Health Technology Assessment Report 3: Prevention and relapse in alcohol dependence
Update December 2005

Introduction
Scotland has a significant alcohol misuse problem that can lead to a range of physical, psychological and social problems. The extent of the problem was reviewed in the Scottish Executive’s Plan for Action on Alcohol Problems (Scottish Advisory Committee on Alcohol Misuse, 2002), which estimated that associated problems cost Scotland at least £1 billion each year.\(^1\) In response to the Plan of Action, the Health Technology Board for Scotland (now part of NHS Quality Improvement Scotland) undertook a comprehensive review of current and optimal use of interventions to prevent relapse in alcohol dependent individuals who had undergone detoxification. This review was published as Health Technology Assessment Report 3: Prevention of relapse in alcohol dependence, in December 2003.\(^2\) Since the publication of this report a number of new randomised clinical trials, considering pharmacological intervention strategies, have been reported. This Update presents a re-analysis of the available clinical trial data incorporating findings published since 2003.

Pharmacological interventions used in alcohol dependence for prevention of relapse include medication such as:

- **Disulfiram** (Antabuse\(^5\)) which induces unpleasant symptoms if the patient consumes alcohol.
- **Acamprosate** (Campral\(^6\)) designed to prevent alcoholic relapse by decreasing cravings and countering the reinforcing properties of alcohol.
- **Naltrexone** (Revia\(^5\)) an opioid antagonist believed to act through the modulation of reward mechanisms.

These treatments represent an additional therapeutic option for use as adjunct to or in conjunction with psychosocial interventions.\(^2\) New data considered for inclusion in this update comprised four placebo-controlled trials using acamprosate and eight using naltrexone. In addition, a number of studies are discussed that directly compare various pharmacological therapies.

Acamprosate

Two recent clinical trials of acamprosate used suitable patient populations and considered outcomes appropriate for inclusion in the new meta-analysis of clinical effectiveness.\(^3-6\) The incorporation of these studies resulted in a slight
change in the odds ratio for treatment success from 1.73 (95% CI: 1.36, 2.20) to 1.75 (95% CI: 1.43, 2.15), confirming the statistically significant beneficial effect of acamprosate in preventing relapse in newly detoxified alcohol dependent patients.\(^2\)

Keifer et al. (2003/2004) enrolled 160 patients, who were randomised to three months of treatment with acamprosate, and assessed the proportion able to control their alcohol consumption. A statistically significant reduction in relapse rate was seen following acamprosate treatment compared with placebo after 12 weeks of therapy (50% vs. 75%, p<0.05).\(^3\),\(^4\)

The second study compared 75 patients, who were randomised to three months of treatment with either placebo or acamprosate, and assessed the proportion who abstained from drinking. A statistically significant difference (p=0.048) was seen between treatment groups by the end of the study, with 43% of patients in the acamprosate treatment group and 20% of patients in the placebo group remaining abstinent.\(^5\),\(^6\)

**Naltrexone**

Five randomised clinical trials of naltrexone used suitable patient populations and considered outcomes appropriate for inclusion in the new meta-analysis.\(^3\),\(^4\),\(^7\)\(^-\)\(^10\) The incorporation of these studies resulted in a slight change in the odds ratio for treatment success from 1.46 (95% CI: 1.12, 1.90) to 1.50 (95% CI: 1.18, 1.92), confirming the statistically significant beneficial effect of naltrexone in preventing relapse in newly detoxified alcohol dependent patients.\(^2\)

Keifer et al. (2003/2004) enrolled 160 patients, who were randomised to three months of treatment with either placebo or naltrexone, and assessed the proportion able to control their alcohol consumption. A statistically significant reduction in relapse rate was seen following naltrexone treatment compared with placebo after 12 weeks of therapy (35% vs. 75%, p<0.05).\(^3\),\(^4\) Naltrexone also reduced the rate of relapse to heavy drinking from 18.8% in the placebo treated patients to 7.9% (p=0.05) in a study by Guardia et al. (2002).\(^7\) In addition, naltrexone in combination with cognitive behavioural therapy reduced the number of heavy drinking days (p=0.045) and the severity of alcohol cravings (p=0.029) during treatment over a six-month period.\(^8\)

In a study of 111 patients receiving limited psychosocial therapy, naltrexone treatment showed a statistically significant benefit in preventing relapse to heavy drinking compared with placebo (63% vs. 90% relapse rate, p=0.017), though not beneficial in maintaining abstinence.\(^9\) In a similar study Latt et al. (2002) showed a statistically significant reduction in the proportion of patients relapsing to heavy drinking following naltrexone treatment compared with placebo (33.9% vs. 52.9%; p=0.047). In addition the median time to relapse was higher in the active treatment group (90 vs. 42 days).\(^10\)
Active comparator trials
In addition to the placebo controlled trials described, two active comparator studies have been published since preparation of Health Technology Assessment Report 3. Data from these studies were not included in the meta-analysis described in this update. Rubio et al. (2001) undertook an open, randomised direct comparison of the efficacy of naltrexone and acamprosate in reducing relapse in patients with alcohol dependence, over a 12-month period. This study showed naltrexone to result in a significantly longer time to first relapse (63 days vs. 42 days, p=0.02). At the end of the study 41% of patients in the naltrexone group and 17% in the acamprosate group had not relapsed (p=0.0009). In addition, a reduction in the severity of cravings and better compliance with psychosocial therapy were seen in the naltrexone treatment group.

In comparison the study by Kiefer et al. (2004) showed that 35% of patients relapsed after receiving naltrexone and 50% after receiving acamprosate during 12 weeks of therapy (not statistically significant). In this trial a group of patients was also treated with naltrexone and acamprosate in combination, which further reduced relapse rate to 28%. Combination therapy was reported to result in an additive effect, showing a statistically significant reduction in relapse rate compared with acamprosate (p<0.05).

In a second direct comparison study de Sousa and de Sousa (2004) showed that disulfiram was superior to naltrexone in terms of time to relapse (119 vs. 63 days, p=0.02) and abstinence at the end of the one-year study period (86% vs. 44% of patients, p=0.0009).

Conclusions
The inclusion of data from recent randomised clinical trials into the meta-analysis previously published in Health Technology Assessment Report 3 (2003), made no difference to consideration of the overall efficacy of acamprosate and naltrexone in preventing alcoholic relapse. As a result, acamprosate and naltrexone are both considered effective as adjuncts to psychosocial interventions in the treatment of alcohol dependence. Limited data indicates that naltrexone treatment may also be useful in cases where the availability of psychosocial interventions is restricted.

References


