Journal of Alcoholism & Drug Dependence

Andal et al., J Alcohol Drug Depend 2018, 6:3
DOI: 10.4172/2329-6488.1000314

Research Article Open Access

Topiramate for the Treatment of Methamphetamine Addiction: A Meta-Analysis

Vida Margarette de Vera Andal*, Nikolai Gil Diwa Reyes and Carissa Paz Dioquino Maligaso

University of the Philippines-Philippine General Hospital, Manila, Philippines

Corresponding author: Vida Margarette de Vera Andal, University of the Philippines-Philippine General Hospital Manila, Philippines, Tel: 639175339292; E-mail: vdandal@gmail.com

Received date: June 24, 2018; **Accepted date:** July 19, 2018; **Published date:** July 25, 2018

Abstract

Methamphetamine (MAP) is one of the most abused recreational drug worldwide and its abuse creates a socio-economic burden for developed and developing countries alike. It is hypothesized to act on various receptors to facilitate the release of catecholamines such as dopamine to provide a euphoric effect. As of date, there are no pharmacologic interventions approved yet for the treatment of MAP addiction. Topiramate is an anti-epileptic drug that works on multiple pathways to modulate other catecholamines such as gamma-aminobutyric acid (GABA) to decrease the reinforcing effects of stimulants like MAP. Two randomized controlled trials done by Elkashef et al. and Razeai et al. investigated the effectiveness of topiramate in the treatment of MAP addiction. To the authors knowledge, this is the first meta-analysis on topiramate for methamphetamine addiction. This study aims to evaluate the effectiveness of topiramate in the treatment of methamphetamine addiction among diagnoses methamphetamine dependents. Randomized controlled trials were searched through PubMed and other databases. Fixed variant analysis was applied to compare dichotomous outcomes. Two randomized controlled trials comparing maximum topiramate dose tolerated and placebo were included. The primary outcome was negative MAP use using urine test on the 10th week of study. There was no significant difference between the topiramate and placebo groups (RR 1.03, 95% CI [0.85,1.26], p=0.73). There is insufficient evidence to show that topiramate significantly promotes MAP abstinence on MAP abusers compared to placebo. Due to paucity of controlled studies, firm recommendation for its routine use for MAP addiction cannot be established.

Keywords: Topiramate; Methamphetamine addiction; Methamphetamine; Addiction

Introduction

Methaphetamine or MAP is a synthetic substance that causes the release and inhibits the metabolism and reuptake of neurotransmitters such as dopamine, norepinephrine and serotonin [1]. It produces different cardiovascular and neurologic effects depending on its dose. At low doses, it increases the blood pressure and causes palpitations, chest pains, sweating, shortness of breath and tremors. It creates a feeling of euphoria and increases alertness, concentration and physical performance. However, at high doses, it can cause seizures, nausea, vomiting, anxiety, agitation, paranoia and hallucinations. Worse outcomes include arrhythmia and cerebral haemorrhage, to name a few. Long term use of methamphetamine results in dependence, malnutrition, poor cognitive functioning, sleep problems and psychotic symptoms.

It is marketed as Desoxyn and Adderall and is used for the treatment of attention deficit hyperactive disorder (ADHD) and obesity [1].

However, methamphetamine has garnered its reputation for being a drug of abuse. The United Nations Office for Drug and Crime (UNODC) estimates that in 2014, an estimated 35.65 million or 0.8% of the world's population aged 15-64 is using methamphetamine. The highest prevalence was recorded in Asia, particularly East and Southeast Asia. Methamphetamine abuse creates a substantial socio-economic burden worldwide [2].

After ingestion, inhalation or intravenous injection, methamphetamine enters the bloodstream rapidly. Because it is lipophilic, it crosses the blood-brain barrier and reaches the brain parenchyma. Despite extensive animal studies, there is still no definite evidence as to which part of the brain and which neurotransmitters are responsible for the development of addiction to it. However, there are neuroimaging studies and autopsies that suggest increased release of dopamine from the striatum during methamphetamine intake. It promotes dopamine and other catecholamines' release inside vesicles in the presynaptic neuron by (1) blocking vesicular monoamine transporter 2 (VMAT2), (2) by decreasing the expression of the dopamine transporter (DAT) at the cell surface, and (3) by inhibiting the activity and the expression of tyrosine hydroxylase. These result in increasing dopamine in the cytoplasm and neuromuscular junction. The abundance of dopamine gives the feeling of euphoria to methamphetamine users. However, prolonged use of methamphetamine leads to rapid and massive dopamine release therefore easily depleting the body's dopamine stores. In addition, there is also down-regulation of dopamine D2-rceptors at uptake sites [3]. This explains the feeling of being unwell by methamphetamine dependents at times of withdrawal and low dopamine levels, hence the need for more and more stimulation.

Pharmacologic interventions aim to modulate other non-dopamine reward systems in the brain such as gamma-aminobutyric acid (GABA), serotonin and opioid pathways. These agents decrease the amount of catecholamines available and therefore reduce the stimulating effect of methamphetamine. One such agent is topiramate.

Topiramate has been investigated in the treatment of methamphetamine dependence. It acts by blocking voltage-gated sodium channels, enhancement of GABA transmission, blocking glutamate receptors and inhibiting carbonic anhydrase. These mechanisms help antagonize the surges in dopamine in response to methamphetamine by affecting the non-dopamine reward pathways [3].

As of date, there are no approved medications for the treatment of methamphetamine addiction in the United States of America, Australia, and the Philippines [4,5]. There is a paucity of research studying pharmacologic interventions that may help conventional treatment towards methamphetamine addiction such as cognitive behavioural therapy and contingency management intervention.

This paper primarily aims to evaluate the published evidence on the effectiveness of topiramate in treating methamphetamine addiction in known methamphetamine dependents.

Method

A comprehensive literature review was conducted to search for randomized-controlled clinical trials that presented data on the effectiveness of topiramate as treatment for methamphetamine addiction. The authors were able to identify two combinable randomized controlled clinical trials. These are studies by Rezaei et al. [6] ("Topiramate for the management of methamphetamine dependence: a pilot randomized double-blind, placebo-controlled trial") and by Elkashef et al. [7] ("Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial") (Figure 1).

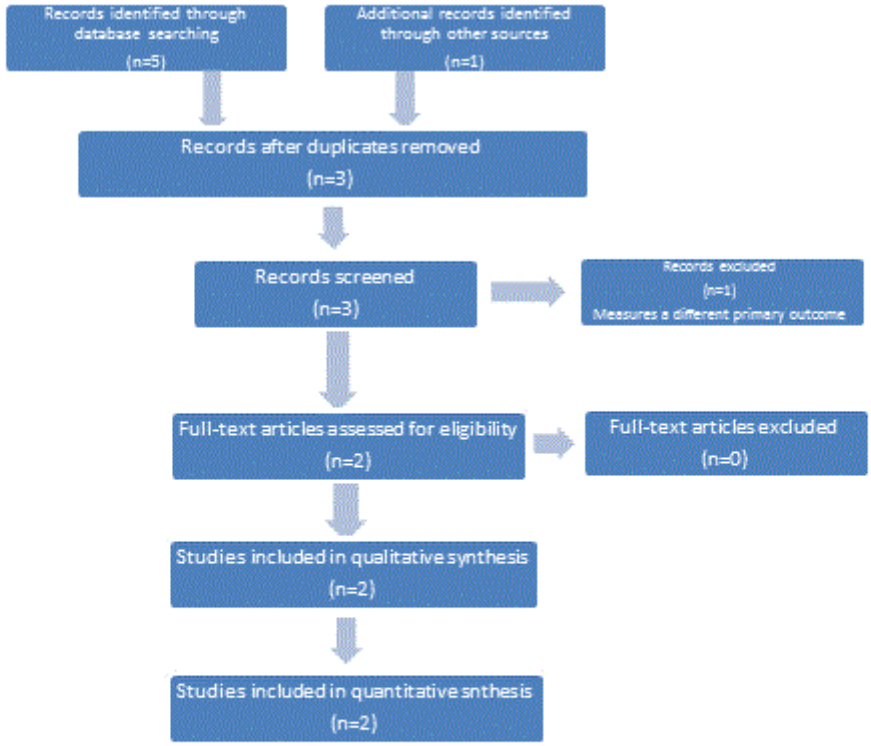

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram illustrating the process of selection of studies.

Results

Assessment of risk of bias

Both studies included individuals above 18 years of age who were diagnosed with methamphetamine dependence based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). The studies did not explicitly specify the technique but they reported randomization into treatment and control groups for eligible subjects. Allocation concealment was also not described in both studies. This makes selection bias unclear for both studies.

Elkashef et al. evaluated their data using intention-to-treat analysis. Of the 140 subjects that were randomized, a total of 37 subjects were lost to follow up but a total of 140 outcomes were analyzed. On the other hand, Razeai et al. analyzed only 57 outcomes out of the 62 subjects who underwent randomization. The percentage of randomized subjects that completed the study was almost the same for both groups. Figure 2 summarizes the risk of bias for both studies.

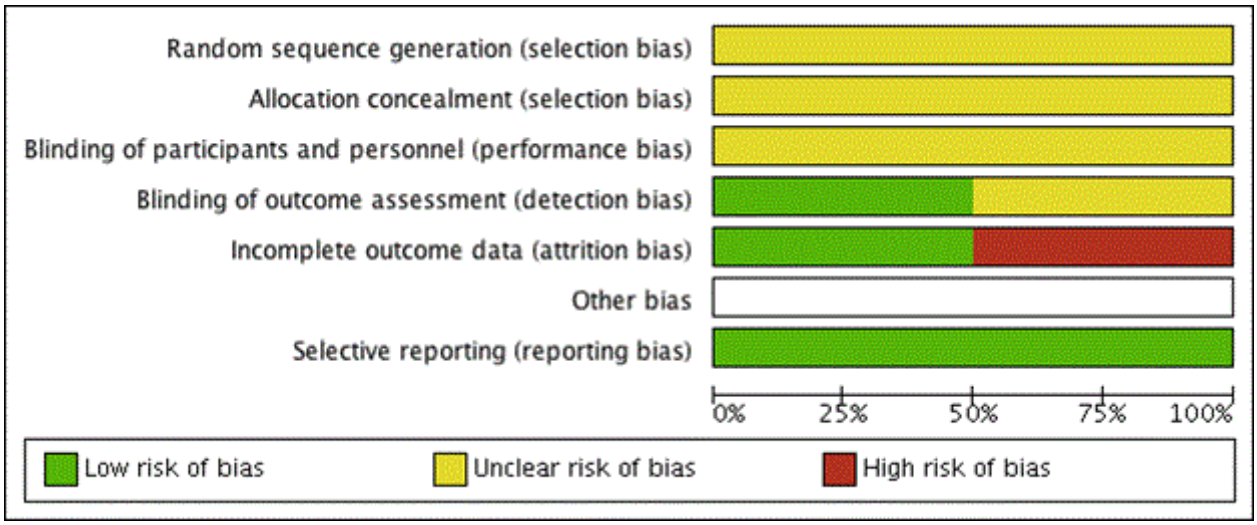

Figure 2: Cochrane collaboration tool for assessing risk of bias.

Effects of intervention

The effectiveness of topiramate as treatment for methamphetamine addiction was measured through urine MAP studies at pre-determined times after receiving topiramate and placebo doses. Topiramate dosing was not fixed as these were adjusted based on patient tolerance but a minimum of 50 mg per day was given to experimental subjects. Using fixed effects model, the pooled analysis showed that there is no significant difference in the risk ratio of negative urine MAP study between topiramate and placebo among patients diagnosed to have MAP addiction (RR 1.03, 95% CI [0.85,1.26], p=0.73). No significant heterogeneity was found between the two studies (I2=6%, p=9.30) (Figure 3).

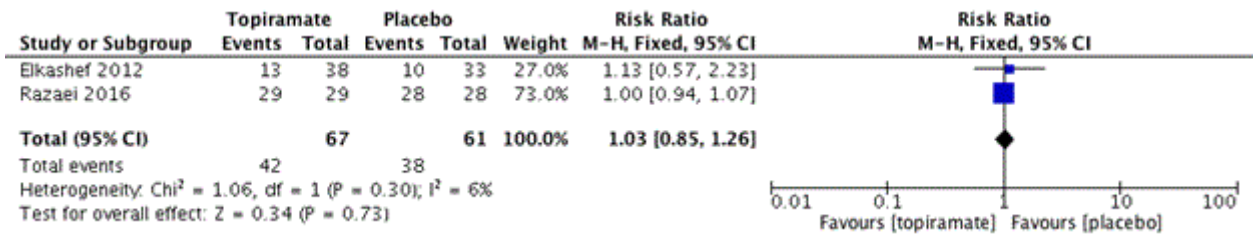

Figure 3: Percentage of subjects with negative methamphetamine use week 10.

Both studies also compared the effect of topiramate on reducing MAP craving over time through the Brief Substance Craving Scale (BSCS). This tool measures cravings using three domains: intensity, frequency and duration. The study by Elkashef et al. showed a strong relationship between the baseline BSCS score and the subsequent weekly mean BSCS scores for both populations. Razaei et al. also showed a decline in the weekly mean BSCS score for both populations but without statistical significance between the two groups.

Both studies also measured depression during the study weeks but used different tools. Elkashef et al. used the Montgomery-Asberg Depression Rating Score while the study by Razaei et al. used the Beck Depression Rating Scale. The studies showed no significant treatment effect on depression scores between topiramate and placebo groups.

Adverse effects

A total of 1,121 adverse events were observed during the trial of Elkashef et al. 53% of which occurred in the topiramate group while 47% occurred in the placebo group. The most common adverse effect observed was headache as it was experience by 70% of all subjects (48% in topiramate and 42% in placebo). Gastrointestinal symptoms such as nausea and vomiting were experienced by 57% of the topiramate group and 38% of the placebo group (p=0.04).

Discussion

This study showed that topiramate doses of 50 mg to 200 mg daily have insufficient evidence to demonstrate a difference compared to placebo in the treatment of methamphetamine addiction. Both groups showed a steady decline in the number of negative urine MAP-weeks after 10 weeks of treatment.

Both studies included subjects who were not abstinent at baseline but they were not stratified as to the chronicity of MAP use and intensity of consumption. Though studies show that there are significant changes in the grey matter of the cingulate cortex, subgenual cortex and paralimbic areas of MAP abusers, it is still unclear how and how fast these changes happen through time [8]. It is possible that chronic MAP abuse may lead to more cortical and subcortical changes in the brain making it more challenging to treat chronic MAP addicts compared to acute MAP addicts.

Moreover, certain characteristics predispose drug dependents to better treatment outcomes such as chronicity of abuse, route of administration (specifically injecting), and shorter abstinence at pre-treatment period, MAP use during treatment period, presence of depression and Asian ethnicity [9].

Both treatment groups also underwent cognitive-behavioral therapy (CBT) during the treatment period. A meta-analysis of 53 controlled trials by Magill et al. showed that CBT produced a small but statistically significant treatment effect (g=0.154, p<0.005) for adults diagnosed with alcohol or illicit drug use [10]. Therefore, CBT may have an unmeasured treatment effect on both topiramate and placebo groups.

The two studies measured their primary outcome using urine MAP assays for both topiramate and placebo groups during the treatment period. This technique is an easy, non-invasive, accurate, relatively cheap and quick way of measuring the presence and levels of MAP in the subject's body. The study by Elkashef et al. used gas chromatography/mass spectrometry which is a good confirmatory test for urine MAP levels while the study by Rezaei used urine immunoassay, a technique prone to false-negative and false-positive results. Urine assays are subject to cross-reactivity with other substances which may be structurally-related or not. Labetalol, buprorion, chlorpromazine, ofloxacin, dimethylamylamine, phenylpropanolamine, ranitidine, phenylephrine, fluoxetine and even metformin are some of the drugs that may produce a false-positive result [11,12]. Both studies included in this meta-analysis did not specify investigation on the concomitant use of the aforementioned drugs in the subjects under each study group during randomization and treatment weeks. Moreover, urine assays can yield false-negative results depending on the amount of drugs taken, body fat level and other metabolic factors [11].

Measures to prevent tampering of urine samples were also not mentioned in both studies. To achieve false-negative results, subjects may dilute their urine through excessive water intake or by ingestion of substances that may interfere with testing such as table salt, vinegar, bleach, etc. Subjects could also have submitted clean urine samples that are not theirs [11]. Specimen validity testing on urine specimens through measurement of creatinine, specific gravity, pH and nitrates were not done. Other measures that could have minimized tampering include protocols that would require subjects to leave their personal belongings in exam rooms or to show pocket contents prior to urine collection [13].

Moreover, there is no sufficient evidence that topiramate actually improves abstinence as there is no statistically significant difference between topiramate and placebo groups. Though studies showed high validity for self-report of MAP use among patients seeking treatment for MAP addiction [14,15], these studies do recognize that the knowledge of the participants that they are being studied may have affected the internal validity of results. In addition, the mere participation in a clinical trial may have promoted a sense of wellness in the subjects.

The study duration of 10 weeks may also be insufficient to observe treatment effect among subjects in the experimental group. Studies on treatment addiction usually measure treatment effect after 90 days of intervention [16].

Finally, caution in interpreting this pooled data should also be practiced due to paucity of studies included in this meta-analysis. This underscores the need for more randomized controlled trials to measure the efficacy of topiramate in the treatment of methamphetamine addiction.

Conclusion

As of this writing, there is still no pharmacological therapy with established efficacy in the treatment of MAP addiction. Cognitive-behavioral therapy, contingency management, motivational interviewing or a combination of these remain the interventions showing consistent results in promoting abstinence and self-efficacy to quit [17]. Topiramate shows no significant effect compared to placebo in the treatment of MAP addiction and should be used judiciously.

Future studies investigating the efficacy of topiramate for MAP addiction should involve larger sample sizes and should attempt to stratify the subjects based on duration, frequency and intensity of MAP use as these may have effects on the outcomes. Interventions and results should be properly concealed from subjects, investigators and data analyzers to avoid biases in reporting and evaluation of outcomes. Currently, there are no alternative scales to measure craving and abstinence other than self-reports so these may still pose subject reporting bias on future trials. Confirmatory tests like gas chromatography and mass spectrometry should be employed in future studies to avoid cross-reactivity and measurement bias in results.

References

1. Kish SJ (2008) Pharmacologic mechanisms of crystal meth. Cmaj 178: 1679-1682.
2. United Nations Office for Drug and Crime World Drug Report 2016 (2016) Vienna.
3. Karila L, Weinstein A, Aubin HJ, Benyamina A, Reynaud M, et al. (2010) Pharmacological approaches to methamphetamine dependence: A focused review. British J Clin Pharmacol 69: 578-592.

4. Methamphetamine (2017) Retrieved from https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/df_methamphetamine_february2017_1.pdf
5. Lee N, Johns L, Jenkinson R, Johnston J, Connolly K, et al. (2007) Methamphetamine dependence and treatment. Clinical Treatment Guidelines for Alcohol and Drug Clinicians 14: 131.
6. Rezaei F, Ghaderi E, Mardani R, Hamidi S, Hassandazeh K (2016) Topiramate for the management of methamphetamine dependence: a pilot randomized, double-blind, placebo-controlled trial. Fundam Clin Pharmacol 30: 282-289.
7. Elkashef A, Kahn R, Yu E, Iturriaga E, Li S, et al. (2012) Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. Addiction 107: 1297-1306.
8. Thompson PM (2004) Structural Abnormalities in the Brains of Human Subjects Who Use Methamphetamine. Journal of Neuroscience 24: 6028-6036.
9. Hillhouse MP, Marinelli-Casey P, Gonzales R, Ang A, Rawson RA, et al. (2007) Predicting in-treatment performance and post-treatment outcomes in methamphetamine users. Addiction 102: 84-95.
10. Magill M, Ray LA (2009) Cognitive-Behavioral Treatment With Adult Alcohol and Illicit Drug Users: A Meta-Analysis of Randomized Controlled Trials. Journal of Studies on Alcohol and Drugs 70: 516-527.
11. Riahi-Zanjani B (2014) False positive and false negative results in urine drug screening tests: Tampering methods and specimen integrity tests. Pharmacologyonline 1: 102-108.
12. Saitman A, Park HD, Fitzgerald RL (2014) False-positive interferences of common urine drug screen immunoassays: A review. Journal of Analytical Toxicology 38: 387-396.
13. Report 1 of the Council on Science and Public Health (I-16) (2016) Retrieved from https://www.ama-assn.org/sites/default/files/media-browser/2016-interim-csaph-report-1.pdf
14. Napper LE, Fisher DG, EJM, Wood MM (2010) The Reliability and Validity of Drug Users' Self Reports of Amphetamine Use Among Primarily Heroin and Cocaine Users. Addict Behav 35: 1-11.
15. Solbergsdottir E, Bjornsson G, Gudmundsson LS, Tyrfingsson T, Kristinsson J (2004) Validity of self-reports and drug use among young people seeking treatment for substance abuse or dependence. Journal of Addictive Diseases 23: 29-38.
16. Volkow ND (2012) Principles of Drug Addiction Treatment: A Research-Based Guide. National Institute on Drug Abuse pp: 1-43.
17. Lee NK, Rawson RA (2008) A systematic review of cognitive and/or behavioural therapies for methamphetamine dependence. Drug Alcohol Rev 27: 309-317.