



Pharmacotherapy Utilisation in Alcohol Dependence

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EXECUTIVE SUMMARY

This study used the Clinical Practice Research Datalink (CPRD) to explore drug utilisation in the treatment of alcohol dependence. An initial process was undertaken to develop a case definition for alcohol dependence in CPRD. This process resulted in a case definition that was highly specific for alcohol dependence, thus meaning that our cohort was likely to contain those with more severe manifestations of the condition.

When our criteria were applied to CPRD, we identified 43,087 cases. Searches were performed on each patient's prescription data for the 12 months immediately after diagnosis. During this timeframe, 5,047 patients (11.7%) received at least one prescription for the treatment of alcohol dependence. Of the 38,040 that did not receive pharmacotherapy, 3,502 had documented psychosocial support. There was 17% of the cohort that received pharmacotherapy that had a record of adjunct psychosocial support. A total of 34,548 (80.1%) had no record for pharmacotherapy or psychosocial support in the first 12 months after diagnosis.

Males and those from the most deprived areas (indexed by practice location) were less likely to receive pharmacotherapy. Northern Ireland had the lowest rates of prescribing compared with the other UK Home Nations; Scotland and Wales had superior rates than England, which was used as the reference group. The rate of prescribing improved over time. The age at diagnosis also influenced prescribing with older patients (≥ 55) less likely to receive pharmacotherapy.

We also reported on the persistence of prescribing, which was 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-up for 18 months from the date of first prescription. Over 6 months, persistence (i.e. number still receiving pharmacotherapy) 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.

Within the final section of this report we provide some potential implications for these findings, and outline where opportunities might be being missed in this hard to engage population. We also compare our findings to other published work, and outline scope for future research.

INTRODUCTION

The term alcohol use disorder spans a spectrum of conditions with alcohol dependence as the most extreme phenotype. Alcohol dependence manifests from chronic, repeated exposure to ethanol which results in a cluster of behavioural, neurological, and physiological adaptations (WHO, 2010). The condition is complex with heterogeneous symptoms and various degrees of severity. However, it is well established that consumption of alcohol at the levels synonymous with dependence has substantial negative impact on the individual (Cargiulo, 2007) and society at large (Rehm et al., 2009, Newton et al., 2015).

Alcohol dependence is a major global public health concern, with the use and abuse of alcohol considered a leading risk factor for many non-communicable diseases (Jones et al., 2008). The mortality rate is high in this clinical population, being nearly four times the age-adjusted rate for people without alcohol dependence (NICE, 2009). There are further social and economic costs linked to excessive alcohol drinking, with the annual global bill estimated at 760 billion Euros (Rehm et al., 2009), and nationally £3.5 billion to the NHS (Department of Health, 2014).

The treatment options for those with alcohol dependence are limited, and most studies examining the outcome of people attending alcohol treatment find that 70% to 80% will relapse in the year following treatment, with the highest rate of relapse taking place in the first three months (Hunt et al., 1971, Raistrick, 2006). Those that remain abstinent from alcohol for the first year after treatment have a relatively low risk of relapse thereafter (Schuckit, 2009). In the UK, The National Institute for Health and Care Excellence (NICE) provides treatment guidelines that advocate psychological/social support and pharmacotherapy. Psychological interventions represent an important therapy in this patient group, but often need to be used in conjunction with other forms of treatment including pharmacotherapies. There are three pharmacotherapies that are indicated for use in this patient population in the UK: acamprosate, disulfiram and naltrexone. Each has its own specific mechanism of action but none are universally accepted by healthcare professionals, and medication appears to be under-utilised in this population.

Acamprosate is assumed to act by inhibiting the activity of N-methyl-D-aspartate (NMDA) receptors and thereby decreasing glutamatergic excitation associated with chronic alcohol intake and subsequent withdrawal (Tsai and Coyle, 1998, Mann et al., 2008). However, a series of animal and human studies postulated that the effects of acamprosate could be attributed solely to the active calcium component of the drug (Spanagel et al., 2013). Disulfiram is an aversive medication that blocks the enzyme aldehyde dehydrogenase. Thus, when alcohol is consumed there is an accumulation of acetaldehyde that cannot be metabolised, which results in an unpleasant reaction. Naltrexone's mechanism of action in the treatment of alcohol dependence has not been fully elucidated; however, interaction with the endogenous opioid system is suspected to play an important role. Naltrexone acts as a competitive antagonist at the opioid receptors in the central and peripheral nervous systems where it prevents binding of exogenous and endogenous ligands. This blockade decreases dopaminergic activity and thereby reduces the rewarding/pleasurable effects of alcohol (Ray et al., 2010).

A US survey revealed that only 9% of people needing treatment for alcohol dependence received pharmacotherapy for the disorder (Mark et al., 2009). In England, data from the Health and Social Care Information Centre indicate that there has been a year-on-year rise in the prescription of acamprosate and disulfiram, from 2003-2012; in 2012 there were a total of 178,247 prescriptions in primary and secondary care. However, this data does not account for other drugs that can be used for alcohol dependence and it fails to identify the number of patients prescribed medication alongside factors that determine drug choice.

By exploring the extent to which medications are utilised we can help provide a baseline for future quality targets and perhaps motivate healthcare providers to consider their current practice against quality standards provided in national guidelines. Although it should be noted that other factors may determine pharmacotherapy use for alcohol dependence including contraindications, patients' preferences and cost effectiveness. Furthermore, as advances are made in certain areas (e.g. pharmacogenomics) other factors may need to be considered to ensure good practice.

This project will use a longitudinal primary care database, the Clinical Practice Research Datalink (CPRD), to explore the utilisation of pharmacotherapy in the treatment of this clinical cohort. An important initial aspect of this work is to develop a case definition for alcohol dependence in CPRD. Although specific Read code exist for alcohol dependence, it is likely that these coding will not be uniform both within and between practices. Therefore, developing a strategy to capture the highest proportion of appropriate cases is required. The primary aims of this study are to: develop a case definition for alcohol dependence in CPRD and describe the utilisation of medication prescribed in primary care for the treatment of alcohol dependence.

The objectives for the study are:

1. Use expert clinical 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.

METHODS

The data was sourced from the Clinical Practice Research Datalink, 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. Quality checks are performed on all data to ensure that they reach the required standards for inclusion. Detailed information on CPRD is available elsewhere (Williams et al., 2012, Herrett et al., 2015). The study was approved by the Independent Scientific Advisory Committee on 27th August 2014 (protocol 14_151). Patient and practice confidentiality was maintained in accordance with the CPRD policy on personal data.

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, multiphase 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 ≤ 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); and
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; baclofen and topiramate are clustered as “other” for the purposes of data analyses. Nalmefene was provisionally considered but excluded due to the low number of prescriptions that existed in the cohort. Some included medications have indications that are not relevant for alcohol dependence. For each medication the British National Formulary (version 66) was consulted to identify other indications. Medications were deemed prescribed for other conditions if a patient had a diagnosis that was relevant to other indications up to 18 months before the medication in question being prescribed.

Secondary outcomes included whether patients were referred for psychosocial support and the factors that are associated with patients receiving a relevant pharmacotherapy. These factors were: gender; age across seven bands (16-24, 25-34, 35-44, 45-54, 55-64, 65-74, and 75 years and above); Index of Multiple Deprivation (IMD) 2010 quintiles (1 = least deprived; 5 = most deprived); UK Home Nations (England, Northern Ireland, Scotland, and Wales); and year of diagnosis across five bands (1990-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2013). Univariable and multivariable logistic regression was used to analyse factors associated with prescribing relevant medication. In the multivariable logistic model, we included all risk factors.

Where medication was prescribed, a subgroup analysis for prescribing persistence was performed in patients diagnosed between 2008 and 2013. 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. For example, if a patient had an acamprosate prescription that lasts 28 days, a repeat would need to be issued within 90 days otherwise persistence would be deemed to have “failed” and the patient would be censored. 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, which resulted in both medications being considered. Patients who died or left the practice during the time period for repeat prescribing were censored. Life tables analysis was used to estimate the duration of medication persistence.

All other data are presented using descriptive statistics. All analyses were performed using R. Statistical significance was considered as $P < 0.05$.

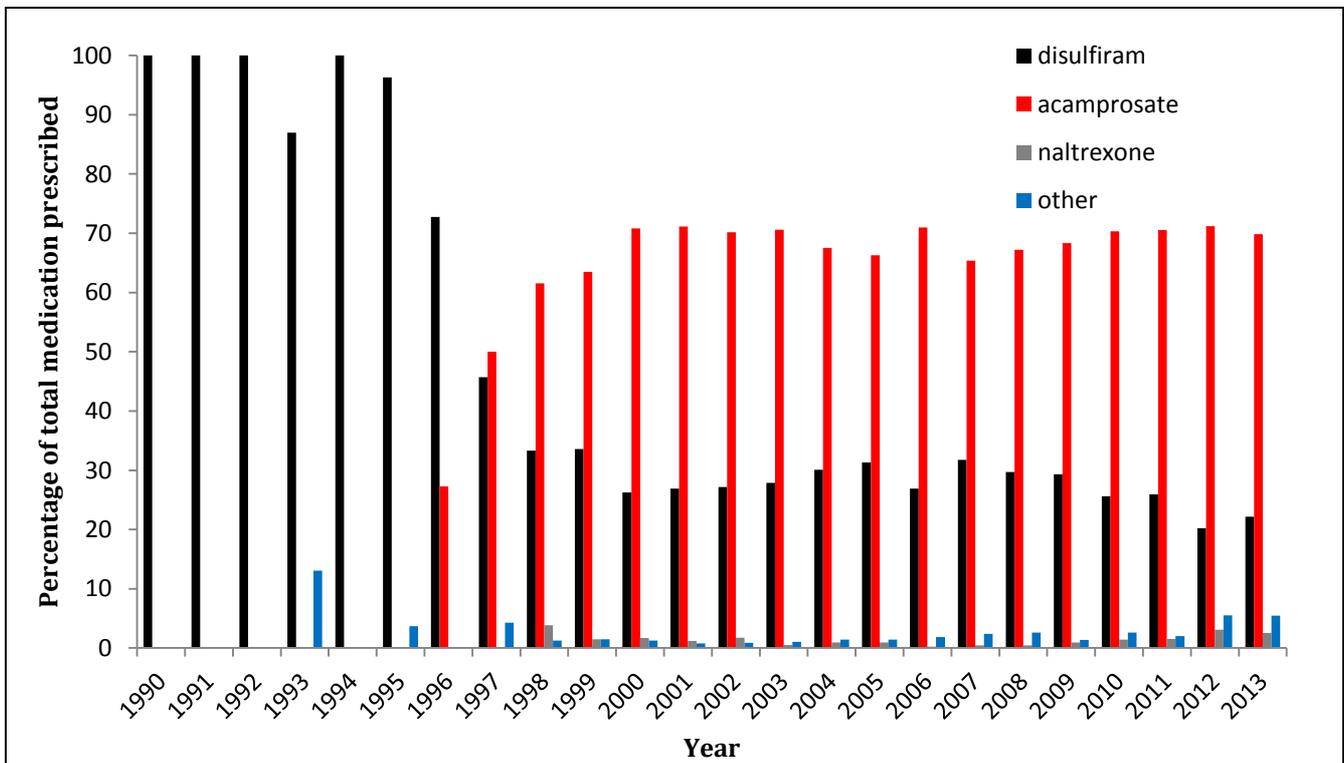
RESULTS

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: 29,132 (67.6%) were males, and the mean age at diagnosis was 45 years (SD = 14).

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 first 12 months after diagnosis.

Prescribing practices appear to have changed over time. Figure 1 shows the proportion of relevant medication users per drug by calendar year. All prescriptions were considered, thus some patients may have contributed to more than one medication group in a given year. During the early 1990s disulfiram was the predominant drug. By the late 1990s acamprosate had been introduced and became the most likely drug to be prescribed. The proportions of each drug prescribed remained relatively stable from 1998 onwards, when patients were around two times more likely to receive acamprosate than disulfiram. Naltrexone and other medications were used infrequently during the entire analysis period.

Figure 1: Medication as a proportion of total prescribing for alcohol dependence in each year (1990-2013)



Several factors that were considered in the univariable logistic regression analysis were predictors of treatment with pharmacotherapy (Table 1). 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 more recent years (inclusive of 2000-2013) were significantly more likely to receive medication than those diagnosed in earlier years (1990-1994).

In multivariable analysis including individual risk factors, the likelihood of receiving a prescription of a drug under investigation was strongly associated with several factors (Table 2). First, being male (Odds Ratio 0.74; 95% CI 0.70-0.79); from a practice based in the most deprived quintile (Odds Ratio 0.58; 95% CI 0.52-0.63); diagnosed at an older age (age 65-74 years Odds Ratio 0.59; 95% CI 0.48-0.74; age 75 years and above Odds Ratio 0.20; 95% CI 0.12-0.30); and diagnosed in Northern Ireland (Odds Ratio 0.79; 95% CI 0.68-0.91) were associated with decreased likelihood of receiving a prescription. Second, being diagnosed more recently (incident diagnosis made 2010-2013 Odds Ratio 2.64; 95% CI 2.16-3.25); diagnosed in Scotland (Odds Ratio 1.59; 95% CI 1.47-1.72) or Wales (Odds Ratio 1.43; 95% CI 1.29-1.59); and receiving a diagnosis at certain ages (age 25-34 years Odds Ratio 1.85; 95% CI 1.59-2.17; age 35-44 years Odds Ratio 2.05; 95% CI 1.77-2.38; age 45-54 years Odds Ratio 1.56; 95% CI 1.34-1.82) were associated with increased likelihood of receiving a prescription.

Table 1: Univariable analysis of factors associated with prescribing drugs for alcohol dependence

Risk Factor	OR	95% CI	P
Gender – Men vs Women	0.73	0.69 to 0.78	<0.0005
Age (years)			
16-24 (Reference)	1.00	Reference	Reference
25-34	1.73	1.49 to 2.02	<0.0005
35-44	1.95	1.69 to 2.27	<0.0005
45-54	1.52	1.31 to 1.77	<0.0005
55-64	1.07	0.91 to 1.26	0.407
65-74	0.60	0.48 to 0.74	<0.0005
≥75	0.20	0.12 to 0.31	<0.0005
IMD			
1 (least)	1.00	Reference	Reference
2	0.84	0.76 to 0.93	<0.0005
3	0.95	0.86 to 1.05	0.281
4	0.95	0.87 to 1.05	0.315
5 (most)	0.61	0.56 to 0.67	<0.0005
UK Home Nation			
England	1.00	Reference	Reference
Northern Ireland	0.80	0.69 to 0.93	0.004
Scotland	1.49	1.38 to 1.60	<0.0005
Wales	1.41	1.27 to 0.56	<0.0005
Year of Diagnosis			
1990-1994	1.00	Reference	Reference
1995-1999	1.21	0.97 to 1.52	0.100
2000-2004	2.26	1.86 to 2.78	<0.0005
2005-2009	2.52	2.08 to 3.09	<0.0005
2010-2013	2.80	2.30 to 3.44	<0.0005

OR = odds ratio, CI = confidence interval

Table 2: Multivariable odds ratios for the association between individual patient factors and prescription of drugs for alcohol dependence

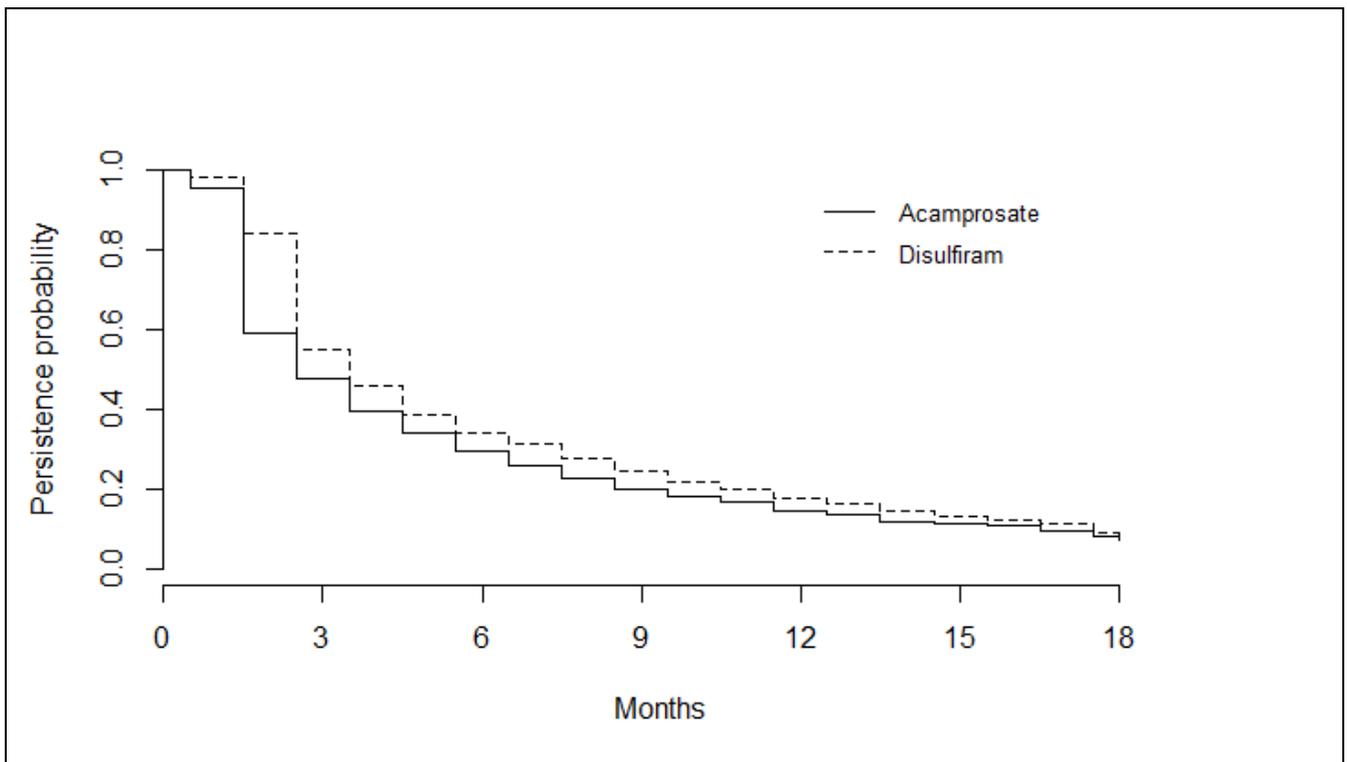
Risk Factor*	OR	95% CI	P
Gender – Men vs Women	0.74	0.70 to 0.79	<0.0005
Age (years)			
16-24 (Reference)	1.00	Reference	Reference
25-34	1.85	1.59 to 2.17	<0.0005
35-44	2.05	1.77 to 2.38	<0.0005
45-54	1.56	1.34 to 1.82	<0.0005
55-64	1.08	0.92 to 1.27	0.370
65-74	0.59	0.48 to 0.74	<0.0005
≥75	0.20	0.12 to 0.30	<0.0005
IMD			
1 (least)	1.00	Reference	Reference
2	0.83	0.75 to 0.92	<0.0005
3	0.92	0.83 to 1.02	0.122
4	0.94	0.85 to 1.03	0.200
5 (most)	0.58	0.52 to 0.63	<0.0005
UK Home Nation			
England	1.00	Reference	Reference
Northern Ireland	0.80	0.69 to 0.93	0.002
Scotland	1.49	1.38 to 1.60	<0.0005
Wales	1.41	1.27 to 0.56	<0.0005
Year of Diagnosis			
1990-1994	1.00	Reference	Reference
1995-1999	1.19	0.95 to 1.49	0.138
2000-2004	2.18	1.79 to 2.68	<0.0005
2005-2009	2.38	1.95 to 2.92	<0.0005
2010-2013	2.64	2.16 to 3.25	<0.0005

OR = odds ratio, CI = confidence interval

*Each risk factor is independently adjusted for other risk factors

Persistence analysis revealed that many patients never received a repeat prescription, meaning there was a big drop in the number of persistent patients within two months of the first prescription being issued (Figure 2). Over 6 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.

Figure 2: Persistence of prescribing for acamprosate and disulfiram for 18 months after the date of first prescription



DISCUSSION

In this project we have undertaken a process to develop a case definition for alcohol dependence in CPRD, and subsequently performed a drug utilisation study for the treatment of alcohol dependence. As outlined above, our major finding is the low utilisation of pharmacotherapy in the first 12 months after diagnosis in this cohort. Furthermore, many patients had no recorded pharmacotherapy or psychosocial support. The level of persistence for prescribing was generally low with less than a third of patients in both acamprosate and disulfiram subgroups still engaged with treatment at six months.

Implications

The data presented within this project highlight potentially 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 treatment pathway where extra attention is required to maintain engagement. Treatment retention and adherence are well-established predictors of long term outcomes (Gastfriend, 2014), and it has been found that patients who receive an alcohol-related medication have lower healthcare utilisation than those who did not (Mark et al., 2010, Baser et al., 2011). 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-use disorder, although the principal care of these patients is often devolved to secondary or tertiary services.

Although the utilisation of pharmacotherapy was limited across all assessed factors considered, certain trends deserve discussion and possibly further investigation as our cross-sectional design means we are unable to infer causality. First, females were significantly more likely to receive pharmacotherapy. We are aware that females are more likely to suffer harm from alcohol (Ashley et al., 1977, Nolen-Hoeksema, 2004) but this does not explain the reported gender-gap. It is posited that females may be more willing to engage with treatment pathways and thus accept intervention for their alcohol dependence. 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. Given the increased harm from alcohol reported in this group (i.e. the alcohol paradox) it is perhaps surprising that this group appears to be poorly managed against quality standards reported in NICE guidelines (NICE, 2009). Third, the upward trend in prescribing in recent years can be seen as encouraging but 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.

Comparison with other research

Data from the United States (US) (Mark et al., 2009) support our findings for the UK. However, it should be noted that the definition of alcohol dependence between studies may vary and comparisons should be considered with this caveat. It was estimated that 9% of the US population with alcohol dependence received at least one pharmacotherapy, compared with 11.7% in the present study. In the US there was an increase in the number of prescriptions for alcohol dependence, with an annual growth rate of 12.9% between 2003 and 2007. Furthermore, acamprosate was soon established as the market leader and the number of disulfiram prescriptions reduced. In further support of our findings and as mentioned in the introduction, data from the Health and Social Care Information Centre indicate that there has been a year-on-year (2003-2012) increase in the prescription of acamprosate and disulfiram in England. General Practitioners in the US prescribed proportionately more disulfiram than any other observed practitioner group, whether that is the case in the UK cannot be elucidated in this project.

The use of standardised methods across three healthcare databases revealed some variation in the level of prescribing in alcohol use disorder treatment. The number of patients that filled at least one prescription for alcohol pharmacotherapy ranged from 2.6 to 16.4% in 2006 (Thomas et al., 2013). Results from a study investigating medication use in the biggest of the aforementioned databases (Veterans Health Administration), found that approximately 3% of militarily veterans received pharmacotherapy for an alcohol use disorder (Harris et al., 2010). Some of our findings regarding patient factors that predict receipt of pharmacotherapy were supported by this study. Females were reported to be more likely to receive medication, as were those aged less than 55 years. Follow-up surveys with healthcare providers suggested several prominent barriers to prescribing including, perceived low patient demand, pharmacy procedures or formulary restrictions, lack of provider skills or knowledge regarding pharmacotherapy for alcohol dependence, and lack of confidence in treatment effectiveness (Harris et al., 2013). Some of these barriers were drug-specific meaning that individual strategies may be required to improve prescribing levels of each drug.

Persistence at six months for the two medications analysed in the current project was 25.6% for acamprosate and 31.3% for disulfiram. A study investigating persistence for naltrexone reported 14.2% of patients remained engaged at six months (Kranzler et al., 2008). Although we did not analyse naltrexone because of the low number of prescriptions, this comparison highlights the global issue of treatment retention in this clinical cohort.

Other psychiatric conditions are generally managed to a greater extent with pharmacotherapy. Further data from the Veterans Affairs healthcare system demonstrate that patients with dual diagnosis (i.e. alcohol use disorder and at least one other comorbid psychiatric condition) were less likely to receive pharmacotherapy for their alcohol disorder than their co-occurring condition (Rubinsky et al., 2015). The proportion receiving pharmacotherapy for alcohol ranged from 7% to 11%, whereas psychiatric conditions (i.e. bipolar, schizophrenia, major depressive disorder and posttraumatic stress disorder) ranged from 69 to 82%.

Tobacco addiction pharmacotherapy was also investigated with receipt reported at 34%.

Limitations

Our work is not without limitations, and some of the findings and inferences from this work need to be considered in the context of the following:

- 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. Although not unique, this treatment pattern means that patients on these pathways require GPs to follow-up and subsequently record any diagnosis in their primary care records to be eligible for our cohort.
- The entry of patients into this study depends on accurate coding by GPs. We are also restricted in our interpretation of incidence rates, as we rely upon the first recording in CPRD. There are possibilities that patients may have had alcohol dependence prior to either seeking medical help or registering with the practice.
- Medication use was defined as a prescription in the GP system, and not by actual issue of medication to the patient. Therefore, misclassification of medication use is possible since prescriptions recorded in the GP system may not have been dispensed by the pharmacy, or actually used by the patient. Furthermore, we are unable to monitor actual patient compliance to drugs, even if a repeat prescription is issued, as this does not imply that the medication is being used as directed by the medical practitioner.
- Data for deprivation status was obtained at practice level rather than for each individual. This is due to either missing data at patient level for this variable or lack of consent for data linkages from practices. Although practices are shown to be generally representative of their registered population, having individual deprivation status would have been informative due to the strong association with alcohol dependence.

CONCLUSION

Pharmacotherapy in this cohort has the potential to increase success of clinical pathways but still appears to be under-utilised in practice. This patient cohort is often difficult to engage and resistant to change. This may be compounded however by lack of education and poor 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.

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