ALCOHOL HISTORY AND SMOKING CESSION IN NICOTINE REPLACEMENT THERAPY, BUPROPION SUSTAINED RELEASE AND VARENCLINE TRIALS: A REVIEW

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Abstract — Aims: We conducted a review of published reports of smoking cessation pharmacotherapy trials in order to address the following: (i) the generalizability of findings to smokers with a history of alcohol problems; (ii) the extent to which alcohol use affects smoking cessation overall and the efficacy of pharmacotherapy specifically and (iii) the effect of smoking cessation on alcohol use. Methods: We located published reports of nicotine replacement therapy (NRT), bupropion sustained release (SR) and varenicline clinical trials using an approach based on prior Cochrane reviews. The reports were searched for alcohol-related inclusion/exclusion criteria and for findings related to alcohol. Results: The present review included 212 published reports from 149 trials. Alcohol-related exclusion criteria appeared frequently (41.6% of trials)—45/125 NRT trials (36%), 15/22 bupropion SR trials (68.2%) and 3/3 varenicline trials—and most commonly involved exclusion of participants with past or recent alcohol problems. Most studies failed to provide any baseline alcohol-related characteristics. Eleven trials reported on the relationship between alcohol history and likelihood of smoking cessation. In the majority of these studies, smokers with a past history of alcohol problems were not at a disadvantage, although contrary findings exist. Only two studies examined the potential influence of smoking cessation on alcohol use. Conclusions: Smokers with alcohol problems, particularly those with current or recent problems, are underrepresented in studies of approved pharmacotherapy for smoking cessation. Future trials should assess alcohol use at baseline and during treatment and examine reciprocal influences between alcohol consumption and smoking cessation.

INTRODUCTION

There is strong evidence of co-morbidity between nicotine and alcohol problems. According to data from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), 12 month co-morbidity of alcohol use disorders among those with nicotine dependence is 22.8%, and 12 month co-morbidity of nicotine dependence among those with alcohol use disorders is 34.5% (Grant et al., 2004). Among individuals attempting to abstain from cigarettes, alcohol consumption has been frequently cited as a precipitant of smoking relapse (Krall et al., 2002). As a result, the most recent guidelines for smoking cessation treatment advocate that smokers attempting to quit also make an effort to avoid drinking (Fiore et al., 2000). The clinical-practice guidelines also recommend that all patients be offered pharmacotherapy if not contraindicated. At the time of the guidelines’ publication, the U.S. Food and Drug Administration (FDA) had approved five pharmacotherapies for smoking cessation: four types of nicotine replacement therapy (NRT) (i.e. gum, patch, nasal spray and inhaler) and a non-nicotine-based antidepressant, bupropion sustained-release (SR) (Zyban, Wellbutrin). Since then, another form of NRT (i.e. lozenge) and the partial nicotinic agonist varenicline (Chantix) have been granted FDA approval for smoking cessation treatment. All five types of NRT and bupropion SR have been approved in Europe as well, and European approval for varenicline has been recommended by the Committee for Medicinal Products for Human Use (see http://emea.europa.eu). Research findings suggest that these medications are safe and effective (Hughes et al., 2004b; Silagy et al., 2004; Gonzales et al., 2006; Jorenby et al., 2006; Tonstad et al., 2006).

While it is important for all smokers to quit, those with histories of co-morbid alcohol problems face added risks. In addition to the increase in risk for certain cancers among individuals who smoke and drink heavily (e.g. hepatocellular carcinoma, Kuper et al., 2000), recent research suggests that smoking exacerbates the deleterious effects of alcohol dependence on brain neurobiology (Gazdzinski et al., 2006) and that smoking retards neurobiologic recovery among alcoholics in treatment (Durazzo et al., 2006). Moreover, smokers with a history of alcohol problems tend to be more heavily dependent on nicotine (Hughes and Kalman, 2006) and may experience more intense withdrawal symptoms (Marks et al., 1997). Thus it is important to determine whether FDA-approved pharmacotherapies for smoking cessation are efficacious for use on the large population of smokers with past or current alcohol use disorders. Exclusion of individuals with a history of alcohol problems from smoking cessation trials may limit the generalizability of the results to this subpopulation of smokers.

Among smokers who currently drink, it is conceivable that quitting smoking may also reduce alcohol consumption given that nicotine is known to increase alcohol tolerance (Madden et al., 1995) and alcohol reinforcement (at least in men; Acheson et al., 2006). Findings reported by Prochaska et al. (2004) are suggestive of this possibility. They conducted a meta-analysis and found that smoking cessation interventions offered during treatment for other addictive substances were associated with a 25% increased likelihood of long-term abstinence from alcohol and illicit drugs. Alternatively, it is possible that smoking cessation could lead to an increase in alcohol consumption should these substances be substitutable rather than complementary in nature. Also, among smokers already abstaining from or regulating their alcohol consumption, a smoking cessation attempt may interfere with their efforts (Joseph et al., 2004). Studies that include an assessment of drinking behaviour at baseline and during treatment could inform our understanding of the interaction between
alcohol consumption and smoking cessation and could also be used to examine potential effects of pharmacotherapy on alcohol consumption.

To address these issues, we reviewed published reports of smoking cessation trials using FDA-approved pharmacotherapy in light of guidelines supporting the use of approved pharmacotherapy for smoking cessation treatment (Fiore et al., 2000). Inclusion of the pharmacotherapies that have been approved since the publication of these guidelines made the present review up-to-date with respect to the current state of smoking cessation treatment. Pharmacotherapies not FDA-approved for smoking cessation treatment were excluded given the uncertain evidence for their efficacy and safety. While there have been several reviews addressing smoking cessation treatment for those with co-morbid alcohol problems (e.g., Sussman, 2002; Prochaska et al., 2004; Hughes and Kalman, 2006), none have systematically reviewed the literature on FDA-approved smoking cessation pharmacotherapy.

Given the evidence of co-morbidity and the related treatment implications, we focused our review on the following three issues:

1. The generalizability of findings in the NRT, bupropion SR and varenicline literatures to smokers with current or past histories of alcohol problems.
2. The extent to which alcohol use affects smoking cessation overall and specifically the efficacy of pharmacotherapy.
3. The likelihood that smoking cessation will result in a reduction or increase in alcohol use.

METHOD

Our goal was to review published papers assessing the efficacy of the pharmacotherapies for smoking cessation that were FDA-approved as of July 2006: five forms of NRT—nicotine gum, patch, nasal spray, inhaler and sublingual tablet/lozenge—and two non-nicotine-based pharmacotherapies—bupropion SR (Zyban, Wellbutrin) and varenicline (Chantix). Meta-analyses of literatures on NRT (Silagy et al., 2004) and antidepressants for smoking cessation (Hughes et al., 2004b) found in the Cochrane Database of Systematic Reviews were used as the basis for the present review.

The literature reviews that formed the basis for the two Cochrane reviews were completed in March 2004. The literature searches for both reviews make use of the specialized register of the Cochrane Tobacco Addiction Group. For the NRT review, the specialized register ‘was searched for trials with any reference to the use of NRT of any type in the title, abstract or keywords’ (Silagy et al., 2004, p. 4). The search also included the following databases: EMBASE, MEDLINE (PubMed), MEDLINE Express, PsychLIT/PsychINFO, Science Citation Index (Web of Science) and the Cochrane Central Register of Controlled Trials (CENTRAL). A similar strategy was used for the antidepressant review; in this case, the specialized register was searched for ‘trials using pharmacotherapy other than nicotine, clonidine or lobeline for smoking cessation... and those using medications generally classified as having an antidepressant effect’ (Hughes et al., 2004b, p. 3). Searches were then carried out in MEDLINE and EMBASE for each such medication found in the review of the specialized register.

Trials were included in the Cochrane review of NRT if they met four main criteria: (i) use of random or quasi-random assignment to groups; (ii) a study design that allowed for a comparison between different doses of active NRT or between active NRT and either a placebo or no NRT condition; (iii) reporting of smoking cessation or reduction outcomes and (iv) the reporting of a smoking cessation or reduction outcome at least 6 months after the beginning of treatment with a 6-week window period to account for trials making use of varying endpoints. To these criteria, we added two of our own: (i) reports must have been peer-reviewed prior to publication and (ii) reports must have been published in English. The requirements for the antidepressant review were similar. Criteria number (i), (iii) and (iv) were the same with the exception that the possibility of a 6-week window for reporting outcome measures was not mentioned. For criterion number (ii), a comparison had to be made between different doses of active antidepressants or between an active antidepressant and either a placebo or an alternative therapeutic control. Only reports involving bupropion SR were considered for the present review, given that it is the only antidepressant with FDA approval for smoking cessation treatment (see the Cochrane reviews—Hughes et al., 2004b; Silagy et al., 2004—for further detail about their methods).

In order to make the present review as current as possible, we conducted our own searches using the same databases employed in the Cochrane review of NRT from 2004 to June 2006 for NRT and to July 2006 for bupropion SR and for varenicline. The inclusion of the entire year of 2004 in the updated review ensured that there would be no gap between the end of the Cochrane reviews and the start of our updated review. The following keywords—‘patch,’ ‘gum,’ ‘inhaler,’ ‘spray,’ ‘lozenge,’ ‘tablet,’ ‘bupropion,’ ‘Wellbutrin,’ ‘Zyban,’ ‘varenicline’ and ‘Chantix’—were all paired with ‘nicotine,’ ‘cigarette,’ ‘tobacco’ and ‘smoking.’ The same inclusion criteria from the Cochrane reviews were used for this updated literature search. We also checked the reference sections of review papers addressing interactions between smoking and alcohol (Sussman, 2002; Prochaska et al., 2004; Hughes and Kalman, 2006) and repeated the search detailed above in the Scopus database for the years up to and including 2004 to ensure that no secondary publications from trials included in the Cochrane reviews were omitted.

To address the first goal of this review—assessment of the generalizability of findings in the NRT, bupropion SR and varenicline literatures to smokers with histories of alcohol problems—we evaluated the presence or absence of alcohol-related inclusion or exclusion criteria, the type of alcohol history excluded (e.g., dependence, abuse, frequency/quantity of alcohol use above a certain threshold) and the time frame considered (e.g., current, recent, lifetime). To address the second and third goals of this review, we looked for any information about the influence of past or current alcohol use at baseline on smoking cessation outcome and for reported effects of smoking cessation on drinking behaviour in the course of trials.
RESULTS

A total of 212 articles from 149 clinical trials were included in the present review. Of these, 164 were NRT articles (from 124 trials); 41 were bupropion SR articles (from 21 trials) and three were varenicline articles (from 3 trials). In addition, four papers were published from one trial that was included in both the NRT and antidepressant Cochrane reviews (Jorenby et al., 1999). Data from this trial are reported in this section under both NRT and bupropion SR. Other trials (e.g. Simon et al., 2004) included both NRT and bupropion SR but would have met criteria only for the antidepressant Cochrane review, thus findings from these trials are reported under bupropion SR only. Of the 149 trials included in the review, 126 were taken from the two Cochrane reviews (111 NRT, 14 bupropion SR, 1 NRT and bupropion SR). Of the articles taken from the Cochrane reviews, only those cited in the text are included in the references. A complete reference list can be obtained from the authors. Our updated search of the NRT literature yielded seven eligible trials: Aubin et al., 2004; Myles et al., 2004; Simon et al., 2004; Evins et al., 2005; Zellweger et al., 2005; Haggström et al., 2006; Killen et al., 2006. Three varenicline trials were found to be eligible: Gonzales et al., 2006; Jorenby et al., 2006; Tonstad et al., 2006.

Generalizability of findings

Table 1 provides details regarding the reporting of alcohol-related inclusion and exclusion criteria by type of medication. Alcohol-related inclusion criteria were reported in only two trials, both of which involved NRT (Hughes et al., 2003b; Kalman et al., 2006). Both studies recruited smokers with a past history of alcohol dependence who reported a period of current abstinence at the time of enrollment. Alcohol-related exclusion criteria were reported frequently, in 41.6% (62/149) of trials — 45/125 NRT trials (36%), 15/22 bupropion SR trials (68.2%) and 3/3 varenicline trials. The reporting of alcohol-related exclusion criteria in NRT trials is a relatively recent trend. Of the 34 NRT trials published before 1990, only

<table>
<thead>
<tr>
<th>Type of information</th>
<th>Total NRT</th>
<th>Total Bupropion SR</th>
<th>Total Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of trials</td>
<td>149</td>
<td>125</td>
<td>22</td>
</tr>
<tr>
<td>Any inclusion criteria</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Any exclusion criteria</td>
<td>63 (42%)</td>
<td>45 (36%)</td>
<td>15 (68%)</td>
</tr>
<tr>
<td>Criteria unclear'</td>
<td>7 (5%)</td>
<td>6 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Abuse</td>
<td>38 (26%)</td>
<td>25 (20%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>No time qualifier or other information given</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Any history (recent or past)</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Recent history'</td>
<td>17</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Current history'</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Dependence</td>
<td>17 (11%)</td>
<td>14 (11%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>No time qualifier or other information given</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Any history (recent or past)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Recent history'</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Frequency/quantity only</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Prevalence of alcohol-related problems at baseline presented</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Typical frequency and/or quantity of alcohol consumed at baseline presented</td>
<td>6 (4%)</td>
<td>5 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Influence of alcohol history on cessation reported</td>
<td>11 (7%)</td>
<td>7 (6%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Influence of smoking cessation on alcohol use reported</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

' One trial (Jorenby et al., 1999) met criteria for inclusion in both the NRT and antidepressant Cochrane reviews, thus data for this trial are counted under both NRT and bupropion. Other trials (e.g. Simon et al., 2004) included both NRT and bupropion but would have met criteria only for the antidepressant Cochrane review. These trials were counted under bupropion only.

' The inclusion criterion for the Hughes et al. (2003); Kalman et al. (2006) trials was a history of dependence according to DSM-IV criteria but no alcohol consumption within the past 30 days in the Hughes trial and within the past 2 months in the Kalman trial.

' Criteria included 'excessive alcohol use,' 'alcohol problems' and 'alcohol misuse.'

' Recent history includes trials stipulating a history within the past 12 months and those simply reporting a 'recent history' criterion. This history could be a current diagnosis or a recent but not current diagnosis. Includes one bupropion trial where the criteria were a recent history or a particular frequency/quantity of consumption.
three (3/34, 8.8%) reported alcohol-related exclusion criteria, whereas among the more recent NRT trials, 42 of 91 (46.2%) reported alcohol-related exclusion criteria.

A recent history of alcohol abuse (i.e. in the past 12 months or simply stated as ‘recent history’ with no time frame given) was the most common exclusion criterion for all three medication types. Because alcohol dependence is considered to be a more severe alcohol use disorder than alcohol abuse, we presume that these trials also excluded patients with recent alcohol dependence, even when not explicitly stated. Seventeen trials specifically excluded participants based on alcohol dependence criteria, principally a current or recent history.

Seven trials reported excluding participants with any history (i.e. current, recent or past) of alcohol abuse or dependence. One bupropion SR study used a quantity/frequency measure of drinking as an exclusion criterion. Only three trials—all bupropion SR—reported the percentage of ineligible participants who were excluded due to alcohol-related criteria. Two trials reported modest exclusion rates (13% in Swan et al., 2003 and 7% in Killen et al., 2006), while one study (Ahlulwalia et al., 2002) reported that 35.5% of the ineligible participants were excluded due to ‘excessive alcohol use.' Few trials (6/149, 4%) provided any information about baseline drinking behaviour beyond the percentage of subjects with a past alcohol problems, which was reported in 14 trials (9.4%).

In summary, exclusion of individuals with histories of alcohol problems from pharmacotherapy trials is common. Fortunately, few studies made use of blanket policies excluding participants with any history of alcohol abuse or dependence. However, individuals with recent or current alcohol abuse or dependence are likely underrepresented compared to their prevalence among smokers in the general population. Unfortunately, few papers provide any information beyond alcohol-related inclusion or exclusion criteria, such as rates of prior alcohol problems or current frequency/quantity of alcohol use.

Effects of alcohol use on smoking cessation

Eleven trials (7.4%) reported data pertaining to effects of alcohol history on smoking cessation. Seven trials involved NRT and four involved bupropion SR; there were no such studies involving varenicline. We reviewed the findings of these trials to determine whether there were any significant differences in overall likelihood of smoking cessation based on alcohol history either at the end of treatment or 6–12 months following the beginning of treatment. We also examined the efficacy of pharmacotherapy as a function of alcohol history if this interaction was tested in the trial. This and other detailed information about these trials is provided in Table 2.

NRT. Six trials reported findings at the end of a treatment period lasting less than 6 months. Of these, four reported no difference in likelihood of smoking cessation based on alcohol history, including a multi-site, double-blind, placebo-controlled study of the patch (Hurt et al., 1994; alcohol findings reported in Hurt et al., 1995); a large, multi-site trial involving smokers of 30 or more cigarettes/day with double-blind administration of placebo or one of three doses of active patch (Hughes et al., 1999; alcohol findings reported in Hughes et al., 2003a); a large, multi-site trial of open-label nicotine nasal spray, 15 mg transdermal patch or both treatments (Croghan et al., 2003) and a double-blind, placebo-controlled study of the patch in a sample of heavy smokers who all reported a past history of alcohol dependence and current abstinence from alcohol (Hughes et al., 2003b). Alcohol-related exclusion criteria were reported for the trials by Hurt et al. (1994) and Hughes et al. (1999), but not for Croghan et al. (2003) trial. In Hughes et al. (2003b) paper, the sample of individuals with a past history of alcohol problems was compared with a matched sample of participants without alcohol histories from the 1999 trial, and no significant differences were found between the two samples in either likelihood of continuous abstinence from smoking or efficacy of pharmacotherapy.

The findings at follow-up for these four studies were similar to the end of treatment results, although findings 1 year later in Hurt et al. (1994) trial showed a trend favouring those without an alcohol history in point-prevalence abstinence. This difference was not statistically significant, likely because of the small number of recovering alcoholics remaining in the sample through follow-up (N = 31) (reported in Hurt et al., 1995).

Contrasting results at the end of treatment were reported by Hays et al. (1999), Kalman et al. (2006). In a secondary analysis of data from a double-blind, dose-ranging study of the patch (Jorenby et al., 1995). Hays et al. (1999) categorized subjects into those with current, past or no history of alcohol problems and examined smoking cessation rates. Smokers without a history of alcohol problems were more likely to be abstinent at the end of treatment than smokers with either a current or past history. No alcohol-related exclusion criteria were reported for this trial. Kalman et al. (2006) recruited a sample of smokers who all reported a past history of alcohol dependence and a current period of abstinence, similar to the study by Hughes et al. (2003b). The Kalman trial was also a dose-ranging study of the patch but did not include a placebo control. Although smokers were required to have a longer current period of abstinence (i.e. 2 months) than smokers in the Hughes trial (i.e. 1 month), the typical duration of abstinence turned out to be much shorter (median = 4 months vs 60 months). In the Kalman trial, a longer duration of alcohol abstinence at enrollment was associated with an increased likelihood of smoking cessation at the end of treatment.

Similar findings were obtained at the follow-up time points. The difference based on alcohol history at the end of treatment in Jorenby et al. (1995) trial continued to be observable but was no longer statistically significant (reported in Hays et al., 1999). Kalman et al. (2006) reported that the advantage associated with longer duration of alcohol abstinence at enrollment was still statistically significant after 36 weeks.

The one long-term treatment study, a double-blind nicotine gum trial (Hughes et al., 1989) reported a significant advantage in continuous abstinence over the course of a year for smokers without a history of alcohol problems. While participants were instructed to begin tapering their gum use after 3 months, gum was available to them for an entire year. Smokers with current alcohol abuse were excluded from this trial.

Four trials examined whether alcohol history influenced response to NRT at the end of a treatment period lasting less than 6 months, and a fifth trial examined this question...
Table 2. Findings related to influence of alcohol status on smoking cessation and influence of smoking cessation on alcohol use

<table>
<thead>
<tr>
<th>1st Author, year (secondary publications in parentheses)</th>
<th>Design and n’s by randomized group</th>
<th>Definition of alcohol problem and baseline alcohol characteristics</th>
<th>Type of smoking outcome</th>
<th>Smoking abstinence rate at end of treatmenta</th>
<th>Smoking abstinence rate at 6–12 months follow-up</th>
<th>Percent lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croghan et al., 2003</td>
<td>Open-label patch (N = 459), spray (N = 463), both (N = 462)</td>
<td>Definition: History of alcohol problems = SAAST score of 7 or higher</td>
<td>Seven day point-prevalence</td>
<td>AH: 19.7% NH: 20.8% Interaction not significant</td>
<td>AH: 5.6% NH: 8.4% Interaction not significant</td>
<td>70%</td>
</tr>
<tr>
<td>Hughes et al., 1993 (Hughes, 1993)</td>
<td>Placebo (N = 105) gum (N = 210)</td>
<td>Definition: Response to ‘have you ever had a problem from alcohol or drug use’ (12%, N = 38) Baseline data: Median drinks per week = 2 (non-history), 0 (past alcohol history); weekly drinking reported by 76% (non-history), 42% (past alcohol history)</td>
<td>Continuous (i.e. point-prevalence abstinence at 1, 6 &amp; 12 months assessments)</td>
<td>AH: 10% (active) 2% (placebo) NH: 20% (active) 18% (placebo)b</td>
<td>Interaction significant</td>
<td>17%</td>
</tr>
<tr>
<td>Hughes et al., 2003a (Hughes et al., 2003b)</td>
<td>Placebo patch, 21 mg, 35 mg, 42 mg Total N = 1039</td>
<td>Definition: Past alcohol problems = SADD score ≥9 reporting on drinking 1 year ago and prior (15%, N = 160) Mean past SADD = 19 (9), Mean current SADD = 3 (4); 46% reported at least 1 current problem</td>
<td>Continuous with 2 week grace period</td>
<td>AH: 14% NH: 11% Interaction not significant</td>
<td>AH: 10% NH: 8% Interaction not significant</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hughes et al., 2003b</td>
<td>Placebo patch (N = 54), 21 mg (N = 61)</td>
<td>Definition: DSM-IV dependence diagnosis; mean number of past dependence criteria endorsed = 6 (1) mean past MAST = 34 (12) Baseline data: 79% current AA attendee; 75% past alcohol treatment, 7% current alcohol treatment; median abstinence: 60 months (35 months), fewer than 10% abstinent ≤1 year</td>
<td>Continuous with 2 week grace period</td>
<td>AH: 25% (active) 19% (placebo)</td>
<td>AH: 21% (active) 15% (placebo)</td>
<td>73%</td>
</tr>
<tr>
<td>Hurt et al., 1994 (Hurt et al., 1995)</td>
<td>Placebo patch (N = 120), 22 mg (N = 120)</td>
<td>Definition: Recovering alcoholic = 7 or higher on SAAST; no drinking in past year (13%, N = 31) End of treatment: 7 day point-prevalence; 1 yr. follow-up: 3 month point-prev.</td>
<td>AH: 46% (active) 17% (placebo) NH: 47% (active) 21% (placebo) Interaction not significant</td>
<td>AH: 9% (active) 11% (placebo) NH: 31% (active) 15% (placebo) Interaction: non-significant trend</td>
<td>AH: 25% (active) 15.1% (past) NH: 26.7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Jorenby et al., 1995 (Hays et al., 1999)</td>
<td>Double-blind 22 mg (N = 190) or 44 mg (N = 192) patch followed by open-label tapering</td>
<td>Definition: Past problems = no to ‘Do you have a drink now and then’ and yes to ‘If you don’t drink now, did you stop drinking because of problems with alcohol?’ (14%, N = 53) Remaining subjects classified by SAAST: No alcohol problem: &lt;7 Current alcohol problem: ≥7</td>
<td>Seven day point-prevalence</td>
<td>AH: 41.7% (current) 34% (past) NH: 58%b Interaction not reported</td>
<td>AH: 25% (current) 15.1% (past)</td>
<td>16.5%</td>
</tr>
</tbody>
</table>

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et al measured by abstinence rates at the end of treatment (Hurt problems as it is for those without alcohol histories as NRT is at least as effective among smokers with past alcohol after 1 year. Findings from the shorter trials suggested that NRT is more effective than placebo among smokers with past drug/alcohol problems but not significantly more effective than placebo among smokers without past drug/alcohol problems.

In summary, the limited data available suggest that smokers with past alcohol histories have overall success rates similar to those without past alcohol histories and that they benefit from NRT to the same degree. However, very little information is available on individuals with a current history of alcohol problems, who may find it particularly difficult to quit smoking. Consistent with this hypothesis, Kalman et al.
(2006) found that a shorter period of alcohol abstinence was associated with decreased likelihood of smoking cessation. In the only NRT study in the present review to define a group of smokers with current alcohol problems for the purpose of analysis, smokers with current alcohol problems were less likely to be abstinent at the end of treatment than individuals without a history of alcohol problems (Hays et al., 1999).

**Bupropion SR.** Three of the four bupropion SR trials reported no end-of-treatment difference in likelihood of smoking cessation based on alcohol history (Hurt et al., 1997; Hayford et al., 1999; Aubin et al., 2004; Simon et al., 2004). The one exception was a trial conducted by Hays et al. (2001), who reported a significant advantage for smokers with no alcohol history at the end of a 7-week open-label period that was not seen among responders in a subsequent 45-week placebo-controlled maintenance study (reported in Hurt et al., 2002). In this trial, alcohol consumption was commonly cited as a reason for smoking relapse regardless of whether participants received bupropion SR (22.4%) or placebo (20.3%) (reported in Durcan et al., 2002). These data were not broken down by alcohol history. All four bupropion SR trials reported some sort of alcohol-related exclusion criteria.

A slightly different pattern of findings was observable at follow-up. Aubin et al. (2004) reported an advantage for smokers without current alcohol problems in 6-month continuous abstinence, but not point-prevalence abstinence. In contrast, Simon et al. (2004) reported a significant advantage in cessation for smokers with alcohol histories at 6-month follow-up, and Hayford et al. (1999) reported a nonsignificant trend in the same direction after 1 year (data from the Hurt et al., 1997 trial).

Three trials evaluated whether the efficacy of bupropion SR differed according to past history of alcohol problems. Two trials reported no significant differences in efficacy by alcohol history either at end of treatment or at follow-up (Hurt et al., 1997; Hayford et al., 1999; Aubin et al., 2004), and a third trial reported no significant interaction between treatment and alcohol history after a year of treatment (Hays et al., 2001; Hurt et al., 2002).

In summary, very limited information exists on how individuals with histories of alcohol problems fare in bupropion SR trials. What evidence exists favours a conclusion of no difference in likelihood of quitting smoking in bupropion trials and no differential efficacy of bupropion SR at end of treatment based on past alcohol history. However, no study has examined how current alcohol use or problems influence treatment response.

**Effects of smoking cessation on alcohol use**

Only the two NRT trials that specifically recruited patients with past alcohol dependence reported on the effect of smoking cessation on alcohol use. Hughes et al. (2003b) reported that none of their participants relapsed to alcohol use. In contrast, Kalman et al. (2006) reported that 36 weeks following the beginning of treatment, 19% ($N=25$) had relapsed to alcohol use, all of whom eventually relapsed to smoking as well. Of these, 23 had less than 6 months of alcohol abstinence at the time of enrollment. For 15 of the 25, smoking relapse occurred before alcohol relapse.

**DISCUSSION**

Based on the present review, we conclude that smokers with recent or current alcohol histories have been excluded from a high proportion of smoking cessation pharmacotherapy trials, calling into question the generalizability of findings to this considerable subgroup of smokers. Further, it is possible that the proportion of trials excluding individuals with alcohol histories, current or past, has been underestimated. The standards for describing study methods have grown more stringent since the earliest NRT trials were published, and some trials may have excluded subjects based on alcohol-related variables but not included this information in the methods sections of the reports. Fortunately, few trials reported blanket policies excluding participants with any history of alcohol abuse or dependence, an extremely restrictive exclusion criterion. Several trials, including a number of recent ones, report their alcohol-related exclusion criteria with a lack of precision. We recommend that researchers be precise in specifying the instruments used to inform decisions regarding exclusion, the classifications used (e.g., a hazardous level of drinking, abuse, dependence) and the time frames involved (i.e., current, in the past 12 months).

The potential for increased seizure activity among those who are current heavy users of alcohol (Thomson/PDR, 2005) legitimizes the exclusion of these smokers from studies of bupropion SR. Also, the three trials of varenicline that qualified for inclusion in the present review were all conducted prior to the drug’s approval by the FDA. Given the strict controls that are the norm in efficacy trials aimed at obtaining FDA approval, the exclusion of smokers with alcohol abuse or dependence in the past year from these trials was justifiable. Given that there are no known or hypothesized contraindications to alcohol consumption with varenicline, future trials will hopefully address the efficacy of varenicline among those who drink heavily or have a history of alcohol problems.

Another conclusion is that few trials provide any alcohol-related information beyond inclusion/exclusion criteria, resulting in a dearth of information about the effects of alcohol use on smoking cessation and vice-versa. Further, the data that are available typically concern only classifications of patients as having or not having a history of alcohol problems. While co-morbidity between nicotine and alcohol dependence is common (Grant et al., 2004), current smokers are also more likely than nonsmokers to drink at subclinical (i.e., hazardous) levels (Kranzler et al., 2002), yet the representation of smokers who drink at hazardous levels in clinical trials is unknown.

The available data regarding effects of alcohol use on smoking cessation favour the conclusion that a past history of alcohol problems does not put smokers at a considerable disadvantage in smoking cessation attempts with NRT or bupropion SR. Hughes and Kalman (2006) arrived at a similar conclusion in their review. However, no definitive conclusion can be made, given that 7 of the 11 trials that examined the effect of alcohol history on smoking cessation reported some type of alcohol-related exclusion criteria, meaning that the findings of these trials are not necessarily representative of the subgroup of smokers with current alcohol problems. Also, six trials (four NRT, two bupropion SR) reported data favouring the opposing conclusion—that smokers with a past alcohol
history are at a disadvantage in smoking cessation—although these findings all had important caveats, such as statistically significant differences at end of treatment but not at follow-up or vice-versa. (See Hughes and Kalman, 2006 for discussion of reasons why smokers with alcohol histories may be less successful with smoking cessation.)

The two NRT trials that exclusively recruited participants with a history of alcohol dependence offered findings suggesting that a longer history of alcohol abstinence puts a smoker at an advantage over short-term abstainers with respect to both smoking cessation and maintaining abstinence from alcohol. The great success enjoyed by participants in Hughes et al. (2003b) trial in maintaining their alcohol abstinence in the course of their smoking cessation attempts (i.e. 100% success rate) was likely due in large part to the extensive period of alcohol abstinence they had already achieved prior to treatment. Kalman et al. (2006) reported on a subgroup of their participants who had difficulty maintaining abstinence from alcohol and smoking. An overwhelming percentage of this subgroup had less than 6 months of abstinence from alcohol prior to enrollment. Assessment of the impact of smoking cessation on maintaining alcohol abstinence was not a main goal of Kalman and colleagues’ study. Accordingly, they did not include a waiting list control or comparison group of alcohol dependent smokers who were not attempting to quit smoking in order to determine more definitively whether smoking cessation increases the risk of alcohol relapse above that expected in early abstinence from alcohol.

Our focus was on trials of approved pharmacotherapy that met or would have met criteria for inclusion in the NRT (Silagy et al., 2004) or antidepressant (Hughes et al., 2004) meta-analyses from the Cochrane group. Thus, the main limitation of this review is that our findings do not apply to nonpharmacologic, behavioural-only treatments for smoking cessation (see Sussman, 2002; Prochaska et al., 2004; Hughes and Kalman, 2006 for reviews including nonpharmacotherapy trials), nor do our findings apply to non-approved pharmacotherapies or to trials of approved pharmacotherapy not meeting standards for inclusion in a Cochrane review.

The clear implication of this review is that too few smoking cessation trials involving pharmacotherapy report data on prevalence of past alcohol problems or alcohol consumption. This trend should be reversed in subsequent research in order to assess the generalizability of pharmacotherapy efficacy to smokers with alcohol histories, both diagnostic and subclinical, and to determine whether pharmacotherapy-assisted smoking cessation might also decrease alcohol consumption among smokers who drink. It is particularly important that this issue be addressed for both NRT and varenicline since these medications have no known or hypothesized contraindications to alcohol consumption. At a minimum, information on drinking patterns at baseline should be reported in all trials, including the percentage of participants who abstain from alcohol (defined as no alcohol consumption over the past year), the percentage who meet criteria for hazardous drinking over the past year (defined as five or more drinks for men or four or more drinks for women on one or more occasions), and for drinkers, the frequency of any drinking and of hazardous drinking over a recent period, such as the past month. We also advise that alcohol consumption data be collected during treatment given the strong association between drinking and smoking (Grant et al., 2004). These data could be used to examine alcohol consumption as a precipitant of smoking relapse and to examine the effects of smoking cessation on alcohol consumption. For studies of novel pharmacotherapies, preliminary information about whether the medication affects drinking independent of smoking cessation could be ascertained, thereby furthering drug development. For example, there are several classes of new medications that may alter smoking and drinking behaviour (e.g. Corticotropin Releasing Factor antagonists, cannabinoid antagonists).

There are a number of methods for obtaining valid and reliable alcohol data regardless of the time and space limitations faced by researchers. Diagnostic and alcohol consumption information can be obtained using a brief self-report measure such as the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), which is made up of 10 items: 3 on alcohol dependence, 4 on alcohol-related problems and 3 on typical frequency and quantity of consumption. If time and staffing allow it, researchers might administer a clinical interview such as the alcohol disorders section of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al., 2002). It should be noted that the SCID does not include a measure of frequency and quantity of alcohol consumption. To date, the use of diagnostic measures in smoking cessation studies has typically been limited to screening/exclusion purposes. However, number of symptoms reported on measures such as the SCID or scores on measures such as the AUDIT could be examined as predictors for smoking cessation outcome.

To assess patterns of alcohol consumption, a task force appointed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommended the use of five self-report questions concerning typical frequency, typical quantity, peak quantity in a 24-h period, frequency with which this peak was reached and frequency of binge drinking, all in the past 12 months. A sixth question concerns lifetime peak quantity of alcohol consumed within a 24-h period (see www.niaaa.nih.gov/Resources/ResearchResources/TaskForce.htm). Other options include a portion of the Daily Drinking Questionnaire (DDQ; Collins et al., 1985), in which participants are asked to report on the frequency and quantity of alcohol consumption on each of the 7 days of the week during the past 3 months. Another more detailed method is the Timeline Follow-back Interview (TLFB; Sobell and Sobell, 1992) in which participants are presented with a calendar including holidays and other notable dates for a specified period. Participants are asked to indicate their quantity of consumption for each day on the calendar. The Form 90 interview (Miller and DelBoca, 1994) is essentially a combination of “grid” measures like the DDQ and calendar measures like the TLFB. While use of a TLFB or Form 90 is more time consuming than pencil-and-paper methods, the TLFB and Form 90 can be used simultaneously to obtain both alcohol and smoking data, potentially minimizing the additional time required. There are several biological measures of alcohol and its metabolites that can be used to verify participants’ self-reports, although there is currently no “gold standard” biological measure that supersedes all others in terms of reliability and validity and all are relatively...
CONCLUSIONS

Our review suggests that smokers with current alcohol problems are underrepresented in pharmacotherapy trials, raising questions about the generalizability of the results to this important subgroup of smokers. The studies that have examined specifically how a past history of alcohol problems influences treatment outcome generally support the conclusion that those with a past history of alcohol problems can quit smoking using NRT or bupropion SR at a rate that is similar to those without a history of alcohol problems. Almost all studies fail to report on the drinking patterns of participants at baseline and during treatment, and so very little information is available to examine whether smoking cessation pharmacotherapies alter alcohol drinking. Assessment of drinking-related variables in all future clinical trials of approved and novel smoking cessation pharmacotherapies would advance the field with minimal additional expenditures of time. Following up on the trials conducted by Hughes et al. (2003b) and Kalman et al. (2006), further trials are needed in which smokers with co-morbid alcohol histories, both diagnostic and subclinical, are actively sought in order to design effective treatment strategies for this considerable subgroup of smokers.

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REFERENCES

* Indicates a paper that was included in the review

See Hughes et al. (2004) for bupropion SR articles from the Cochrane Review of antidepressants for smoking cessation that were included in the review but not cited in the text and see Silagyi et al. (2004) for articles from the Cochrane Review of nicotine replacement therapy that were included in the review but not cited in the text.


