., Saar, J., Carius, A., Harle, M. *et al.* (2007) The influence of antiepileptic drugs on cognition: a comparison of levetiracetam with topiramate. *Epilepsy Behav* 10: 486–494.
- Groselj, J., Guerrini, R., Van Oene, J., Lahaye, M., Schreiner, A. and Schwalen, S. (2005) Experience with topiramate monotherapy in elderly patients with recent-onset epilepsy. *Acta Neurol Scand* 112: 144–150.
- Gross-Tsur, V. and Shalev, R. (2004) Reversible language regression as an adverse effect of topiramate treatment in children. *Neurology* 62: 299–300.

- Hill, M., Gordon, C., Situnayake, R. and Heath, D. (1994) Sulfasalazine induced seizures and dysphasia. *J Rheumatol* 21: 748–749.
- Huang, C., Pai, M. and Tsai, J. (2008) Comparative cognitive effects of levetiracetam and topiramate in intractable epilepsy. *Psychiatry Clin Neurosci* 62: 548–553.
- Jansen, J., Aldenkamp, A., Marian Majoie, H., Reijs, R., De Krom, M., Hofman, P. *et al.* (2006) Functional MRI reveals declined prefrontal cortex activation in patients with epilepsy on topiramate therapy. *Epilepsy Behav* 9: 181–185.
- Jette, N., Hemming, K., Hutton, J. and Marson, A. (2008) Topiramate add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev*: CD001417.
- Johannessen Landmark, C. (2008) Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 22: 27–47.
- Kang, H., Eun, B., Wu Lee, C., Ku Moon, H., Kim, J., Wook Kim, D. *et al.* (2007) The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign Rolandic epilepsy. *Epilepsia* 48: 1716–1723.
- Kanner, A., Wu, J., Faught, E., Tatum, W., Fix, A. and French, J. (2003) A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy Behav* 4: 548–552.
- Kennedy, G. and Lhatoo, S. (2008) CNS adverse events associated with antiepileptic drugs. *CNS Drugs* 22: 739–760.
- Keskinbora, K. and Aydinli, I. (2008) A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. *Clin Neurol Neurosurg* 110: 979–984.
- Kluger, G., Schauble, B., Rettig, K., Schreiner, A. and Holthausen, H. (2009) Effectiveness of low dose of topiramate following rapid titration in multiply handicapped children and difficult-to-treat epilepsy. *Neuropediatrics* 40: 61–65.
- Kockelmann, E., Elger, C. and Helmstaedter, C. (2003) Significant improvement in frontal lobe associated neuropsychological functions after withdrawal of topiramate in epilepsy patients. *Epilepsy Res* 54: 171–178.
- Krakow, K., Lengler, U., Rettig, K., Schreiner, A. and Schauble, B. (2007) Topiramate in add-on therapy: results from an open-label, observational study. *Seizure* 16: 593–600.
- Kuzniecky, R., Hetherington, H., Ho, S., Pan, J., Martin, R., Gilliam, F. *et al.* (1998) Topiramate increases cerebral GABA in healthy humans. *Neurology* 51: 627–629.
- Kuzniecky, R., Ho, S., Pan, J., Martin, R., Gilliam, F., Faught, E. *et al.* (2002) Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. *Neurology* 58: 368–372.
- Lee, H., Jung, D., Suh, C., Kwon, S. and Park, S. (2006) Cognitive effects of low-dose topiramate monotherapy in epilepsy patients: a 1-year follow-up. *Epilepsy Behav* 8: 736–741.
- Leniger, T., Thone, J. and Wiemann, M. (2004) Topiramate modulates Ph of hippocampal Ca³ neurons by combined effects on carbonic anhydrase and Cl[–]/HCO₃[–] exchange. *Br J Pharmacol* 142: 831–842.
- Lewis, D., Winner, P., Saper, J., Ness, S., Polverejan, E., Wang, S. *et al.* (2009) Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. *Pediatrics* 123: 924–934.
- Lhatoo, S., Sander, J. and Wong, I. (2000) Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 54: 270–271; author reply 271–272.
- Lipton, R., Silberstein, S., Dodick, D., Cady, R., Freitag, F., Mathew, N. *et al.* (2011) Topiramate intervention to prevent transformation of episodic migraine: the Topiramate Intrepid Study. *Cephalalgia* 31: 18–30.
- Loring, D., Williamson, D., Meador, K., Wiegand, F. and Hulihan, J. (2011) Topiramate dose effects on cognition: a randomized double-blind study. *Neurology* 76: 131–137.
- Luykx, J., Mason, M., Ferrari, M. and Carpay, J. (2009) Are migraineurs at increased risk of adverse drug responses? A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine. *Clin Pharmacol Ther* 85: 283–288.
- Magis, D. and Schoenen, J. (2011) Treatment of migraine: update on new therapies. *Curr Opin Neurol* 24: 203–210.
- Malessa, R., Gendolla, A., Steinberg, B., Schmitt, L., Bornhoevd, K., Djelani, M. *et al.* (2010) Prevention of episodic migraine with topiramate: a prospective 24-week, open-label, flexible-dose clinical trial with optional 24 weeks follow-up in a community setting. *Curr Med Res Opin* 26: 1119–1129.
- Marino, S., Meador, K., Loring, D., Okun, M., Fernandez, H., Fessler, A. *et al.* (2009) Subjective perception of cognition is related to mood and not performance. *Epilepsy Behav* 14: 459–464.

- Marson, A., Al-Kharusi, A., Alwaidh, M., Appleton, R., Baker, G., Chadwick, D. *et al.* (2007a) The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 369: 1000–1015.
- Marson, A., Al-Kharusi, A., Alwaidh, M., Appleton, R., Baker, G., Chadwick, D. *et al.* (2007b) The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 369: 1016–1026.
- Martin, R., Kuzniecky, R., Ho, S., Hetherington, H., Pan, J., Sinclair, K. *et al.* (1999) Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 52: 321–327.
- McLean, M., Bukhari, A. and Wamil, A. (2000) Effects of topiramate on sodium-dependent action-potential firing by mouse spinal cord neurons in cell culture. *Epilepsia* 41(Suppl. 1): S21–S24.
- Meador, K., Loring, D., Hulihan, J., Kamin, M. and Karim, R. (2003) Differential cognitive and behavioral effects of topiramate and valproate. *Neurology* 60: 1483–1488.
- Meador, K., Loring, D., Vahle, V., Ray, P., Werz, M., Fessler, A. *et al.* (2005) Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. *Neurology* 64: 2108–2114.
- Mecarelli, O., Piacenti, A., Pulitano, P., Vicenzini, E., Rizzo, C., Rinalduzzi, S. *et al.* (2001) Clinical and electroencephalographic effects of topiramate in patients with epilepsy and healthy volunteers. *Clin Neuropharmacol* 24: 284–289.
- Muehlbacher, M., Nickel, M., Kettler, C., Tritt, K., Lahmann, C., Leiberich, P. *et al.* (2006) Topiramate in treatment of patients with chronic low back pain: a randomized, double-blind, placebo-controlled study. *Clin J Pain* 22: 526–531.
- Mula, M., Hesdorffer, D., Trimble, M. and Sander, J. (2009) The role of titration schedule of topiramate for the development of depression in patients with epilepsy. *Epilepsia* 50: 1072–1076.
- Mula, M., Pini, S. and Cassano, G. (2007) The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. *J Clin Psychopharmacol* 27: 263–272.
- Mula, M., Sander, J. and Trimble, M. (2006) The role of hippocampal sclerosis in antiepileptic drug-related depression in patients with epilepsy: a study on levetiracetam. *Seizure* 15: 405–408.
- Mula, M. and Trimble, M. (2006) Neuropharmacological aspects of cognitive neurorehabilitation in epilepsy. *Behav Neurol* 17: 69–75.
- Mula, M. and Trimble, M. (2009) Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. *CNS Drugs* 23: 121–137.
- Mula, M., Trimble, M., Lhatoo, S. and Sander, J. (2003a) Topiramate and psychiatric adverse events in patients with epilepsy. *Epilepsia* 44: 659–663.
- Mula, M., Trimble, M., Thompson, P. and Sander, J. (2003b) Topiramate and word-finding difficulties in patients with epilepsy. *Neurology* 60: 1104–1107.
- Nelles, G., Delbruck, A., Schulze, L., Kademmann, B., Bornhoevd, K., Schafer, S. *et al.* (2009) Topiramate for migraine prevention in a naturalistic setting: results from an open label, flexible dose study. *Headache* 49: 1454–1465.
- Nelles, G., Schmitt, L., Humbert, T., Becker, V., Sandow, P., Bornhoevd, K. *et al.* (2010) Prevention of episodic migraines with topiramate: results from a non-interventional study in a general practice setting. *J Headache Pain* 11: 33–44.
- Novotny, E., Renfro, B., Yardi, N., Nordli, D., Ness, S., Wang, S. *et al.* (2010) Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures. *Neurology* 74: 714–720.
- Ojemann, L., Ojemann, G., Dodrill, C., Crawford, C., Holmes, M. and Dudley, D. (2001) Language disturbances as side effects of topiramate and zonisamide therapy. *Epilepsy Behav* 2: 579–584.
- Ondo, W., Jankovic, J., Connor, G., Pahwa, R., Elble, R., Stacy, M. *et al.* (2006) Topiramate in essential tremor: a double-blind, placebo-controlled trial. *Neurology* 66: 672–677.
- Pandina, G., Ness, S., Polverejan, E., Yuen, E., Eerdekens, M., Bilder, R. *et al.* (2010) Cognitive effects of topiramate in migraine patients aged 12 through 17 years. *Pediatr Neurol* 42: 187–195.
- Pina-Garza, J., Schwarzman, L., Wiegand, F. and Hulihan, J. (2011) A pilot study of topiramate in childhood absence epilepsy. *Acta Neurol Scand* 123: 54–59.
- Privitera, M., Fincham, R., Penry, J., Reife, R., Kramer, L., Pledger, G. *et al.* (1996) Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. Topiramate YE Study Group. *Neurology* 46: 1678–1683.
- Ramsay, E., Faught, E., Krumholz, A., Naritoku, D., Privitera, M., Schwarzman, L. *et al.* (2010) Efficacy, tolerability, and safety of rapid initiation of topiramate versus phenytoin in patients with new-onset epilepsy: a randomized double-blind clinical trial. *Epilepsia* 51: 1970–1977.

- Ramsay, R., Uthman, B., Pryor, F., Rowan, A., Bainbridge, J., Spitz, M. *et al.* (2008) Topiramate in older patients with partial-onset seizures: a pilot double-blind, dose-comparison study. *Epilepsia* 49: 1180–1185.
- Rizzato, B., Leone, G., Misaggi, G., Zivi, I. and Diomedi, M. (2011) Efficacy and tolerability of pregabalin versus topiramate in the prophylaxis of chronic daily headache with analgesic overuse: an open-label prospective study. *Clin Neuropharmacol* 34: 74–78.
- Rowan, A., Ramsay, R., Collins, J., Pryor, F., Boardman, K., Uthman, B. *et al.* (2005) New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 64: 1868–1873.
- Sachdeo, R., Glauser, T., Ritter, F., Reife, R., Lim, P. and Pledger, G. (1999) A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate Y1 Study Group. *Neurology* 52: 1882–1887.
- Salinsky, M., Storzach, D., Oken, B. and Spencer, D. (2007) Topiramate effects on the EEG and alertness in healthy volunteers: a different profile of antiepileptic drug neurotoxicity. *Epilepsy Behav* 10: 463–469.
- Shank, R., Gardocki, J., Streeter, A. and Maryanoff, B. (2000) An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia* 41(Suppl. 1): S3–S9.
- Shank, R., Gardocki, J., Vaught, J., Davis, C., Schupsky, J., Raffa, R. *et al.* (1994) Topiramate: preclinical evaluation of structurally novel anticonvulsant. *Epilepsia* 35: 450–460.
- Silberstein, S., Lipton, R., Dodick, D., Freitag, F., Mathew, N., Brandes, J. *et al.* (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache* 49: 1153–1162.
- Silberstein, S., Lipton, R., Dodick, D., Freitag, F., Ramadan, N., Mathew, N. *et al.* (2007) Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 47: 170–180.
- Smith, M., Gevins, A., McEvoy, L., Meador, K., Ray, P. and Gilliam, F. (2006) Distinct cognitive neurophysiologic profiles for lamotrigine and topiramate. *Epilepsia* 47: 695–703.
- Spina, E. and Perugi, G. (2004) Antiepileptic drugs: indications other than epilepsy. *Epileptic Disord* 6: 57–75.
- Stefan, H., Hubbertz, L., Peglau, I., Berrouschot, J., Kasper, B., Schreiner, A. *et al.* (2008) Epilepsy outcomes in elderly treated with topiramate. *Acta Neurol Scand* 118: 164–174.
- Stewart, S. (2005) The effects of benzodiazepines on cognition. *J Clin Psychiatry* 66(Suppl. 2): 9–13.
- Thompson, P., Baxendale, S., Duncan, J. and Sander, J. (2000) Effects of topiramate on cognitive function. *J Neurol Neurosurg Psychiatry* 69: 636–641.
- Tremont-Lukats, I., Megeff, C. and Backonja, M. (2000) Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs* 60: 1029–1052.
- Wang, W., Li, J. and Wu, X. (2003) Quantitative EEG effects of topiramate. *Clin Electroencephalogr* 34: 87–92.
- Werz, M., Schoenberg, M., Meador, K., Loring, D., Ray, P., Kaul-Gupta, R. *et al.* (2006) Subjective preference for lamotrigine or topiramate in healthy volunteers: relationship to cognitive and behavioral functioning. *Epilepsy Behav* 8: 181–191.
- White, H. (2003) Mechanism of action of newer anticonvulsants. *J Clin Psychiatry* 64(Suppl. 8): 5–8.
- White, H., Brown, S., Woodhead, J., Skeen, G. and Wolf, H. (1997) Topiramate enhances gaba-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. *Epilepsy Res* 28: 167–179.
- Wilensky, A., Friel, P., Ojemann, L., Dodrill, C., McCormick, K. and Levy, R. (1985) Zonisamide in epilepsy: a pilot study. *Epilepsia* 26: 212–220.
- Winner, P., Pearlman, E., Linder, S., Jordan, D., Fisher, A. and Hulihan, J. (2005) Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. *Headache* 45: 1304–1312.
- Zhang, L., Huang, J., Zhuang, J., Huang, L. and Zhao, Z. (2011) Topiramate as an adjunctive treatment for refractory partial epilepsy in the elderly. *J Int Med Res* 39: 408–415.
- Zhang, X., Velumian, A., Jones, O. and Carlen, P. (2000) Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. *Epilepsia* 41(Suppl. 1): S52–S60.