

Evaluating the efficacy of topiramate in the reduction of drinking behaviours amongst alcohol dependent individuals

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ABSTRACT

Alcohol dependence is a complex and multi-faceted problem, with alcohol misuse costing the NHS an estimated £3.5 billion annually. Appropriate pharmacological treatment, alongside behavioural therapy, is essential to the proper management of dependent individuals.

NICE recommended pharmacotherapies are still relatively under prescribed, despite their relatively low number-needed-to-treat (NNT), perhaps owing to mixed evidence across the literature. Topiramate (currently licensed for migraine prophylaxis and epilepsy) has been proposed as one drug with potential efficacy in reducing drinking behaviours. Hence, the aim of this paper is to evaluate the efficacy of topiramate in promoting and maintaining abstinence in alcohol dependence, through a review of the current literature.

Seven papers are reported after a systematic database search (PubMed, Medline, Embase, Web of Science); statistical manipulation of results has been performed to present findings in a common format. Results were consistent and showed the effectiveness of topiramate in all outcome measures evaluated: heavy drinking days (HDDs), plasma gamma-glutamyl transferase (GGT) concentration and abstinence rate. These differences over placebo reached statistical significance in all seven studies.

This paper supports the efficacy of topiramate in treating alcohol dependence. There are several recommendations for further research, including comparisons to currently licensed alcohol dependence medications (namely naltrexone) and the pharmacogenetic influence of a GRIK1 polymorphism on the efficacy of topiramate. Further research into the tolerability of topiramate is required, although evaluation of adverse events within this paper has been positive.

INTRODUCTION

Alcohol dependence demonstrates a significant challenge to public health. In 2020, there were 8,974 alcohol-specific deaths registered across the United Kingdom (UK), with a significantly greater indirect mortality rate assumed owing to co-morbidities arising from excessive consumption.¹ Acute alcohol intoxication also precipitates a number of social risks, encompassing unintentional injury, motor vehicle accidents, suicide, and interpersonal violence – all of which are under-represented in the statistics.²

An estimated 602,391 individuals in England are classified as dependent drinkers, with only 18% receiving active pharmacological treatment (down from 29% in 2017).^{1,3} The National Institute for Health and Care Excellence (NICE) define dependent drinking as “characterised by craving, tolerance, a preoccupation with alcohol and continued drinking in spite of harmful consequences”.⁴

Despite the magnitude of this problem, uncertainty remains as to the exact pathophysiology underlying alcohol use disorders – although the consensus within medical literature points towards the involvement of the dopaminergic

mesolimbic reward system.⁵ This pathway runs from the ventral tegmental area (VTA) of the midbrain, terminating in the nucleus accumbens (NAcc) and limbic regions. Upon exposure to a ‘rewarding’ stimulus, dopamine neurons, projecting from the VTA to the NAcc, are activated – ultimately increasing dopaminergic transmission in the latter.⁵ One such rewarding stimulus is ethanol.

Ethanol (a neurotropic agent capable of crossing the blood-brain barrier) acts to increase extracellular dopamine levels in the NAcc through two primary mechanisms: stimulation of interneuron activity in the VTA, and simultaneous potentiation of dopamine receptors (particularly D₁ and D₂ subtypes, with preferential activation in a dose-dependent fashion).⁶ Studies have yielded results supporting the involvement of this mechanism in alcohol-reinforcing behaviours; Samson *et al* and Czachowski *et al* demonstrated that injection of raclopride (a specific D₂/D₃ receptor antagonist) into the NAcc of rats significantly reduced the frequency of ethanol-seeking behaviour.^{7,8} Prolonged exposure to elevated dopamine is suggested to propound neuroplastic changes in the mesolimbic system, altering reward-seeking behaviours.⁷ However, whilst the dopaminergic mesolimbic system constitutes a significant component of the alcohol reinforcement response, alcohol dependence cannot be exclusively attributed to it. Instances have been noted in which lesions of the mesolimbic system fail to abolish ethanol-reinforcement behaviour, suggesting the involvement of a more complex neuroadaptive process.⁹

Ethanol has also been found to increase GABA (gamma-aminobutyric acid) activity in the brain through either stimulation of presynaptic neurons to produce more GABA, or via postsynaptic modulation of the GABA_A receptor.¹⁰ Chronic ethanol exposure therefore prolongs the increase in GABA transmission in the central nucleus of the amygdala, engendering alterations to emotional regulation in states of withdrawal and abstinence.¹⁰

In a similar fashion, ethanol reduces activity of glutamate, the main excitatory CNS neurotransmitter, decreasing extracellular levels in the striatum. Consequently, acute administration of ethanol inhibits glutamate-mediated neurotransmission in the amygdala – an effect that is enhanced in chronic alcohol consumption. It is hypothesised that upregulated functionality of N-methyl-D-aspartate (NMDA) receptors, in response to ethanol-induced glutamate release over prolonged periods, increases sensitivity of receptors to excitatory glutamate signals.¹¹

This is the perhaps the most clinically significant mechanism and is targeted by acamprosate, the most prescribed pharmacotherapy for alcohol dependence. This drug accounts for 87% of prescriptions for alcohol dependence, modulating NMDA receptor activity to reduce cravings once abstinence has already been achieved.¹² However, the evidence supporting the efficacy of acamprosate in detoxification of alcohol-dependent individuals is mixed – despite first-line recommendation in NICE guidelines.^{4,13} This differs from the alternative first-line therapy, naltrexone, which is more

effective at initial moderation of heavy drinking behaviours through reduction of cravings but less effective at maintaining long-term abstinence.¹²

Topiramate, a fructose-substituted pyranose derivative, was initially licensed for use as an anti-epileptic monotherapy – before subsequently being approved for the purpose of migraine prophylaxis.¹⁴ The pharmacodynamic basis to these applications is multifaceted; primarily, it antagonises voltage-gated sodium ion channels which prevents sustained CNS depolarisation during seizures. Incidentally, topiramate also mediates GABA-mediated neurotransmission through enhancement of ionotropic GABA_A receptor activity – as well as inhibiting glutamate activity at NMDA receptors.¹⁵ The combined effect is a decrease in neuronal excitability. Topiramate is also a weak carbonic anhydrase inhibitor; whilst this is unlikely to contribute to its anticonvulsive properties, it has been proposed that the induction of a mildly acidotic state in the brain downregulates NMDA receptors – further inhibiting excitatory synaptic transmission.¹⁶

Hypothetically, these effects on neurotransmission could indicate topiramate for use in decreasing alcohol reinforcement, hence maintenance of abstinence. The reasoning behind this is that topiramate administration would decrease dopamine activity in the mesolimbic system, through the two fundamental processes described – GABA potentiation and glutamate inhibition.¹⁷ Hence, ethanol consumption would produce a deficient response in the mesolimbic reward system, decreasing positive reinforcement of drinking behaviours.

The aim of this paper is to evaluate the efficacy of topiramate as a means of maintaining abstinence in alcohol-dependent individuals (despite not yet being approved for this application by NICE). A range of doses will be reviewed to assess for clinically observable effects.

METHODS

The methodology of this paper comprised searching databases for randomised controlled trials (RCTs) evaluating the efficacy of topiramate in the treatment of alcohol dependence. As no quantitative measure for alcohol dependence is universally defined, trials were only considered if they recorded results in at least one of three identified forms: heavy drinking days, abstinence rate and plasma gamma-glutamyl transferase (GGT) concentration. Of the seven relevant RCTs identified, only two presented plasma GGT reduction as a log GGT ratio. As such, I performed statistical analyses on the results of the remaining trials to present their data in this established format ($\log \text{GGT ratio} = (\log[\text{end-point conc}^{\text{d}}] - \log[\text{baseline conc}^{\text{d}}]) / \log[\text{baseline conc}^{\text{d}}]$). Likewise, data on heavy drinking days (HDDs) was standardised to the format of percentage heavy drinking day (PHDD) reduction, to aid interpretation.

RESULTS

This paper reviewed seven RCTs directly comparing the efficacy of topiramate against placebo, when applied to promotion and maintenance of abstinence amongst alcohol dependent individuals (Table 1 presents a comparative summary of these results).

B A Johnson et al – 2003:

This was the earliest RCT investigating the efficacy of topiramate for the treatment of alcohol dependence – a

12-week double-blind trial of 150 individuals diagnosed with alcohol dependence, in accordance with DSM-IV criteria.¹⁸ Equally sized groups, with statistically insignificant demographic differences, were counselled on adherence to a treatment regimen of topiramate (dosage escalating from 25-300mg/day, reaching maximum dose by week eight) or indistinguishable placebo capsules. The topiramate group reported a 60% reduction in PHDDs, compared to a 33% reduction in the placebo group ($P=0.0003$). Likewise, self-reported alcohol cravings were significantly lower in the topiramate group ($P<0.0001$). This was corroborated by a 0.11 decrease in log plasma GGT ratio, significantly greater than the 0.04 decrease observed in the placebo group ($P=0.0046$). Moreover, this study demonstrated the greatest completion rate of any examined (95.6%). Perhaps this was due to the implementation of brief behavioural compliance-enhancement treatment (BBCET) – a psychosocial intervention which emphasises that medication compliance is imperative to reducing alcohol consumption. This feature further increases the internal validity of the trial.

H R Kranzler et al – 2014:

Kranzler et al produced the first study investigating the influence of a single nucleotide polymorphism (SNP) in GRIK1, in the moderation of topiramate's effect in alcohol dependent individuals.²⁰ Following the 12-week treatment period, with equal completion rates in the placebo ($n=71$) and topiramate ($n=67$) groups at 84.9%, findings were significant in corroborating the conclusions of the previous studies. 35.8% fewer HDDs were reported in the topiramate group (receiving a 25-200mg/day titration), in contrast to a 16.9% reduction in the placebo group ($P<0.001$). Correspondingly, topiramate produced a mean plasma GGT concentration decrease of 19.8 versus a statistically insignificant reduction of 8.2 in the placebo group. The study also determined a significant moderating effect of the rs2832407 SNP on the efficacy of topiramate, in terms of reducing heavy drinking days. This study was unique within the literature as it was supported by a 6-month follow-up, however the difference between topiramate and placebo in terms of PHDDs reverted to statistical insignificance by the 3-month mark.²¹ This may indicate that longer treatment periods are required to sustain changes in drinking behaviours, hence this is a hypothesis recommended for future research.

H R Kranzler et al – 2021:

In attempt to reproduce the results of the previous study, Kranzler et al conducted a larger, prospective pharmacogenetic trial re-testing the same hypothesis ($n=170$).²² This RCT also utilised the most expansive age range assessed (18-70). Whilst conclusions regarding the superiority of topiramate to placebo were maintained – measuring PHDD reduction ($P=0.01$) and median GGT decrease ($P=0.04$) – the pharmacogenetic effect of the rs2832407 SNP polymorphism could not be replicated. This conjecture is substantiated by a lack of evidence in similar pharmacogenetic RCTs throughout the literature, suggesting that the results of the initial trial were somewhat insubstantial.^{23, 24, 25} Nevertheless, whilst statistically insignificant, the SNP did increase the efficacy of topiramate as hypothesised – indicating this as a promising area for future research through higher-powered trials.

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R R Wetherill et al – 2021:

Utilising the smallest number of participants thus far (n=29), this RCT only reached a completion rate of 69% at a maximum dosage of 200mg/day topiramate.²⁶ As such, the conclusion of a statistically greater reduction in PHDDs in the topiramate group at P=0.04 (49.8% and 28.6%, respectively) must be considered in context.

B A Johnson et al – 2007:

The largest RCT evaluated recruited 371 participants diagnosed with alcohol dependence in accordance with DSM-IV.¹⁷ This multi-site 14-week trial assessed the efficacy of topiramate against placebo, titrating from 25-300mg/day over five weeks – resulting in reduced PHDDs, drinks per drinking day and GGT concentration in the topiramate group. However, the therapeutic effect of topiramate was not observed beyond week four. This would indicate that reducing the maximum topiramate dosage and slowing the titration may be of clinical interest.^{19, 20, 22, 26} Whilst the specific dropout rate was undeclared, all dropouts were considered as relapsing to baseline statistics – negating uncertainty that a poor completion rate may have impacted the significance of the results. More participants in the topiramate population (than control) reported attending alcoholics anonymous, 5% and 2.7% respectively, however this difference was statistically insignificant (so did not impose performance bias).

D A Baltieri et al – 2008:

This study was the only trial to compare the efficacy of topiramate with naltrexone – a first-line NICE-recommended medication for alcohol dependence.^{4, 27} In all areas, topiramate (25-300mg/day) was found to be more efficacious than both placebo and naltrexone, though rarely were the differences statistically significant in comparisons with the latter. Nonetheless, the changes effectuated by topiramate consistently approached significance in terms of superiority over naltrexone (at the 95% confidence level), indicating that topiramate may have been found more efficacious in a larger

study – with a greater overall completion rate than 54.8% (n=155).

T Paparrigopoulos et al – 2011:

This open-label RCT was the only trial which failed to record data on HDDs, with median duration of abstinence utilised as the sole outcome measure.¹⁹ Participants were assigned to treatment groups in a 2:1 ratio; the placebo group (n=60) underwent standard psychosocial detoxification protocol, whereas the intervention group (n=30) additionally received topiramate doses escalating from 25-75mg/day. This maldistribution of the sample size, whilst not preferable, indicated no significant differences in the sociodemographic characteristics of the study populations. The absence of blinding also pre-disposes this trial to a criticism of performance bias, reducing the validity of its results. Nevertheless, findings were still positive for the efficacy of topiramate in maintaining abstinence; a median duration of 10 weeks abstinence (of the 16-week trial) was observed in the treatment group compared to four weeks in the control group (P=0.008).

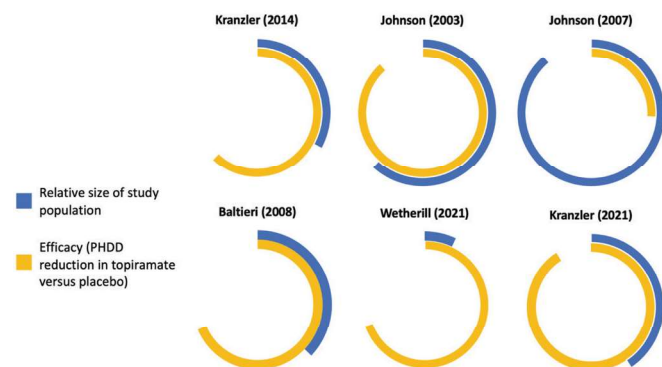


Figure 1: Infographic demonstrating the results of the six studies utilising HDDs as an outcome measure, and their relative sample sizes, to provide visual representation of the power of their findings. See appendix for methods used in design of infographic.

		Kranzler (2014)	Paparrigopoulos (2011)	Johnson (2003)	Johnson (2007)	Baltieri (2008)	Wetherill (2021)	Kranzler (2021)
Design		Double-blind	Open-label	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
Recruitment metric		/	DSM-IV	DSM-IV	DSM-IV	ICD-10	DSM-V	DSM-V
Sample size		138	90	150	371	155	29	170
Participant age range		18-65	18-65	21-65	18-65	18-60	18-60	18-70
Completion rate (%)		84.9	94.4	95.6	81.4	54.8	69.0	91.8
Treatment period (weeks)		12	16	12	14	12	12	12
Dosage titration (mg/d)		25-200	25-75	25-300	25-300	25-300	25-200	25-200
Reduction in HDDs (%)	Topiramate	35.8	/	60.0	38.1	71.7	49.8	59.6
	Placebo	16.9	/	33.0	30.1	50.8	28.6	31.9
Log GGT ratio	Topiramate	-0.14	/	-0.11	-0.05	-0.11	/	-0.08
	Placebo	-0.08	/	-0.04	-0.02	-0.06	/	-0.04
End-point abstinence rate (%)	Topiramate	38.6	71.4	44.5	37.6	46.2	/	/
	Placebo	21.4	33.3	18.0	29.0	27.8	/	/

Table 1: Summary of seven assessed RCTs directly comparing topiramate with placebo.^{17, 18, 19, 20, 22, 26, 27}

DISCUSSION

All studies evaluated were placebo-controlled RCTs, the highest quality study in terms of the hierarchy of evidence. Additionally, all except one trial (Paparrigopoulos et al)¹⁹ used double-blinding measures to reduce performance bias.

Comparative Summary of Findings:

Six of the seven trials surmised that topiramate was significantly superior to placebo in terms of reducing PHDDs (P values ranging from 0.0003 – 0.04); Paparrigopoulos¹⁹ did not assess HDDs as a measure of efficacy but did find a significant increase in end-point abstinent rate versus control. Likewise, every study that outlined abstinence rate as an outcome measure found a significant difference between treatment groups – consistently in favour of topiramate (P values between <0.001 – 0.04). Regarding plasma GGT, end-point concentrations were significantly lower in the topiramate group than the placebo group (adjusting for variation in baseline levels) in all but one trial; Baltieri²⁷ found no statistically significant difference in mean GGT decrease between placebo, naltrexone and topiramate treatment groups at the 95% confidence level (p=0.42). Some limitations to this study must be considered when appraising the evidence, however. These include a disproportionately high dropout rate; a lack of structure regarding implementation of psychosocial interventions between groups (despite the author listing this as a strength that improved external validity); and the discrepancy that the naltrexone and placebo group required once daily dosing whereas topiramate was dosed twice daily. The latter may have led to greater variation between groups in terms of medication adherence, skewing the results.

Limitations:

One frequently occurring limitation was the reliance on self-reporting methods as a means of monitoring participants' alcohol consumption. This inevitably precipitates an element of measurement bias due to inherent mismatches between reported and actual drinking behaviours. However, five RCTs validated self-reported alcohol consumption with objective laboratory markers – plasma GGT concentration. This has been confirmed as a reliable indicator for detecting alcohol relapse in alcohol-dependent individuals.²⁸

The two remaining studies that did not report any verifiable outcome measures for drinking behaviour corroborated the participants' responses through weekly (Paparrigopoulos)¹⁹ and endpoint (Wetherill)²⁶ alcohol breath tests – for which the latter produced no readings above zero.

A limitation found to be consistent throughout the literature was the exclusion of participants with clinically significant co-existing medical conditions, with some trials explicitly outlining 'alcoholic cirrhosis' as an exclusion criterion. This will have likely resulted in the heaviest drinkers being removed from the initial study population, a selection bias that reduces the external validity of the study. This point is particularly pertinent to the Baltieri 2008 study,²⁷ which directly compared the efficacy of topiramate with naltrexone – a pharmacotherapy characteristically efficacious within the specific demographic of heavy drinkers. Hence, any discernible superiority of topiramate over naltrexone may be over-estimated. As aforementioned, more inclusive, higher-powered studies must be conducted before any reliable conclusions can be drawn in this respect.

Study power:

The study with the largest sample size was conducted by Johnson,¹⁷ with 371 participants (significantly increasing its statistical significance). Coincidentally, this was also the study which demonstrated the smallest difference between treatment groups in terms of end-point abstinence rate, reduction in PHDDs and reduction in plasma GGT – despite titrating to the highest ceiling dose of topiramate observed in the literature (300mg). Likewise, the study which was most rigorous in reducing random error, by accounting for extraneous variables, (Kranzler)²⁰ presented the second lowest difference in PHHD reduction and difference in abstinence rate between groups. The authors improved statistical power of the study in this regard, through post-randomisation stratification for age, sex and pre-treatment drinking frequency.

Comparability of Studies:

Baltieri²⁷ and Paparrigopoulos¹⁹ produced particularly distinctive studies. Baltieri designed the first trial in the literature to recruit participants on an outpatient basis (Clinical Hospital of the University of São Paulo), whereas the latter recruited exclusively based on attendance of a community addition clinic (Clinic of the Athens University Psychiatric Clinic). Paparrigopoulos also used the lowest maximum dose of topiramate of any study assessed (75mg) – yet still demonstrated efficacy through a 38.1% greater end-point abstinence rate than seen in the placebo group. The maximum 300mg topiramate dosage in Baltieri's study appeared to yield similarly significant results (P=0.02, P=0.008) however the open-label design of the later trial restricts comparability between studies. More research is undoubtedly required in this domain, as low-dose topiramate has now proven promisingly efficacious in a number of trials.^{19, 29}

Overall, the extent to which comparisons between studies can be made is limited, due to the different diagnostic tools used to classify participants as alcohol dependent. Three different diagnostic criteria for recruiting participants were identified, with Wetherill²⁶ combining DSM-V with their own rigorous inclusion criteria (considering pattern of alcohol consumption and intelligence quotient). This contrasts to Kranzler²¹, who opted not to use any established criteria for diagnosing dependency, with a single inclusion criterion of ≥ 24 standard units/week average consumption.

Safety and Tolerability:

Whilst not outlined within the aims of this paper, the tolerability of topiramate amongst the study populations was considered. The most frequently reported side effects were paraesthesia, headaches, somnolence, diarrhoea, impairment of concentration, taste alteration and loss of appetite – with significantly greater effects reported in the topiramate group, in all studies except Baltieri²⁷ (P=0.09). Only Johnson¹⁷ and Kranzler²² observed serious adverse events in the topiramate treatment groups (one case of cholelithiasis and myopia, and one asthma exacerbation, respectively).

Attrition rates due to adverse events was only found to be statistically significant between groups by Johnson.^{17, 18} However, it is also worth considering that pregnancy was an exclusion criterion for all seven studies, hence the safety of topiramate in pregnant/lactating women may be an area for future research.

CONCLUSION

Alcohol dependence is a condition which precipitates a range of physical and psychosocial implications for both the individual and their family. However, it is a condition for which NICE-recommended pharmacological therapies are relatively under prescribed – despite a relatively low NNT.³⁰

Notwithstanding, this review found consistency throughout the literature supporting the efficacy of topiramate for the treatment of alcohol dependence, in both the initial reduction of heavy drinking and the maintenance of abstinence in detoxified individuals. These findings are supported by a theoretical neuropsychological basis, with an understood mechanism of action through which topiramate can act to reduce positive reinforcement of alcohol-promoting behaviours.

Findings from studies such as Baltieri²⁷ further suggest that topiramate may have potential to surpass currently licensed drugs for this application, advocating further research in this area through higher-powered studies. Likewise, follow-up research to the RCTs conducted by Kranzler et al^{20, 22} may endorse prescription of topiramate for alcohol dependence on a pharmacogenetic basis, owing to potentially superior efficacy in individuals possessing SNP polymorphisms in GRIK-1.

APPENDIX

The infographic was designed by multiplying both metrics (difference in PHDDs between topiramate and placebo groups, and sample size) to fit on a single unitary scale. This combined scale was established by multiplying the PHDD values, for each study, by 13.7; the sample sizes were multiplied by one. The maximum recorded value for this combined metric was 417.4, which represented 360° of the donut charts. The values for both metrics, on this combined scale, were then subtracted from the maximum value (417.4, 360°) to give the circumferential.

As a result, the blue portion of each donut chart represents the sample size of the study and the orange portion represents the effectiveness of topiramate presented in its results (based on the HDD outcome measure), relative to the findings of the other studies.

PHDDs was chosen as the outcome measure for use in this infographic, as it is the outcome measure recorded most frequently across the studies investigated (six out of the seven trials measured HDDs).

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(a full list available on request)