

Real-world effectiveness of pharmacological treatments of alcohol use disorders in a Swedish nation-wide cohort of 125 556 patients

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ABSTRACT

Background and aim Pharmacotherapy for alcohol use disorder (AUD) is recommendable, but under-used, possibly due to deficient knowledge of medications. This study aimed to investigate the real-world effectiveness of approved pharmacological treatments (disulfiram, acamprosate, naltrexone and nalmefene) of AUD. **Design** A nation-wide, register-based cohort study. **Setting** Sweden. **Participants** All residents aged 16–64 years living in Sweden with registered first-time treatment contact due to AUD from July 2006 to December 2016 ($n = 125\,556$, 62.5% men) were identified from nation-wide registers. **Measurements** The main outcome was hospitalization due to AUD. The secondary outcomes were hospitalization due to any cause, alcohol-related somatic causes, as well as work disability (sickness absence or disability pension), and death. Mortality was analysed with between-individual analysis using a traditional multivariate-adjusted Cox hazards regression model. Recurrent outcomes, such as hospitalization-based events and work disability, were analysed with within-individual analyses to eliminate selection bias. **Findings** Naltrexone combined with acamprosate [hazard ratio (HR) = 0.74; 95% confidence interval (CI) = 0.61–0.89], combined with disulfiram (HR = 0.76, 95% CI = 0.60–0.96) and as monotherapy (HR = 0.89, 95% CI = 0.81–0.97) was associated with a significantly lower risk of AUD-hospitalization compared with no use of AUD medication. Similar results were found for risk of hospitalization due to any cause. Benzodiazepine use and acamprosate monotherapy were associated with an increased risk of AUD-hospitalization (HR = 1.18, 95% CI = 1.14–1.22 and HR = 1.10, 95% CI = 1.04–1.17, respectively). No statistically significant effects were found for work disability or mortality. **Conclusions** Naltrexone as monotherapy and when combined with disulfiram and acamprosate appears to be associated with lower risk of hospitalization due to any and alcohol-related causes, compared with no use of alcohol use disorder (AUD) medication. Acamprosate monotherapy and benzodiazepine use appear to be associated with increased risk of AUD-associated hospitalization.

Keywords Acamprosate, alcohol use disorder, disulfiram, effectiveness, hospitalization, mortality, nalmefene, naltrexone, work disability.

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INTRODUCTION

Alcohol use disorders (AUD) cause health problems and are one of the leading causes of mortality and morbidity world-wide [1–3]. More than 5% of the global disease burden is caused by harmful use of alcohol, and in 2016 more than 3 million people died due to alcohol-related causes [1]. The harmful use of alcohol is associated with risk of mental and behavioral disorders, and regular alcohol abuse

can lead to serious somatic diseases [4]. Alcohol use also increases the risk of injuries resulting from violence and accidents [1].

The mainstay of AUD treatment is psychosocial intervention, but combining psychosocial treatments with pharmacotherapy can lead to better outcomes [5]. Disulfiram, naltrexone and acamprosate are approved for the treatment of AUD in the United States and Europe. Nalmefene is also approved in Europe [2]. According to

the latest meta-analyses and systematic reviews on randomized controlled trials (RCTs), these medications have shown their efficacy in comparison with placebo: disulfiram under supervision to advance treatment adherence, acamprosate in maintaining abstinence, naltrexone, especially in reducing binge drinking, and nalmefene in reducing heavy drinking days [6–9]. Despite their potential to improve clinical outcome for individuals with AUD, these medications are under-utilized. Deficient knowledge of these medications and possible doubts about their effectiveness may lead to the low utilization rate. [5,10]. Benzodiazepines are generally accepted as pharmacotherapy for managing alcohol withdrawal, but not recommended for use after detoxification [11]. Nonetheless, benzodiazepine misuse is common among people with AUD [12]. All mentioned medications can cause some adverse effects [13,14], disulfiram even fatal ones [15], but very little is known about overall health outcomes (such as risks of hospitalization and mortality) associated with specific treatments in real-world circumstances. Furthermore, the possible association of specific treatments with work-related outcomes (such as sickness absences and disability pensions) is less well established, despite the fact that AUD has a strong effect on work performance [16]. As patients included in RCTs are highly selected populations, it is not known how effective treatments are in non-selected patient population in real-world treatment settings.

The aim of this study is to investigate the real-world effectiveness of pharmacological treatments of alcohol dependence on (1) risk of hospitalization due to AUD as a main outcome and (2) hospitalization due to any cause, alcohol-related somatic causes and work disability and death as secondary outcomes.

METHODS

Nation-wide register-based data were used to conduct a prospective population-based cohort study of patients with AUD. The project was approved by the Regional Ethics Board of Stockholm (decision 2007/762–31). No informed consent is required for register-based studies using anonymized data.

Study population

Data were gathered prospectively from nation-wide Swedish registers. People with a diagnosis of AUD were identified based on four register sources: inpatient and specialized outpatient care from the National Patient Register, disability pension from the MiDAS register (Microdata for analyses of social insurance) and sickness absence data from the MiDAS register. Drug use data were gathered from the Prescribed Drug Register since July 2005. Dates of death were obtained from the Causes of Death Register

and demographic characteristics for the cohort were obtained from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) Register.

All residents aged 16–64 years (at the time of diagnosis) living in Sweden with registered first-time treatment contact due to AUD between 1 July 2006 and 31 December 2016 were included into this study. All individuals with a diagnosis of AUD, according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) classification [17] (F10.0–F10.9) were identified from inpatient, specialized outpatient, sickness absence and disability pension (MiDAS) registers. Individuals were chosen based on not having had a previous diagnosis of schizophrenia or bipolar disorder. All Swedish residents were assigned a unique personal identification number which enabled linkage between various registers.

Exposure

Drug use data was gathered from the Prescribed Drug Register. Drug use information in the register is categorized according to the anatomical therapeutic chemical (ATC) classification [18] and recorded as defined daily doses (DDD), together with information on drug package and formulation. Exposure to AUD medications was categorized as follows: disulfiram (ATC N07BB01), acamprosate (N07BB03), naltrexone (N07BB04) and nalmefene (N07BB05). In addition to monotherapies of these medications, drug combinations were also analysed as follows: disulfiram and acamprosate, disulfiram and naltrexone and acamprosate and naltrexone. In some secondary analyses (hospitalization due to alcohol-related somatic causes and work disability) all drug combinations were grouped into one ‘polytherapy’ category (any combination of studied medications), because of the low rate of events. In addition, we analysed the risk of main and secondary outcomes associated with benzodiazepine and related drug (N05BA, N05CD, N05CF) use.

Drug use periods (i.e. when drug use started and ended) were constructed using the prescription drug purchases to drug use periods—a second-generation method (PRE2DUP). The method is based on the calculation of sliding averages of daily dose (in DDDs), the purchased amounts of drugs and personal drug use patterns [19]. The method takes into account hospital stays (when drug use is not recorded in the register) and stockpiling of drugs when constructing use periods.

Outcomes

The main outcome measure was hospitalization due to alcohol use disorder (AUD hospitalization, ICD-10-code F10). Hospitalizations were derived from the National Patient

Register and defined as an inpatient stay of at least 24 hours. The secondary outcomes were hospitalization due to any cause and to alcohol-related somatic causes (Supporting information, Table S1), all-cause mortality and work disability, defined as start of sickness absence or disability pension (regardless of level of compensation or diagnoses).

Covariates

Within-individual analyses were adjusted for temporal order of treatments, time since cohort entry (i.e. time since first AUD diagnosis) and use of psychotropic drugs; antidepressants (N06A), benzodiazepines and related drugs, mood stabilizers (N03AF01, N03AG01, N03AX09, N05AN01) and anti-psychotics (N05A). Between-individual analyses were additionally adjusted for sex, age, educational level, the number of previous hospitalizations due to AUD, time since first AUD diagnosis, comorbidities and other medication use (Supporting information, Table S1).

Statistical analysis

Hospitalizations and work disability were treated as recurrent events and analysed with the within-individual Cox regression model [20]. The within-individual model is a stratified Cox regression model in which each individual forms his or her own stratum. This reduces selection bias. The follow-up time is reset to zero after each outcome event to allow comparison of treatment periods within each individual. Mortality was analysed with the traditional multivariate-adjusted Cox regression model as between-individual analysis, and between-individual analyses were also used as sensitivity analyses for the main outcome and for analyses on duration of use and associated risk of AUD hospitalization. Only individuals with variation in outcome and exposure contribute to the model in within-individual analysis, whereas in between-individual analysis, all individuals contribute to the model. The follow-up started at the first diagnosis of AUD and ended at death, emigration, diagnosis of schizophrenia or bipolar disorder and end-of-study follow-up (31 December 2016). In analyses of sickness absence, the follow-up also ended at start of disability pension. In analyses of work disability outcomes (sickness absence, disability pension), people already on disability pension at cohort entry were excluded and analyses were censored when they reached the age of 65 years, when old-age pension typically starts. Subgroup analyses for the main outcome were performed by tightening the criteria for AUD first by restricting analyses to people without any other substance use disorder than AUD, and secondly by including only individuals either diagnosed with acute alcohol intoxication

(F10.0) more than once or having other diagnoses of alcohol-related disorders, indicating a more serious alcohol problem (F10.1–F10.9) before start of follow-up. Nominal *P*-values are displayed throughout the paper. Significance level was set at 0.05 using the Benjamini–Hochberg false discovery rate (FDR) method.

The primary research question and analysis plan were not pre-registered on a publicly available platform; thus, the results should be considered exploratory.

RESULTS

In the total cohort, including 125 556 patients with a diagnosis of AUD, 78 434 individuals (62.5%) were men, and the mean age was 38.1 [standard deviation (SD) = 15.9] years. The median follow-up time was 4.6 [interquartile range (IQR) = 2.1–7.2] years. During follow-up, 32 129 (25.6%) of the patients used any of the following drugs: 19 274 (15.4%) patients used disulfiram, 11 432 (9.1%) acamprosate, 10 872 (8.7%) naltrexone, 693 (0.6%) nalmefene and 6398 (5.1%) used two or more of the above-mentioned medications concomitantly. The clinical and socio-demographic characteristics of the cohort are described in Supporting information, Table S2; Supporting information, Table S3 shows the numbers of events for each exposure and outcome analysed.

During the follow-up (median = 4.6, IQR = 2.1–7.2 years), 30 044 (23.9%) patients had a main outcome event (AUD hospitalization). Naltrexone combined with acamprosate (HR = 0.74; 95% CI = 0.61–0.89), combined with disulfiram (HR = 0.76, 95% CI = 0.60–0.96) and as monotherapy (HR = 0.89, 95% CI = 0.81–0.97) was associated with a significantly lower risk of AUD-hospitalization compared to those time-periods when the same individual did not use any AUD medication. The use of acamprosate was associated with a significantly increased risk of hospitalization due to AUD (Fig. 1). The results were similar in the between-individual model (Supporting information, Fig. S1), and longer duration of naltrexone use was associated with lower risk of AUD hospitalization (Supporting information, Table S4). Similar results were also found when the outcome was hospitalization due to any cause. Naltrexone combined with either disulfiram or acamprosate and as monotherapy was associated with decreased risk of any hospitalization (HR = 0.77, 95% CI = 0.64–0.94; HR = 0.80, 95% CI = 0.69–0.94; HR = 0.89, 95% CI = 0.83–0.96, respectively) (Fig. 2). Acamprosate monotherapy was not associated with a higher risk of hospitalization due to any cause.

During the follow-up, 3173 (2.5%) of the patients were hospitalized due to alcohol-related somatic causes. Polytherapy was associated with a significantly decreased risk of hospitalization due to alcohol-related somatic causes (HR = 0.31, 95% CI = 0.12–0.83) compared with no use

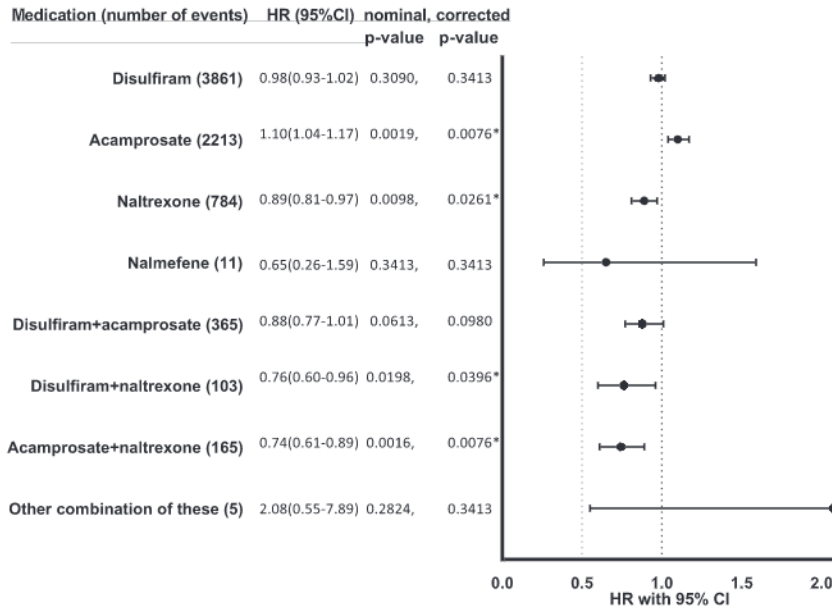


Figure 1 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of hospitalization due to alcohol use disorder (AUD) during pharmacotherapy compared with no use of medication in within-individual analyses. *Results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold

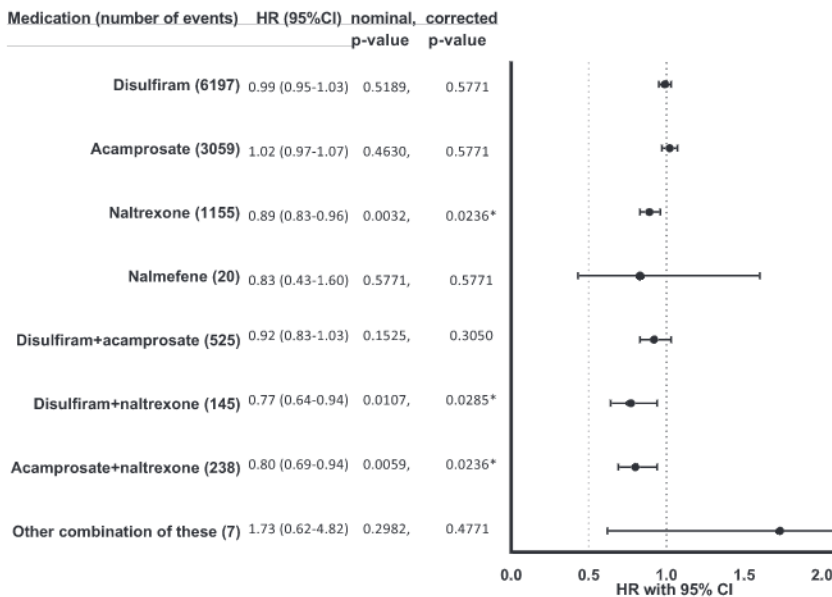


Figure 2 Risk of hospitalization due to any cause during follow-up. Within-individual model. *Results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold

of AUD medications (Fig. 3). In addition, disulfiram monotherapy was associated with a significantly decreased risk of hospitalization due to alcohol-related somatic causes (HR = 0.61, 95% CI = 0.42–0.89).

Altogether, 13 031 (10.4%) of patients with diagnosis of AUD were also diagnosed with some other substance use disorder (ICD-10: F11–F16, F18–F19) during the follow-up. Two or more of the studied medications used concomitantly (polytherapy) was associated with a

non-significant (when FDR-corrected) trend towards a lower risk of hospitalization due to AUD in patients diagnosed with AUD only (HR = 0.81, 95% CI = 0.71–0.91) (Supporting information, Fig. S2). As a sensitivity analysis for risk of AUD-hospitalization, we performed a subgroup analysis including only individuals diagnosed with acute alcohol intoxication (F10.0) more than once or having other alcohol-related diagnoses (F10.1–F10.9) before the start of follow-up, indicating a more serious alcohol

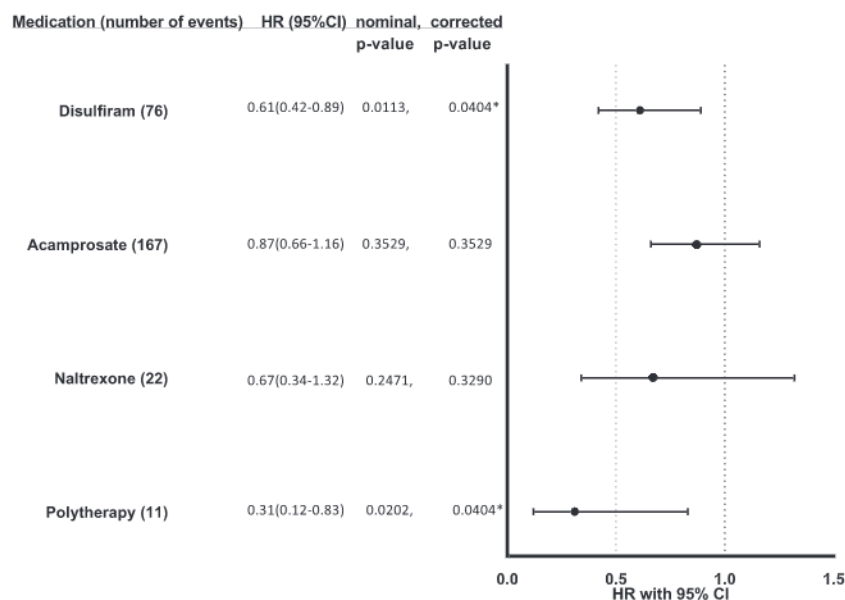


Figure 3 Risk of hospitalization due to alcohol-related somatic cause during exposure of studied medications (all drug-combinations grouped into 'polytherapy' category because the low rate of events). Nalmefene monotherapy was not analysed due to the small number of events. *Results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hospitalization due to alcohol-related somatic diagnoses (ICD-10: E51.2, E24.4, G31.2, G40.51, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.00, K86.01, K86.08, O35.4; Supporting information, Table S1)

problem. In this analysis as well, naltrexone combined with acamprosate and as monotherapy was associated with lower risk of hospitalization due to AUD (HR = 0.71, 95% CI = 0.58–0.87; HR = 0.89, 95% CI = 0.81–0.98, respectively) (Supporting information, Fig. S3).

During the follow-up, 42 678 (34.0%) of patients used benzodiazepines and related drugs. The use was associated with a significantly increased risk of hospitalization due to AUD (HR = 1.18, 95% CI = 1.14–1.22, $P < 0.0001$) compared with no use. No significant increase in the risk of hospitalization due to alcohol-related somatic causes was detected (HR = 0.99, 95% CI = 0.88–1.12, $P = 0.9036$).

Overall, 7832 (6.2%) of the patients died during the follow-up time. The adjusted risk of all-cause mortality was not significantly lower with any of the studied medications (disulfiram, acamprosate, nalmefene, naltrexone) (Supporting information, Fig. S4). However, 1211 (2.8%) of patients who used benzodiazepines and related drugs died, and the adjusted risk of all-cause mortality was significantly higher with these drugs (HR = 1.11, 95% CI = 1.04–1.19, $P = 0.0034$).

Altogether, 4719 (4.2%) of patients had sickness absence or disability pension during the follow-up time. The risk of work disability (either sickness absence or disability pension) did not significantly decrease during use of any studied drug (Supporting information, Fig. S5). In fact, use of disulfiram, acamprosate or polytherapy (two or more studied drugs combined) were associated with a non-significant trend towards an increased risk of

work disability (HR = 1.37, 95% CI = 1.00–1.86; HR = 1.59, 95% CI = 1.07–2.37; HR = 1.98, 95% CI = 1.09–3.61, respectively).

DISCUSSION

To the best of our knowledge, no other prospective cohort study has studied the real-world effectiveness of pharmacotherapy in AUD during a long-term follow-up period. We found that in comparison to personal no-use periods of any AUD medication, naltrexone as a monotherapy and combined with acamprosate and disulfiram was associated with a reduced risk of hospitalization due to AUD and any causes. Polytherapy of the studied medications and disulfiram monotherapy were associated with lower risk of hospitalization due to alcohol-related somatic causes. Benzodiazepines and acamprosate as a monotherapy were associated with an increased risk of hospitalization due to AUD and use of benzodiazepines was associated with a higher mortality rate.

In this study, based on a cohort of more than 125 000 patients diagnosed with AUD, 25.6% of the individuals used some of the studied AUD drugs during the follow-up. Previous studies have shown that medications for treating AUD are under-prescribed and under-utilized and, depending on the study, only approximately 10–20% of patients with AUD receive prescribed medication for their AUD [2,5,6,21]. Even though the proportion of AUD medication users was low, 34% of the cohort had used benzodiazepines. Increased use of benzodiazepines has been linked to

onset of AUD in a naturalistic 12-year follow-up study in the United States [11], and use of benzodiazepines was associated with an increased risk of mortality in our study. The problem is thus not only under-prescription of medications, but also prescribing the wrong medications. Naltrexone as monotherapy and combined with disulfiram and acamprosate was associated with a reduced risk of hospitalization due to AUD. These results are in line with previous reviews which have found naltrexone to be effective in treatment of AUD, especially in reducing binge drinking [6]. Naglich *et al.* concluded in their systematic review in 2018 that naltrexone is the medication most combined with other AUD drugs. Drug combinations studied in the review were extremely heterogenous, and no significant benefit was found for combinations over monotherapies. However, reviewers assumed that benefit may be observed when targeting the drug combination for specific symptoms or subpopulations [22]. Naltrexone is also used in other substance use disorders, such as opioid dependence. In subgroup analyses censoring follow-up to the occurrence of any other substance use disorder, the association between naltrexone and risk of AUD hospitalization lost statistical significance, although the point estimate remained the same. Lack of association may be due to lack of statistical power, as this censoring also restricted follow-up time and the number of events. However, drug combinations of naltrexone, acamprosate, disulfiram or nalmefene were associated with a significantly reduced risk of hospitalization due to AUD. Combining drugs may increase their effectiveness by impacting upon separate symptoms [22]. Thus, the effect of polytherapy might be explained by either an increase in effectiveness due to combining drugs affecting different systems or a more resilient striving towards abstinence by the patient, indicated by the willingness to ingest multiple different medications with a potential for increased side effects and out-of-pocket costs.

The use of disulfiram or a combination of two or more studied drugs was associated with a reduced risk of hospitalization due to alcohol-related somatic diagnoses. Alcohol-related somatic hospitalizations are usually due to long-term heavy alcohol consumption. Because of the aversive reaction to alcohol caused by disulfiram it necessitates total abstinence, which might explain its effect in reducing the risk of hospitalization due to alcohol-related causes.

Nalmefene was approved by the European Medicines Agency (EMA) as a treatment for alcohol dependence in 2013 [23]. The results of efficacy of nalmefene in previous studies are mixed, and it seems to have limited efficacy in reducing alcohol consumption [23,24]. We found no statistically significant association between use of nalmefene and risk of hospitalization, work disability or death, possibly due to a low number of events. Nalmefene also seems to be less used in other studies [21,25]. Acamprosate seems to

have efficacy in reducing alcohol craving and relapse [9,26]. In our study, acamprosate was the second most used drug, but it did not reduce the risk for hospitalization, work-related outcomes or mortality as a monotherapy. Instead, it was associated with an increased risk of AUD-hospitalization. However, acamprosate combined with naltrexone was associated with a reduced risk of hospitalization due to AUD and any cause. According to a recent review, acamprosate seems to be generally well-tolerated [13]. Therefore, the increased risk of hospitalization due to AUD may be a signal of acamprosate monotherapy's deficient efficacy in treating active AUD, while its efficacy is usually shown in maintaining abstinence [6,27]. Also, acamprosate needs to be administered three times a day (whereas, e.g. naltrexone only once daily) [28]. The need for stricter adherence and consequent risk of suboptimal dosing with acamprosate may somewhat explain the poor results seen for acamprosate use.

Benzodiazepines and related drugs were associated with a higher risk of mortality and hospitalization due to AUD. Benzodiazepines are used to reduce alcohol withdrawal symptoms and decrease the risk of seizures [14], although they may also be used for treatment of other comorbid problems (such as anxiety disorders or insomnia), which may confound our results. Altogether, the evidence shows that AUD increases the risk of benzodiazepine misuse [12], and because of their addictive potential, risk of tolerance and side effects, they are not safe to use when combined with alcohol [14]. Thus, the use of benzodiazepines in treating AUD should be carefully considered and should not be used for the maintenance of alcohol abstinence.

None of the studied AUD medications (disulfiram, acamprosate, naltrexone or nalmefene) were associated with a higher risk of mortality, which is a positive safety signal, as some of these medications have been associated with severe adverse effects. For example, disulfiram may cause hepatitis, neuropathy, optic neuritis, psychosis, myocardial infarction, congestive heart failure, respiratory depression and, rarely, death [26]. Usually, however, these medications are well tolerated and have only mild side effects. Because the mortality risk did not increase during drug use (even during combination use), our results suggest that the studied medications are safe to use, and concerning the efficacy on reducing hospitalizations, recommendable.

None of the studied drugs were associated with a reduced risk of mortality or work disability. In fact, disulfiram, acamprosate and polytherapy of two or more studied drugs showed a non-significant trend towards increased risk of work disability. The association between AUD medication and risk of work disability may reflect the situations where AUD medication use is started too late in relation to the ongoing process of increasing alcohol use and decreasing



work capacity. Another possible explanation for this association may be that people still working but with AUD might be more easily referred to treatment. However, there are many confounding factors in the association between work disability and alcohol consumption, as alcohol has a strong effect on overall work performance [29]. It has been shown that risky alcohol consumption predisposes to unemployment, and only approximately 20% of inpatients with alcohol addiction are employed [30,31]. Conversely, job loss is associated with increased frequency of AUD [32]. Thus, work disability (such as sickness absences and disability pension) is not only affected by poor health, but is also determined by socio-economic and work-related factors. As individuals often try to hide their substance abuse, pharmacological treatment of AUD may be deficient to stop the retirement process at the point when they are discovered. Hereby, a reduction of the stigma of substance abuse problems and their earlier discovery and treatment should be worked towards.

Strengths and limitations

The main strengths of this study are the nation-wide coverage of all AUD patients and the significant follow-up time up to 7 years. For these reasons, the results are generalizable to real-world patients with AUD in countries with state-funded health-care systems providing care and medications with no or very small co-payments. In addition, we used data on actually purchased medications instead of data on prescriptions given to the patients. We analysed the risk of hospitalization-based outcomes and sickness absence by using a within-individual design, where each individual acts as his or her own control, which reduces selection bias. Drug use was modelled with the PRE2DUP-method, which describes actual drug use well when compared with interview-reported use [33].

The limitations of this study include that there was no information on possibly reduced days and levels of alcohol consumption, so the effectiveness of studied medications was evaluated with secondary measures, such as risk of hospitalization due to alcohol-related causes, mortality and work disability. However, these outcomes represent severe and significant disadvantages for both the individual and society. Another limitation is that we did not know the severity of AUD or the use of psychosocial treatments combined with pharmacotherapy. However, because the effectiveness of the studied drugs varied, the existence of possible psychosocial treatment combined to pharmacotherapy seems not pivotal.

CONCLUSION

The risk of alcohol-related hospitalizations is lower when patients with AUD are treated with naltrexone or with

combinations including naltrexone, disulfiram or acamprosate. Polytherapy of the studied medications was also associated with lower risk of hospitalization due to any cause. Acamprosate monotherapy was not associated with beneficial effects, defined in the study as decreased risk for hospitalization due to AUD or for any cause, alcohol-related somatic causes, work disability or death. Benzodiazepines were associated with a higher risk of hospitalization due to AUD and should not be administered other than in alcohol withdrawal symptoms. Pharmacotherapies of AUD are under-utilized, whereas benzodiazepine use was strikingly common among people with AUD. According to the data presented here, naltrexone and drug-combinations in particular seem to be effective in the treatment of AUD and are recommended to be used as part of treatment protocol; the use of benzodiazepines should be avoided.

Declaration of interests

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Author contributions

Milja Heikkinen: Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization. **Heidi Taipale:** Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization. **Antti Tanskanen:** Conceptualization; data curation; formal analysis; investigation; methodology; software; validation.



Ellenor Mittendorfer-Rutz: Conceptualization; supervision.
Markku Lähteenvuuo: Conceptualization; formal analysis; validation; visualization. **Jari Tiihonen:** Conceptualization; formal analysis; funding acquisition; investigation; project administration; resources; supervision; validation.

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Supporting Information

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

Table S1. Covariate definitions for between individual analyses. Anatomical Therapeutic Chemical (ATC) classification codes for covariate medications and International Classification of Diseases (ICD) version 10 codes for alcohol-related somatic diseases are described in the table.

Table S2. Description of the cohort of persons with alcohol use disorder (AUD), ($N=125\,556$), including all residents aged 16–64 living in Sweden with registered first-time treatment contact due to AUD during 2006–2016.

Table S3. The numbers of events for each exposure and for each outcome analyzed.

Table S4. The risk of AUD hospitalization in between-individual model by duration of use for disulfiram, acamprosate and naltrexone monotherapies.

Figure S1. The risk of AUD hospitalization in between-individual analyses. *denote results significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold.

Figure S2. Sensitivity analysis for the risk of hospitalization due to AUD in persons without other substance use disorders than alcohol use disorder (F10) during follow-up. Within-individual model. None of the associations survived significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons.

Figure S3. Sensitivity analyses for risk of AUD-hospitalization in patients who were diagnosed with

acute intoxication of alcohol (F10.0) at least twice or with other alcohol use disorder (F10.1 – F10.9) before the follow-up (59.1% of the total cohort included). Within-individual model. * denote results significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold.

ICD-code F10: Mental and behavioural disorders due to use of alcohol. F10.0 Acute intoxication, F10.1 Harmful use, F10.2 Dependence syndrome, F10.3 Withdrawal state, F10.4. Withdrawal state with delirium, F10.5 Psychotic disorder, F10.6 Amnesic syndrome, F10.7 Residual and late-onset psychotic disorder, F10.8 Other mental and behavioural disorders, F10.9 Unspecified mental and behavioural disorder

Figure S4. The adjusted risk of all-cause mortality, between-individual model. Nalmefene monotherapy or the other combinations of studied drugs were not analysed due to the small number of events. Adjusted for baseline covariates (age, gender, education, order of treatment, concomitant use of psychotropic drugs), other medication use (opioid and non-opioid analgesics, cardiovascular medications, alimentary tract and metabolism medications, antiepileptic drugs), and comorbidities (alcohol-related somatic diseases, the number of previous hospitalizations due to AUD, cardiovascular disease, diabetes, asthma/COPD, previous cancer and renal disease).

Figure S5. The risk of sickness absence (SA) or disability pension (DP). All drug-combinations grouped into 'polytherapy' category because the low rate of events. Nalmefene was not analysed due to a small number of events. None of the associations survived significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons.