

## Pharmacotherapy Utilisation in Alcohol Dependence

June 2016

### Key findings

- Drug utilisation for severe alcohol dependence is low.
- Of 43,087 patients, only 11.7% received pharmacotherapy to promote abstinence or reduce consumption in the first 12 months following diagnosis.
- 80.1% of patients did not receive psychosocial support or pharmacotherapy in the first 12 months following diagnosis.
- Males and those from the most deprived areas are least likely to receive pharmacotherapy.
- Persistence of prescribing appears poor for acamprosate and disulfiram, with less than 31% in both medication groups still receiving the medication after 6 months. This reduces to less than 17% after 12 months.

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### Background

This project used a longitudinal primary care database, the Clinical Practice Research Datalink (CPRD), to explore the utilisation of pharmacotherapy in the treatment of this clinical cohort. The treatment options available to reduce alcohol consumption are limited and a potential barrier to successful outcomes (e.g. abstinence). Pharmacotherapy is one available treatment option but appears to have low levels of utilisation in practice; however, no large-scale studies have been conducted in the UK to provide empirical evidence of relevant drug use.

The objectives of this project are:

1. Use expert knowledge and systematic investigation to develop a case definition for alcohol dependence in CPRD;
2. Compare treatment utilisation for patients with alcohol dependence;
3. Explore factors that may influence the treatment pathway;
4. Explore the national-level variation in the overall usage of medication for alcohol dependence; and
5. Compare the attrition of drugs used in alcohol dependence as indexed by persistence of prescribing.



## Outline of Methods

The data was sourced from the Clinical Practice Research Datalink (CPRD), a large database which contains anonymised primary care data from about 8% of the UK population. CPRD has been shown to be broadly representative of the UK population (Herrett et al., 2015) and at the time of data analysis covers 689 contributing practices with approximately 14 million patients. Data in the CPRD is routinely collected and includes patient demographic information, diagnoses, hospital referrals, prescription details, laboratory test results, and lifestyle variables such as smoking status and body mass index. The study was approved by the Independent Scientific Advisory Committee on 27 August 2014 (protocol 14\_151).

Diagnostic information is recorded in CPRD by General Practitioners using a hierarchical system of coding known as Read codes. Due to the large number of coding options available for many diagnoses, we undertook a systematic, multistep process to produce a case definition for alcohol dependence when using CPRD:

- 1) Exploration of the Read code database identified an initial list of 289 codes of interest, of which 144 were excluded after review because of lack of relevance or potential to indicate alcohol dependence.
- 2) Following extraction of the remaining codes in CPRD, we undertook several queries relating to code frequency and identifying patients with only one code of interest, which resulted in the decision to remove all codes relating to screening tools (e.g. FAST and AUDIT) and those appearing on  $\leq 10$  occasions.
- 3) All codes which describe an alcohol consumption pattern rather than an overt diagnosis were excluded because 'hard' clinical outcomes are more readily recorded in CPRD.
- 4) Our initial code list included a number of codes that referred to some level of treatment for alcohol misuse. These codes vary from brief interventions to admission to a detoxification facility. As one of the aims of our work is to understand how individuals identified as alcohol dependent are treated, it was decided that these codes should not be used to identify alcohol dependence. Furthermore, following a discussion with a clinical alcohol treatment specialist, it was proposed that these codes alone were in general not good indicators of alcohol dependence (i.e. many of the patients may be harmful or hazardous users rather than dependent).
- 5) Two clinical experts were asked to independently review the remaining 84 codes and dichotomise according to whether they believed the codes likely identified a case of alcohol dependence. Where agreement was clear between reviewers, codes were included or excluded accordingly. Discordant codes were discussed between the reviewers and members of the research team, and grouped according to consensus. This process resulted in 47 codes being included in the case definition for "alcohol dependence".

We utilised an 'open' cohort study design, such that each patient's time at risk commenced at a different time point, and some exited prior to the end of the study period. The study population consisted of all individuals in CPRD aged 16 years or older between 1 January 1990 and 31 December 2013. An incident (new) case of alcohol dependence was defined as: patients had to be registered at the start of the year (1 January), be in their current registration phase with the practice, be contributing data to CPRD throughout the year, and have no recorded history of alcohol dependence prior to start of the year. The date of incident diagnosis for alcohol dependence is known as the index date.

All patients were followed-up for treatment outcomes from the index date for either 12 months, the date of transfer of the patient out of the practice area, or the patient's death as recorded in the CPRD database, whichever came

first. The main treatment outcome was whether the patient was or was not treated with medication to promote abstinence from alcohol or reduce drinking to safe levels. The medications selected were acamprosate, disulfiram, naltrexone, baclofen and topiramate.

Secondary outcomes included whether patients were referred for psychosocial support and the factors that are associated with patients receiving a relevant pharmacotherapy. Where medication was prescribed, a sub-group analysis for prescribing persistence was performed. This analysis was only performed for acamprosate and disulfiram because of the low levels of utilisation of other pharmacotherapies. Prescribing persistence is defined as a patient having a record of a repeat prescription within 90 days of the expected end date of their last prescription. Patients were followed for persistence for 18 months after the issue of the first prescription. This timeframe allows observation of persistence beyond the initial six months of pharmacotherapy recommended by NICE, and particularly the use of acamprosate beyond its 12 month UK licence where continued use requires written consent from the patient. Patients were only able to contribute one event unless both acamprosate and disulfiram commenced on the same date.

Univariable and multivariable logistic regression was used to analyse factors associated with prescribing relevant medication. Life tables analysis was used to estimate the duration of medication persistence. All other analysis was performed using descriptive statistics. Statistical significance was considered as  $P < 0.05$ .

## Findings

Our case definition is designed to have high specificity for alcohol dependence. This decision was taken to ensure that our cohort was not skewed by individuals who had non-dependent alcohol use disorders (e.g., hazardous or harmful drinkers). When our selection criteria were applied, we identified 43,087 eligible patients.

Of this cohort, 5,047 (11.7%) were treated with a relevant pharmacotherapy in the 12 months following incident diagnosis. In addition, 856 (17.0%) of the patients who received medication also received adjunct psychosocial support during the same time period. Of the 38,040 that did not receive medication, 3,502 (9.2%) were reported to have received psychosocial support. The remaining 34,538 (80.1%) did not receive either mode of treatment in the 12 months after diagnosis.

Several factors that were considered in the logistic regression analysis produced significant results for association with prescribing. Males were significantly less likely to receive pharmacotherapy for their alcohol dependence. Those aged 16-24 were significantly less likely to receive medication than those aged 25-54, but the youngest age group were more likely to receive medication than those aged 65 and above. Compared with the least deprived quintile, those from the most deprived quintile were significantly less likely to receive medication. Patients from the other deprivation quintiles were also less likely to receive pharmacotherapy compared with the least deprived group, but statistical significance was only observed in the second least deprived quintile. Using England as the reference nation, patients diagnosed in Northern Ireland were significantly less likely to receive pharmacotherapy, whereas those diagnosed in Scotland or Wales were significantly more likely. The likelihood of receiving pharmacotherapy appears to have increased over time. Patients diagnosed with alcohol dependence in the more recent years (inclusive of 2000-2013) were significantly more likely to receive medication than those diagnosed in earlier years (1990-1994). These significant findings held when all variables were considered in a single model (multivariable analysis).

Persistence analysis revealed that many patients never received a repeat prescription, meaning there was a big drop in the number of persistent patients within the first two months after the first prescription being issued. Over six months, persistence was 25.6% for acamprosate and 31.3% for disulfiram; over 12 months persistence was 13.4% and 16.3%

respectively; and over 18 months persistence was 7.4% and 8.3% respectively.

## Implications

The data presented within this project summary highlight potential missed opportunities to engage patients with alcohol dependence on appropriate treatment pathways. Only 19.9% of the cohort received formal intervention (pharmacotherapy or psychosocial support), that was recorded in their primary care records. Drug utilisation was low in the cohort, 11.7%. Furthermore, of the patients that did receive either acamprosate or disulfiram, many did not receive a repeat prescription 90 days after the expected end of their first prescription, potentially highlighting a time point in the pharmacotherapy treatment pathway where extra attention is required to maintain engagement. General practitioners have previously been identified as being well-placed to identify (Rehm et al., 2015) and treat (Üstün and Sartorius, 1995) patients with alcohol problems, although the primary care of these patients is often devolved to secondary or tertiary services.

Although the utilisation of pharmacotherapy was limited across all assessed factors, certain trends deserve discussion and possibly further investigation. First, females were significantly more likely to receive pharmacotherapy, and potentially higher levels of harm among female dependent drinkers (Ashley et al., 1977, Nolen-Hoeksema, 2004) do not explain the reported gender-gap. It is possible that females may be more willing to engage with treatment pathways and thus accept pharmacological intervention for their alcohol dependence, but this requires further research. Second, although no linear trend was observed for deprivation and likelihood of receiving pharmacotherapy, those from the most deprived quintile were least likely to receive medication. This is perhaps surprising given the increased harm from alcohol reported in this group (Bellis et al., 2015), and suggest they may be poorly managed against quality standards reported in NICE guidelines (NICE, 2009). Third, the upward trend in prescribing in recent years means appropriate training and support needs to be given to GPs and other primary care staff to ensure they have the knowledge, skills and confidence that enables them to deliver appropriate clinical pathways, including both psychosocial support and pharmacotherapy.

We believe it is important to highlight some limitations of our work:

- Although we view the process adopted to create our case definition for alcohol dependence as a strength, we also recognise that it may have limitations. The definition was designed to have high negative predictive value and thus will likely capture patients with more severe alcohol dependence and will miss those with milder manifestations of the condition. This may have led to an underestimation of the incidence and annual presentation when alcohol dependence is defined according to NICE criteria (NICE, 2009).
- CPRD is a database that reflects primary care. Theoretical and empirical evidence suggests that many patients who are dependent on alcohol may attend secondary or tertiary services to receive either planned or emergency treatment that is related to their alcohol consumption.
- The entry of patients into this study depends on accurate coding by GPs.

## Conclusion

Pharmacotherapy in this cohort has the potential to increase success of clinical pathways but may be under-utilised in practice. This patient cohort is often difficult to engage and resistant to change. This may be compounded however by our lack of understanding of what therapies will be effective for each individual. This lack of stratification early in the treatment pathway may lead to a negative treatment outcome that disengages the patient. Looking ahead, translational research is required to identify novel therapeutic targets that can be developed into targeted therapies

for alcohol dependence or broader alcohol use disorders. A strong scientific grounding is required to ensure any stratification markers or therapies that are developed are effective and provide confidence to the prescriber and patient.

## Further Information

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## References

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