ALCOHOL RESEARCH UK

Effects of varenicline on alcohol enjoyment and consumption

Dunja Przulj
Hayden McRobbie
Oliver Knight-West
Peter Hajek

January 2016

AUTHOR DETAILS

Dunja Przulj[1], Hayden McRobbie[1], Oliver Knight-West[2], Peter Hajek[1]

[1]Health and Lifestyles Research Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, UK.

[2] National Institute for Health Innovation, School of Population Health, University of Auckland, New Zealand.

Corresponding Author
Dr Dunja Przulj, 2 Stayner's Road, London E1 4AH, UK
Tel: 0207 882 5949
Email: d.przulj@qmul.ac.uk

This report was funded by Alcohol Research UK. Alcohol Research UK is an independent charity working to reduce alcohol-related harm through ensuring policy and practice can be developed on the basis of reliable, research-based evidence.
www.alcoholresearchuk.org

EXECUTIVE SUMMARY

Background and Aims

One of the most commonly used stop smoking medicines, varenicline, may also have potential as a treatment for alcohol dependence. Alcohol may produce mesolimbic activation, in part due to its effect on nicotinic acetylcholine receptors.

We aimed to examine the differences in enjoyment of drinking and change in alcohol consumption in smokers treated with varenicline compared to those treated with nicotine replacement treatment (NRT).

Methods

We conducted a data audit of The Royal London Hospital Smokers' Clinic. From 2009- 2013, 412 clients (NRT=94, varenicline=318) provided details of their alcohol consumption (units/week) and enjoyment, before and on their target quit day (TQD), and at 1 and 4-weeks post-TQD.

Results

- There was no difference in change in alcohol consumption between NRT and varenicline users at any time point.
- At four weeks post-TQD, 20% (n=42) of varenicline users compared with 6% (n=3) of NRT users reported they enjoyed alcohol less (p=0.014).
- Varenicline, compared to NRT, had no effect on alcohol consumption or reduced enjoyment in a sub-sample of hazardous-harmful drinkers.
- There were no differences between Varenicline 'reactors' (clients who reported a 50% reduction in smoking in the first week of use) and non-reactors on consumption or enjoyment of alcohol.

Conclusions

Varenicline may reduce enjoyment of drinking, but this was only observed in small number of clients. Its potential to alter drinking behaviour is likely to be small.

BACKGROUND

A relationship exists between smoking and alcohol consumption where heavy drinkers are also more likely to be highly dependent smokers (Rimm et al., 1995). Among smokers, trying to quit alcohol consumption is often cited as a reason for relapse (Lisha et al., 2014).

One of the most commonly used stop smoking medicines, varenicline, may also have potential as a treatment for alcohol dependence. Alcohol may produce mesolimbic activation, in part due to its effect on nicotinic acetylcholine receptors (nAChR) (Li et al., 2007, Davis and de Fiebre, 2006, Larsson and Engel, 2004, Söderpalm et al., 2000); varenicline, which reduces tobacco withdrawal symptoms and diminishes the reinforcing aspects of smoking, could also act to modify alcohol reactivity and thus drinking behaviour. It has also been suggested that varenicline might decrease motivation and incentive salience of alcohol by decreasing neural activity in the amygdala, insula, and ventral striatum, which are involved in reward pathways (Vatsalya et al., 2015).

In the laboratory, varenicline has been shown, more than placebo, to acutely decrease enjoyment and consumption of alcohol among heavy-drinking smokers (McKee et al., 2009) and to increase the negative effects of alcohol (Childs et al., 2012). Two randomised controlled pilot studies (n=30 (Fucito et al., 2011) and n=64(Mitchell et al., 2012)) involving heavy-drinking smokers found that, relative to placebo, varenicline was associated with a greater reduction in alcohol craving and fewer heavy-drinking days in the short-term.

However, several larger trials have not confirmed these findings. A randomised study (n=200) of alcohol dependent smokers and non-smokers observed similar results, but compared to placebo, varenicline did not affect alcohol abstinence rates at 12 weeks (Litten et al., 2013). Another, which randomised 160 participants to a 12 week course of varenicline or placebo (de Bejczy et al., 2015), found no effect of varenicline on the number of heavy drinking days. However, varenicline use was associated with a significant reduction, relative to placebo, in blood phosphatidylethanol levels (a specific marker of alcohol consumption) as well as alcohol craving and Alcohol Use Disorders Identification Test (AUDIT) scores.

The Royal London Hospital Smokers' Clinic provides a combination of multi-session behavioural support and pharmacotherapy (nicotine replacement treatment [NRT], bupropion or varenicline) to people seeking help to stop smoking. From 2009-2013, clients have been routinely asked to provide details of their alcohol consumption and enjoyment, both at baseline (before quitting smoking) and at several time points throughout treatment. Using this data, we aimed to examine the differences in enjoyment of drinking and change in alcohol consumption in clients using varenicline compared to those using NRT.

METHODS

Design

Audit of data from the Royal London Hospital Smokers' Clinic clients using NRT and clients using varenicline. Only a small proportion of clients use bupropion and these smokers were not included in the analysis.

Participants

570 consecutive clients who received free National Health Service Stop Smoking Service (NHS-SSS) treatment that involved the use of either NRT (N=138) or varenicline (N= 432) over a four-year period between January 2009 and January 2013.

Setting and description of treatment

Smokers receive withdrawal-oriented treatment (Hajek, 1989) delivered face-to-face, either in groups or individually. There are seven weekly visits, each lasting approximately one hour (groups) or 20 minutes (individuals). In addition to motivational support, patients also select their choice of either NRT or varenicline. NRT use (usually a combination of nicotine patch with a faster-acting preparation: gum, lozenge, mouth spray, nasal spray, or inhalator) begins on the target quit date (TQD; third visit), whilst varenicline use begins one week prior to the TQD. There is an up-titration schedule during the first week of varenicline use (Days 1-3: 0.5mg/day; days 3-7: 1.0mg/day; Day 8 onwards: 2.0mg/day). Both medications are prescribed for up to twelve weeks.

Measures

Standard Clinic questions on demographics (age, sex, socio-economic status, nicotine dependence, current and ever treatment for alcohol problems) were asked at baseline (two weeks prior to the smoking TQD).

Self-reported weekly alcohol consumption (number of units consumed/week) was collected at baseline, TQD, and one and four week's post-TQD. We also asked clients to rate their subjective enjoyment of alcohol at each of the four post-TQD sessions using a question based on previous work assessing the enjoyment of smoking among patients using varenicline (Hajek et al., 2011). Clients were asked to answer 'Compared to how you felt about alcohol before coming to the smokers' clinic, how did you find it during the last week?' by selecting one of six responses: much more enjoyable; slightly more enjoyable; same as before; slightly less enjoyable; much less enjoyable; did not drink any alcohol.

Smoking status was ascertained weekly and self-reports of abstinence are verified by a carbon monoxide (CO) reading in expired breath of < 10ppm.

Analyses

For the purposes of this audit we split the sample, based on baseline reported alcohol consumption, into 'moderate' (≤ 21 units/week for men, ≤ 14 units/week for women) 'hazardous' (14-34 units for women or 21-49 units for men) and 'harmful' (50+ units/week for men and 35+ units/week for women) drinkers. Clients who reported at baseline that they do not normally consume alcohol were excluded from analyses. Reponses to the enjoyment of alcohol question were dichotomised into those who experienced a decreased enjoyment and those who did not.

Repeated measures ANOVAs and chi-squared tests were used as appropriate to compare differences between NRT and varenicline users in consumption and enjoyment of alcohol over time. Analyses were conducted on both the whole sample, including those who attended the TQD session but did not manage to stop smoking, and on abstainers only. Abstinence at 1-week post-TQD was defined as not a single puff since TQD, and at 4 weeks, as not a single puff in the last 2 weeks of treatment, verified by a CO reading of <10 ppm.

For exploratory purposes, we also ran the analyses on the sample of clients who were defined as either 'hazardous' or 'harmful' drinkers. We conducted two further exploratory analyses: (i) comparing patients who showed an initial favourable treatment reaction to varenicline (reduced cigarette consumption by more than 50% in the first week of taking it) with those who did not experience such a reaction. Varenicline reactors have higher rates of smoking cessation than non-reactors (Hajek et al., 2011) so it was of interest to determine if this indicator also predicts any effect of varenicline on alcohol use and enjoyment. And (ii), we compared enjoyment of alcohol in varenicline users who had abstained from smoking vs. those who did not. A previous study reported an effect of varenicline on alcohol consumption in those who had also reduced their smoking (Litten et al., 2013).

RESULTS

Client characteristics

Client characteristics are shown in Table 1. There were missing data on baseline alcohol consumption for 77 clients and 81 (16%) reported not drinking alcohol (removed from analyses). There were no significant differences in baseline characteristics between varenicline and NRT users except that those using varenicline had significantly higher baseline cigarette consumption and CO levels than those who used NRT. Baseline alcohol consumption was correlated with baseline cigarette consumption (Pearson Chi-square=0.21, p<0.001).

Table 1: Baseline Characteristics

	Total sample (n=412)	Varenicline (n=318)	NRT (n=94)
Mean age	41.3 (SD=11.0)	41.6 (SD=11.0)	40.3 (SD=11.2)
% Male	61.4%	61.6%	60.6%
% employed (n=397)*	74.8%	75.8%	71.4%
Mean daily cigarette consumption (n=409)*	17.1 (SD=8.3)	17.6 (SD=8.4)	15.3 (SD=7.3)**
% who smoke within 30 minutes of waking (n= 406)*	69.3%	71.2%	62.8%
% with a past history of problem drinking (n=407)*	4.7%	4.1%	6.5%
Alcohol consumption			
Moderate	76.5%	76.4%	60%
Hazardous	18.7%	18.2%	20.2%
Harmful	4.9%	5.3%	3.2%
Mean carbon monoxide in expired breath (n= 204)	19.8 (SD=11.7)	20.6 (SD=11.2)	16.4 (SD=13.2)***

**N varies due to missing data ** p= 0.017 ***p= 0.041*
Definitions of alcohol consumption:
Moderate: up to 21 units/week for men and 14 units/week for women
Hazardous: 22-49 units/week for men and 15-34 units/week for women
Harmful: 50+ units/week for men and 35+ units/week for women

Alcohol consumption

A total of 218, 242, and 221 clients provided data on alcohol consumption at the TQD, 1 week post-TQD, and 4 weeks post-TQD, respectively. Clients reported drinking marginally less, overall, than they did at baseline (see Table 2). This reduction was only statistically significant in the total sample at one-week post-TQD (p<0.001). There was no significant difference in change in alcohol consumption from baseline between NRT and varenicline users at any time point.

In those clients who were confirmed abstinent at 1 week post-TQD (N= 146), there was an overall significant reduction in alcohol consumption from baseline to 1 week post-TQD (p=0.023), but no significant interaction with medication type. In clients who were confirmed abstinent at 4 weeks post-TQD (N= 117), there were no changes in alcohol consumption form baseline to 4 weeks post-TQD, overall, and by medication type.

Table 2: Alcohol consumption (units/week) at baseline and at 1 and 4 weeks post-TQD

	Varenicline	NRT	Medication*Time
	Mean (SD)		p value
Baseline:	14.9 (12.9)	14.1 (14.7)	0.778
TQD:	14.0 (13.2)	13.5 (12.7)	
N=218 (V= 169,NRT= 49)*			
Baseline:	14.9 (12.9)	15.6 (18.0)	0.302
1-week post-TQD:	13.0 (13.0)	11.9 (12.1)	
N=242 (V=185, NRT=57)			
Baseline:	14.2 (12.1)	13.6 (15.2)	0.501
4-weeks post-TQD:	13.2 (11.9)	11.4 (10.7)	
N=221 (V=170, NRT=51)			

**V= Varenicline, NRT= Nicotine Replacement Treatment*

Enjoyment of alcohol

The data on enjoyment of alcohol are presented in Table 3. At the smoking TQD, there was no significant difference between NRT and varenicline users in the proportion of clients who reported they enjoyed alcohol less versus those who did not since they enrolled in treatment. There was also no difference at one week post-target quit date, but by four weeks post-TQD, some 20% (n=42) of varenicline users compared with 6% (n=3) of NRT users reported they enjoyed alcohol less (p=0.014). The pattern of results were similar when enjoyment ratings were examined in 1 and 4 week abstainers from smoking, although the difference between medications did not reach statistical significance at four weeks post-TQD (20% vs. 8%, p=0.124), due to the decreased sample size (N=221).

Table 3: Enjoyment of alcohol at follow-up

Follow-up point	% (N) reporting less enjoyment of alcohol		
	Varenicline users	NRT users	Difference (p value)
Target Quit Date Total N=292	20% (47)	10% (6)	0.05
1-week post-TQD Total N=280	19% (42)	20% (12)	0.93
4-weeks post-TQD Total N=260	20% (42)	6% (3)	0.014

Exploratory analyses: hazardous-harmful drinkers

Restricting the analyses to the heavy-harmful drinkers who provided data on alcohol consumption at baseline and at the three follow-up points showed a significant reduction in alcohol consumption from baseline to the TQD (p= 0.033) and from baseline to 1- and 4-weeks post-TQD (p= 0.003 and 0.004, respectively), but no interaction with medication type (see Table 4).

A total of 21 (22%) clients who were hazardous-harmful drinkers at baseline reported drinking within 'moderate' limits at the 4-week follow-up point. This was not significantly related to medication type (16 [31%] varenicline users vs. 5 [33%] NRT users, ns) or smoking status (3 [75%] smokers vs 18 [29%] abstainers, p=0.052).

At 4-weeks post TQD 17% (n=9) versus 8% (n=1) of varenicline and NRT users reported less enjoyment of alcohol, but this difference was not significant.

Table 4: Alcohol consumption (units/week) in hazardous and harmful drinkers at baseline and at 1 and 4 week follow-up

	Varenicline users	NRT users	Medication*Time
	Mean (SD)		p value
Baseline:	32.1 (13.8)	31.2 (19.0)	0.890
TQD:	28.6 (15.0)	27.2 (11.7)	
N=54 (V=41, NRT= 13)*			
Baseline:	31.7 (13.2)	36.3 (25.8)	0.270
1-week post-TQD:	26.4 (13.9)	25.0 (14.0)	
N=60 (V= 46, NRT=14)			
Baseline:	31.7 (12.3)	34.2 (23.7)	0.376
4-weeks post-TQD:	25.4 (13.3)	22.6 (11.2)	
N=47 (V= 47, NRT=10)			

**V= Varenicline, NRT= Nicotine Replacement Treatment*

Exploratory analyses: varenicline 'reactors'

Finally, we also explored whether varenicline reactors (clients who reduced cigarette consumption by at least 50% by TQD) were more likely than non-reactors to experience a greater reduction in alcohol consumption and enjoyment, but found no such effect (data not shown).

We also re-analysed the enjoyment of alcohol data in varenicline users only, to see if there was any effect of abstinence. At 1-week post-TQD, 21% of those abstinent reported reduced enjoyment of alcohol vs. 18% of those who had smoked (ns); and at 4 weeks post-TQD, 19% of abstainers vs. 30% of smokers reported a reduction in alcohol enjoyment (ns).

CONCLUSIONS

In this data audit, we explored whether smokers treated with varenicline experienced greater reductions in enjoyment and consumption of alcohol than those using NRT. Clients using varenicline were more likely to report reduced enjoyment of drinking compared to those using NRT at 4 weeks post-TQD, but there were no effects of varenicline on alcohol consumption overall, or on alcohol consumption in a subgroup of hazardous-harmful drinkers. This was also the case for those clients who reported a strong reaction to varenicline during the first week of use.

The audit has some limitations: medication type was self-selected; although the overall sample was large, missing data, removal of non-drinkers, and sub-group analyses, led to modest sample sizes for some comparisons. In some analyses, the proportion of NRT users was considerably less compared with varenicline. In addition, alcohol consumption was self-reported and data on medication compliance was not captured.

The findings reported here have implications for considerations of the potential of varenicline to treat alcoholism. There is a hint that varenicline may reduce enjoyment of alcohol, but this has been observed in only a minority of clients, and did not translate to an overall reduction in alcohol consumption. In conclusion, the potential of varenicline to alter drinking behaviour is likely to be small.

Conflicts of interest

PH and HM have received research funds and/or consultancy fees from manufacturers of smoking cessation medications. The remaining authors have no conflicts of interest to declare.

REFERENCES

Childs, E., Roche, D. J. O., King, A. C. & De Wit, H. (2012). Varenicline Potentiates Alcohol-Induced Negative Subjective Responses and Offsets Impaired Eye Movements. *Alcoholism: Clinical and Experimental Research,* 36**,** 906-914.

Davis, T. J. & De Fiebre, C. M. (2006). Alcohol's actions on neuronal nicotinic acetylcholine receptors. *Alcohol Research & Health,* 29**,** 179-185.

De Bejczy, A., Lof, E., Walther, L., Guterstam, J., Hammarberg, A., Asanovska, G., Franck, J., Isaksson, A. & Soderpalm, B. (2015). Varenicline for Treatment of Alcohol Dependence: A Randomized, Placebo-Controlled Trial. *Alcoholism: Clinical and Experimental Research,* 39**,** 2189-99.

Fucito, L. M., Toll, B. A., Wu, R., Romano, D. M., Tek, E. & O'malley, S. S. (2011). A preliminary investigation of varenicline for heavy drinking smokers. *Psychopharmacology (Berl),* 215**,** 655-63.

Hajek, P. 1989. Withdrawal-oriented therapy for smokers. *British Journal of Addiction,* 84**,** 591-8.

Hajek, P., Mcrobbie, H. J., Myers, K. E., Stapleton, J. & Dhanji, A. R. (2011). Use of Varenicline for 4 Weeks Before Quitting Smoking Decrease in Ad Lib Smoking and Increase in Smoking Cessation Rates. *Archives of Internal Medicine,* 171**,** 770-777.

Larsson, A. & Engel, J. A. (2004). Neurochemical and behavioral studies on ethanol and nicotine interactions. *Neuroscience and Biobehavioral Reviews,* 27**,** 713-720.
Li, T. K., Volkow, N. D., Baler, R. D. & Egli, M. (2007). The biological bases of nicotine and alcohol co-addiction. *Biological Psychiatry,* 61**,** 1-3.

Lisha, N. E., Carmody, T. P., Humfleet, G. L. & Delucchi, K. L. (2014). Reciprocal effects of alcohol and nicotine in smoking cessation treatment studies. *Addictive Behaviors,* 39**,** 637-643.

Litten, R. Z., Ryan, M. L., Fertig, J. B., Falk, D. E., Johnson, B., Dunn, K. E., Green, A. I., Pettinati, H. M., Ciraulo, D. A., Sarid-Segal, O., Kampman, K., Brunette, M. F., Strain, E. C., Tiouririne, N. A., Ransom, J., Scott, C., Stout, R. & Group, N. S. (2013). A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *Journal of Addictiont Medicine,* 7**,** 277-86.

Mckee, S. A., Harrison, E. L. R., O'malley, S. S., Krishnan-Sarin, S., Shi, J., Tetrault, J. M., Picciotto, M. R., Petrakis, I. L., Estevez, N. & Balchunas, E. (2009). Varenicline Reduces Alcohol Self-Administration in Heavy-Drinking Smokers. *Biological Psychiatry,* 66**,** 185-190.

Mitchell, J. M., Teague, C. H., Kayser, A. S., Bartlett, S. E. & Fields, H. L. (2012). Varenicline decreases alcohol consumption in heavy-drinking smokers. *Psychopharmacology,* 223**,** 299-306.
Rimm, E. B., Chan, J., Stampfer, M. J., Colditz, G. A. & Willett, W. C. (1995). Prospective-Study of Cigarette-Smoking, Alcohol-Use, and the Risk of Diabetes in Men. *British Medical Journal,* 310**,** 555-559.

Söderpalm, B., Ericson, M., Olausson, P., Blomqvist, O. & Engel, J. A. (2000). Nicotinic mechanisms involved in the dopamine activating and reinforcing properties of ethanol. *Behavioural Brain Research,* 113**,** 85-96.

Vatsalya, V., Gowin, J. L., Schwandt, M. L., Momenan, R., Coe, M. A., Cooke, M. E., Hommer, D. W., Bartlett, S., Heilig, M. & Ramchandani, V. A. (2015). Effects of Varenicline on Neural Correlates of Alcohol Salience in Heavy Drinkers. *International Journal of Neuropsychopharmacology*.