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Pharmacological treatments for alcohol dependence: Evidence on uptake, inequalities and comparative effectiveness from a UK population-based cohort

Francesco Manca[1] | **Lisong Zhang**[1] | **Niamh Fitzgerald**[2] | **Frederick Ho**[1] | **Hamish Innes**[3] | **Bhautesh Jani**[1] | **Srinivasa Vittal Katikireddi**[1] | **Andrew McAuley**[3] | **Clare Sharp**[2] | **Jim Lewsey**[1]

[1]School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

[2]Faculty of Health Sciences and Sport & Institute for Social Marketing, University of Stirling, Stirling, United Kingdom

[3]School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, United Kingdom

Correspondence
Jim Lewsey, School of Health and Wellbeing, University of Glasgow, Clarice Pears Building, 90 Byres Road, Glasgow G12 8TB, United Kingdom.
Email: jim.lewsey@glasgow.ac.uk

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Abstract

Introduction: We assessed the prevalence of prescribing of certain medications for alcohol dependence and the extent of any inequalities in receiving prescriptions for individuals with such a diagnosis. Further, we compared the effectiveness of two of the most prescribed medications (acamprosate and disulfiram) for alcohol dependence and assessed whether there is inequality in prescribing either of them.

Methods: We used a nationwide dataset on prescriptions and hospitalisations in Scotland, UK ($N = 19{,}748$). We calculated the percentage of patients receiving alcohol dependence prescriptions after discharge, both overall and by socio-economic groups. Binary logistic regressions were used to assess the odds of receiving any alcohol-dependence prescription and the comparative odds of receiving acamprosate or disulfiram. Comparative effectiveness in avoiding future alcohol-related hospitalisations ($N = 11{,}239$) was assessed using Cox modelling with statistical adjustment for potential confounding.

Results: Upto 7% of hospitalised individuals for alcohol use disorder received prescriptions for alcohol dependence after being discharged. Least deprived socio-economic groups had relatively more individuals receiving prescriptions. Inequalities in prescribing for alcohol dependence existed, especially across sex and comorbidities: males had 12% (odds ratio [OR] 0.88, 95% confidence interval [CI] 0.81–0.96) and those with a history of mental health hospitalisations had 10% (OR 0.90, 95% CI 0.82–0.98) lower odds of receiving prescriptions after an alcohol-related hospitalisation. Prescribing disulfiram was superior to prescribing acamprosate in preventing alcohol-related hospitalisations (hazard ratio ranged between 0.60 and 0.81 across analyses). Disulfiram was relatively less likely prescribed to those from more deprived areas.

Francesco Manca and Lisong Zhang are joint first authors.

Discussion and Conclusions: Inequalities in prescribing for alcohol dependence exists in Scotland with lower prescribing to men and disulfiram prescribed more to those from least deprived areas.

KEYWORDS
acamprosate, alcohol dependence, comparative effectiveness, disulfiram, inequality

1 | INTRODUCTION

Excessive alcohol use is related to a range of adverse health outcomes and causes societal as well as individual harm. Alcohol dependence, as defined by the National Institute for Health and Care Excellence, is 'characterised by craving, tolerance, a preoccupation with alcohol and continued drinking in spite of harmful consequences' [1]. Globally, in 2016, the estimated age-standardised prevalence of alcohol dependence was 1320.8 cases per 100,000 people [2]. In the United Kingdom, between 1990 and 2013, the estimated rate of presentation to general practice with alcohol dependence was 171 and 76 per 100,000 male and female patients, respectively [3].

International guidelines recommend pharmacological treatments for patients with alcohol dependence subsequent to detox and alongside psychosocial support, with specific medications suggested based on patients' goals (reduction in consumption or abstinence), comorbidities and capabilities to cope with potential side effects [4-6]. Concerning the United Kingdom, the National Institute for Health and Care Excellence clinical guidelines recommend that for people with mild alcohol dependence a psychological intervention is offered, and for those with moderate/severe alcohol dependence these psychological interventions can be used in combination with pharmacological treatments [1]. In the United Kingdom, nalmefene, naltrexone, acamprosate and disulfiram are the medications for treating alcohol dependence, with the last two by far the most frequently prescribed. Acamprosate helps to maintain abstinence by restoring neurotransmitters affected by excessive alcohol use and contributing to managing alcohol cravings, but it is generally effective only in someone already sober [7,8]. Disulfiram causes unpleasant symptoms if alcohol is consumed, functioning as a deterrent to alcohol drinking [9]. Due to its strong effects, manufacturers suggest that patients and their carers are counselled on the disulfiram-alcohol reaction and the National Institute for Health and Care Excellence advises monitoring patients in the initial phases of treatment [10]. The evidence directly comparing disufiram and acamprosate is based on two open-label randomised trials [11,12] and one observational study. The trials had different outcomes. One showed disulfiram to be more effective in reducing alcohol intake, increasing the number of abstinence days and reducing risks of relapse [12]. The second found that disulfiram increased the percentage of abstinent patients and reduced risk of relapse [11]. In a small observational study ($N = 353$) that directly compares the two medications, it was found that disulfiram led to a longer duration of time to alcohol relapse and higher cumulative abstinence [13]. To enhance this evidence base, as well as further randomised trials with longer-term clinical outcomes, high-quality comparative effectiveness research is needed from large, unselected cohorts identified in routine care databases.

Despite evidence on effectiveness and their inclusion in clinical guidelines, pharmacological intervention for treating alcohol dependence is underutilised in clinical practice [14,15]. When there is evidence of underutilisation, it is important to understand whether this is caused, at least in part, by some groups being less likely to receive prescriptions than others. If this happens, inequalities in health outcomes can be exacerbated if those less likely to receive prescriptions are those who are most in need (i.e., more likely to experience severe alcohol dependence). Previous studies showed potential disparities in receiving pharmacotherapy for alcohol use disorder (AUD) across ethnic [16] and socio-economic [17] groups. Studies on the United Kingdom found similar patterns [15], with males and more deprived groups less likely to receive medication. However, specific variables such as comorbidities were not considered. Further, no study analysed the inequality of prescribing across medications with the same indication of alcohol dependence but different effectiveness on alcohol abstinence. Indeed, the health inequalities associated with the burden of alcohol could be also related to imbalances in prescribing medications with different levels of effectiveness across different groups beyond the prescribing action itself.

Using a nationwide routine health-care dataset of hospitalisations in Scotland (United Kingdom), we aimed to identify the rate of people hospitalised with a diagnosis of alcohol dependence and assess the percentage of patients receiving alcohol dependence prescriptions and the extent of any difference in the odds of receiving prescriptions (by age, sex and socio-economic deprivation). Further, we compare the real-world effectiveness of

acamprosate and disulfiram in avoiding the first alcohol-related hospitalisation. Lastly, we assess whether there are differences in prescribing between these two medications. Our intention is to add evidence on the inequality of the burden of alcohol associated with access to pharmacological treatment, as well as the relative effectiveness of the two most used medications for alcohol dependence in a nationwide study.

2 | METHODS

This study is composed of four different analyses included in three sections. Section 1 describes an analysis of rates of alcohol-related hospitalisations and prescriptions for alcohol dependence in this population. Section 2 analyses prescription inequality in two ways: first, the differences in odds of receiving any prescription for alcohol dependence across subpopulation groups; and second considering differences between those who receive prescriptions for acamprosate or disulfiram. Section 3 compares the effectiveness of disulfiram and acamprosate. The data sources were the same across analyses. Differences in cohort definition, size and methods of investigation are described in each section below, detailed cohort identification diagrams are in Data S1, Supporting Information.

2.1 | Data sources

We utilised a Scottish dataset linking three nationwide administrative health-care databases containing data from 2010 to 2019, dispensed prescriptions in the community (Scottish National Prescribing Information System [18]), general and acute hospitalisations (Scottish hospital records [SMR01] [19]) and deaths (National Records of Scotland) [20]. SMR01 uses International Classification of Diseases 10th Revision (ICD-10) codes to categorise patients' diagnoses.

2.2 | Analyses and pharmacological treatments

We evaluated rates and variations in the odds of receiving prescriptions for all medications in the UK guidelines with an exclusive indication for the treatment of moderate or severe alcohol dependence [1]: acamprosate, disulfiram and nalmefene. However, nalmefene was rarely prescribed and we focused on the two most common prescriptions: acamprosate and disulfiram and compared their effectiveness separately. We then ran a further analysis assessing imbalance in prescriptions between these two medications across different groups. Naltrexone is another medication that can be used for the treatment of alcohol dependence. However, in the United Kingdom, naltrexone was initially licensed only for the treatment of opioid dependence, and while it was used off-label for alcohol dependence, it became licensed for this purpose only in October 2022 [21] (out of our study period). Given that naltrexone is not exclusively indicated for alcohol dependence, and its extremely low prescription levels compared to acamprosate and disulfiram in the United Kingdom [15], we excluded it from our analyses.

2.3 | Statistical analyses

Table 1 summarises the outcome of each analysis, which are explained in detail in the sections below.

2.3.1 | Rates

We assessed the incidence rates of alcohol dependence over time. Specifically, we checked the rate of patients with a first hospitalisation of 'mental and behavioural disorders due to alcohol' (ICD F10.x, main diagnostic position). We used data from national Scottish population records as denominators to compute the percentage of individuals with alcohol dependence medications dispensed within 60 days after discharge. We determined 60 days after discharge as the maximum window to link the alcohol dependence prescription with the hospitalisation event. We assessed differences in prescriptions across age, sex and socio-economic group.

2.3.2 | Inequality

We identified a cohort between January 2010 and March 2019 with a first hospitalisation of AUD diagnoses in the main diagnostic position (see above for inclusion criteria) screening back for 10 years to avoid previous alcohol-related hospitalisation. We determined whether patients received prescriptions within 60 days from their diagnosis. We repeated the same analysis on prescriptions received any time after the diagnosis. Logistic regression was used to assess whether age, sex and socio-economic deprivation area of the patient (measured through the Scottish index of multiple deprivation [22]) were associated with the odds of receipt of prescriptions for alcohol dependence. We also adjusted for comorbidities

TABLE 1 Summary sections and outcomes.

Summary section	Outcome
Rate	a. Incidence of first AUD hospitalisation in the Scottish population b. Percentage of AUD hospitalised individuals receiving prescriptions for alcohol dependence after discharge
Inequality	
Inequality in prescription	Odds of receiving prescription ever before, 60 days before, 60 days after or ever after the first AUD hospitalisation
Inequality between acamprosate and disulfiram	Odds of receiving acamprosate vs disulfiram prescriptions 60 days after or ever after the first AUD hospitalisation
Comparative-effectiveness	Time to first AUD hospitalisation

Abbreviation: AUD, alcohol use disorder.

(measured through Charlson comorbidity score [23]), previous hospitalisation related to mental health (any ICD-10F code) and for receipt of alcohol dependence prescriptions before hospitalisation. Whenever the relationship between covariates and the dependent variable was not linear (e.g., for age), restricted cubic splines [24] were used to allow for curvi-linear associations. After excluding missing data on sex, level of deprivation or age ($n = 278$), the final sample in this inequality analysis was 19,748 individuals. We also ran an additional analysis using as the dependent variable obtaining a prescription before the hospitalisation (yes/no). This was to assess imbalances of prescriptions that aim to prevent patients being hospitalised.

2.3.3 | Comparative effectiveness

We identified patients with a first prescription of acamprosate or disulfiram without any previous hospitalisation for F10.x in the previous 10 years. The outcome under study was time to first hospitalisation for F10.x after prescription, the independent variable of interest was whether the patient was prescribed acamprosate or disulfiram. We assessed time to first hospitalisation using four approaches—Cox regression: unadjusted, adjusted for covariates (age, sex, socio-economic deprivation), covariates used in propensity scores (inverse probability weight) and an instrumental variable approach using physician prescribing preferences (IV PPP) [25]. For IV PPP, we implemented two-stage residual inclusion (2SRI) models which provide consistent estimators in non-linear models [26]. The instrument we used in our 2SRI-Cox model is the proportion of acamprosate prescribed by a particular physician in the last 10 prescriptions. While the first two approaches controlled for measured confounding by indication, the third one, providing assumptions are met, accounted for potential unmeasured confounding. Instrumental variables are useful whenever there is likely to be unmeasured confounding that would create bias in comparative effectiveness estimates that only account for measured covariates. After excluding for missing data across the covariates ($n = 67$), the sample size for the comparative effectiveness analysis was ($N = 11{,}238$).

The goodness of fit of every model and test for survival analyses assumptions are reported in Data S1. The analysis was performed with Stata 17 [27] and the instrumental variable models for the comparative effectiveness analyses was performed in R, using packages 'AER' and 'survival'.

3 | RESULTS

The socio-demographics regarding the imbalance in receiving prescriptions and comparative effectiveness cohorts are summarised in Table 2. Individuals in the inequality cohort had an average of 44.8 (±18) years of age, and 68% were male. Individuals receiving prescriptions were on average more than 1 year older. In the comparative effectiveness analysis cohort acamprosate was prescribed more than twice as frequently as disulfiram and it was prescribed relatively to less males and to more deprived areas.

3.1 | Rates

The rate of AUD hospitalisation slightly increased over the years (see Figure 1); it was between 3 and 4 per 10,000 inhabitants in our study period, with 6–7% individuals receiving a prescription for alcohol dependence medications within 60 days after their first hospitalisation. This percentage varied across socio-economic groups, with the least deprived groups receiving more, in percentage terms, prescriptions after hospital discharge compared to the most deprived groups (apart from in 2016). There were also differences between age categories with groups between 36 and 65 years of age receiving more prescriptions in percentage terms. In contrast, there were no relevant differences in receiving prescriptions between sexes (for figures by age groups and sex see Data S1).

TABLE 2 Summary of socio-demographic variables for cohorts with a diagnosis of alcohol dependence.

			Sex		Charlson comorbidity index		Previous hospitalisations for mental health	Socio-economic deprivation in quintiles				
	N.	Age, years mean (±SD)	Male	Female	0	≥1		First (most deprived)	Second	Third	Fourth	Fifth (least deprived)
Inequality												
Total (%)	19,748	44.8 (±18)	13,463 (68%)	6285 (32%)	14,049 (71%)	5699 (29%)	6086 (31%)	5853 (30%)	4896 25%)	3925 (20%)	2964 (15%)	2110 (11%)
Individuals receiving prescriptions	1240	46.1 (±11)	841 (68%)	399 (32%)	888 (72%)	352 (28%)	408 (33%)	275 (22%)	340 (27%)	278 (22%)	205 (17%)	142 (11%)
Acamprosate[a]	840	46.5 (±11)	541 (64%)	299 (36%)	584 (70%)	256 (30%)	267 (32%)	197 (23%)	236 (28%)	183 (22%)	136 (16%)	88 (10%)
Disulfiram[a]	349	45.3 (±11)	222 (64%)	127 (36%)	262 (75%)	87 (25%)	120 (34%)	67 (19%)	92 (26%)	80 (23%)	61 (17%)	49 (14%)
Not receiving prescriptions	18,508	44.2 (±18)	12,662 (68%)	5846 (32%)	13,161 (71%)	5347 (29%)	5678 (31%)	5578 (30%)	4556 (25%)	3647 (20%)	2759 (15%)	1968 (11%)
Comparative effectiveness												
Acamprosate	8016	44.9 (±12)	4911 (61%)	3105 (39%)	-	-	-	2874 (36%)	1969 (25%)	1451 (18%)	1030 (13%)	692 (9%)
Disulfiram	3223	43.2 (±11)	2088 (65%)	1135 (35%)	-	-	-	964 (30%)	814 (25%)	626 (19%)	473 (15%)	346 (11%)

[a]The number of patients receiving acamprosate and disulfiram prescriptions does not equate to total number of patients as nalmefene was also prescribed.

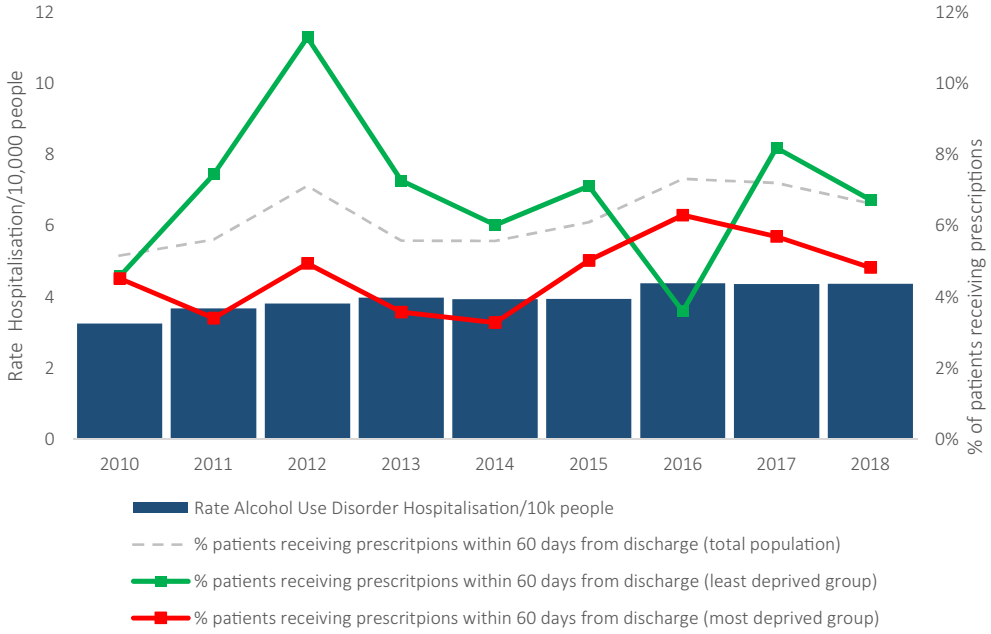

FIGURE 1 Trends and rates of alcohol use disorders hospitalisation and percentage of such individuals receiving alcohol dependence prescriptions within 60 days of the discharge date. In the figure, 2019 was removed as data were only until March.

3.2 | Inequality

The odds of receiving prescriptions with indications for alcohol dependence after 60 days from an AUD hospitalisation was associated with sex (males had 12% lower odds of receiving a prescription than females, odds ratio [OR] 0.88, 95% confidence interval [CI] 0.77–1.00—see Table 3, column 1) and age (odds increasing until 43 years of age and then decreasing in older individuals—see Data S1 for graphs showing curvi-linear association with age). Socio-economic deprivation was also associated with odds of receiving prescriptions after a secondary health-care episode: living in least deprived areas was significantly associated with an increase in odds of receiving prescriptions of at least 41% (OR 1.41, 95% CI 1.18–1.68—for the second most deprived quintile compared to the most deprived) (Table 3, column 1). Lastly, receiving prescriptions prior to hospitalisation was associated with a 23-fold increase (OR 23.42, 95% CI 19.63–27.94) in the odds of receiving prescriptions later. Being previously hospitalised for other mental health diagnoses did not have a strong association with prescriptions just after being discharged but became more precise and statistically significant (OR 0.90, 95% CI 0.82–0.98) when we did not include the 60 days constraint after hospitalisation (Table 3, column 2). In contrast, socio-economic deprivation reduced its impact in odds of receiving prescriptions after removing the 60 days constraint.

When we analysed odds of receiving prescriptions before hospitalisation (Table 3, columns 3 and 4), comorbidities (and in particular mental health comorbidities) were associated with increased odds of receiving prescriptions (OR 1.32, 95% CI 1.20–1.44). In contrast, they were associated with reduction in the odds of getting prescriptions after hospitalisation in the long term (OR 0.90, 95% CI 0.82–0.98—Table 3, column 2). We found that the odds of receiving disulfiram instead of acamprosate were associated with deprivation and with the kind of medication received before hospitalisation (Table 3, columns 5 and 6). Receiving disulfiram prior to hospitalisation was associated with an increase in odds of receiving disulfiram after (OR 6.01, 95% CI 4.08–9.08). Conversely, receiving acamprosate before hospitalisation was associated with a decrease in the odds of getting disulfiram after.

3.3 | Comparative effectiveness

The comparative effectiveness modelling shows that prescribing disulfiram, compared to acamprosate, was associated with a reduced risk of first alcohol-related hospitalisation. All three methods were consistent in their findings (Figure 2). Instrumental variable modelling produced point estimates showing larger associations but with wider confidence intervals. Point estimates across the four methods varied from hazard

TABLE 3 Inequality models of prescriptions after alcohol dependence diagnosis in primary care and AUD hospitalisations in secondary care (odds ratios and confidence intervals shown).

	Any alcohol dependence prescription after 60 days from hospitalisation (1)	Any alcohol dependence prescription ever from hospitalisation (2)	Any alcohol dependence prescriptions 60 days prior first hospitalisation (3)	Any alcohol dependence prescription ever before first hospitalisation (4)	Acamprosate versus disulfiram prescriptions within 60 days of hospitalisation—acamprosate reference (5)	Acamprosate versus disulfiram prescriptions ever after hospitalisation—acamprosate reference (6)
Sex (female reference)	0.88 (0.77–1.00)	0.88 (0.80–0.96)	0.79 (0.67–0.94)	0.72 (0.65–0.78)	1.00 (0.76–1.32)	1.10 (0.93–1.29)
Charlson Comorbidity Index (0 reference)						
≥1	0.92 (0.80–1.07)	0.91 (0.834–1.00)	1.04 (0.87–1.24)	1.09 (0.99–1.20)	0.84 (0.67–1.15)	0.77 (0.64–0.93)
Mental health comorbidity	0.92 (0.80–1.05)	0.90 (0.82–0.98)	1.28 (1.09–1.51)	1.32 (1.20–1.44)	1.11 (0.83–1.48)	1.14 (0.96–1.35)
Socio-economic deprivation (1 = most deprived, reference)						
2	1.41 (1.18–1.68)	1.05 (0.94–1.17)	1.57 (1.25–1.95)	1.28 (1.13–1.44)	1.20 (0.81–1.78)	1.42 (1.14–1.77)
3	1.62 (1.35–1.96)	1.11 (0.99–1.25)	1.33 (1.04–1.70)	1.32 (1.16–1.50)	1.41 (0.94–2.13)	1.29 (1.02–1.63)
4	1.54 (1.25–1.89)	1.07 (0.94–1.22)	1.52 (1.17–1.96)	1.37 (1.19–1.58)	1.41 (0.91–2.19)	1.47 (1.14–1.90)
5	1.45 (1.16–1.83)	1.12 (0.97–1.29)	1.63 (1.23–2.16)	1.50 (1.29–1.75)	1.92 (1.187–3.10)	1.78 (1.35–2.35)
Previous prescription in the previous 60 days[a]						
Any	23.42 (19.63–27.94)					
Acamprosate						0.51 (0.37–0.70)
Disulfiram						6.48 (4.82–8.71)
Previous prescription ever[a]						
Any		5.12 (4.66–5.63)				
Acamprosate					0.45 (0.30–0.69)	
Disulfiram					6.08 (4.08–9.07)	

Note: As the relationship with age was not linear, we applied spline, see graph for interpretation of spline in Data S1.

Abbreviation: AUD, alcohol use disorder.

[a]Any stands for 'any kind of prescription for alcohol dependence' and it is used in models referring to the overall inequality after hospitalisation (1) and (2), the variable is a dichotomous (0 = no prescriptions and 1 = prescriptions). Models (5) and (6), comparing acamprosate and disulfiram, specify the kind of prescription received before hospitalisation in a trichotomous variable (0 = no previous prescriptions, 1 = previous acamprosate prescriptions, 2 = previous disulfiram prescriptions) where the reference is 'no previous prescription'.

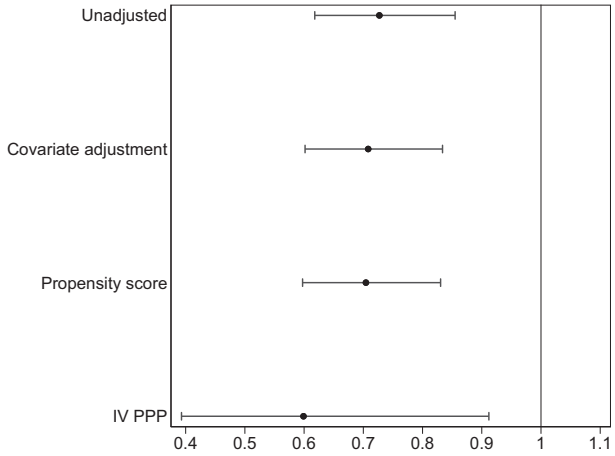

FIGURE 2 Representation of hazard ratio point estimate and 95% confidence intervals of models measuring comparative effectiveness of disulfiram and acamprosate. Acamprosate is the reference category. Circles are for point estimate related to models. IV PPP stands for instrumental variable based on Physician Prescribing Preferences.

ratio 0.60 (95% CI 0.39–0.91) for IV PPP to 0.73 (0.62–0.86) for unadjusted regression, indicating that disulfiram was associated with a reduction in the risk of alcohol-related hopitalistation between 40% and 27% compared to acamprosate. For detailed results of comparative-effectiveness analysis, see Data S1.

4 | DISCUSSION

4.1 | Prescription rates and inequality in prescription

We found the rate of alcohol-related hospitalisation to be between 3 and 4 per 10,000 population between 2010 and 2018 with 6–7% receiving a prescription for alcohol dependence medication after discharge. Our analyses highlighted that several socio-demographic factors were associated with the prescribing for alcohol dependence. Some factors such as sex, age and socio-economic areas were associated with differences in receiving prescriptions for alcohol dependence. Specifically, living in the most socio-economically deprived areas was associated with lower odds of receiving prescriptions within 60 days after the first AUD hospitalisation. The comparative effectiveness modelling suggests that patients in receipt of disulfiram had a lower risk of a first alcohol-related hospitalisation compared with those in receipt of acamprosate. Furthermore, we showed that those living in the least socio-economic deprived areas were associated with an increase in odds of being prescribed the most effective medication (disulfiram) after hospitalisation. We believe that these findings have important implications for socio-economic health inequalities for the alcohol dependent population.

Our findings are in line with other UK studies, showing a low percentage of pharmacotherapy treatment for patients with alcohol dependence. A study of patients diagnosed with alcohol dependence in primary care found that 11.7% received relevant pharmacotherapy, concluding that the prescribing of drug therapy was 'low' [13]. Our study, evaluating the percentage of prescriptions for alcohol dependence after any AUD hospitalisations (including alcohol dependence) found that between 6% and 8% of patients received alcohol dependence prescriptions, confirming that prescribing remained 'low' in secondary care.

Regarding prescription inequality, Thompson et al. [15] in a similar study regarding primary care data between 1990 and 2013, found comparable inequality patterns for sex and age and socio-economic deprivation in determining differences in odds of receiving alcohol dependence prescriptions. We found that socio-economic deprivation status was associated with disparities in receiving prescriptions within 60 days from discharge. However, in contrast, the extent of such disparities decreased for prescribing if we removed the 60 days constraint. This could suggest that distinct deprived groups can have different ease and access to care in the initial phase after hospital discharge, which is the most critical period in avoiding relapses [28]. Indeed, individuals with alcohol dependence requiring hospitalisation often require specialist alcohol treatment in hospitals or in community settings. Studies describing a lower utilisation of specialist care in groups with lower levels of educational attainment [29], can explain why we found lower prescription rates in the most deprived areas. With our data, we cannot attribute the overall inequality we found in prescriptions concerning sex and age (which are consistent across primary and secondary health care), to practitioners or to services prescribing the medications. On the contrary, we believe that a combination of factors such as the lower propensity to seek help of certain patient groups (e.g., males are less likely to seek consultation [30], especially regarding psychological matters [31]) may be responsible for this. We also found that comorbidities and previous alcohol dependence medications were associated with the odds of receiving prescriptions.

Regarding comorbidities, a history of previous mental health hospitalisations was associated with an increase in the odds of being issued prescriptions before the hospitalisation and with a reduction in the odds of getting prescriptions afterwards. This could suggest that patients with certain comorbidities are also more likely to be in contact for mental health

assistance and more likely to be treated with alcohol dependence pharmacotherapies aimed to prevent a future hospitalisation. On the contrary, after a hospitalisation, existing or previous mental health conditions decreased the odds of receiving alcohol dependence prescriptions. This could imply that after severe episodes such as alcohol-related hospitalisations, patients with such comorbidities may have other recovery goals rather than abstinence (e.g., consumption reduction), or alternatively, the potential interaction with other psychotropic therapies may reduce the odds of getting alcohol dependence prescriptions.

4.2 | Comparative effectiveness

Our analysis of real-world data on a nationwide cohort in Scotland, UK shows that disulfiram was superior to acamprosate in avoiding a first alcohol-related hospitalisation. Our results are in accordance with previous evidence from small randomised control trials [11,12] and a small observational study [13] that reported disulfiram to be more effective in maintaining abstinence, craving, days until relapse and consumption and abstinence, respectively. Our instrumental variable analysis showing similar results to methods that adjust for measured confounders by indication only, strengthens the internal validity of our study. The wider confidence intervals of the IV PPP models can be ascribed to the fact that such intervals from two stage least square models have a 'tendency' to be 'large' [32]. The point estimates of the propensity score and covariate adjustment models being closer to the null may be due to a positive correlation between unmeasured confounders (captured by IV PPP) and probability of being prescribed disulfiram. Potential unmeasured confounding factors are initial alcohol dependence severity [13], as well as motivation and supervision of the patient. As disulfiram's mechanism of action is to cause unpleasant symptoms if alcohol is consumed, patients deemed more motivated to abstinence or with greater supervisory support could be more likely to be prescribed disulfiram than acamprosate. It is worth noting that we do not link the results of our comparative effectiveness analysis to the medication's pharmacological substances only, but it could be generated by a mixture of other factors such as the close monitoring suggested for disulfiram administration.

4.3 | Inequality between disulfiram and acamprosate

In our inequality analysis (Table 3, models 5 and 6), we showed how living in the most deprived areas decreased the odds of being prescribed the most effective medication to avoid alcohol-related hospitalisation compared to living in the least deprived areas. This remained the only driver of prescription imbalances between the two medications. We believe this has important implications for health inequality. However, it is not possible from this study to understand the reasons for this inequality. We attribute this to potential unmeasured factors such as likely less available assistance, supervision or close clinical monitoring (recommended for disulfiram [10]) in individuals living in more deprived areas. Other factors may be patient preference, severity of dependence or also prescriber factors. The general inequality of prescriptions for alcohol dependence combined with the inequality of the most effective in favour of the least deprived groups can partially explain the social imbalance of the burden of alcohol. In considering implications for services, we believe that improving patient access to specialist services after being hospitalised for alcohol-related reasons and developing new integrated care pathways is essential.

4.4 | Strengths and limitations

Our findings regarding prescription inequality are novel, especially on differences in prescribing of acamprosate and disulfiram, and they have relevance for current practice in care and treatment of patients with alcohol dependence after alcohol-related hospitalisations. We also believe we provided the most robust real-world comparative effectiveness evidence to date by using several different methods to account for measured and unmeasured confounders. Further, we utilised nationwide dataset for Scotland, while previous real-world studies had lower statistical power [13].

A potential limitation was that we looked at all the ICD-10 codes identifying all AUD hospitalisations rather than alcohol dependence only. We included all AUD diagnoses mainly to correct for possible errors in recording data across different alcohol-related diagnostic codes which are possible in general/acute hospital records. Indeed, in the datasets, some of the people not hospitalised for alcohol dependence but for other AUD conditions (e.g., withdrawal or intoxication) received alcohol dependence prescriptions. We are also aware that some potentially key variables were not always considered across our analyses. Specifically, both disulfiram and acamprosate (which are the most prescribed in the United Kingdom with an indication of alcohol dependence) are aimed at abstinence. However, some individuals may have moderation rather than abstinence as a goal, and this may be one of the reason for the low percentage of prescribing we found. Similarly, we used 'first alcohol-related hospitalisation' as the only outcome

variable in our analysis which does not reflect other important recovery outcomes which may be important to patients but for which robust data is lacking. Some other variables describing risk factors for AUD as well as potential choice of one pharmacological therapy over another were not available to us (e.g., marital status as a risk factor for AUD [33]—but also potential proxy for support when an individual is prescribed disulfiram and/or other opportunities of direct patient supervision). While the instrumental variable analysis should have attenuated this potential source of bias, to be conservative, we discuss diverse explanations for our findings that go beyond the pharmacology of the medication to other factors such as close monitoring or patient motivation.

5 | CONCLUSIONS

Alcohol dependence medications are not extensively prescribed in Scotland, UK. Differences in prescribing exist, especially across categories of sex, age and socioeconomic status. People living in the most deprived areas have lower odds of receiving a prescription following an alcohol-related hospitalisation, which is the most critical period to avoid further hospital episodes. Living in the most deprived areas also has lower odds of receiving disulfiram. Yet, receipt of disulfiram is strongly associated with a lower chance of a further alcohol-related hospitalisation. Further consideration is needed to understand these inequalities in prescribing and to develop new strategies to reduce the societal imbalance in the burden of alcohol.

AUTHOR CONTRIBUTIONS

Francesco Manca and Lisong Zhang contributed equally to the study. Jim Lewsey, Niamh Fitzgerald, Hamish Innes and Andrew McAuley initial conception/design and funding acquisition for the study. Jim Lewsey, Francesco Manca and Lisong Zhang extension of initial project ideas/design and adaptation of the original design to the data. Francesco Manca and Lisong Zhang data analysis, visualisation. Jim Lewsey, Francesco Manca and Lisong Zhang data interpretation. Francesco Manca original draft of the study. Jim Lewsey supervision and management of Francesco Manca and Lisong Zhang. Jim Lewsey and Francesco Manca data acquisition. Jim Lewsey, Niamh Fitzgerald, Hamish Innes, Andrew McAuley, Clare Sharp, Frederick Ho, Bhautesh Jani, Srinivasa Vittal Katikireddi and Lisong Zhang editing of manuscript.

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CONFLICT OF INTEREST STATEMENT

He declares no other conflicts of interest. All other authors have no conflict of interests to disclose.

ORCID

Francesco Manca https://orcid.org/0000-0002-2954-6774
Niamh Fitzgerald https://orcid.org/0000-0002-3643-8165
Srinivasa Vittal Katikireddi https://orcid.org/0000-0001-6593-9092
Jim Lewsey https://orcid.org/0000-0002-3811-8165

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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