The Role of Topiramate in the Management of Cocaine Addiction: A Possible Therapeutic Option

Antonio Siniscalchi1,*, Antonello Bonci2, Nicola Biagio Mercuri3, Domenico Pirritano4, Aida Squillace5, Giovambattista De Sarro5 and Luca Gallelli5

1Department of Neurology, “Annunziata” Hospital, Cosenza, Italy; 2Intramural research program, National Institute on Drug Abuse, NIH, Baltimore, 21224, USA; 3IRCCS-Fondazione S. Lucia and Department of Neurophysiopathology University “Tor Vergata”; Rome, Italy; 4Diagnostic Center Igea SRL, Catanzaro; 5Chair of Pharmacology, Department of Health Science, School of Medicine, University of Catanzaro, Clinical Pharmacology and Pharmacovigilance Unit, Mater Domini University Hospital, Catanzaro, Italy.

Abstract: Topiramate (TPM) is an antiepileptic drug able to play a role in both neurological and psychiatric disorders. TPM facilitates gamma-aminobutyric acid (GABA) transmission and inhibits glutamatergic transmission (i.e. AMPA/kainate receptors).

Several studies reported that the modulation of GABAergic and glutamatergic synaptic transmission may reduce cocaine reinforcement. Therefore, TPM could be used in the management of cocaine dependence.

Keywords: Cocaine dependence, gamma-aminobutyric acid neurotransmission, glutamatergic neurotransmission, topiramate.

INTRODUCTION

Topiramate (TPM; 2,3,4,5-bis-O-(1-methylethylidene)-b-D-fructopyranosulfamate) is an O-alkyl sulfamate derivative of the naturally occurring monosaccharide D-fructose that showed efficacy in epilepsy [1, 2]. Recently, TPM has been reported to be effective also in drug resistance partial epilepsy [2, 3], refractory partial and secondary generalized seizures [2, 4], primary generalized tonic/clonic seizures [2, 4] and tonic/atonic seizures associated with Lennox- Gastaut syndrome [5] and may also improve myoclonic movements [3, 6]. Although in elderly patients with epilepsy TPM does not represent the first choice, it may be used in cognitively healthy elderly patients, for both high safety and low drug-drug interactions respect to other antiepileptic drugs [1, 7]. Preliminary data suggested that, in addition to its use in epilepsy, TPM may have therapeutic effects also in other neurological disorders and in psychiatric conditions, sinecother studies are needed to confirm these preliminary findings [3]. The efficacy of TPM in bipolar and schizoaffective disorders, bulimia, neuropathic pain syndrome, migraine and cluster headache prophylaxis has been reported [7-11]. Moreover, recently reviewing the literature about the use of TPM in hyperkinetic movement disorders, we described that the effectiveness of this drug is still inadequate and conclusive evidence has not been published [3]. Finally, TPM seems to play a role in the treatment of cocaine addiction [12, 13], gambling relapse [14, 15], compulsive eating and sexual behavior [13, 16, 17]. However clinical efficacy of topiramate is associated with regular cognitive-behavioural therapy, suggesting that a combined effort can be used to improve psychiatric symptoms [18].

TPM facilitating gamma-aminobutyric acid (GABA) transmission and inhibiting glutamatergic transmission via AMPA/kainate receptors [1, 3, 7] decreases the dopamine release in the cortico-mesolimbic system, which is involved in mechanisms of reward and reinforcement [19, 20]. Secondly, TPM blocks AMPA-type glutamate receptors in the nucleus paragigantocellularis through the inhibition of noradrenergic neurons in the locus coeruleus, the activation of which seems to be involved in the development of autonomic symptoms of withdrawal [19]. Finally, TPM is a carbonic anhydrase inhibitor; this effect is involved in its anticonvulsant effects, and could be important in the management of withdrawal [3, 19].

This review aims to delineate efficacy and safety of TPM in the treatment of cocaine addiction.

METHODS

PubMed, Embase, Cochrane library and reference lists were searched for articles published until July 5, 2015 using the keywords: topiramate and mechanism of actions, topiramate and cocaine, topiramate and substance abuse. Secondary searches included articles cited in sources identified by the previous search. We enclosed randomized control trials (RCTs), open trials, case series, and case reports.

ROLE OF EXCITATORY AND INHIBITORY NEUROTRANSMISSION IN COCAINE DEPENDENCE

Experimental studies documented that substances able to modify the effects of excitatory amino acids (EAA s), such as
glutamate, or facilitate the actions of GABA neurons in several areas of the brain may reduce cocaine reinforcement [13, 21]. Bonci and colleagues [22] showed that long-time cocaine self-administration decreased ex vivo intrinsic excitability of deep-layer pyramidal neurons in the prelimbic cortex, which was significantly more pronounced in compulsive drug-seeking. Additionally, inhibition of corticofugal glutaminergic pathways or activation of GABA pathways may decrease the extracellular release of dopamine [23, 24], an acutely neurotransmitter in cocaine reinforcement pathway. Stuber et al. [25], reviewing literature, documented in dopaminergic neurons of ventral tegmental area as well as in medium spiny neurons of nucleus accumbens, exposed to passive or active cocaine, an increase in excitatory synaptic strength.

Take together these data suggest that drugs able to restore the GABA/glutamate balance could reduce cocaine use. In this light, TPM, modulating the excitatory and inhibitory neurotransmission, could be a good candidate in the treatment of cocaine dependence (Fig. 1) [23, 25]. In fact, Muriach et al., [26] documented in cocaine treated rats, a decreased activity of NFkappaB in the frontal cortex, and of GSH concentration and glutathione peroxidase activity in the hippocampus, with an impairment of memory. Suggesting a role of oxidative and nitrosative stress in the alterations induced by cocaine. In contrast, the same authors documented that TPM was able to prevents these effects suggesting a neuroprotective effects of TPM in cocaine injury.

Moreover, in a rat model, Echeverry-Alzate et al., [27] evaluating the effects of TPM, on operant ethanol self-administration with the co-administration of cocaine documented that topiramate prevents the cocaine-induced increase in the response to ethanol in a dose-dependent manner without motor impairments and these effects were explained by the suppression of the expression of the effects of cocaine rather than the blockade of the acquisition of the effects of cocaine.

**CLINICAL USE OF TOPIRAMATE IN COCAINE DEPENDENCE**

To date there are few studies reporting the effect of TPM in cocaine dependence. In particular, in 13-week double-blind RCT, Kampman et al. [28], enrolled 40 treatment-seeking cocaine dependent subjects, age from 18 to 60 years old, without other substance dependence except nicotine. TPM was administered at 25 mg/day, with an increase of 25 mg/week up to maximum dosage of 200 mg/day at week 8. All subjects received a cognitive behavioral relapse prevention therapy, twice a week. At the end of the study, 82% of subjects completed the trial, the authors documented that TPM treatment induced a decrease in cocaine use and in cocaine craving respect to placebo group, without the development of serious side effects.

In an open-label, uncontrolled trial of 28 cocaine dependent males (age 18–55 years), Reis et al. [29], evaluated the effects of a 12-week treatment with TPM (25–300 mg/day, mean dose 127 mg/day). TPM induced a significant decrease in craving intensity and duration in 25% of the peoples without the development of side effects. However, in this as well as in the previous studies the sample size is very little, so it is not possible to calculate the power of the study and the results are difficult to interpret.

In a randomized, double-blind, placebo-controlled trial performed in 24 cocaine-dependent peoples, Johnson et al. [13], documented that TPM pretreatment (100 mg twice a day) reduced cocaine-related craving and monetary value in

---

**Fig. (1).** Proposed sites of action of Topiramate on the treatment of cocaine dependence. NA= nucleus accumbes, GABA= γ-aminobutyric acid, TPM= topiramate, VTA=ventral tegmental area.
presence of high-dose cocaine treatment; in contrast during a treatment with low-dose of cocaine, TPM increased the monetary value, euphoria, and stimulant effects. The authors suggested that these bidirectional effects, in presence of low and high cocaine dose, could be related with the mood-stabilizing effect of TPM [30], since a mechanism of sensitization can’t be rule out.

In agreement in a double-blind, randomized, placebo-controlled, 12-week trial of 142 cocaine-dependent adults, it has been reported that TPM(from 50 mg/day to 300 mg/day) + weekly cognitive-behavioral treatment, increase the cocaine nonuse days (period weeks 6 to 12), respect to placebo treatment [31].

In a double-blind, placebo-controlled trial, Kampman et al. [32], after a high number of participants who did not complete treatment, evaluated in 170 cocaine and alcohol users, the ability of TPM (300 mg/day) + cognitive behavioural psychotherapy respect to placebo + cognitive behavioural psychotherapy, to induce cocaine and alcohol abstinence in patients addicted to both drugs. After 13 weeks (end of the study), authors recorded that TPM reduces both cocaine and alcohol abuse respect to placebo, but it was not able to reduce cocaine-craving and to prevent relapse.

However, in contrast to these positive effects on cocaine dependence, recently Umbricht et al. [33], in a double-blind controlled clinical trial performed in 171 cocaine dependent methadone maintenance patients, reported that the TPM treatment (final dosage of 300 mg/day) is not able to increase cocaine abstinence.

In an open-label, randomized feasibility trial, Nuijten et al. reported a safety of use of TPM (200 mg/die) in 74 crack-cocaine dependent patients, since they documented a limited efficacy of this drug probably related to low acceptance of the treatment [34].

CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH

TPM is used on-label in patients with epilepsy or migraine. Main TPM targets include enhancement of GABAergic inhibition and reduction of AMPA receptors activity [3] that are involved in neuronal excitability control. Therefore TPM stabilizes neurons and decreases mesocorticolimbic dopamine release and could represent a potential candidate inco-cocaine-dependence treatment. In fact, attenuating the midbrain dopamine release, TPM could reduce the reinforcing and rewarding activities of drug abuse, and because it is a non-addictive agent, could be a more desirable alternative to other agents with abuse liability. Moreover, TPM may be used in several psychiatric disorders (e.g. obsessive compulsive disorder, trichotillomania, bulimia nervosa, binge-eating disorder, and pathologic gambling) [19]. These psychiatric diseases show some similarities with drug-dependence, i.e. repetitive behaviors persisting minimal self-control despite significant negative consequences. TPM may be effective in these clinical conditions because it is able to reduce the reinforcing properties of these compulsive behaviors.

In the future, TPM could represent a therapeutic option in the management of cocaine dependence.

However, to data there are only few clinical studies regarding its role in cocaine users. Data from these clinical studies showed that the efficacy of TPM in cocaine treatment are often limited by total number of subjects that was relatively small and by number of participants who did not complete treatment. Despite its weaknesses the results of these trial suggest that TPM may be beneficial for the treatment of comorbid cocaine (i.e. reducing anxiolytic and euphoric effects).

A recent Cochrane review of 20 studies with 2068 participants, regarding the efficacy and safety of anticonvulsant drugs for cocaine dependence, reported no conclusive significant evidence for use of TPM in the management of cocaine addiction [35]. Probably due to the number of participants who did not complete treatment (557 partecipants, RR 0.92, 95% CI 0.73 to 1.16).

Moreover Minozzi et al., [35] in this paper did not reveal any significant difference in both use of cocaine (210 participants, RR 1.19, 95% CI 0.48 to 2.98) and in development of side effects (261 partecipants RR 2.42, 95% CI 0.27 to 21.87) in peoples treated with TPM vs placebo.

So, research supporting the effectiveness of TPM in cocaine addiction is still inadequate and conclusive evidences have not been published. Thus, prospective clinical trials are needed to confirm TPM efficacy in cocaine dependence treatment, particularly in the treatment of comorbid cocaine. (i.e. reducing anxiolytic and euphoric effects), and to better define the proportion of responders in larger groups of patients, including analysis of genetic variants associated with TPM response.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Siniscalchi, A.; Gallelli, L.; Russo, E.; De Sarro, G. A review on antiepileptic drugs-dependent fatigue: pathophysiological mechanisms and incidence. Eur. J. Pharmacol., 2013, 718(1-3), 10-16. http://dx.doi.org/10.1016/j.ejphar.2013.09.013
[2] Labate, A.; Siniscalchi, A.; Mummoli, L.; Aguglia, U.; Quattrone, A.; Gambardella, A. Topiramate and temporal lobe epilepsy: an open-label study. Epileptic Disorders. Inter. Epilepsy J. Videotape, 2012, 14(2), 163-166.
[3] Siniscalchi, A.; Gallelli, L.; Girofie, C.; De Sarro, G. What's the role of topiramate in the management of patients with hyperkinetic movement disorders? Pharmacol. Rep., 2012, 64(1), 24-30.
[4] Privitera, M.D. Topiramate: a new antiepileptic drug. Ann. Pharmacother., 1997, 31(10), 1164-1173.
[5] Sachdeo, R.C.; Glaser, T.A.; Ritter, F.; Reife, R.; Lim, P.; Pledger, G. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate, Y.L. Study Group. Neurology, 1999, 52(9), 1882-1887. http://dx.doi.org/10.1212/WNL.52.9.1882
[6] Siniscalchi, A.; Mancuso, F.; Russo, E.; Ibbadu, G.F.; De Sarro, G. Spinal myoclonus responsive to topiramate. Movement disorders. Ann. Labate, A.; Siniscalchi, A.; Mumoli, L.; Aguglia, U.; Quattrone, A.; Gambardella, A. Topiramate and temporal lobe epilepsy: an open-label study. Epileptic Disorders. Inter. Epilepsy J. Videotape, 2012, 14(2), 163-166.
[7] Siniscalchi, A.; Gallelli, L.; De Sarro, G.; Malferri, G.; Santangelo, E. Antiepileptic drugs for central post-stroke pain management. Pharmacol. Res., 2012, 65(2), 171-175.
plasticity induced by psychostimulants: the past, present, and therapeutic future. *Neuron*, 2010, 67(1), 11-24. http://dx.doi.org/10.1016/j.neuron.2010.06.004

Dewey, S.L.; Chaurasia, C.S.; Chen, C.E.; Volkow, N.D.; Clarkson, F.A.; Porter, S.P. GAABergic attenuation of cocaine-induced dopamine release and locomotor activity. *Synapse*, 1997, 25(4), 393-398. http://dx.doi.org/10.1002/syn.19970425-4:393::AID-SYN11-3.0.CO;2-W

Suber, G.D.; Hopf, F.W.; Tye, K.M.; Chen, B.T.; Bonci, A. Neuroplastic alterations in the limbic system following cocaine or alcohol exposure. *Curr. Top. Behave. Neurosci.*, 2010, 3, 3-27. http://dx.doi.org/10.1007/978-540-2009.23

Muriach, M.; Pedrajas, R.L.; Barcia, J.M.; Villarroyo, M.V.S.; Almansa, I.; Romero, F.J. Cocaine causes memory and learning impairments in rats: involvement of nuclear factor kappa B and oxidative stress, and prevention by topiramate. *J. Neurochem.*, 2010, 114(3), 675-684. http://dx.doi.org/10.1111/j.1471-4159.2010.06794.x

Alzate, V.E.; Gine, E.; Buhler, K.M.; Conde, J.C.; Oloros, M.; Gorrini, M.A. Effects of topiramate on ethanol-cocaine interactions and DNA methyltransferase gene expression in the rat prefrontal cortex. *Br. J. Pharmacol.*, 2014, 171(12), 3023-3036. http://dx.doi.org/10.1111/bph.12636

Kampman, K.M.; Pettinati, H.; Lynch, K.G.; Daickis, C.; Sparkman, T.; Weigley, C. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend.*, 2004, 75(3), 233-240. http://dx.doi.org/10.1016/j.drugalcdep.2004.03.008

Reis, A.D.; Castro, L.A.; Faria, R.; Laranjeira, R. Craving decrease with topiramate in outpatient treatment for cocaine dependence: an open label trial. *Rev. Bras. Psiquiatr.*, 2008, 30(2), 132-135. http://dx.doi.org/10.1590/S1516-444620080005000012

Correll, C.U.; Sheridan, E.M.; DeBello, M.P. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord.*, 2010, 12(2), 116-141. http://dx.doi.org/10.1111/j.1399-5618.2010.00798.x

Johnson, B.A.; Daoud, N.A.; Wang, X.Q.; Penberthy, J.K.; Javors, M.A.; Sereviatine, C. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry*, 2013, 70(12), 1338-1346. http://dx.doi.org/10.1001/jamapsychiatry.2013.2295

Kampman, K.M.; Pettinati, H.M.; Lynch, K.G.; Spratt, K.; Wierzbicki, M.R.; O'Brien, C.P. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug Alcohol Depend.*, 2013, 133(1), 94-99. http://dx.doi.org/10.1016/j.drugalcdep.2013.05.026

Umbricht, A.; DeFulio, A.; Winstanley, E.L.; Tompkins, D.A.; Peirce, J.; Mintzer, M.Z. Topiramate for cocaine dependence during methadone maintenance treatment: a randomized controlled trial. *Drug Alcohol Depend.*, 2014, 140, 92-100. controlled trial. Drug and alcohol dependence. 2014; 140: 92-100. Epub 2014/05/13. http://dx.doi.org/10.1016/j.drugalcdep.2014.03.033

Nuijten, M.; Blanken, P.; van den Brink, W.; Hendriks, V. Treatment of crack-cocaine dependence with topiramate: a randomized controlled feasibility trial in The Netherlands. *Drug Alcohol Depend.*, 2014, 138, 177-184. http://dx.doi.org/10.1016/j.drugalcdep.2014.02.024

Minozzi, S.; Cinquini, M.; Amato, L.; Davoli, M.; Farrell, M.F.; Pan, P.P. Anticonvulsants for cocaine dependence. *Cochrane Database Syst. Rev.*, 2015, 4, CD006754. http://dx.doi.org/10.1002/14651858.cd006754.pub3