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MILJA HARTIKAINEN

REAL-WORLD EFFECTIVENESS OF PHARMACOLOGICAL TREATMENTS OF ALCOHOL, OPIOID AND AMPHETAMINE USE DISORDERS

FINDINGS FROM SWEDISH NATIONAL REGISTER-BASED STUDIES

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Real-world effectiveness of pharmacological treatments of alcohol, opioid and amphetamine use disorders – Findings from Swedish national register-based studies
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ABSTRACT

Substance use disorders are a substantial health and social burden, and increase the risk of premature death. The treatment of substance use disorders can be remarkably improved with pharmacotherapy; however, pharmacological treatments are underused, partly due to insufficient knowledge about the comparative effectiveness of different medications. Health authorities have approved medications for the treatment of alcohol use disorder (AUD) and opioid use disorder (OUD), while no officially accepted pharmacotherapy for (meth)amphetamine use disorders (MAUD) is currently available. Studies concerning the efficacy of medications used to treat substance use disorders are generally limited due to small and highly specific patient populations, along with low rates of treatment adherence or completion. As such, real-world studies on the effectiveness of these medications which would involve large cohorts and long follow-up periods are rare or do not exist.

The research underlying this dissertation aimed to investigate the real-world effectiveness of pharmacotherapies for persons with AUD, OUD and

MAUD based on long-term outcomes, such as hospitalisation and death. The data were gathered prospectively between July 1, 2006 and December 31, 2016 from Swedish nationwide registers, such as the National Patient Register (NPR), Causes of Death Register, LISA Register (The Longitudinal Integration Database for Health Insurance and Labor Market Studies), MiDAS Register (Micro Data for Analyses of Social Insurance), and Prescribed Drug Register (PDR). The data present in different registers can be linked through a unique personal identification number. All Swedish residents aged 16–64 with a diagnosis of either AUD or MAUD (Studies I and III), or who had purchased medication for OUD (Study II) were included in the research. In the case of Study III, the follow-up time was extended until December 31, 2018. Recurrent outcomes, such as hospitalisation, were analysed via within-individual models to eliminate selection bias. In this model, individual acts as his or her own control and only factors which vary over time (e.g., temporal order of treatments, concomitant use of medications and time since cohort entry) need to be adjusted for. In addition to the within-individual approach, the main outcomes were also analysed using a between-individual model to ensure that the results represent all members of the study cohort. One-time-events, such as death, were also analysed using the between-individual approach.

The results of Study I showed that only 25% of patients diagnosed with AUD used any type of AUD medication during the follow-up period. The use of naltrexone, either alone or combined with acamprosate or disulfiram, was associated with a reduced risk of hospitalization due to AUD (a reduction of 11%, 26% and 24%, respectively) when compared with no use of AUD medications. Furthermore, the concomitant use of different AUD medications or the use of disulfiram were associated with a reduced risk of alcohol-related hospitalisation (reductions of 69% and 39%, respectively). The results of Study II revealed that the use of buprenorphine or methadone was associated with reduced risk of hospitalisation due to OUD (reductions of 27% and 26%, respectively), all-cause mortality (reductions of 55% and 49%, respectively), and death due to external causes (reductions of 61% and 60%, respectively), compared

with no use of OUD medications. The longer duration of treatment was associated with better outcomes. Study III reported that lisdexamphetamine, known as medication for attention deficit hyperactivity disorder (ADHD), was consistently associated with the best comparative effectiveness among generally used medications in persons with MAUD. The use of lisdexamphetamine was associated with 18% reduced risk of hospitalisation due to substance use, 14% reduced risk of any hospitalisation or death and 57% reduced risk of all-cause mortality, compared with no use of ADHD medications. The results of Studies I and III revealed that the use of benzodiazepines was associated with an increased risk of hospitalisation and death among persons with AUD and MAUD. All of the aforementioned results were statistically significant.

The results of studies included in this dissertation demonstrate that safe and effective medications for treatment of AUD and OUD do exist, and could thus be included in treatment protocols. Unfortunately, the use of pharmacotherapies for the treatment of AUD remains low, although the results of Study I clearly demonstrated that naltrexone use, alone and in combination with disulfiram and acamprosate, was associated with favorable treatment outcomes. The consistent results obtained from the large dataset can be generalised to the general population, and highlight the need to prescribe effective treatments to individuals with AUD. Prior research has shown that opioid agonists are effective in the treatment of OUD, with the results of Study II confirming this view. The consistent beneficial findings concerning the use of lidsexamphetamine in Study III pave a way for future research using randomized controlled designs.

Keywords: Amphetamine Related Disorders; Alcohol Use Disorder; Cohort Studies; Hospitalisation; Mortality; Opioid Use Disorder; Pharmacotherapy; Sweden

Hartikainen, Milja
Alkoholi-, opioidi- ja amfetamiiniongelmaisten käyttämien lääkehoitojen tosielämän vaikuttavuus – Löydöksiä kansallisista ruotsalaisista rekisteritutkimuksista
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TIIVISTELMÄ

Maailmanlaajuisesti yleistyvät päihdeongelmat aiheuttavat terveydellisiä ja sosiaalisia haittoja ja lisäävät ennenaikaisen kuoleman riskiä. Päihdeongelmien lääkehoidolla hoitotuloksia voitaisiin merkittävästi parantaa, mutta lääkehoito on alikäytettyä. Lääkkeiden määräämistä päihdeongelmaisille voi vähentää lääkehoitojen vaikuttavuutta vertailevien tutkimusten puute. Alkoholiriippuvuuteen ja opioidiriippuvuuteen on olemassa viranomaisten hyväksymiä lääkkeitä, kun taas amfetamiiniriippuvuuden hoitoon ei virallisesti hyväksyttyä lääkehoitoa ole. Päihderiippuvuuksissa lääkehoitojen tehokkuutta koskevat tutkimukset ovat usein pieniä, koskevat valikoitunutta joukkoa ja keskeytyvät usein. Tosielämän vaikuttavuutta selvittävät, laajoilla joukoilla ja pitkällä seuranta-ajalla totetutetut tutkimukset ovat harvinaisia tai niitä ei ole.

Tässä väitöskirjassa selvitettiin alkoholi-, opioidi- ja amfetamiiniongelmaisilla käytössä olevien lääkehoitojen tosielämän vaikuttavuutta pitkän ajan päätetapahtumiin, kuten sairaalaan joutuminen tai kuolema. Tutkimusaineisto kerättiin 1.7.2006–31.12.2016 väliseltä ajalta

ruotsalaisiin kansallisiin rekistereihin ja niistä saatuja tietoja voitiin yksilöidyn tunnistusnumeron avulla yhdistää. Kolmanteen osajulkaisuun mennessä seuranta-aika pidentyi 31.12.2018 asti. Tutkimusaineisto koostui työikäisistä ruotsalaisista, joilla oli diagnosoitu alkoholi- tai amfetamiiniongelma (tutkimukset I ja III) tai jotka olivat ostaneet apteekista opioidiriippuvuuteen käytettyjä lääkkeitä (tutkimus II). Valikoitumisharhan eliminoimiseksi toistuvat päätetapahtumat, kuten sairaalahoidot, analysoitiin tilastollisesti käyttämällä within-individual-menetelmää. Menetelmässä jokainen tutkittava henkilö toimii omana verrokkinaan, jolloin vain ajasta riippuvaiset muuttujat (kuten hoitojen ajallinen järjestys, muiden lääkkeiden samanaikainen käyttö ja sairauden kesto) tarvitsee vakioida. Pääasialliset päätetapahtumat analysoitiin within-individual-menetelmän lisäksi myös between-individual-menetelmällä, jotta tulokset edustaisivat koko tutkimuskohorttia. Between-individual-menetelmällä analysoitiin myös päätetapahtumat, jotka voivat tapahtua vain kerran (kuten kuolema).

Alkoholiongelmaisia koskevassa osajulkaisussa (tutkimus I) havaittiin, että vain noin 25 % tutkituista käytti jotain alkoholiongelmaan tarkoitettua lääkehoitoa. Naltreksonin käyttö yksin ja yhdessä akamprosaatin tai disulfiraamin kanssa oli yhteydessä pienentyneeseen riskiin joutua sairaalahoitoon alkoholiongelman vuoksi (riski väheni 11 %, 26 % ja 24 %, tässä järjestyksessä). Eri lääkkeiden yhteiskäyttö sekä disulfiraami puolestaan olivat yhteydessä vähentyneeseen riskiin joutua sairaalaan alkoholinkäyttöön liittyvien somaattisten syiden vuoksi (riski pieneni 69 % ja 39 %, tässä järjestyksessä), verrattuna siihen, ettei yksilö käyttänyt alkoholiongelmaan tarkoitettua lääkettä. Toisessa, opioidiagonistien käyttöön liittyvässä osajulkaisussa havaittiin buprenorfiinin ja metadonin käytön olevan yhteydessä pienentyneeseen riskiin joutua sairaalaan opioidiriippuvuuden vuoksi (buprenorfiinin käytön aikana 27 % pienempi riski, metadonin käytön aikana 26 % pienempi riski) tai kuolla mistä tahansa syystä (buprenorfiinin käytön aikana 55 % pienempi riski, metadonin käytön aikana 49 % pienempi riski) verrattuna siihen, ettei henkilö käyttänyt kumpaakaan lääkettä. Buprenorfiinin käyttöön liittyi

myös 61 % ja metadoniin 60 % pienempi riski kuolla ulkoisesta syystä, verrattuna siihen, ettei yksilö käyttänyt kumpaakaan tutkittua lääkettä. Lääkehoidon pidempi kesto näytti parantavan ennustetta. Kolmannessa, amfetamiiniongelmaisten käyttämiä lääkehoitoja tutkivassa osajulkaisussa aktiivisuuden ja tarkkaavuuden häiriön (ADHD) lääkkeenä tunnettu lisdexamfetamiini oli yhteydessä kaikkiin tutkittuihin päätetapahtumiin suotuisasti. Lisdexamfetamiinin käyttö oli yhteydessä 18 % pienentyneeseen riskiin joutua päihdeongelman vuoksi sairaalaan, 14 % pienentyneeseen riskiin joutua sairaalaan tai kuolla, sekä 57 % pienentyneeseen riskiin kuolla, verrattuna ajanjaksoihin, jolloin henkilö ei käyttänyt mitään ADHD-lääkettä. Bentsodiatsepiinien käyttö oli osajulkaisuissa I ja III yhteydessä lisääntyneeseen riskiin joutua sairaalaan tai kuolla. Kaikki mainitut tulokset olivat tilastollisesti merkitseviä.

Tutkimustulokset osoittivat, että opioidi- ja alkoholiongelmiin on olemassa turvallisia ja tehokkaita lääkehoitoja, joita voisi useammin liittää osaksi hoitoprotokollaa. Etenkin alkoholiongelmien hoidossa lääkkeiden määrääminen on edelleen vähäistä, vaikka ensimmäisen osajulkaisun mukaan naltreksonin käyttö yksin ja yhdessä disulfiraamin ja akamprosaatin kanssa oli yhteydessä suotuisiin päätetapahtumiin. Suuresta aineistosta saadut yhteneväiset tulokset ovat yleistettävissä koko väestöön rohkaisten lääkkeiden määräämiseen ja alkoholiongelman hoidon tehostamiseen. Opioidiriippuvuuden hoito opioidiagonisteilla on aiemmissa tutkimuksissa osoitettu tehokkaaksi ja toinen osajulkaisu vahvisti tätä käsitystä. Kolmannen osajulkaisun yksiselitteisen positiiviset löydökset koskien lisdexamfetamiinin käyttöä, rohkaisevat jatkotutkimusten tekemiseen satunnaistetuissa kontrolloiduissa tutkimusasetelmissa.

Avainsanat: Amfetamiiniin Liittyvät Häiriöt; Alkoholiongelma; Kohorttitutkimus; Kuolleisuus; Lääkehoito; Opioidiriippuvuus; Ruotsi; Sairaalahoito

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Milja Hartikainen, Kuopio, May 2024

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Heikkinen M, Taipale H, Tanskanen A, Mittendorfer-Rutz E, Lähteenvuo M, Tiihonen J. Real-world effectiveness of pharmacological treatments of alcohol use disorders in a Swedish nation-wide cohort of 125 556 patients. Addiction. 2021 Aug;116(8):1990–1998. doi: 10.1111/add.15384.

II Heikkinen M, Taipale H, Tanskanen A, Mittendorfer-Rutz E, Lähteenvuo M and Tiihonen J. Real-world effectiveness of pharmacological treatments of opioid use disorder in a national cohort. Addiction. 2022 Jun;117(6):1683–1691. doi: 10.1111/add.15814.

III Heikkinen M, Taipale H, Tanskanen A, Mittendorfer-Rutz E, Lähteenvuo M and Tiihonen J. Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients. JAMA Psychiatry. 2023 Jan 1;80(1):31–39. doi: 10.1001/jamapsychiatry.2022.3788.

CONTENTS

ABBREVIATIONS

ADHD	Attention Deficit Hyperactive Disorder
ATC	Anatomical Therapeutic Chemical Classification System
AUD	Alcohol use disorder
CBT	Cognitive Behavioral Therapy
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DALY	Disability-adjusted Life Year
DDD	Defined Daily Dose
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDR	False discovery rate
GABA	Gamma-aminobutyric acid
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
MAUD	Methamphetamine/ amphetamine use disorder
MiDAS	Micro Data for Analyses of Social Insurance
NPR	National Patient Register
OAT	Opioid agonist therapy
OUD	Opioid use disorder
PDR	Prescribed Drug Register
PRE2DUP	From Prescriptions to Drug Use Periods -method
RCT	Randomized controlled trial
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
TCA	Tricyclic antidepressant
WHO	World Health Organization

1 INTRODUCTION

Substance use disorders (SUDs) represent a global health burden which significantly impacts individuals, family members, and society at large. These disorders are characterised by the compulsive and harmful use of substances, and contribute to a range of adverse consequences, such as physical and mental health problems, increased mortality, social disruption, and economic burden. Hence, the prognosis for SUDs without treatment is unfavourable. The treatment of SUDs includes psychosocial interventions, but the effectiveness of treatment strategies could be significantly improved with the inclusion of pharmacological treatment. However, medications that have been approved by the relevant health authorities are limited to the treatment of nicotine, opioid and alcohol use disorders. As such, no officially approved medications for the treatment of stimulant use disorders, such as amphetamine use disorder, are currently available. Furthermore, pharmacotherapy for alcohol and opioid use disorders remain largely underused, potentially due to insufficient knowledge of the comparative effectiveness of medications and the stigma associated with SUDs. (1,2)

Studies concerning the pharmacotherapies available for SUDs are often constrained by limited sample sizes, which describe highly spesific populations, and by low rates of treatment adherence or completion. The effectiveness of medications for alcohol use disorder (AUD) and amphetamine use disorders (MAUD) have mainly been investigated through randomized controlled trials, and observational studies with large cohorts and long follow-up periods are rare. The maintenance treatment of opioid use disorder (OUD) is quite well established and associated with a better prognosis (3–5). However, there is still a clear lack of real-world evidence concerning the outcomes of different SUDs, such as hospitalisation and death (especially among persons with AUD and MAUD). The continuously increasing prevalence of SUDs means, that it is

imperative to deepen our understanding of effective treatment strategies to prevent the substantial harm and costs caused by SUDs to both individuals and society. It is important to state that real-world studies with large, unselected cohorts and extensive follow-up periods, would provide comprehensive and generalisable information on the effectiveness of various medications and provide valuable guidance for further studies. (1,6)

AUD, OUD and MAUD represent the majority of the health burden caused by SUDs and were therefore selected as the disorders for investigation in the papers appended to this dissertation. The research underlying this dissertation utilised nationwide Swedish registers to investigate the real-world effectiveness of different medications used to treat these disorders. The main aim of the research presented in this dissertation was to investigate, whether different medications approved for the treatment of SUDs, or otherwise generally used among persons with SUD, were associated with hard outcomes, such as hospitalisation or death. This type of evidence, when considered in the light of the elevated relapse rates and consequential health and social challenges linked with SUDs, could enhance our understanding of the effectiveness of different pharmacological treatments for individuals with AUD, OUD and MAUD. This could be pivotal in improving clinical outcomes for this population as well as mitigating the harm linked to these disorders.

2 REVIEW OF THE LITERATURE

2.1 SUBSTANCE USE DISORDERS

Substance use disorders (SUDs) are psychiatric disorders characterised by the continuous and compulsive use of a substance despite physical, psychological and/or social harm (1). The most severe form of these disorders is dependence (i.e.,"addiction"), which is defined as an inability to control the compulsive use of substance and physiological withdrawal symptoms when the use of the substance ceases or decreases. (7) The development of any SUD is a complex, multifactorial process, and several biological and social factors (i.e., male sex, genetics, initiation of substance use at a young age, childhood trauma, and psychiatric comorbidities) have been associated with the increased risk of development of SUDs (1,7). SUDs are now known to form as a consequence of repeated activation of reward systems within the brain following the use of a specific substance. The main component of the reward system is the dopamine pathway, which projects from the midbrain to the nucleus accumbens, where addictive substances directly or indirectly increase levels of the neurotransmitter dopamine. Dopamine is generally associated with feelings of pleasure and reward, along with the avoidance of negative stimuli; as such, this neurotransmitter plays a key role in reward and reinforcement mechanisms. (1,8) Various drug classes elevate dopamine levels through unique molecular targets and mechanisms. Hence, various substances show differential magnitudes and velocities of dopamine increase, which, in turn, contribute to the potential for addiction to a specific substance (1). During prolonged substance use, the functional control of the frontal lobe decreases, which makes the stress systems of the brain more sensitive. The repeated use of a substance induces neuroplastic alterations in the glutamatergic connections to the striatum and midbrain dopamine neurons. This mechanism amplifies the responsiveness of the brain to drug-related stimuli, diminishes sensitivity

to non-drug rewards, impairs self-control (which predisposes an individual to relapses in substance abuse), and heightens sensitivity to stress and negative emotional states, especially when access to the substance is limited. As such, chronic exposure of to a certain substance has been associated with reduced levels of dopamine 2-receptors in the striatum, which could explain impulsive behaviour and compulsive use of a substance despite negative consequences. (8,9) Thus, different addictive substances cause both rewarding effects and adaptation in the brain over repeated consumption, which culminates persistent alterations in brain networks and functioning underlying the development of substance dependence. (1,7,8,10–12)

The clinical diagnosis of a SUD is based on two main classification systems: the ICD-11, developed by the World Health Organization (WHO), with the most recent update in 2022 (13); and the DSM-5 (14), generated by the American Psychiatric Association. In European countries, the diagnostic criteria for SUDs are mainly based on the ICD-coding. The newest version, ICD-11, is not yet implemented in all countries, with the tenth edition (ICD-10) still widely used (15). Both the DSM-5 and ICD-10/11 include diagnoses for SUDs, albeit with slight variations in the diagnostic criteria. Depending on diagnostic tool used to define SUD, it consists of substance dependence and substance abuse or substance dependence and harmful use of substance. ICD-10 includes distinct diagnoses for different types of substance use-related conditions, i.e., harmful use and acute intoxication. In ICD-10, substance use disorders are defined with the codes F10–F19, which describe different mental and behavioural disorders due to psychoactive substance use. The third digit in the code (0–9) denotes the substance involved, while the fourth character indicates the clinical condition or state. For example, alcohol dependence is coded as F10.2, where “0” means that the substance involved is alcohol and the number “2” describes the clinical state, which is dependence. However, the term SUDs usually refers to substance dependence and harmful use, which are identified with fourth characters in the code. (16) The diagnostic criteria for harmful use and dependence used in ICD-10 are presented in **Tables 1** and

2. In contrast, ICD-11 (the most recent update of the ICD) distinguishes only three separate disorders: episode of harmful substance use; harmful pattern of substance use; and substance dependence (13). In DSM-5, substance abuse and substance dependence classifications are merged into a unified condition ranging from mild to severe (17), with addiction representing the most severe manifestation of a SUD. In the studies presented in this dissertation, substance use problems were defined in a comprehensive manner, i.e., using only three characters of the ICD-10, if not stated otherwise.

Table 1. The diagnostic criteria for the harmful use of a psychoactive substance, in the ICD-10 (F1x.1)

- The utilisation of the substance has clearly led to mental and/or physical damage, including compromised judgment or disrupted behaviour that could lead to impairments in interpersonal relationships or result in adverse consequences within them.
- The damage caused by the substance must be explicitly specifiable and describable.
- The pattern of harmful use of a substance has persisted for a minimum of one month or has recurred consistently over the past twelve months.
- The diagnostic criteria for another mental or behavioral disorder attributed to the same substance are not met concurrently (excluding acute intoxication, F1x.0)

The diagnosis of harmful use should not be applied if there is concurrent presence of dependence syndrome (F1x.2), psychotic disorder (F1x.5) or another defined substance- or alcohol-related disorder.

Table 2. The diagnostic criteria for psychoactive substance dependence, provided in ICD-10 (F1x.2)

Three or more of the following criteria have been identified simultaneously for a minimum of one month, or recurrently over a one-year period, in cases where the continuous periods last less than one month: • An intensive craving or compulsive urge to consume the psychoactive substance. • Impaired control over the initiation, cessation, or quantity of substance intake, resulting in the consumption of larger quantities or over a longer duration than initially intended. The persistent craving for substance use remains, and efforts to regulate or diminish substance use fail. • Experiencing a physiological withdrawal state upon discontinuation or reduction of substance use, manifesting as the typical withdrawal syndrome associated with the specific substance. Alternatively, using the same substance or a closely related one to alleviate withdrawal symptoms. • Observable signs of tolerance, where higher doses of the psychoactive substance are required to attain effects that were initially achieved with lower doses. • Progressive neglect of alternative other enjoyable activities due to psychoactive substance use. • Continued substance use despite clear evidence of harmful mental and/or physical consequences.

At present, SUDs are noticeably prevalent in societies around the world and significantly contributes to global health issues, mortality rates, as well as financial and social burdens (1,2). The most prevalent of the substance use disorders is AUD, followed by cannabis dependence and opioid dependence. (18) The harmful use of alcohol is a contributing factor to more than 5% of the worldwide disease burden and is responsible for 10% of all deaths in individuals aged 15–49. In total, around 35 million individuals worldwide are thought to be impacted by drug use disorders, leading to approximately 0.5 million annual deaths that can be attributed to drug use. (19) Among various drug categories, opioids pose the highest fatality risk, and are responsible for two-thirds of deaths directly associated with drugs; the most common opioid-linked cause of death is overdose

(20). The prevalence of amphetamine use disorders is lower than that of AUDs or OUDs (18). However, qualitative information suggests that amphetamine use noticeably increased in 2020, and that mortality related to amphetamine or methamphetamine use is also on the rise (20–22). SUDs predispose individuals to adverse health consequences, such as liver diseases, infections and cancers. In addition, SUDs are associated with negative behavioural changes, including harming oneself and/or others. (18) The progression of any SUD can disrupt an individual's self-care practices, impact adherence to treatment, or exacerbate pre-existing medical conditions, all of which can increase hospitalisation rates and mortality (23). SUDs are also associated with personal social and economical burden with individuals with SUDs less likely to be employed (1).

Even though SUDs have been repeatedly associated with harm and the availability of evidence-based treatments, SUDs remain largely untreated. (2). The treatment coverage varies across countries, but still shows a worrying low average. (24,25). This dissertation will discuss the pharmacological treatments available for SUDs at length.

2.2 ALCOHOL USE DISORDERS

Alcohol is a psychoactive substance with addictive properties; it has been widely used for centuries in many cultures (19). When used at low doses, alcohol has anxiolytic and rewarding effects (26). Alcohol consumption activates the reward system of the brain, with the dopamine pathway (projected from the midbrain to the nucleus accumbens) playing a central role. Drinking alcohol increases dopamine level, particularly in the nucleus accumbens area, and this mechanism contributes to the rewarding effects of alcohol, explaining the initiation and persistence of alcohol use. (26,27) Alcohol also interacts with other neurotransmitter systems (e.g., serotonin, gamma-aminobutyric acid [GABA], glutamate, acetylcholine, and opioid systems); in this way, prolonged alcohol use can disrupt the neural networks regulating rewards, motivation, decision-making, stress

response, and emotions. (9) The repeated activation of the reward system may lead to AUD. Risk factors for the development of AUD include early initiation of alcohol use and hazardous drinking during adolescence. Furthermore, a family history of AUD, poor family support, potentially including low parental monitoring, as well as impulsivity and childhood conduct disorders may predispose an individual to developing AUD. (26)

AUDs cover alcohol dependence, alcohol abuse, and dependence or harmful use (27). In AUD, the consumption of alcohol is accompanied by a strong craving for more alcohol and the continuation of use despite negative consequences (27).

2.2.1 Definition and prevalence

According to ICD-10, the diagnosis of AUD requires the harmful use of alcohol for at least one month or repeatedly over the past twelve months (harmful use), or the fulfilment of at least three dependence syndrome criteria over the same time-period (28) (**Tables 1 and 2**). On a global level, AUD is the most prevalent substance use disorder (18); according to the 2018 Global Status Report on Alcohol and Health by the World Health Organization, approximately 237 million men and 46 million women are estimated to be affected by AUDs (24). The number of people afflicted by AUDs has increased substantially since the 1990's (18).

In Sweden, the prevalence of AUDs was 14% in males and 7.3% in females in 2016 (24). In 2021, around 20% of men and 13% of women were estimated to engage in hazardous drinking. Moreover, the prevalence of alcohol dependence in Sweden was recently estimated to be between 4% and 5%. (29)

2.2.2 Morbidity and mortality

AUDs represent one of the primary causes of mortality and morbidity worldwide. Globally, 5.3% of all deaths can be attributed to harmful alcohol use. (24) Previous evidence has shown that mortality among men with AUD

is over three-fold higher, and among women with AUD over four-fold higher, compared with general population (30). A register-based study that focused on the Nordic countries (Denmark, Finland and Sweden) revealed that persons with AUD have 24–28 years shorter life expectancy when compared with the general population and that AUD is associated with a higher risk of mortality due to all causes of death, diseases and medical conditions, as well as suicide. (31) The global burden of the disease and injuries caused by harmful alcohol use is over 5% when measured in disability-adjusted life years (DALYs); this exceeds the burdens caused by many other health conditions that are high on the global health agenda. (24) Chronic exposure to alcohol exerts significant impacts on various systems within the human body and is associated with liver diseases, diabetes, gastrointestinal diseases, cancers, cardiovascular diseases, tuberculosis and HIV/AIDS. (9,24) AUD significantly affects the nervous system, and predisposes an individual to cognitive deficits (such as amnesias and difficulties in problem-solving, abstraction and learning) as well as peripheral neuropathy (27). Persons with AUD may suffer from malnutrition and severe vitamin deficiencies, of which vitamin B1 deficiency (thiamine deficiency) is the most common. The most severe manifestation caused by thiamine deficiency is Wernicke encephalopathy, which is potentially fatal. In addition, the harmful use of alcohol plays a noticeable role in road injuries, violence, and suicides. Overall, AUD may also co-occur with psychiatric disorders (e.g., other substance use disorders, major depressive and bipolar disorders, and personality disorders). (32) Individuals who consume large quantities of alcohol are also more likely to frequently consume other psychoactive substances. The simultaneous usage of alcohol and drugs, especially opioids or benzodiazepines, frequently plays a role in overdoses and fatalities from poisoning. (24) AUDs also exert negative effects on social and economic functioning, including work performance (9,33).

2.2.3 Treatment

Currently, several treatments are available for AUD. The cornerstone of treatment is psychosocial intervention, e.g., cognitive behavioural therapy (CBT), motivational interviewing, support groups, and group therapies. (9,34) However, psychosocial treatments, when provided alone, are associated with high relapse rates; as such, combining these types of interventions with pharmacotherapy can lead to better outcomes (34). Various pharmacotherapies are discussed in more detail in Chapter 2.5.1. A systematic review and meta-analysis published in 2020 suggests that combining CBT with pharmacotherapy enhances treatment adherence and retention, and supports patients with AUD before the effects of their medication becomes apparent (35). Despite the availability of evidence-based treatment methods, access to treatment remains an issue and varies widely across countries (9,24,25). More specifically, only approximately one in six people with AUDs will receive treatment (36). The low treatment rate may be explained by the stigma associated with addiction and insufficient screening of AUD in health care services (25). In addition, financial restrictions as well as limited understanding of medications and uncertainties regarding their efficacy can result in a low rate of utilisation (9,34,37). Untreated AUD may result in clinical and medical consequences, psychosocial dysfunction and functional impairments, and adversely affect work performance (9,33).

2.3 OPIOID USE DISORDERS

Opioids are a class of drugs with analgesic and euphorgenic effects; they represent one of the most commonly used group of illicit drugs worldwide (18,38,39). Opioids acts as agonists on the mu (μ), delta (Δ), and kappa (K) opioid receptors within the human body. By engaging the endogenous opioid system, these compounds depress breathing, enhance sensations of pleasure and inhibit the transmission of pain signals within the nervous system. (38,40) The agonist action of opioids (either prescribed

medications or illicit drugs) at the mu-receptor is responsible for the analgesic and rewarding effects of opioids (41). The development of OUD is quite well understood as it is the most intensely studied substance use disorder (42). The repeated use of opioids, both in patients receiving pain relief and persons misusing these compounds, can rapidly progress to physical dependence and may lead to the emergence of acute withdrawal symptoms when opioid use is discontinued (43). The misuse of opioids disrupts the natural reward mechanism governed by endogenous opioids and severely alters reward, brain stress, and pain systems. In contrast to many other substances, the probability of developing OUD after using opioids is high, due to the complex interplay between structural, developmental, social, and behavioral risk factors. (40) Significant psychopathology (such as anxiety, depression, and trauma-related disorders) often precedes the use of opioids (42). Moreover, genetic factors, unfavourable early-life experiences, societal norms, exposure to drugs, and accessibility to drugs on the market can impact patterns of drug use (40). Roughly 50% of individuals who misuse opioids for non-medical reasons will develop OUD within a median period of two years, while more than 20% will develop a dependence syndrome (20). After opioid addiction has developed, the purpose of opioid use often shifts from seeking euphoria to preventing withdrawal symptoms. It is important to state that opioid use-related neuroplastic adaptations are long-lasting and can persist for years after drug discontinuation (43).

2.3.1 Definition and prevalence

OUD is characterised by a problematic pattern of opioid use that results in notable distress or impairment. Severe OUD arises from neuroplastic changes in brain circuits related to rewards and motivation, self-regulation and decision-making, as well as mood and stress responsiveness. (43) The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has consolidated previous diagnoses of opioid abuse and dependence into a unified disorder, OUD, with the severity categorised

based on the number of symptoms present. (17) The International Classification of Diseases 10th or 11th Revision (ICD10/11) is widely utilised in numerous countries, and is particularly popular in Europe. Under this classification system, abuse and dependence are still considered distinct disorders. Under ICD definitions, a person must show a greater number of symptoms to be described as having opioid dependence, which is considered more severe than abuse (40). However, OUD is broadly characterised as a problematic pattern of opioid use that leads to substantial impairment or distress. Individuals with OUD continue to use opioids despite experiencing additional physical, mental, social, or legal issues, developing tolerance, or having to use opioids to alleviate withdrawal symptoms. (40) Craving, which is defined as an intense and irresistible urge or compulsion to use a drug that is driven by the memory of the pleasurable rewarding effects combined with a negative emotional state, is now included in the recently updated ICD-11 definition of opioid dependence (44).

According to the 2016 Global Burden of Disease study, approximately 26.8 million individuals are suffering from OUD on a global level (18). More recent estimates of OUD, performed in 2019, revealed a slight decrease in prevalence, to 21.4 million individuals (95%CI=17.4–26.9) (45). However, it is difficult to accurately estimate the prevalence of OUD because of geographical variation in the availability and quality of OUD data (40). In the United States, the prevalence of opioid misuse and OUD has increased over the last two decades, culminating in the so-called opioid crisis, which represents great public health challenge. This opioid crisis, which can be traced back to the misuse of prescription analgesics, is currently characterised by the use of heroin and synthetic opioids (such as fentanyl), and seems to be expanding to other countries as well. (41)

2.3.2 Morbidity and mortality

OUD is marked by excessive morbidity, mortality and other negative consequences (42). Nevertheless, persons with OUD will keep using opioids

and progressively develop a tolerance to the effects of the compound they abuse. This will result in withdrawal symptoms (such as piloerection, cold sensations, insomnia, diarrhoea, nausea, vomiting and muscle pain) when the use of opioids ceases or decreases. People with OUD are at high risk of all-cause and overdose-specific mortality, while OUD causes significant challenges for the affected individual, their family members, and the broader community. (39,40) OUD is associated with severe health consequences, such as mental health disorders, bloodborne viruses (such as HIV-infection and hepatitis), severe injection-related infections, hepatitis-related liver cancer and cirrhosis, injuries, suicide, homicide, overdose and premature death (20,40,41,46). OUD is also linked to social issues, including challenging family environments and criminal activities related to drug use (40). The mortality rate among opioid users is approximately 10–20 times higher than the figures for the general population of the same age and gender. Moreover, 25–50% of individuals who used opioids and were followed over a 20-year period were deceased by the end of that timeframe (20). Of the approximately 600 000 global deaths attributable to drug use, close to 80% of those deaths are related to opioid use, and it was estimated that 125 000 people died of opioid overdose in 2019 (47). Thus, opioids account for a significant share of drug-related deaths , which have increased by 41% in the past decade (1). OUD is considered to be chronic and relapsing disorder, and poses a heightened risk of serious adverse outcomes (e.g., overdose, suicide and injuries) associated with relapses even after a period of abstinence (40).

In Sweden, opioid overdoses contributed to over two-thirds of drug-related deaths, the rate of which increased from 3.6 to 8.1 per 100 000 individuals between 2006 and 2014 (48). A study examining fatal poisonings in individuals with SUDs in Nordic countries reported that poly-drug use mainly involved the injection of opioids in combination with benzodiazepines, pregabalin, or alcohol. (49) These substances may interact synergistically leading to depression of the central nervous system. For example, buprenorphine – which exhibits a ceiling-effect – rarely leads to fatal poisoning when used in the absence of other drugs. However, the

combination of opioids and benzodiazepines can lead to a life-threatening situation. (49) A Finnish study conducted in 2011 found that the majority of buprenorphine poisonings did not involve opioids other than buprenorphine. However, benzodiazepines were discovered in 82% of the cases, and alcohol was involved in 58% of the cases. (50) Furthermore, a Swedish study of opioid-related deaths in Sweden between 2006–2014 reported a consistently high percentage of cases which benzodiazepines were involved, regardless of the primary drug involved in the fatality. Pregabalin was most frequently identified in deaths where buprenorphine was the primary drug. Overall, benzodiazepines, pregabalin, and alcohol were forensically detected in 61%, 15% and 24%, respectively, of the 2 834 opioid-related deaths. The presence of another opioid than the main drug at death was detected in 17% of the cases. (48)

2.3.3 Treatment

Several evidence-based treatments for OUD are available. Despite the availability of effective treatments, medications are not utilised to the full potential, treatment adherence tends to be suboptimal, dropout rates are high, and a substantial risk of relapse remains once treatment concludes. (40,41,46,51) The treatment of OUD can include acute intervention, stabilisation and long-term care (40). Psychosocial interventions, such as behavioural therapies, group therapy (e.g., Narcotics Anonymous, NA) and residential rehabilitation, lack robust scientific evidence and are mostly considered as a potential complementary service to pharmacological treatments (40).

The Food and Drug Administration (FDA) has approved three medications for the treatment of OUD, namely, the opioid agonists buprenorphine and methadone, and the opioid antagonist naltrexone; all of these compounds are meant to be used for long-term maintenance treatment. Pharmacotherapies for opioid addiction also include alpha-2-adrenergic agonists (lofexidine, clonidine), which serve to detoxify opioids.

(40,52) The pharmacotherapies available for OUD are explained further in chapter 2.5.2.

2.4 AMPHETAMINE USE DISORDERS

Amphetamines, including amphetamine sulfate and methamphetamine, act on the central nervous system by increasing the levels of dopamine, serotonin, noradrenaline, and adrenaline to produce mainly stimulant effects (53,54). The use of amphetamines induces heightened alertness, increased energy levels, intensified curiosity, reduced fatigue, anorexia and an elevated mood. In addition, amphetamines can exert positive effects on focus, attention and concentration; for this reason they have been used to treat conditions such as attention deficit hyperactivity disorder (ADHD), narcolepsy and excessive eating. (54,55) Amphetamines are also used recreationally for pleasure, to enhance work performance, or as ”self-medication” for stressful life events or weight-related issues (53,55). Non-medical use typically involves higher doses than what is prescribed for oral ingestion, with recreational users commonly using routes of administration that lead to a more rapid onset, e.g., inhalation, intravenous injection, or intra-nasal administration (55). However, amphetamines have high addiction potential; as such regular, long-term use may lead to (meth)amphetamine use disorder (MAUD), which is characterised by social and physiological deterioration, including withdrawal symptoms and the development of tolerance (55,56). The main neurobiological mechanism involved in amphetamine dependence involves dopamine dysfunction. Despite the initial increase in dopamine in the nucleus accumbens during amphetamine use, prolonged exposure results in a hypo-dopaminergic state. The cessation of amphetamine use and the emergence of withdrawal symptoms may be attributed to functional dopamine hypoactivity in the striatum. (57) As is the case with many other substance use disorders, MAUD is considered a chronic and relapsing condition; in this way, persons who do not participate in treatment exhibit five-year remission rates of only up to 30%. Of the individuals with MAUD who undergo treatment, 61%

will experience a relapse within the initial 12 months, and an additional 14% will relapse within 2–5 years (53).

2.4.1 Definition and prevalence

The course of MAUD development is typically marked by recurring phases of intense substance use interspersed with periods of sobriety and subsequent relapses (53). In ICD-10, amphetamine and methamphetamine use disorders are included under the code F15, which covers other stimulant related disorders (excluding cocaine), and defined by a pattern of amphetamine use that ultimately leads to significant impairment or distress, defined by the presence of certain symptoms over a spesific time period (28) (**Tables 1** and **2**). It is noteworthy that the global market for amphetamines continues to expand. In 2017, an estimated 29 million persons had used amphetamines during the past year, with this number rising to 34 million users in 2020. (20,58) A global surveys from 2016 estimated 4.9 million cases of amphetamine use disorder, with 65% of the cases describing males (18). However, the estimate in 2019 increased to 7.3 million cases (62% of which were males) (59). According to the World Drug Report of 2022, seizures of amphetamine-type stimulants show an increasing trend; the quantities of seized methamphetamine have grown five-fold and the quantities of seized amphetamine four-fold over the decade (20). Thus, MAUD seems to be re-emerging as a significant public health burden (53).

2.4.2 Morbidity and mortality

Amphetamine use can cause a range of adverse effects, ranging from heart palpitations, sweating, hyperthermia and seizures, headache, tremor, paranoia and other symptoms of psychosis to aggressive behavior (60,61). Regular and long-term use can lead to mental (e.g., psychosis, depression and suicide attempts) and physical (e.g., cardiovascular disease, blood borne viruses and infections) health consequences, and the increased

prevalence of violent behavior (56,62). The adverse consequences can also be fatal, especially among people who regularly use amphetamines, especially via the injection route, and have become dependent on them (60). The most critical medical issues, and primary cause of death, linked with MAUD are cardiovascular and cerebrovascular diseases (53). Amphetamine use is considered to be toxic for the heart and blood vessels and, as such, increases the risk of myocardial infarction, aortic dissecation, acute coronary syndrome, cardiomyopathy and cardiac arrhythmias, all of which can be fatal (61,62). Cerebrovascular disease includes stroke, aneurysm, and cerebral haemorrhage (60). People who abuse stimulants are subjected to six-fold higher risk of mortality relative to the general public. In 2017, amphetamine dependence was linked with approximately 326 000 excess deaths (0.56% of all deaths) on a global level. Overall, suicide, overdoses, and fatal cardiovascular disease are the most common causes of death for persons who use amphetamines, with accidental injuries and homicide also cited as reasons for death among users. (62)

Persons with MAUD also commonly abuse other substances, which increases the risk of combined adverse consequences. The substances which are most commonly abused in tandem with amphetamines are cannabis, other stimulants, alcohol and opioids. Individuals who use stimulants often heavily consume alcohol, which increases the risk of cardiotoxic effects and violent behaviour. (62) Possibly the most dangerous combination of substances is combining amphetamines with opioids. The combined use of amphetamines and opioids increases the risk of cardiotoxic effects, and adverse outcomes associated with the central nervous system and respiratory system, as well as the risk of fatal overdose. Moreover, the concurrent use of amphetamines and opioids heightens the risk of exposure to bloodborne viruses, such as HIV and hepatitis. This association is linked to users requiring multiple injections per day and the reuse of syringes. (62,63) Also, benzodiazepines are often combined with stimulants, such as amphetamines, to “come down from” or decrease the excitatory effects of these substances (e.g., anxiety, irritation, insomnia) (64).

2.4.3 Treatment

Despite the alarming public health impact of MAUD, no pharmacotherapies have yet been officially accepted by the relevant health authorities (55). While promising candidates do exist, no pharmacotherapy for the treatment of MAUD has provided robust and convincing results. Research findings are frequently constrained by small sample sizes within specific populations, along with low rates of treatment adherence or completion. (55,56) Psychosocial interventions, such as cognitive behavioral therapy, behavioural activation and contingency management have shown modest efficacy. The current evidence base demonstrates mixed results, and the positive effect of therapy does not usually persist after termination, nor does it seem to help with more severe problems (frequent or long-term amphetamine use). (53,55,56,62) The effectiveness of different medications generally used among persons with MAUD will be presented further in Chapter 2.5.3.

2.5 PHARMACOLOGICAL TREATMENT OF SUBSTANCE USE DISORDERS

The United States Food and Drug Administration (FDA) has only approved medications for the treatment of the following SUDs: nicotine, opioid, and alcohol use disorders (1). The pharmacological treatment options for opioid and alcohol use disorders are reviewed below. At present, no approved medications for treating amphetamine use disorders exist. However, as the pharmacotherapies used by persons with MAUD were studied in third study included in this dissertation, the present knowledge concerning pharmacotherapy for MAUD is also presented below.

2.5.1 Pharmacotherapy of AUD

The FDA has approved three medications for the treatment of alcohol use disorder: disulfiram, acamprosate, and naltrexone. In addition to these

three compounds, the European Medicines Agency (EMA) has approved nalmefene for the treatment of AUD. (1,65)

Disulfiram has been used in the treatment of AUDs for decades, since being approved in the 1940's. Instead of reducing an individual's craving for alcohol, disulfiram works mainly by eliciting an aversive reaction when used concomitantly with alcohol. This is a result of disulfiram inhibiting the metabolism of the toxic metabolite of alcohol, acetaldehyde. The accumulation of acetaldehyde causes unpleasant, potentially dangerous physical symptoms, such as tachycardia, sweating, flushing, nausea, vomiting and hypotension. Thereby, the effectiveness of disulfiram is based on the patient's fear of experiencing uncomfortable symptoms rather than direct pharmacological action. Even though the main effect of disulfiram is psychological fear, disulfiram has nevertheless been shown to increase dopamine concentrations in the brain. Dopamine has a remarkable role in rewarding craving. (32,65,66) Due to the aversive reaction experienced once drinking alcohol, disulfiram treatment necessitates total abstinence. The treatment dosage varies from 125–500 mg/day, with 200 mg/day the most common dosage. (34,67) The most common side effects of disulfiram include headache and drowsiness (67), but treatment can also involve severe side effects, including hepatitis, psychotic symptoms, neuropathy, and potentially life-threatening conditions such as myocardial infarction, congestive heart failure, respiratory depression, and rarely, death. Thus, disulfiram should be avoided in the case of previous psychosis or renal failure, cardiovascular or pulmonary disease or diabetes. In addition, disulfiram is not recommended for use in persons over the age of 60 or as a first-line treatment of AUD. (68) Numerous clinical studies have been conducted to investigate the effectiveness of disulfiram in AUD treatment. However, these findings exhibit limited consistency. (69) The largest meta-analysis of RCTs concerning disulfiram (**Table 3**) included 22 RCTs (N=2 414) and compared the success rate (various outcome measures, such as continuous abstinence, mean days of alcohol use, and time to first relapse) of disulfiram and controls (66). This analysis revealed that disulfiram

achieves a significant success rate when compared to the controls (Hedges' g=0.58; 95%CI=0.35–0.82), where a Hedges' g-value of 0.2–0.3 denotes a "small" effect, value of 0.5 denotes a "medium" effect, and a value over 0.8 denotes a "large" effect. However, the significant effects were observed only in open-label studies, whereas blinded studies showed no significant effects. The authors suggest that this discrepancy can be explained by the primary action mechanism of disulfiram, i.e., the expectation of an aversive reaction. In a blinded study design, these expectations can also be expected to affect the placebo group, which may bias the between-group differences. In addition, disulfiram was significantly more effective when treatment was supervised. (66) A similar phenomenon was observed in, for example, a randomized open-label comparative trial of disulfiram, naltrexone and acamprosate. Treatment with all of the studied medications, when combined with brief manual-based cognitive behavioural therapy, significantly reduced alcohol consumption; however, it is notable that the supervised use of disulfiram was most effective, particularly throughout the continuous medication period. (70) The results including effect sizes are presented in **Table 3**.

Acamprosate is the calcium salt of N-acetyl-homotaurine and modulates glutamatergic and GABA-ergic neurotransmission, with potential effects on calcium-channels (65,67,68). In 2004, the FDA approved acamprosate to help maintain abstinence in persons with AUD who are abstaining from alcohol at treatment initiation (32,65). Acamprosate is usually well tolerated. The typical dose of acamprosate is 666 mg, taken three times/day. (34) The exact mechanism through which acamprosate works remains unclear, although it appears to be effective in diminishing alcohol craving and lowering the risk of relapse (68,71). A meta-analysis of 16 RCTs concluded that treatment with acamprosate, when compared to the placebo, significantly decreases the risk of drinking among abstinent patients, although this form of treatment did not show a reduction in the likelihood of binge drinking (72). Another meta-analysis also found acamprosate to be effective in reducing relapses when compared to a placebo (73). Moreover, Bahji et al. found acamprosate to be effective in

both improving abstinence and reducing heavy drinking in a meta-analysis conducted in 2022 (74). More details about these meta-analyses are provided in **Table 3**.

Naltrexone has been used in AUD treatment since the 1990's. It is an opioid receptor antagonist, and has also been used for the treatment of OUD. Naltrexone blocks the mu-opioid-receptor and – by modulating the dopaminergic mesolimbic pathway – dampens the euphoric effect of alcohol and reduces cravings. (34,71) The common side effects reported for naltrexone include gastrointestinal issues (e.g., nausea, vomiting, abdominal pain, and diminished appetite), dizziness, and drowsiness (32), but these usually ease with time. Naltrexone treatment also involves a low risk for hepatoxicity and should thus be avoided in persons with acute hepatitis or liver failure (1). However, a recent retrospective cohort study (N=9 131) found that use of acamprosate or naltrexone in persons with alcohol-associated cirrhosis and high-risk alcohol use behavior is linked with a 20% improvement in survival compared with the case that no pharmacotherapy is used; this indicates that naltrexone can be considered safe among persons with liver-disease (75). As an opioid antagonist, naltrexone is contraindicated in patients using opioids. The dosage on oral naltrexone is usually 50 mg/day, although treatment can be started with 25 mg/day. (34,67) An extended-release injection formulation of naltrexone, which is administered as a monthly injection, has been approved by the FDA in the United States (76). In Europe, the extended-release naltrexone injection has been approved in France, Germany, Greece, Ireland, and the United Kingdom. (77) Multiple meta-analyses of RCTs have provided strong support for the efficacy of naltrexone in treating AUD, especially in terms of reducing heavy drinking and cravings (72–74,78); more details are presented in **Table 3**. The use of naltrexone, either the oral or extended-release injection formulation, has been shown to decrease the amount of drinking days (76,79,80), and reduce the consumption of alcohol based on the reduction of rewarding effects (81). However, it is only moderately effective in reducing relapses, as reported in a meta-analysis of 53 RCTs (72).

Nalmefene, like naltrexone, is an opioid antagonist that targets the mu and delta opioid receptors. However, unlike naltrexone, nalmefene also acts as a partial agonist at the kappa-opioid receptor. (82) Nalmefene was approved in Europe in 2013 for the reduction of alcohol consumption among adult patients with alcohol dependence and who exhibit a highly risky drinking behaviour (defined as alcohol consumption exceeding 60 g/day for men and 40 g/day for women). This recommendation is applicable to individuals without physical withdrawal symptoms and who do not require immediate detoxification (83). The approved dosage for nalmefene in Europe is 18 mg/day and is usually well tolerated, with adverse effects similar to what has been observed for naltrexone. (32,71) However, nalmefene therapy has not been linked to serum hepatic enzyme elevations or acute liver injury and does not appear to exacerbate chronic liver diseases, such as alcohol liver disease or hepatitis (84). Nalmefene exhibits a similar effect as naltrexone, with the advantages of greater bioavailability and an extended effect. (1,34) Nalmefene have shown limited efficacy in reducing alcohol consumption, especially heavy drinking days (72,85,86). A systematic review and meta-analysis from 2017 found that nalmefene exhibited a limited impact on overall alcohol consumption and the number of drinks per drinking day when compared to a placebo. However, the evidence was not considered to be robust. (87) Also, the studies that led to the European approval of nalmefene were met with criticism due to limitations in the evidence of efficacy, more specifically a retrospective definition of a subgroup of patients, the absence of an *a priori* definition for outcome measures and sensitivity analyses, and comparisons of nalmefene with a placebo instead of appropriate comparators. (32) More recent research has found nalmefene therapy to be associated with high dropout rates (74,88). The studies regarding nalmefene pharmacotherapy are presented in detail in **Table 3.**

It should be noted that persons with AUD face a risk of alcohol withdrawal symptoms when they substantially reduce alcohol consumption following an extended period of heavy drinking. Withdrawal symptoms can include nausea or vomiting, hyperactivity of the autonomic

nervous system, inability to sleep, increased anxiety, tremor and seizures. (89) Benzodiazepines are generally used to reduce alcohol withdrawal symptoms and decrease the risk of seizures (90). These compounds act as agonists at GABA-receptors and decrease the severity and length of withdrawal symptoms, along with the frequency of seizures and risk of delirium (89). Furthermore, diazepam is widely used to treat withdrawal symptoms because it is characterised by rapid onset and longer duration of action. Depending on the severity of symptoms, patients receive either a 5 or 10 mg oral or intravenous formulation of diazepam, with repeated doses until sedation is achieved. After the stabilisation of withdrawal symptoms, benzodiazepine treatment will be gradually tapered off within a few days. (91,92) It should be noted that the use of benzodiazepines after detoxification among patients with AUD is not accepted (93).

To summarise, the latest available meta-analyses and systematic reviews of RCTs (presented in **Table 3)**, have provided sufficient evidence for the efficacy of disulfiram, acamprosate, naltrexone and nalmefene in treating AUD based on comparisons with a placebo (71). However, knowledge about the overall health outcomes (e.g., risks of hospitalisation and mortality) associated with these treatment alternatives in real-world circumstances remains scarce. For instance, no previous experimental studies have been designed to measure and compare the risks of all-cause hospitalisation or death for these AUD medications. The only real-world study that investigated whether AUD medications are associated with hospitalisations and death focused on how baclofen use compares with acamprosate, naltrexone and nalmefene treatment. The study (N=165 334) concluded that treatment with baclofen for AUD is associated with a 13% increased risk of hospitalisation and a 31% increased risk of death compared to treatment with the other, approved drugs (94). Another real-world study (N=61 904) investigated prescription patterns of AUD-medications (naltrexone and acamprosate) in Australia and found that only 15–25% of participants received the recommended alcohol pharmacotherapy for a minimum period of three months (95). This finding

is in line with previous knowledge of the underutilisation of AUD pharmacotherapies (34,37,72).

In Sweden, the Swedish Medical Products Agency has approved these four pharmacotherapies (disulfiram, acamprosate, naltrexone and nalmefene) for the treatment of AUD. Moreover, the Swedish National Board of Health and Welfare has given their highest recommendation to acamprosate, disulfiram and naltrexone, which means that every person diagnosed with AUD who is seeking treatment should be offered these therapies. Nalmefene has received a lower recommendation, which means that it can be offered when treating AUD. (96) In Sweden, naltrexone is only available as an oral formulation (tablet) (97).

Table 3. The results of meta-analyses of randomized controlled trials (RCTs) focusing on pharmacotherapies of AUD.

Study	Study design	Inclusion criteria	Exposure(s) and treatment duration	Outcome(s)	Number of patients	Main results (with effect sizes)
Bahji A. et al. 2022 (Journal of Addiction Medicine) (74)	A systematic review and network meta-analysis of RCTs	RCTs of any pharmacotherapy of AUD and control interventions	**Disulfiram, acamprosate, naltrexone and nalmefene** Trial durations: 4–52 weeks.	Alcohol consumption (total abstinence and reduced heavy drinking), dropouts, and dropouts due to adverse events.	156 RCTs N=27 334	Disulfiram (13 studies), acamprosate (35 studies) and oral naltrexone (54 studies) **improved abstinence** (RR=1.71, 95%CI=1.39–2.10; RR=1.33, 95%CI=1.15–1.54 and RR=1.15, 95%CI=1.01–1.32, respectively) and **reduced heavy drinking** (RR=0.19, 95%CI=0.10–0.35; RR=0.78, 95%CI=0.70–0.86 and RR=0.81, 95%CI=0.73–0.90, respectively) over placebo. There were no beneficial results reported for nalmefene. Nalmefene caused more **dropouts** than placebo (RR=1.17, 95%CI=1.01–1.35), also due to adverse events (RR=3.26, 95%CI=2.34–4.55)

Donoghue et al. 2015 (Addiction) (73)	A systematic review and meta-analysis of RCTs	RCTs studying naltrexone and acamprosate for the treatment of AUDs	**Acamprosate** Treatment duration 56–365 days	At least one of the following outcomes: any/heavy drinking and discontinued treatment due to any cause or adverse effect	22 RCTs N=5 236	The **risk of returning to any drinking** at 6 months was significantly lower for acamprosate compared with placebo (RR=0.83, 95%CI =0.78–0.89).
			Oral naltrexone Treatment duration 77–365 days		27 RCTs N=4 199	The risk of **returning to any drinking** at 3 months was significantly reduced in naltrexone group (RR=0.92, 95% CI=0.86–1.00), as was the risk of **relapsing to heavy drinking** at 3 months (RR=0.85, 95% CI=0.78–0.93)

Jonas et al. 2014 (JAMA) (72)	A systematic review and meta-analysis of RCTs	Adults with AUD with FDA-approved or off-label medication for at least 12 weeks (outpatient)	**Acamprosate** Treatment duration: 12–52 weeks	Return to any drinking	16 RCTs N=4 847	Acamprosate was associated with a greater **reduction in the risk of drinking** among abstinent patients (RD=−0.09, 95%CI=−0.14–−0.04; NNT=12), but **no reduction in the likelihood of binge drinking.**
				Return to heavy drinking	7 RCTs N=2 496	Acamprosate was not associated with improvement (RD=−0.01, 95%CI=−0.04–0.03) in returning to **heavy drinking**.
			Oral naltrexone Treatment duration: 12–24 weeks	Return to any drinking	16 RCTs N=2 347	Naltrexone with a dose of 50 mg/day was associated with **reduced risk of returning to any drinking** (RD =−0.05, 95% CI=−0.10–-0.002; NNT=20)
				Return to heavy drinking	19 RCTs N=2 875	Naltrexone was also associated with **reduced risk of heavy drinking** (RD=−0.09, 95%CI=−0.13–−0.04, NNT=12)

Maisel et al. 2013 (Addiction) (78)	A meta-analysis of RCTs	RCTs testing the efficacy of naltrexone or acamprosate in treatment of AUDs	**Acamprosate** Lenght of trials: 21–360 days	Abstinence Heavy drinking Craving	16 RCTs N=4 349	The effect size of acamprosate was larger than naltrexone's for **abstinence** outcomes, (g=0.359 vs. g=0.116, P<0.001). The effect size for naltrexone studies (g=0.144) was marginally larger than the effect size for acamprosate studies (g=0.034, P=0.075) for **craving**.
			Oral naltrexone Lenght of trials: 21–365 days		45 RCTs N=5 434	
Murphy et al. 2022 (Addiction) (76)	A systematic review and meta-analysis of RCTs	RCTs that assessed the efficacy of XR-naltrexone on alcohol use and heavy drinking days	**Extended-release naltrexone** Treatment duration: 2–6 months	The number of monthly drinking days	7 RCTs N=1 500	The pooled WMD was -2.0 (95% CI= -3.4–-0.6; P=0.03) in favor of extended-release naltrexone for **drinking days per month** and -1.2 (95%CI=-0.2–-2.1; P=0.02) for **heavy drinking** days per month.[1]

[1] indicating that treatment resulted in two fewer drinking days per month and 1.2 fewer heavy drinking days per month compared with placebo.

Palpacuer et al. 2017 (Addiction) (87)	A systematic review and meta-analysis of RCTs	RCTs assessing the efficacy of nalmefene, naltrexone, acamprosate, baclofen or topiramate against each other or placebo in adults with AUD.	**Nalmefene** Treatment duration: 3–52 weeks	The primary outcome was total alcohol consumption	9 RCTs N=1 693	Nalmefene (SMD=−0.19, 95%CI=−0.29, –0.10) showed superiority over placebo on **total alcohol consumption**. Nalmefene and naltrexone were associated with a significant increase in withdrawals from study. There was no evidence for a significant reduction in serious adverse events or in mortality. Effect sizes were small.
Skinner et al. 2014 (PLoS One) (66)	A meta-analysis of RCTs	RCTs comparing the efficacy of disulfiram to any control group in subjects with AUD	**Disulfiram** The duration of treatment 8–52 weeks	The primary outcomes defined by the authors of each trial.	22 RCTs N=2 414	Disulfiram was associated with **sustained abstinence** from alcohol compared to control conditions only in open-label studies (Hedges' g=0.70, 95% CI=0.46–0.93); there was no significant association in blinded trials (Hedges' g=0.01, 95% CI=−0.29–0.32) A better response was associated with **supervised** disulfiram treatment than control conditions (13 studies; Hedges' g=0.82, 95%CI=0.59–1.05), but not when it was unsupervised (9 studies; Hedges' g=0.26, 95% CI=−0.02–0.53)

Abbreviations: RCT=randomized controlled trial, CI=confidence interval, RD=risk difference, NNT=number needed to treat, RR=risk ratio, WMD=weighted mean difference, SMD= standardized mean difference

2.5.2 Pharmacotherapy of OUD

The most effective treatment approach for preventing overdose mortality and improving outcomes among individuals with OUD is pharmacotherapy. The FDA has approved three medications for the treatment of OUD, namely, methadone, buprenorphine, and naltrexone. Opioid agonist therapy (OAT) includes the use of the full-agonist methadone or the partial agonist buprenorphine and represents the main type of pharmacotherapy available for OUD. (1,98,99) OAT is also referred to as opioid substitution treatment, opioid replacement therapy or methadone/buprenorphine maintenance treatment (40). The less commonly-used heroin-assisted therapy would also belong to this category (40,100). In addition to OAT, opioid agonists can be used in decreasing doses for the supervised cessation of opioid use (101). The opioid antagonist naltrexone has been used to maintain abstinence, reduce relapses, and improve treatment adherence (particularly the extended-release formulation), which are crucial factors for reducing overdose deaths. (1,40,52,99) Several studies have demonstrated that these FDA-approved medications are cost-effective and linked to a decreased risk of death due to overdose, relapses, somatic complications such as infections, and criminal behaviour (40,41,46,98). OAT has received the most robust scientific evidence for the treatment of OUD. According to a wide range of studies, OAT can reduce both overdoses and all-cause mortality among people with OUD (3–5). Medications for OUD also improve treatment retention and remission (46).

Methadone is a long-acting synthetic mu-opioid receptor agonist and has been available the longest. It has the largest evidence base of all pharmacotherapies for OUD regarding efficacy. (52,102) As a full agonist of the mu-receptor, methadone has no ceiling effect. This may be a risk factor for overdoses, especially when used at doses above a person's tolerance or combined with other sedatives, such as alcohol, benzodiazepines or other opioids. (52) When initiating maintenance therapy, the starting dose for methadone is generally 15–30 mg/day. The dose can be adjusted every 3–5

days as needed, controlling possible side effects and withdrawal symptoms. Methadone is administered daily as an oral solution and the maintenance dose reaches typically 80–100 mg/day. (102) There is some evidence that higher methadone doses (up to 100 mg/day) are associated with better outcomes than lower doses (103). Methadone is generally used in patients with severe tolerance. As methadone can prolong the QT-interval, it should be carefully considered for patients with a history of cardiac arrhythmias. (43,102)

Buprenoprhine is a partial mu-opioid receptor agonist (and a kappa-opioid antagonist) that was approved by the FDA in 2002 for the treatment of OUD. Buprenorphine has a long half-life (mean of 37 hours), which allows for sublingual administration every other day in addition to daily dosing. (1,43,98) Buprenorphine is administered through the mucous membranes, either as a sublingual or buccal formulation (for immediate release of buprenorphine) mainly on a daily basis, or as an injection or implant (which represent extended-release buprenorphine) that is typically administered on a weekly or monthly basis (101). Daily doses of buprenorphine typically range between 8–24 mg, with a target daily dose of 16 mg. (1) Buprenorphine has very high affinity for the mu-opioid receptor and is able to displace many full opioid receptor agonists. This can lead to opioid withdrawal when buprenorphine is administrated to persons who have actively used opioids. Unlike methadone, buprenorphine has a ceiling effect and higher doses do not cause respiratory depression or euphoria. However, this protective mechanism, which stems from partial agonism, does not apply to cases where a person concomitantly uses alcohol, benzodiazepines or other sedatives. (1,102)

Naltrexone is an opioid antagonist that is used to block the effects of opioids. Naltrexone can be administered either orally, as an immediate-release formulation, or as an extended-release injection. Oral naltrexone is rarely prescribed due to poor adherence to treatment. (40) Treating OUD with naltrexone requires an individual to have a week-long abstinence of opioids to avoid precipitation of withdrawal symptoms. A period of abstinence this long can be highly challenging or even impossible for many

OUD patients, which explains the poor adherence to naltrexone treatment. (1,43) The goal of OUD treatment with naltrexone is supporting abstinence and maintaining a lifestyle that does not involve repeated opioid use. Naltrexone does not induce positive opioid effects, which can lead to challenges in adherence, early discontinuation, and an elevated risk of fatal overdose after treatment cessation. This risk arises from a decrease in opioid tolerance and the rapid unblocking of mu-opioid receptors following the discontinuation of treatment; as such, an individual who then relapses and uses opioids can experience an overdose. (98,104) However, there is also evidence that treatment with extended-release naltrexone results in significant improvements in terms of treatment retention and prevention of premature mortality (1,99).

Abrupt opioid discontinuation leads to withdrawal symptoms, which can be treated with medications. Acute withdrawal, for example, what occurs during medically-supervised withdrawal, can be treated with opioid agonist (decreasing doses of methadone or buprenorphine) and the goal is usually abstinence. (40) The intensity of withdrawal symptoms can also be relieved with alfa-adrenergic agonists, such as lofexidine and clonidine. (98)

Naloxone, an opioid antagonist, is used to reverse opioid-induced overdose. For this reason, naloxone is usually administered intravenously or intramuscularly in emergency rooms and ambulance settings. However, a concentrated naloxone nasal sprays, i.e., a ”take-home naloxone-kit”, is also available on the market. (98) There has been global tendency to reduce overdose deaths by providing and training the use of naloxone to people likely to witness an opioid overdose (47). In Sweden, the National Board of Health and Welfare, together with Medical Products Agency, updated regulations in 2019 to increase accessibility to naloxone. As such, nurses have been authorised to prescribe naloxone, prescribers are authorised to provide patients with an opioid prescription with naloxone, and ambulance and rescue services personnel are now authorised to administer naloxone. There is also publicly-available information available on how to save life if someone close to you experiences an overdose. (105)

OUD is the most intensely studied SUD; as such, in addition to RCTs, plenty of observational studies have investigated the effectiveness of buprenorphine, methadone, and naltrexone ((3,4), **Table 4**). The efficacy of an OUD treatment is usually measured based on the reduction in opioid use (drug-free urine screens), overdose, all-cause mortality, and treatment retention (106). However, RCTs that focus on the comparative effectiveness of OUD pharmacotherapies are often constrained by small sample sizes, which results in low statistical power for identifying between-group differences. Observational studies, which usually demonstrate large sample sizes and sufficient statistical power, may be negatively affected by the high likelihood of selection bias and possible differences between the studied individuals (6). There is robust evidence that OAT is effective especially in reducing opioid use (107), all-cause and overdose mortality (3), and the risk of blood-borne viruses (5). A systematic review of 19 cohort studies found that during OAT, overdose and all-cause mortality were reduced among people with opioid dependence, compared with being out of OAT. The pooled all-cause mortality rates were 11.3 per 1000 person years for methadone treatment and 36.1 per 1000 person years when methadone was not used, and 4.3 and 9.5 per 1000 person years for those with and without, respectively, buprenorphine treatment. Similar results were found for overdose mortality; more specifically pooled overdose mortality rates of 2.6 and 12.7 per 1000 person years with and without, respectively, methadone treatment and 1.4 and 4.6 per 1000 person years with and without, respectively, buprenorphine treatment. (3) In addition, the same review reported that the highest risk of all-cause and overdose mortality occurs within the initial four weeks after treatment discontinuation; there is also an elevated risk during the first four weeks of OAT compared with the remainder of OAT. (3) Furthermore, a systematic review and meta-analysis of 15 RCTs (N=3 852) and 36 primary cohort studies (N=749 634) found that rate of all-cause mortality during OAT was 53% of the rate observed when OAT was not used (risk ratio: 0.47; 95% confidence interval: 0.42–0.53) across the included cohort studies. Moreover, the rates of all-cause mortality and drug-related poisoning were

nearly twice as high during the initial four weeks of methadone treatment when compared to rates observed at other time points of OAT. However, this pattern was not observed for buprenorphine. There were suggestions that the included RCTs did not show sufficient statistical power to make reliable assessments of mortality risk. (4)

There is far less evidence about how effective these treatments are among non-selected patient populations in real-world treatment settings when considering long-term outcomes (such as hospitalisation). Wakeman et al. retrospectively investigated the comparative effectiveness of different treatment pathways (N=40 885), and found that treatment with buprenorphine or methadone is associated with reductions in overdose (reductions of 76% and 59% at the 3- and 12-month follow-up points, respectively) and serious opioid-related acute care use (reductions of 32% and 26% in the 3- and 12-month follow-up points, respectively) compared with other treatments, such as naltrexone, inpatient detoxification or residential services, intensive or non-intensive behavioral health, or no treatment ((46), **Table 4**). A reduction in overdose deaths was also observed in the register-based study by Molero et al. (N=21 281). However, only buprenorphine showed a reduction in accidental overdoses when comparing periods of pharmacotherapy and periods without pharmacotherapy, whereas methadone use was associated with an increased risk of accidental overdose when comparing these periods. Overall, both buprenorphine and methadone were associated with reductions in criminal behaviour, when compared with no-use of medications. ((108),**Table 4**)

In summary, there is ample evidence that buprenorphine and methadone are effective in the treatment of OUD, especially in the reduction of overdoses, all-cause mortality, criminality, and serious opioid-related acute care use. However, the studies which have evaluated the efficacy of these medications are mainly RCTs or studies with a somewhat short follow-up period. As such, no prospective cohort studies have investigated the long-term health outcomes (such as hospitalisations due to OUD and mortality due to all, external and natural causes) associated

with the use of buprenorphine and methadone in real-world circumstances.

In Sweden, the National Guidelines published by the National Board of Social Affairs and Health, primarily recommends opioid detoxification for persons addicted to opioid analgesics. In the case of opioid addiction, tapering means that the patient's dose of opioids is gradually reduced, in agreement with the patient, and adapted to any withdrawal symptoms. Tapering the dose can take place over a varying length of time, from a few days to several months. Although there are certain exceptions, this tapering is often performed with the same opioid that the patient used, but can also be carried out with buprenorphine or a combination of buprenorphine and naloxone. (105) Medication-assisted treatment for OUD aims, among other things, to prevent relapses, improve social functioning and reduce medical complications, the spread of infection, and mortality. In Sweden, OUD treatment is generally accessible to all citizens without significant costs. In 2016, an individual was eligible to receive maintenance treatment for OUD if they had a diagnosis of OUD that was at least 12 months old and a minimum age of 20 years (with exceptions made for special reasons) (109). Services that offer medication-assisted treatment, are regulated by the National Board of Health and Welfare. Maintenance treatment with opioid agonists must also involve psychological or psychosocial treatment or social support efforts. Swedish national guidelines recommend the combination of buprenorphine and naloxone, or methadone alone, for the treatment of OUD. In exceptional cases, health care and social services can offer long-acting naltrexone for the treatment of OUD. However, in Sweden, extended-release naltrexone is available only on requisition, while oral formulation of naltrexone is not recommended in the treatment of OUD. (105) At the time of the data analysis described in Study II, extended-release naltrexone was not available in Sweden. Swedish national guidelines also recommends that naloxone is kept available for cases in which an individual is at risk of overdose (105).

Table 4. Results of previous studies focusing on the effectiveness of OUD medications.

Study	Study design (N)	Mean follow-up period	Exposure(s) and outcomes	Main results (with effect sizes)
Molero et al. 2018 (American Journal of Psychiatry) (108)	Cohort study (21 281) using within-individual analysis	7.6 years	Exposures: use of acamprosate, naltrexone, methadone, and buprenorphine, compared with non-use of medication Outcomes: suicidal behaviour, accidental overdoses, and crime.	Buprenorphine was associated with reduction in both **arrest rates for all crime categories** (HR=0.77, 95%CI=0.72–0.84) and in **accidental overdoses** (HR=0.75, 95%CI=0.60, 0.93), compared with no-use of medication. Methadone was associated with reductions in the rate of **suicidal behaviour** (HR=0.60, 95%CI=0.40–0.88) and in all **crime categories** (HR=0.87, 95%CI=0.83–0.91), when compared with no-use of medication. Compared with no use of methadone, the use of methadone was associated with increased risk of **overdose** (HR=1.25, 95%CI=1.13–1.38).
Santo et al. 2021 (JAMA Psychiatry) (4)	A systematic review and meta-analysis (15 RCTs, N=3 852 and 36 cohort studies, N=749 634)	90 days to 9 years in observational studies 1 week to 3 years in RCTs (planned)	Exposures: OAT with buprenorphine or methadone Outcomes: Overall all-cause and cause-specific mortality	Among the cohort studies, the rate of **all-cause mortality during OAT** was significantly lower than the rate during time out of OAT (RR=0.47; 95%CI=0.42–0.53). Rates of **all-cause mortality and drug-related poisoning** were significantly higher in the first 4 weeks of methadone treatment, compared with the remainder of OAT (RR=2.01; 95%CI=1.55–5.09), but not for buprenorphine (RR=0.58; 95%CI=0.18–1.85). RCTs of OAT were underpowered to examine mortality risk.

Sordo et al. 2017 (BMJ) (3)	A systematic review and meta-analysis of cohort studies (19 studies, N=122 885 with methadone, N=15 831 with buprenorphine)	1.3–13.9 years for methadone 1.1–4.5 years for buprenorphine	Exposure: opioid substitution treatment with methadone or buprenorphine Outcomes: deaths from all causes or overdose	Pooled **all-cause mortality rates** were 11.3 and 36.1 per 1000 PY with and without, respectively, methadone treatment (unadjusted out-to-in rate ratio 3.20, 95%CI=2.65–3.86) and 4.3 and 9.5 per 1000 PY with and without, respectively, buprenorphine treatment (unadjusted out to in ratio 2.20, 95%CI=1.34–3.61). Pooled **overdose mortality rates** of 2.6 and 12.7 per 1000 PY with and without, respectively, methadone treatment (unadjusted out-to-in rate ratio 4.80, 95%CI=2.90–7.96) and 1.4 and 4.6 per 1000 PY with and without, respectively, buprenorphine treatment.
Wakeman et al. 2020 (JAMA Network Open) (46)	A retrospective comparative effectiveness research study (40 885)	293.2 days	Exposures:1) no treatment, 2) inpatient detoxification/residential services, 3) intensive behavioral health, 4) buprenorphine or methadone, 5) naltrexone, or 6) nonintensive behavioral health. Outcomes: Opioid-related overdose or serious acute care 3- and 12- months after initiation of treatment.	Only buprenorphine or methadone were associated with a reduced risk of **overdose and serious opioid-related acute-care use** during the 3-month follow-up (aHR=0.24; 95%CI=0.14–0.41; aHR=0.68; 95%CI=0.47–0.99, respectively) and the 12-month follow-up (aHR=0.41; 95%CI=0.31–0.55; aHR=0.74; 95%CI=0.58–0.95, respectively), compared with other exposures.

Abbreviations: aHR=adjusted hazard ratio, HR=hazard ratio, CI=confidence interval, CMR=crude mortality rate, RR=rate ratio, PY=person year, RCT=randomized controlled trial, OAT=opoid agonist treatment

2.5.3 Pharmacotherapy of MAUD

Although (meth)amphetamine use disorder is recognised as major public health problem that severely affects both individuals and society, neither the FDA nor EMA has approved any pharmacotherapies for the treament of MAUD (55,56,110). The consumption of amphetamines initiates a cascading release of norepinephrine, dopamine and serotonin within the central nervous system and most of the medications that have been studied for the treatment of MAUD have similar effects (58,111). A few pharmacotherapy candidates have shown some weak positive signals in the treatment of MAUD. However, robust scientific evidence for these therapies is still lacking. At present, the studies which have investigated pharmacotherapies for MAUD include small samples and noticeable bias; as such, it is difficult to determine whether any observed effect on the selected primary outcome is linked to the pharmacotherapy regime (see **Table 5**). In addition, a low share of the participants generally complete the study protocol, which adversely affect the statistical power of results. (55) The most relevant studies are presented in details in **Table 5**.

The most consistently positive findings have been observed for stimulant agonist treatments (e.g., dexamphetamine and methylphenidate), the opioid antagonist naltrexone, and the anticonvulsant topiramate (**Table 5**). The antidepressants bupropion and mirtazapine have shown some, albeit rather inconsistent, benefits, while antidepressants in general (such as selective serotonin reuptake inhibitors, SSRIs, or tricyclic antidepressants, TCAs) have not been found to be effective at reducing amphetamine use (55). Treatment with agonist-like medications has shown efficacy in other SUDs, such as opioid use disorder and nicotine use disorder. The effectiveness of agonist treatment is assumed to be explained by similar pharmacological and behavioural effects as the drug that was being abused. Thus, agonist treatment provides an individual with relief from cravings and withdrawal symptoms, which usually are the factors maintaining the drug use and exposing to relapse after abstinence. (58)

Dexamphetamine is a functional agonist of methamphetamine that has a similar structure as noradrenaline, dopamine and serotonine. It is clinically used for the treatment of ADHD and narcolepsy. (111) The use of dexamphetamine in the treatment of MAUD has shown some positive effects in reducing the severity of withdrawal symptoms along with craving (112,113). However, the studies that have focused on this pharmacotherapy are characterised by rather small sample sizes (a few dozen participants), which limits the generalisability of the results. It should be noted that one study is currently examining the effectiveness of lisdexamphetamine, a pro-drug of dexamphetamine, in a randomized, double-blind, placebo controlled trial for the treatment of MAUD (114). Methylphenidate is a stimulant that increases extracellular monoamine levels. It is approved for the treatment of ADHD and it is also considered to represent an agonist-like medication. (111) There is some evidence, that methylphenidate is effective in reducing the amphetamine use and cravings (56,115,116). However, another studies found that there is no difference between methylphenidate and placebo in reducing amphetamine-positive urine samples or self-reported methamphetamine use (115,117). Modafinil is relatively new wakefulness-promoting agent and there is scarce evidence that this compound can reduce amphetamine use among persons who adhere to their medication regiment (56).

Naltrexone is an opioid-receptor antagonist that does not lead to any psychostimulant effects and which is used to treat AUD and OUD. (55,56) Studies that have investigated the use of naltrexone for treating MAUD show mixed results, although there is certain degree of evidence which suggests that both oral and long-acting formulations of naltrexone may reduce amphetamine use (118,119). This compound may also help reduce cravings and help individuals to maintain treatment and abstinence (118). In addition, treatment with extended-release injectable naltrexone, when combined with daily oral extended-release bupropion over a period of 12 weeks, resulted in a higher response (defined as at least three out of four methamphetamine-negative urine samples) than what was observed for the placebo group (120). Bupropion is an atypical, non-tricyclic

antidepressant that elicits a mild stimulant effect. The effectiveness of using bupropion to treat MAUD remains unclear, with a high degree of variation in the results from different studies, but it has shown some signals in reducing amphetamine use. (56) In addition, there is some evidence that the anticonvulsant medication topiramate can reduce amphetamine use and the severity of addiction, when compared to placebo (55). Use of the antidepressant mirtazapine has also been associated with a reduction of amphetamine use. A RCT that focused on sexually-active homosexual males revealed that mirtazapine use added to substance use counseling decreased methamphetamine use among active users (121). Mirtazapine has also been reported to alleviate amphetamine withdrawal symptoms. (121) The atypical antipsychotic aripiprazole has been previously studied for a potential role in the treatment of MAUD. Studies have shown that aripiprazole is not only ineffective in reducing methamphetamine use, but may in fact increase consumption of methamphetamine (116,122).

In summary, the current evidence base suggests that several medications have some potential in supporting treatment adherence and a reduction in drug use among persons with MAUD (see **Table 5**). However, no pharmacotherapy has yet yielded convincing results for the treatment of MAUD. (55,56)

In Sweden, the National Guidelines of substance use disorders, published by the National Board of Health and Welfare, states that health and social care services ”can offer” naltrexone to people with amphetamine addiction. The current deficient knowledge of effective treatments of MAUD is recognized in Guidelines and it is mentioned to affect prioritization. However, since very few alternative pharmacological treatments for MAUD exist, and naltrexone has been associated with beneficial effects on amphetamine use and treatment adherence, without any notable severe side effects, offering naltrexone is considered valid. (105)

Table 5. The results of effectiveness of MAUD-pharmacotherapy with most consistent findings.

Study	Exposure	Study design (N)	Objective(s)	Main results (with effect sizes)
Longo et al. 2010 (Addiction) (113)	**Sustained-release oral dexamphetamine**	RCT (N=49)	To investigate the safety and efficacy of dexamphetamine 110 mg/day in people who are dependent on methamphetamine over 16 weeks	Dexamphetamine was associated with better **treatment retention** compared to placebo (86.3 days vs. 48.6 days, p=0.014) A post-hoc analysis showed a reduction in **MA dependence symptoms** in the dexamphetamine arm compared with placebo.
Galloway et al. 2011 (Clinical Pharmacology and Therapeutics) (112)		RCT (N=60)	To investigate the safety and efficacy of dexamphetamine (60 mg/day) defined as abstinence from MA and self-reported MA consumption	No differences were found between the placebo and dexamphetamine groups in measures of **MA use.** **Withdrawal and craving scores** were significantly lower in the dexamphetamine group compared with placebo (P<0.05 for both).

Miles et al. 2013 (Addiction) (115)	**Methylphenidate**	RCT (N=74)	To assess the efficacy of methylphenidate 54 mg/day	No statistically significant difference in the **percentage of positive urine samples** was found between the methylphenidate and placebo arms (OR=0.95, 95%CI=0.83–1.08). The methylphenidate group achieved higher study retention.
Ling et al. 2014 (Addiction) (117)		RCT (N=110)	To evaluate efficacy of methylphenidate 54 mg/day in persons with MAUD also receiving psychosocial treatments	No difference between study groups in self-reported **MA use** in planned analysis during the final 30 days of treatment (p=0.22) was found. MA use days reduced from baseline to week 10 in methylphenidate group (6.56 days in methylphenidate group vs. 3.82 days in placebo group, P=0.05).
Rezaei et al. 2015 (DARU, Journal of Pharmaceutical Sciences) (123)		RCT (N=56)	To evaluate the efficacy of sustained-release methylphenidate (18 to 54 mg/day) in the treatment of methamphetamine dependence	A reduction in **craving** in the treatment arm (MD=–10.28, 95%CI=0.88–19.18, p=0.03), and fewer **MA positive urine samples** compared with placebo (p=0.03) was observed by the end of the study.
Tiihonen et al. 2007 (American Journal of Psychiatry) (116)		RCT (N=53)	To compare aripiprazole, methylphenidate and placebo for amphetamine dependence	Patients using methylphenidate had significantly fewer **amphetamine-positive urine samples** than patients who used placebo (OR=0.46, 95%CI=0.26–0.81). There were significantly more amphetamine-positive urine samples in patients using aripiprazole, than patients in the placebo group (OR=3.77, 95%CI=1.55–9.18).

Jayaram-Lindström et al. 2008 (American Journal of Psychiatry) (118)	**Naltrexone**	RCT (N=80)	To investigate the efficacy of naltrexone in comparison with placebo in reducing relapse to amphetamine use	The reduction in **self-reported amphetamine use** was greater in the naltrexone group than in the placebo group (effect size of 0.5 for the intention-to-treat sample) Naltrexone group reported greater reduction of **amphetamine use** during treatment period (from 52.2% of the days before medication to 5.5% during it). The reduction in placebo group was from 38.7% to 16.1% (F=78.38, df=1, 53, p<0.05).
Tiihonen et al. 2012 (American Journal of Psychiatry) (119)		RCT (N=100)	To investigate the overall real-world effectiveness of naltrexone implant in persons with polydrug dependence	The proportion of **drug-free urine samples** was 38% (N=19) in the naltrexone group and 16% (N=8) in the placebo group (c2=6.14, df=1, p=0.01). At the end of the study there were more **amphetamine-free urine samples**, although the difference fell short of significance (40% compared with 24%; c2=2.94, df=1, p=0.09).
Elkashef et al. 2012 (Addiction) (124)	**Topiramate**	RCT (N=140)	To test topiramate for treating MAUD with abstinence from methamphetamine during weeks 6–12 as primary outcome	No statistically significant difference was found between topiramate and placebo on the primary outcome. A ≥50% **reduction of use** by self-report favored a significant topiramate treatment effect versus placebo for both the entire treatment period (37.9% vs. 14.3%; P=0.003) and weeks 6–12 (49.1% vs. 26.9%; P=0.027).
Rezaei et al. 2016 (Fundamental and Clinical Pharmacology) (125)		RCT (N=62)	To investigate topiramate in treating MAUD in persons in opiate replacement therapy, with the outcomes of interest being dependence severity, cravings, depression and MA use.	The topiramate group showed a significantly lower proportion of **methamphetamine-positive urine tests** in week 6 in comparison with the placebo group (P=0.01). There were also significantly lower scores in the topiramate group in **drug use severity** (p<0.001) and **drug need** (p<0.001) in comparison with the placebo group

Trivedi et al. 2021 (New England Journal of Medicine) (120)	**Extended-release injectable naltrexone plus oral extended-release bupropion**	RCT (N=403)	To assess the efficacy and safety of extended-release injectable naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day) in adults with moderate or severe MAUD. Primary outcome was a response, defined as at least three out of four methamphetamine-negative urine samples	**The response** over a period of 12 weeks among participants with studied medication combination was low but higher than that among participants who received placebo. The weighted average response was 13.6% with naltrexone–bupropion and 2.5% with placebo, for an overall treatment effect of 11.1 percentage points (P<0.001).
Colfax et al. 2011 (Archives of General Psychiatry) (121)	**Mirtazapine**	RCT (N=60)	To investigate whether mirtazapine would reduce MA use in men having sex with men	In the primary analysis, mirtazapine group had fewer **MA-positive urine samples** compared with the placebo group (RR=0.57, 95%CI=0.35–0.93, P=0.02). Urine positivity decreased from 67% (20 of 30 participants) to 63% (17 of 27) in the placebo arm and from 73% (22 of 30) to 44% (12 of 27) in the mirtazapine arm. The NNT to achieve a negative weekly urine test result was 3.1.
Coffin et al. 2020 (JAMA Psychiatry) (126)		RCT (N=241)		In the expanded replication trial (126), the rate of **MA-positive urine samples** significantly declined among mirtazapine vs placebo group (RR=0.67, 95%CI=0.51–0.87) by the week 12.

Abbreviations: MA=methamphetamine, OR=odds ratio, MD=mean difference, RR=relative risk, NNT=number needed to treat

2.5.4 Summary of the evidence concerning pharmacotherapies of AUD, OUD and MAUD

SUDs are treatable, with medications for OUD and AUD demonstrating clinically significant benefits; moreover, behavioural therapies (such as cognitive behavioural therapy, motivational therapy and group therapies) can be used in the treatment of all SUDs. The approach to SUD treatment should be tailored based on the severity of the disorder, with the treatment of the associated psychiatric and physical conditions receiving simultaneous consideration. (1) The effectiveness of receiving psychosocial treatments without pharmacotherapy lacks robust scientific evidence, and is commonly associated with higher relapse rates, and thus is not beneficial in the treatment of more severe SUD. Thus, the most effective way to treat SUDs is the combination of pharmacological and behavioural interventions. (34,40,53,55,56) However, for SUDs without any approved pharmacotherapy, such as MAUD, the principal treatment approach is behavioural treatments, for instance cognitive behavioural therapy (CBT). (35)

A total of four medications have been approved by the relevant authorities for treatment of AUD (disulfiram, acamprosate, naltrexone and nalmefene). Previous meta-analyses and systematic reviews of RCTs have provided evidence that these medications are effective when compared with a placebo; more specifically, disulfiram, when administered under supervision, can maintain abstinence (66), acamprosate can reduce heavy drinking and maintain abstinence (72,74), naltrexone is especially beneficial in reducing binge drinking, and nalmefene has been found to reduce total alcohol consumption (87). However, these studies often involve rather short follow-up periods (a maximum of 365 days), while there is a clear lack of observational studies with long-term follow-up periods.

The pharmacotherapy available for OUD, especially opioid agonist treatment, is well established also via observational studies. Notably, there is robust evidence that the use of methadone and buprenorphine is associated with a reduced use of opioids and the risk of death (3–5).

However, the use of methadone has also been associated with an increased risk of overdose (127). Nevertheless, the effectiveness of treatment in non-selected patient populations in real-world treatment settings has been studied far less. A prior real-world study concluded that medications for OUD appear to reduce suicidality and crime (127), while a comparative effectiveness study of different OUD treatments showed that buprenorphine and methadone, when compared with other treatments, such as detoxification or behavioural health approaches, are associated with a lower risk of overdose and serious opioid-related acute care utilisation (46).

The world's health authorities have not authorised any pharmacotherapies for the treatment of MAUD. There is some promising evidence for stimulant agonist treatment (e.g., dexamphetamine and methylphenidate), the opioid antagonist naltrexone and the anticonvulsant topiramate, as well as the antidepressants bupropion and mirtazapine. (**Table 5**). However, the relevant studies do not provide consistent beneficial effects, and the research that has been presented, rarely reaches sufficient statistical power to make reliable statements about the efficacy of a treatment.

Even though accepted pharmacotherapies for AUD and OUD exist, and some promising medication candidates for the treatment of MAUD have been presented, SUDs remain undertreated (128). While SUDs cause a remarkable public health burden, there is an emerging need for further research of comparative effectiveness of medications. Real-world observational studies with large and nationwide cohorts, controlled bias, hard outcomes and long follow-up periods would provide pivotal information in enhancing the effective treatments for persons with SUDs.

3 AIMS OF THE STUDY

The research presented in this dissertation was conducted with the overall aim of investigating the real-world effectiveness of pharmacotherapies of alcohol use disorder, opioid use disorder and amphetamine use disorders. The study-specific aims were as follows:

1. investigate whether exposure to disulfiram, acamprosate, naltrexone or nalmefene is associated with a decreased or increased risk of hospitalisation, death or work-related outcomes among persons with alcohol use disorder. (Study I)

2. explore whether exposure to buprenorphine or methadone is associated with a decreased or increased risk of hospitalisation or death in persons with opioid use disorder. (Study II)

3. assess whether exposure to medications generally used by persons with amphetamine use disorders is associated with a decreased or increased risk of hospitalisation or death in persons with amphetamine use disorders. (Study III)

4 SUBJECTS AND METHODS

4.1 STUDY COHORTS

In Sweden, as well as in other Nordic countries, a wealth of health and socio-economic data are collected in nationwide registers. All Swedish residents have a unique personal identification number which enables linkages between various registers. (129) The registers used in the three studies included in this dissertation, were the National Patient Register (NPR), the Causes of Death Register, the LISA register (The Longitudinal Integration Database for Health Insurance and Labor Market Studies) and the MiDAS register (Micro Data for Analyses of Social Insurance) and the Prescribed Drug Register (PDR).

The National Patient Register (NPR) includes data on patients treated in public hospitals that have been collected since the 1960s. Initially, the register contained information about all psychiatric patients, but only about 16% of somatic hospitalisations. At that time, the register covered only some of Sweden's county councils. In 1984, the Ministry of Health and Welfare required all county councils to participate in the maintenance of the register. Since 1987, the NPR has compiled all inpatient information throughout Sweden. Since 2001, the register also includes outpatient doctor visits. Patient data (e.g., personal registration number, sex, age, place of residence), geographical data (e.g., county council, hospital/clinic), administrative data (i.e., duration of inpatient stay), and medical data (e.g., diagnosis, operations) are stored in the NPR. (130)

The Causes of Death Register includes all deaths in Sweden since 1952. The information stored in the register contains the personal identify number, date of death, and underlying cause of death, which is coded in accordance with the International Classification of Diseases and Related Health Problems (ICD) (recorded according to the current version of ICD). The ICD-classification defines the underlying cause of death as follows: ”a) the disease or injury which initiated the train of morbid events leading

directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury" (28). Thus, when reporting death statistics, the conditions that directly led to the death must be separated from the conditions that contributed to it. (131)

The LISA register (The Longitudinal Intergation Database for Health Insurance and Labor Market Studies), which is maintained by Statistics Sweden, contains information on unemployment, income and education for all individuals who are over 16 years of age and a registered resident of Sweden since 1990. The LISA register also provides information on persons age, sex, civil status, emigration and country of birth. (132) The MiDAS database, which is maintained by the Swedish Social Insurance Agency, contains day-level data on continuous episodes of payment of sickness benefits and granted disability pensions (132,133).

In the research presented in this dissertation, drug use data were collected from the PDR (Prescribed Drug Register). The database contains information on prescriptions dispensed by pharmacies, such as data about the patient, prescriber, drug(s), and pharmacy, since July 2005. (129) In terms of drug data, the register includes the trade name, pharmaceutical form, strength and package size, number of packages dispensed, the Nordic Article number (VNR number), and Anatomical Therapeutic Chemical classification (ATC) (134) code, amount in defined daily doses (DDD (135)), date of prescription, date of sale and price. Thus, these nationwide, electronic data provide a unique potential for cross-national record linkages. (129)

The different cohorts included in the studies underlying this dissertation are presented below. In all cohorts, the individuals were chosen based on not having a previous diagnosis of any psychotic disorder (schizophrenia or bipolar disorder, based on diagnoses recorded in NPR since 1996). The main reason that this exclusion criterion was included was that these conditions can significantly impact certain outcomes, such as psychiatric hospitalisations and the risk of mortality (136,137). In all three studies, dates of death were obtained from the Causes of Death Register and demographic characteristics for the cohort were obtained from the LISA,

NPR, and MiDAS registers. Information regarding employment and source of income was also extracted from the LISA register, which is maintained by Statistics Sweden. The starting point of the follow-up period in each study is specified below, as the starting point varied across the three studies. In all studies, the follow-up ended at death, emigration, diagnosis of schizophrenia or bipolar disorder, or the end of the follow-up period (31 December 2016 in Studies I and II, 31 December 2018 in Study III).

4.1.1 AUD cohort (Study I)

The study cohort was identified using the NPR and MiDAS-registers. The NPR includes data on persons treated in inpatient care or specialized outpatient care, while the MiDAS-register includes data on persons who have had sickness absence or received disability pension. The individuals in these registers with a diagnosis of AUD, according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (16) classification (F10.0–F10.9) were identified. All residents between the ages of 16–64 years with AUD, and who had registered treatment contact in Sweden between July 1, 2006 and December 31, 2016, were included in the cohort.

The study cohort included 125 556 patients with a diagnosis of AUD. The follow-up period started at the first diagnosis of AUD and ended as mentioned in the previous Chapter (4.1).

4.1.2 OUD cohort (Study II)

The second study cohort consisted of all residents of Sweden between the ages of 16–64 who had purchased OUD pharmacotherapy (buprenorphine or oral methadone) between July 1, 2005, and December 31, 2016. The data of purchases were collected from the PDR with the ATC codes N07BC01 (buprenorphine), N07BC51 (combination of buprenorphine and naloxone) and N07BC02 (methadone); tablet formulations of methadone were excluded, as these can be prescribed for other indications, such as

cancer pain. A total of 522 (9.1%) of the patients were diagnosed with schizophrenia or bipolar disorder after cohort entry and were censored at that point.

The study cohort consisted of 5 757 persons. The follow-up period started at the first purchase of buprenorphine (alone or combined with naloxone) or methadone.

4.1.3 MAUD cohort (Study III)

Data were gathered prospectively from nationwide Swedish registers, including the NPR, the Causes of Death register, the LISA register and MiDAS register. Drug use data were gathered from the PDR from July 2005 to December 2018. All Swedish residents between the ages of 16–64 with registered treatment contact due to MAUD (ICD-10 F15.0–15.9, other stimulant use, including amphetamine and methamphetamine) identified from the inpatient, specialized outpatient, sickness absence, and disability pension (MiDAS) registers (time period between July 1, 2006, and December 31, 2018) were included in this study.

The cohort consisted of 13 965 individuals and the follow-up period started at the first diagnosis of MAUD and ended, as in Studies I and II, based on the information provided in Chapter 4.1.

4.2 DRUG EXPOSURES AND DRUG USE MODELING

In all three studies, information on drug purchases was obtained from the PDR, with data dating back to July 2005 (129). All of the studied exposures, including the associated ATC-codes, are specified in **Table 6.**

Table 6. The studied exposures, including the associated ATC-codes.

Study	Exposure (ATC-code)
Study I (AUD)	Disulfiram (N07BB01) Acamprosate (N07BB03) Naltrexone (N07BB04) Nalmefene (N07BB05) Benzodiazepine and related drug (N05BA, N05CD, N05CF)
Study II (OUD)	Buprenorphine (N07BC01, N07BC51) Methadone (N07BC02)
Study III (MAUD)	SUD-medications: disulfiram (N07BB01), acamprosate (N07BB03), naltrexone (N07BB04), methadone (N07BC02) and buprenorphine (N07BC01, N07BC51) ADHD-medications (N06BA): more specifically, amphetamine (N06BA01), dexamphetamine (N06BA02), modafinil (N06BA07), atomoxetine (N06BA09), methylphenidate (N06BA04), and lisdexamphetamine (N06BA12) Mood stabilizers: carbamazepine (N03AF01), valproic acid (N03AG01), lamotrigine (N03AX09), topiramate (N03AX11), and lithium (N05AN01) Benzodiazepine and related medications (N05BA, N05CD, N05CF) Antidepressants (N06A) Antipsychotics (N05A, excluding lithium)

4.2.1 AUD-medications

In the first study, the main exposures were disulfiram, acamprosate, naltrexone and nalmefene. These medications are approved by the authorities for the treatment of AUD in Europe (65). In addition to monotherapies with these medications, the following drug combinations were also analysed: disulfiram and acamprosate, disulfiram and naltrexone and acamprosate and naltrexone. In some secondary analyses, spesific drug-combinations were pooled together (as “polytherapy”, i.e., any combination of the studied medications) due to low rate of events of these

specific combinations. In addition, the risk of main and secondary outcomes associated with benzodiazepines and related drugs (N05BA, N05CD, N05CF) was analysed. The reference was the non-use of medication (i.e., non-use of AUD-medications for AUD-drugs and non-use of benzodiazepines and related drugs for that analyses). The risk of the main outcome was assessed through sensitivity analyses in a between-individual model that included the duration of use for disulfiram, acamprosate, and naltrexone monotherapies.

4.2.2 OUD-medications

In the second study, exposure to OUD medications was categorised as buprenorphine and methadone. For methadone, the analysis specified that only the oral solution constitutes OUD therapy, due to the assumption that tablet forms can be used for cancer-related pain. For buprenorphine, the analysis also considered combinations of buprenorphine and naloxone. In addition to monotherapies, concomitant use of the studied medications was also modelled. However, the results of these analyses could not be reported due to the low number of events (fewer than five). The result also likely represented instances in which an individual switches between buprenorphine and methadone use. Exposure to buprenorphine and methadone, as well as the non-use of both medications (which served as the reference), was followed in time and people could switch between treatments and contribute person-time to both exposures.

4.2.3 MAUD-medications

In the third study, exposure to studied medications was categorized as medications for substance use disorders (SUD), medications for attention-deficit hyperactive disorder (ADHD), mood stabilizers, antidepressants, benzodiazepines and related drugs, and antipsychotics. These specific drugs were compared with the non-use of each drug class. All specific drugs refer to within-class monotherapies and concomitant use of two or more medication from the class was defined as combination use (e.g.

concomitant use of disulfiram and naltrexone). In addition, we analysed the risk of main and secondary outcomes associated with the following drug classes: benzodiazepine and related medications, antidepressants and antipsychotics. Sensitivity analyses were conducted for specific antidepressants, including the ten most common antidepressants: mirtazapine, sertraline, venlafaxine, escitalopram, bupropion, citalopram, fluoxetine, duloxetine, amitriptyline and paroxetine. All analyses were adjusted for the aforementioned drug classes.

4.2.4 Drug use modeling

The aim of all three studies included in this dissertation was to investigate whether the use of studied pharmacotherapies was associated with specific outcomes, such as decreased or increased risk of hospitalisation or death. However, the raw drug data derived from PDR, cannot be used for this purpose without some modifications. To define possible association between exposure and outcome, information on the duration of drug use and exposure status at a spesific date are needed. Drug use periods were constructed with a second-generation mathematical modelling method called PRE2DUP (138) (”From Prescriptions to Drug Use Periods”). This method creates time periods of exposure and estimates of the dose taken during the period by considering the purchased amount in Defined Daily Doses (DDDs), recorded in the PDR database. The method corresponds to the actual use of drugs (when continuous use of drugs started and ended) by using a decision procedure that includes each person’s purchase history for each ATC code, processed in chronological order. When calculating the periods of drug use, PRE2DUP-method takes into account the frequency and regularity of drug purchase, stockpiling of drugs, drug characteristics (i.e., pharmaceutical form, frequency of use, whether units such as tablets can be halved) and hospitalisation periods when drug use is not recorded in the PDR. The periods of use for each drug are formed separately, and it is possible to combine overlapping periods of use of the same group of drugs, e.g. to derive time periods when any medication has been used.

(138) With PRE2DUP-modelled data, exposure is time-varying meaning that the same person can have different exposures and unexposed time periods during the follow-up.

In Study III, a specific PRE2DUP dose tool was used for the dose analyses of lisdexamphetamine (139). In these analyses, the lisdexamphetamine dose was modelled time-dependently in pre-specified dose categories (defined daily doses/day translated into milligrams/day dose), which were formed around capsule strengths as follows: less than 45 mg/day, 45–≤65 mg/day, 65–≤85 mg/day, and 85 mg or more/day.

4.3 OUTCOME MEASURES

The outcome measures included in the research underlying this dissertation are shown in **Table 7**. Data on hospitalisations were derived from the National Patient Register and defined as an inpatient stay of at least 24 hours. Data on mortality were derived from the Causes of Death Register. Only ICD-10-codes were used when describing the outcomes.

Table 7. Outcome measures included in the studies presented in this dissertation.

Study	Main outcome(s)	Secondary outcome(s)
Study I: Real-world effectiveness of pharmacological treatments of alcohol use disorders	Hospitalisation due to alcohol use disorder (ICD-10: F10 as a main diagnosis)	Hospitalisation due to any cause Hospitalisation due to alcohol-related somatic cause (ICD-10 codes E51.2, E24.4, G31.2, G40.5, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, O35.4*) All-cause mortality Work disability defined as start of sickness absence or disability pension (regardless of level of compensation or diagnoses)
Study II: Real-world effectiveness of pharmacological treatments of opioid use disorder	Hospitalisation due to opioid use disorder (ICD-10: F11 as a main diagnosis)	Hospitalisation due to any cause All-cause mortality Death due to natural causes (ICD-10 codes A00–R99) Death due to external causes (ICD-10 codes V01–Y98)
Study III: Real-world effectiveness of pharmacological treatments in amphetamine use disorders	Hospitalisation due to substance use disorder (ICD-10 codes F10-F19 as a main diagnosis) Hospitalisation due to any cause or death	All-cause mortality Death due to overdose (ICD-10-codes X40–X49; X60–X69; Y10–Y19)

*Alcohol-related somatic diagnoses: E51.2 Wernickes encephalopathy, E24.4 Alcohol-induced pseudo-Cushing syndrome, G31.2 Degeneration of nervous system due to alcohol, G40.51 Special epileptic syndromes, G62.1 Alcoholic polyneuropathy, G72.1 Alcoholic myopathy, I42.6 Alcoholic cardiomyopathy, K29.2 Alcoholic gastritis, K70 Alcoholic liver disease, K85.2 Alcohol-induced acute pancreatitis, K86.0 Alcohol-induced chronic pancreatitis, O35.4 Maternal care for (suspected) damage to fetus from alcohol

4.4 COVARIATES

The main analyses of the studies described in this dissertation were made using within-individual model (see Chapter 4.5, Statistical analyses). In within-individual model, all time-invariant covariates are automatically controlled for in the study design, and only time-varying factors (such as order of treatment and concomitant use of other drugs) need to be adjusted for. A traditional between-individual model was utilised when analysing one-time events, such as mortality, as well as for the sensitivity analyses of the main outcomes. Also in the between-individual analyses, exposure to a medication varied over time, with non-use of the medication class serving as the reference. Data concerning covariates were extracted from the PDR, NPR and LISA registers.

Table 8. Covariates and their definitions.

Covariate	Definition (ATC / ICD-10 codes)	Model	Studies using the covariate
Temporal order of treatments	Order of treatment continuously updated in the models, categorized as no treatment, 1st, 2nd, 3rd, >3rd	WM, BM	Study I Study II Study III
Concomitant use of psychotropic drugs	Antidepressants (N06A), antipsychotics (N05A), benzodiazepines and related drugs (N05BA, N05CD, N05CF) and mood stabilizers (valproate, carbamazepine, lamotrigine, lithium) continuously updated in the models	WM, BM	Study I Study II
Time since cohort entry	Time since first AUD (F10) diagnosis in years, categorized as 0–1, 1–2, 2–3 and >3 years, continuously updated in the models	WM, BM	Study I
	Time since first OUD medication purchase in years, categorised as 0–1, 1–2, 2–3 and >3 years, continuously updated in the models	WM, BM	Study II
	Time since first MAUD (F15) diagnosis in years, categorised as 0–1, 1–2, 2–3 and >3 years, continuously updated in the models	WM, BM	Study III

Other medication use	Opioid analgesics (N02A), non-opioid analgesics (N02BE01, M01A), cardiovascular medications (C01–C10, excl. C04, C05), alimentary tract and metabolism medications (A02, A04AA, A05, A07, A10), antiepileptic drugs (N03A excl. valproate, carbamazepine, lamotrigine). Defined time-dependently during the follow-up (current use vs. no use currently)	BM	Study I Study II Study III
The number of previous hospitalisations	Due to AUD (main diagnoses of F10), categorised as ≤1, 2–3, >3*	BM	Study I
	Due to OUD (main diagnoses of F11), categorised as ≤1, 2–3, >3*	BM	Study II
	Due to MAUD (main diagnoses of F15), categorized as ≤1, 2–3, >3*	BM	Study III
	*updated time-dependently during the follow-up		
Comorbidities: updated continuously in the model as "no" before the first diagnoses and "yes" thereafter			
Comorbidities (1)	Cardiovascular disease (I00–I99), diabetes (E10–14, or antidiabetic use A10), asthma/COPD (J42–44), previous cancer (C01–C99), renal disease (N10–N19) and previous suicide attempt (X60–84, Y10–34, Z728, Z915). Updated continuously in the model as "no" before the first diagnoses and "yes" thereafter	BM	Study I Study II Study III
Comorbidities (2)	Other substance use disorder than OUD (F10, F12–F16, F18–F19)	BM	Study II
	Other substance use disorder than MAUD (F10–F14, F16, F19)	BM	Study III
Comorbidities (3)	Depression (F32–33), anxiety disorder (F41), ADHD (F90)	BM	Study III
Age	≤35, 36–55, >55 years at cohort entry	BM	Study I Study II Study III
Sex	Male or female	BM	Study I Study II Study III
Education (years)	Low (<9), medium (10–12), high (>12), missing	BM	Study I Study II Study III

Abbreviations: WM=within-individual model, BM=between-individual model, AUD=alcohol use disorder, OUD=opioid use disorder, MAUD=(meth)amphetamine use disorder, ATC=Anatomical Therapeutic Chemical classification, ICD=International Statistical Classification of Diseases and Related Health Problems, COPD=chronic obstructive pulmonary disease, ADHD=attention deficit hyperactive disorder

4.5 STATISTICAL ANALYSES

All of the statistical analyses were performed using SAS statistical software (version 9.4, SAS Institute Inc., Cary, North Carolina, USA).

Cox regression analysis was utilised in all three studies described in this dissertation. Cox regression is a survival analysis method that measures the risk of an outcome (such as hospitalisation) over time. It allows researchers to assess the effect of multiple covariates (such as exposures) on the rate of the outcome. (140) In a traditional Cox regression, two groups are compared based on a particular covariate. The comparison produces hazard ratio, which indicates the probability of an event occurring in one of the studied groups over a unit of time. For example, the Cox regression model can be used to compare the risk of hospitalisation between a group exposed to disulfiram and a group not exposed to disulfiram. The comparison produces hazard ratio, which indicates a risk for hospitalisation in an exposed group compared to non-exposed group. A hazard ratio over 1 means that persons who take disulfiram have an elevated risk of hospitalisation compared with persons who do not use disulfiram, while a hazard ratio under 1 means that persons who take disulfiram have a decreased risk of hospitalisation compared with persons who do not use disulfiram. When analyzing one-time events, such as death or disability pension, the analyses were conducted as a between-individual analysis. This type of analysis compares exposure and non-exposure periods of all individuals. However, it should be noted that the between-individual approach is limited by an inability to take into account potential unmeasured time-invariant confounders, such as genetics or personality. Thus, there is a risk of selection bias when investigating two different groups of people via between-individual analysis. The bias cannot be completely adjusted for with covariates, especially in register-based studies, because registers do not include sufficient information on all of the possible covariates. To reduce this selection bias, the stratified Cox regression in within-individual design (141) was used in all three studies included in this dissertation.

In the within-individual model each individual forms their own stratum, meaning that drug use periods are compared to non-use periods within the same person. The follow-up time is reset to zero after each outcome event to allow comparison of treatment periods within each individual (141). The within-individual model can be used when analysing recurrent events (which can happen multiple times), such as SUD-linked hospitalisation. Thus, only individuals with variation in exposure and those who experience an outcome event directly contribute to the within-individual model whereas the rest of the cohort contributes indirectly. In the studies presented in this dissertation, hospitalisations and work disability were treated as recurrent events and analysed with the within-individual Cox regression model. However, in the conducted sensitivity analyses, some recurrent events were also analysed using traditional between-individual models to investigate the generalisability of results. In addition, a between-individual model was utilised for analyses of one-time events, such as deaths.

The results are reported as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Significance level was set at $p<0.05$ using the Benjamini-Hochberg false discovery rate (FDR) method.

The validity of the studies included in this dissertation was addressed through several means. The validity of research refers to how well the results represent actual findings and includes two domains: internal and external validity (142). To enhance internal validity, the study design was conceptualised to include specific medical diagnoses (Studies I and III) or specific medication purchases (Study II). Recurrent outcomes were analysed using the within-individual method to reduce selection bias; in addition to analyses of one-time events, the between-individual model was used to investigate the generalisability of the results from within-individual-based analyses. The analyses were adjusted with multiple covariates to enhance internal validity. Between-individual models, as the within-individual models, included time-varying exposure; because data may contain multiple observations from the same person, a robust variance estimator was used to correct standard errors. Also, several

sensitivity analyses were conducted in all three studies included in this dissertation, to prevent biases, more specifically, protopathic bias (meaning that pharmacological treatments are often discontinued when the clinical state has improved, and then started when the clinical state deteriorates, which may underestimate the putative beneficial effect of treatment). The significance of results was ensured by using the Benjamini–Hochberg false discovery rate (FDR) method. The data were gathered from comprehensive registers that have been widely used in other studies. A real-world study, that involves nationwide register-based data, will demonstrate good external validity as it provides information on a large, unselected population.

4.5.1 Study I

Hospitalisations and work disability were treated as recurrent events and analysed with the within-individual Cox regression model. Mortality was analysed with the traditional multivariate-adjusted Cox regression model as between-individual analyses. Between-individual analyses were also applied in the sensitivity analyses for the main outcome and for analyses on the duration of use and associated risk of AUD hospitalisation. The follow-up period started at the first diagnosis of AUD and ended at death, emigration, diagnosis of schizophrenia or bipolar disorder or at the end the specified follow-up period (31 December 2016). In analyses concerning sickness absence, the follow-up period also ended at start of disability pension. When analysing sickness absence and disability pension, people who were already receiving disability pension at cohort entry, were excluded. In addition, analyses were censored when individuals reached an age of 65 years, which is typically when senior pension payments begins.

Subgroup analyses concerning the main outcome were performed by tightening the criteria for AUD by two ways: 1) restricting analyses to people without any other SUD than AUD, and 2) including only individuals diagnosed either with acute alcohol intoxication (F10.0) more than once or

other alcohol-related disorders, indicating a more serious alcohol problem (F10.1–F10.9) before the start of the follow-up period.

4.5.2 Study II

As in Study I, hospitalisations were treated as recurrent events and analysed using the within-individual Cox regression. Mortality was analysed with a traditional multivariate-adjusted Cox regression model as between-individual analysis. In addition, between-individual analyses were used in the sensitivity analyses of the main outcome and for analyses on the duration of use and associated risk of OUD hospitalisation and all-cause mortality. Only persons who had experienced an event such as hospitalisation and variation in exposure status (on-medication/off-medication) over time contribute directly to the model in within-individual analysis, whereas all individuals contribute to the between-individual model. The follow-up period started upon the first dispensing of OUD pharmacotherapy. As in Study I, the follow-up ended at death, emigration, diagnosis of schizophrenia or bipolar disorder, or at the end of the specified follow-up period (31 December 2016).

Subgroup analysis for the main outcome was conducted by tightening the inclusion criteria by restricting the analysis to people without any other SUD than OUD. The sensitivity analysis for the main outcome was performed by including only incident cases (“first-time use”). The reference was non-use of buprenorphine and methadone.

4.5.3 Study III

The main outcomes were treated as recurrent events and analysed with the within-individual Cox regression model. The sensitivity analyses, where the first 30 days of all exposures (use and non-use) were omitted, and analysis on lisdexamphetamine dose categories, also applied a within-individual model. In analysis on lisdexamphetamine dose categories, temporal dose was estimated at each dispensing based on PRE2DUP-modelled data in within-individual design comparing to non-use of

lisdexamphetamine. Dose estimates were calculated by using two previous dispensings and categorised into dose categories (see PRE2DUP, Chapter 4.2.4). The traditional between-individual model was used for analyses of mortality, as well as sensitivity analyses of the main outcomes. Exposure in between-individual analyses was similarly time-varying and the reference was non-use of the medication class. The follow-up period started at the first diagnosis of MAUD and ended at death, emigration, diagnosis of schizophrenia or bipolar disorder, or at the end of specified follow-up period (December 31, 2018). Exposure to medications was modelled as exposure that varies over time and was compared to the non-use of medications.

4.6 ETHICAL CONSIDERATIONS

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 anonymised data.

5 RESULTS

The basic characteristics of the study populations are presented in **Table 9**. Study I included 125 556 persons diagnosed with AUD, while Study II included 5 757 persons, who had purchased medications for OUD. Study III included 13 965 persons with a diagnosis of MAUD. The study populations in all three studies included more men than women.

Table 9. Basic characteristics of the cohorts

	Study I (AUD)	**Study II (OUD)**	**Study III (MAUD)**
Number of people in a cohort	125 556	5 757	13 965
Mean age (SD)	38.1 (15.9)	37.7 (10.1)	34.4 (13.0)
Sex male (%)	78 434 (62.5)	4 136 (71.8)	9 671 (69.3)

The use of pharmacological treatments among the cohorts in the three studies are presented in **Table 10**.

Table 10. The use of medications/medication classes in the three studies.

Study I (AUD)		Study II (OUD)		Study III (MAUD)	
Medication	**Users n (%)**	**Medication**	**Users n (%)**	**Medication**	**Users n (%)**
Disulfiram	19 724 (15.4)	Buprenorphine	3 766 (65.4)	SUD-medications	2 856 (20.5)
Acamprosate	11 432 (9.1)	Methadone	3 425 (56.4)	Antidepressants	7 543 (54.0)
Naltrexone	10 872 (8.7)			Mood stabilizers	1 706 (12.2)
Nalmefene	693 (0.6)			ADHD-medications	3 941 (28.2)
Polytherapy	6 398 (5.1)			Benzodiazepines	6 101 (43.7)
Benzodiazepines	42 678 (34.0)			Antipsychotics	5 067 (36.3)

Table 11. Statistically significant associations between the studied medications and main outcomes in the three studies included in this dissertation.

Study I

Outcome (model)	Exposure associated with decreased risk (HR, 95%CI)	Exposure associated with increased risk (HR, 95%CI)
AUD hospitalisation (WM)	Naltexone+acamprosate HR=0.74, 95%CI=0.61–0.89 Naltrexone+disulfiram HR=0.76, 95%CI=0.60–0.96 Naltrexone HR=0.89, 95%CI=0.81–0.97	Acamprosate HR=1.10, 95%CI=1.04–1.17 Benzodiazepines HR=1.18, 95%CI=1.14–1.22
Any hospitalisation (WM)	Naltrexone+disulfiram HR=0.77, 95%CI=0.64–0.94 Naltrexone+acamprosate HR=0.80, 95%CI=0.69–0.94 Naltrexone HR=0.89, 95%CI=0.83–0.96	-
Alcohol-related somatic hospitalisation (WM)	Polytherapy HR=0.31, 95%CI=0.12–0.83 Disulfiram HR=0.61, 95%CI=0.42–0.89	-
All-cause mortality (BM)	-	Benzodiazepines HR=1.11, 95%CI=1.04–1.19

Study II

OUD hospitalisation (WM)	Buprenorphine HR=0.73, 95%CI=0.54–0.97 Methadone HR=0.74, 95%CI=0.59–0.93	-
All-cause mortality (BM)	Buprenorphine HR=0.45, 95%CI=0.34–0.59 Methadone HR=0.51, 95%CI=0.41–0.63	-
Mortality, external cause (BM)	Buprenorphine HR=0.39, 95%CI=0.27–0.54 Methadone HR=0.40, 95%CI=0.29–0.53	-

Study III

SUD hospitalisation (WM)	Lisdexamphetamine aHR=0.82, 95%CI=0.72–0.94 Polytherapy of SUD-medications aHR=0.78, 95%CI=0.66–0.92	Antidepressants aHR=1.07, 95%CI=1.03–1.11 Benzodiazepines aHR=1.17, 95%CI=1.12–1.22
Any hospitalisation or death (WM)	Lisdexamphetamine aHR=0.86, 95%CI=0.78–0.95 Polytherapy of SUD-medications aHR=0.77, 95%CI=0.66–0.90 Buprenorphine aHR=0.89, 95%CI=0.81–0.97	Antidepressants aHR=1.10, 95%CI=1.06–1.14 Antipsychotics aHR=1.06, 95%CI=1.03–1.10 Benzodiazepines aHR=1.20, 95%CI=1.17–1.24
All-cause mortality (BM)	Lisdexamphetamine aHR=0.43, 95%CI=0.24–0.77 Methylphenidate HR=0.56, 95%CI=0.43–0.74	Benzodiazepines aHR=1.39, 95%CI=1.21–1.60

Abbreviations: WM=within-individual model, BM=between-individual model, HR=hazard ratio, aHR=adjusted hazard ratio, CI=confidence interval

5.1 EFFECTIVENESS OF PHARMACOTHERAPY OF AUD (STUDY I)

The study cohort included 125 556 persons with a diagnosis of alcohol use disorder (AUD), 65.5% of whom were men; the mean age of these individuals was 38.1 years. The median follow-up time was 4.6 years. The hazard ratios and confidence intervals for statistically significant results concerning the main outcomes and analyses are presented in **Table 11**. During the follow-up period, 32 129 (25.6%) of the individuals used any of the studied drugs. The number of individuals taking each studied drug are specified in **Table 10**.

During the follow-up period, 30 044 (23.9%) patients had a main outcome event (AUD-hospitalisation). The use of naltrexone alone, as well as in combination with acamprosate or disulfiram was associated with a significantly lower risk of AUD-hospitalisation in the within-individual model (reductions of 11%, 26% and 24%, respectively). The between-individual model returned similar results (HR=0.77, 95%CI=0.72–0.83; HR=0.77, 95%CI=0.66–0.90; HR=0.74, 95%CI=0.61–0.90, respectively). The use of acamprosate was associated with 10% increased risk of hospitalisation due to AUD. In addition, the use of benzodiazepines and related drugs was associated with a statistically significant increase (18%) in the risk of hospitalisation due to AUD compared with no use.

Similar results were found when the outcome was hospitalisation due to any cause (**Table 11**). The use of naltrexone, either as monotherapy or together with disulfiram or acamprosate was associated with a decreased risk of hospitalisation due to any cause. However, the use of acamprosate was not associated with an increased risk of any cause-hospitalisation.

Altogether, 3 173 (2.5%) of the patients were hospitalised due to alcohol-related somatic causes during the follow-up period. The use of two or more of the studied medications simultaneously was associated with 69% decreased risk of hospitalisation due to alcohol-related somatic cause in within-analysis model (**Table 11**). Similar results were found concerning the use of disulfiram (the risk of hospitalisation due to alcohol-related somatic

cause decreased 39%). The use of benzodiazepines or related drugs had no effect on the risk of hospitalisation due to alcohol-related somatic causes.

Overall, 7 832 (6.2%) of the patients in the total cohort died during the follow-up period. None of the studied AUD medications (naltrexone, acamprosate, disulfiram, nalmefene) was associated with an increased or decreased risk of death (**Table 11**). However, 2.8% of the persons using benzodiazepines died during the follow-up period, and the use benzodiazepines and related drugs was associated with an 11% higher adjusted risk of all-cause mortality.

Slightly more than 10% of the total cohort had been diagnosed with an additional SUD other than AUD. A sensitivity analysis conducted on this subgroup, revealed that none of the studied drugs had a statistically significant association with the risk of hospitalisation due to AUD. In addition, another sensitivity analysis was performed in a subgroup of persons assumed to have a more serious alcohol problem, i.e., one on more diagnoses of acute alcohol intoxication or another alcohol-related diagnosis before the start of the follow-up period. The results of this subgroup analysis, revealed that the combined use of naltrexone and acamprosate (HR=0.71, 95%CI=0.58–0.87) is associated with a lower risk of hospitalisation due to AUD. Also, naltrexone monotherapy showed a trend towards reduced risk of AUD-hospitalisation, but the result was not statistically significant after false discovery rate (FDR) correction. The use of acamprosate was again associated with an increased risk of AUD hospitalisation in this subgroup (HR=1.11, 95%CI=1.04–1.18).

5.2 EFFECTIVENESS OF PHARMACOTHERAPY OF OUD (STUDY II)

The cohort of the second study included 5 757 people, who had purchased medications (buprenorphine, methadone) used in the treatment of OUD. Overall, 71.8% of the persons were men and the mean age of the cohort was 37.7 years. The median follow-up time of the study was 7.3 years. During this time, 65.4% of the persons used buprenorphine, while 56.4% used methadone.

Altogether, 13.9% of the persons in the total cohort were hospitalised due to OUD. Both buprenorphine and methadone use were associated with a significantly reduced risk of hospitalisation due to OUD in the within-analysis model (risk reductions of 27% and 26%, respectively). (**Table 11**) The use of buprenorphine was also associated with a reduced risk of OUD hospitalisation in the between-individual model (HR=0.53, 95%CI=0.42–0.66).

During the follow-up period, 14.7% of the persons died. The use of both studied medications was associated with a significantly lower adjusted risk of all-cause mortality (buprenorphine decreased the risk 55%, methadone 49%) (**Table 11**). The use of buprenorphine and methadone was also associated with a significantly lower (61% and 60%, respectively) risk of mortality due to external causes (i.e., suicide and overdoses). However, the risk of mortality due to natural causes was not significantly affected by buprenorphine or methadone use.

The between-individual analyses were stratified according to duration of use to evaluate the possible effects of retention in OUD treatment, with the results presented in **Table 12** below. All of the analysed categories of duration of use for buprenorphine (less than 30 days, 31–180 days, 181–365 days and over 365 days) decreased the risk of OUD hospitalisation and all-cause mortality. Methadone use throughout the first 30 days of treatment was not associated with a decreased risk of OUD hospitalisation or all-cause mortality. However, the risk of OUD hospitalisation and all-cause mortality was significantly lower across all of the other analysed

duration of use categories for methadone. The lowest risk of all-cause mortality was associated with treatment that lasted 181–365 days, and the result was identical for both buprenorphine and methadone. (**Table 12**)

Altogether, 38.6% of the patients were diagnosed an additional SUD other than OUD. In a subgroup of persons with only OUD, neither buprenorphine or methadone was associated with decreased or increased risk of OUD hospitalisation. Similar results were found, when only incident users of buprenorphine and methadone were included.

Table 12. The risk of OUD-hospitalisation and all-cause mortality for various durations of use for buprenorphine and methadone in between-individual model.

	Risk of OUD hospitalisation	**Risk of all-cause mortality**
Duration of medication use (days)	**HR (95%CI)**	**HR (95%CI)**
Buprenorphine		
≤30	0.55 (0.43–0.71)	0.50 (0.32–0.81)
31–180	0.46 (0.36–0.58)	0.38 (0.25–0.56)
181–365	0.38 (0.26–0.57)	0.35 (0.19–0.67)
>365	0.36 (0.23–0.57)	0.61 (0.37–1.00)
Methadone		
≤30	0.93 (0.78–1.12)	0.83 (0.62–1.11)
31–180	0.77 (0.65–0.92)	0.45 (0.33–0.60)
181–365	0.66 (0.50–0.88)	0.22 (0.13–0.38)
>365	0.70 (0.51–0.95)	0.48 (0.33–0.69)

5.3 EFFECTIVENESS OF PHARMACOTHERAPY OF MAUD (STUDY III)

The cohort in Study III included 13 965 persons with a diagnosis of (meth)amphetamine use disorder (MAUD). Altogether, 9671 (69.3%) of the individuals were men, and the mean age of the cohort was 34.4 years. The median follow-up time in this study was 3.9 years. Data concerning the use of different medications during the follow-up period are presented in **Table 13.**

Table 13. The use of medications among persons with MAUD during the follow-up period.

Medication	Users (%)	Medication	Users (%)
SUD-medications	2 856 (20.5)	**ADHD-medications**	3 941 (28.2)
Disulfiram	1 115 (8.0)	*Methylphenidate*	3 043 (21.8)
Naltrexone	873 (6.3)	*Lisdexamphetamine*	1 511 (10.8)
Buprenorphine	652 (4.7)	*≥ 2 ADHD-medications*	1 190 (8.5)
≥ SUD-medications	592 (4.2)	*Atomoxetine*	881 (6.3)
Acamprosate	579 (4.1)	*Dexamphetamine*	268 (1.9)
Methadone	368 (2.6)	*Modafinil*	62 (0.4)
Antidepressants	7 543 (54.0)	*Amphetamine*	19 (0.1)
SSRI	4 411 (31.6)	**Mood stabilizers**	1 706 (12.2)
≥ 2 antidepressants	2 800 (20.1)	*Lamotrigine*	642 (4.6)
Mirtazapin	2 752 (19.7)	*Carbamazepine*	605 (4.3)
SNRI	1 825 (13.1)	*Valproic acid*	562 (4.0)
Bupropion	960 (6.9)	*Topiramate*	117 (0.8)
Tricyclic	700 (5.0)	*≥ 2 mood stabilizers*	114 (0.8)
Other antidepressants	505 (3.6)	**Benzodiazepines**	6 101 (43.7)
		Antipsychotics	5 067 (36.3)

The total of 74% of the persons in the total cohort were hospitalised due to substance use disorder (SUD hospitalisation). Based on the within-individual analysis, the use of lisdexamphetamine was associated with a 18% reduced risk of SUD hospitalisation compared with non-use of ADHD medication. In addition, polytherapy with medications indicated for substance use disorders, compared with non-use of SUD medications, was associated with a statistically significant 22% lower risk of hospitalisation due to SUD. The use of benzodiazepines and antidepressants was associated with an increased risk of SUD hospitalisation (increases of 17% and 7%, respectively). (**Table 11**)

According to the between-individual analyses, in addition to the use of lisdexamphetamine (aHR=0.75, 95%CI=0.66–0.85), the combination of ADHD medications (aHR=0.82; 95%CI=0.70–0.95), as well as methylphenidate (aHR=0.90, 95%CI=0.86–0.95) was associated with a reduced risk of SUD hospitalisation when compared with non-use of ADHD medications. As in the within-individual analyses, the use of benzodiazepines (aHR=1.15, 95%CI=1.11–1.19) and antidepressants (aHR=1.06, 95%CI=1.02–1.10) was associated with an increased risk of SUD hospitalisation. In addition, the use of methadone (aHR=1.25, 95%CI=1.15–1.36) and antipsychotics (aHR=1.19, 95%CI=1.15–1.23) was found to be associated with an increased risk of SUD hospitalisation in between-individual analyses. The results of omission analyses were in line with the results of the main analyses concerning lisdexamphetamine, antidepressants and benzodiazepine use.

Altogether, 82.3% of the persons in the cohort were hospitalised due to any cause or died within the follow-up period. Within-individual analyses demonstrated that the use of a combination of two or more SUD medications, lisdexamphetamine, and buprenorphine was associated with lower risk of any hospitalisation or death (reductions of 23%, 14%, and 11%, respectively) compared with periods when the individual was not taking the studied classes of medication (**Table 11**). The use of antidepressants, benzodiazepines and antipsychotics was associated with an increased risk of hospitalisation due to any cause or death (risk

increased 6–17%) (**Table 11**). The between-individual analysis results revealed that the use of lisdexamphetamine (aHR=0.86, 95%CI=0.78–0.94) and methylphenidate (aHR=0.94, 95%CI=0.90–0.99) was associated with a lower risk of any hospitalisation or death compared with the non-use of ADHD medication. The use of antidepressants, benzodiazepines, antipsychotics, methadone and carbamazepine, was associated with an increased risk of any hospitalisation or death (the risk increased 6–25%, with methadone and benzodiazepines associated with the highest risk). The results of omission analyses were in line with the results of the main analyses concerning lisdexamphetamine, antidepressants and benzodiazepines.

Overall, 9.5% of the persons died during the follow-up period. The use of lisdexamphetamine and methylphenidate was associated with a significantly lower risk of death (reductions of 57% and 44%, respectively). On the other hand, the use of benzodiazepines was associated with a 39% increased risk of death. (**Table 11**) In addition to all-cause mortality, overdose leading to death was included as an analysed outcome. The use of lisdexamphetamine (HR=0.34, 95%CI=0.14–0.82), methylphenidate (HR=0.60, 95%CI=0.42–0.85), buprenorphine (HR=0.32, 95%CI=0.14–0.73), and methadone (HR=0.44, 95%CI=0.21–0.93) was associated with a reduced risk of overdose death, while the use of benzodiazepines (HR=1.74, 95%CI=1.40–2.17) and antipsychotics (HR=1.29, 95%CI=1.02–1.64) was associated with an increased risk of death due to overdose.

Additional analyses were conducted for lisdexamphetamine to determine which dose range is associated with the most pronounced benefits. The risks of both, SUD hospitalisation and any hospitalisation or death, were significantly lower in the dose categories 45–≤65 mg/d (reductions of 30% and 23%, respectively) and 65–≤85 mg/d (reductions of 25% and 21%, respectively) compared with non-use of lisdexamphetamine.

A sensitivity analysis of the ten most used antidepressants revealed that none of the studied antidepressants are associated with beneficial outcomes among persons with MAUD.

6 DISCUSSION

6.1 EFFECTIVENESS OF PHARMACOTHERAPY OF AUD (STUDY I)

Among persons with AUD, the use of naltrexone either alone or combined with disulfiram or acamprosate was associated with a reduced risk of hospitalisation due to AUD and due to any causes when compared to the non-use of AUD medications. Moreover, polytherapy with the studied medications and the use of disulfiram were associated with a reduced risk of hospitalisation due to alcohol-related somatic causes. These results are in line with what has been reported in previous studies, more specifically that naltrexone is effective at reducing heavy drinking (72,74). A recent meta-analysis of 54 RCTs which focused on naltrexone found a 15% improvement in abstinence and a 19% reduction in heavy drinking relative to the placebo (74). However, the effectiveness of naltrexone in decreasing hospitalisation rates or death has not been assessed before. Another meta-analysis reported that naltrexone is the medication that is most often combined with other AUD medications. However, the meta-analysis found no benefit of drug combinations when compared to naltrexone monotherapy. The reliability of this conclusion could be questioned, however, as the meta-analysis involved multiple treatment groups with small populations, which reduces the statistical power and, thus, the generalisability of results (143). In Study I, the main outcome could only be analysed for specific combinations of medications, whereas other analyses involved pooling these combinations together (as “polytherapy”) due to a low rate of events for specific combinations. Polytherapy with AUD medications was associated with a reduced risk of alcohol-related hospitalisations. There may be multiple possible explanations for this. For instance, this could be the result of the increased effectiveness of medications when different mechanisms of action are combined. The effect may also attributed to a patient’s treatment motivation, i.e., the

patient is willing to take multiple different medications to ensure abstinence. On the other hand, it is possible that the benefits of polytherapy translate to a high risk of the outcome (hospitalisation or death) during medication-free periods, in which case the within-individual model highlights a beneficial result for the period when a medication is used. However, the results from these analyses were similar to what was observed in between-individual analyses, where comparisons included the total patient population (also those who were never prescribed polytherapy), which makes the result more generalisable.

Previous research has established that disulfiram use under supervised settings can maintain abstinence (66). In Study I, disulfiram use was associated with a reduced risk of hospitalisation due to alcohol-related somatic cause, which may be explained by the abstinence that disulfiram use requires. The impact of alcohol consumption on alcohol-related somatic complications, such as liver cirrhosis, certain cancers and cardiovascular disease, is predominantly determined by the total volume of consumed alcohol and the manner in which drinking occurs. (24) Thus, heavy drinking significantly predisposes an individual to these acute and chronic health outcomes, and the abstinence required by disulfiram use may relieve this burden. Disulfiram may cause adverse effects, some of which can be severe. (144) The most serious adverse effect of disulfiram is toxic hepatitis, which is associated with high mortality (69); this adverse event is, fortunately, rare (estimated risk of 1:30000 patients per year) (144). Despite the potential, even fatal, adverse effects associated with disulfiram use, there was no association between disulfiram use and an increased risk of death in Study I. Furthermore, the use of disulfiram had no effect on the risk of hospitalisation due to AUD or due to any cause in Study I.

There is not robust previous evidence on the efficacy of nalmefene for the treatment of AUD, and the EMA approval of nalmefene for the treatment of AUD was met with criticism. (88,145,146) A few European countries, including Sweden, have outlined the use of nalmefene as secondary in the treatment of AUD in treatment guidelines (88,96), which

may reduce the use of nalmefene. In 2013, nalmefene was approved for the treatment of AUD by EMA, with the specification that it should be administered on ”as needed” basis (147). The follow-up period of Study I ended in 2016. Possibly due to these facts, only 0.6% of the cohort in Study I had used nalmefene; most analyses concerning nalmefene were impossible to conduct due to the low rate of events. However, nalmefene monotherapy showed a positive trend in reducing the risk of hospitalisation due to AUD and any cause. Nevertheless, this result lacked statistical power and was not significant due to wide confidence intervals.

The results of Study I strengthened the previous conception that AUD medications are grossly underused, as only about 25% of the AUD patients used some of the studied pharmacotherapies. This is in line with what has been reported in previous studies, such as estimates that only approximately 10–20% of AUD patients receive prescribed medication (32,34,65,148). Existing studies, which are predominantly from the United States, suggest that individuals with concurrent comorbidities are more likely to receive pharmacological treatment for AUD than those suffering solely from AUD. However, the literature concerning the utilisation of AUD pharmacotherapy is limited. According to the previous evidence, the distribution of treatment is uneven based on various demographic factors; for example, older age, lower income, lower education, and co-morbid somatic diagnoses are all linked to a lower likelihood of prescription. (96) Potential obstacles to the use of pharmacotherapy for AUD involve perceptions of low patient demand, inadequate skills or knowledge about addiction, and a healthcare professional’s lack of confidence in the effectiveness of a medication (149). In 2017, Thompson et al. found, in a cohort study spanning 39 980 individuals with newly diagnosed alcohol dependence, that merely 11.7% of patients received appropriate pharmacotherapy in the year following diagnosis. Additionally, only 9.2% of those who did not receive pharmacotherapy received psychosocial support. Hence, a substantial majority, or 80.2% (32 048 individuals), did not receive either form of treatment. (148) In Study I, the register-based data did not provide information about whether psychosocial treatment

was combined with the pharmacotherapy. However, as the medications investigated in Study I were found to vary largely in terms of effectiveness, it can be assumed that psychosocial treatment did not have a sizeable impact on the described results on hard outcomes.

6.2 EFFECTIVENESS OF PHARMACOTHERAPY OF OUD (STUDY II)

The results of Study II showed that the use of the opioid agonists buprenorhine or methadone was associated with a reduced risk of hospitalisation due to OUD (a possible indicator of overdose) and mortality due to any-cause and external causes, in comparison to the non-use of these medications. These results are in line with previous evidence from RCTs and observational studies, which has shown that opioid agonist treatment (OAT) with both buprenorphine and methadone reduces overdoses and all-cause mortality (3,4).

In Study II, the use of buprenorphine was associated with a 27% reduced risk of hospitalisation due to OUD in the within-individual analyses. In comparison, the use of methadone was associated with a 26% reduced risk of OUD hospitalisation. This result is in line with what was reported in the comparative effectiveness study by Wakeman et al., i.e., treatment with buprenorphine or methadone was shown to reduce serious opioid-related acute care during both the 3-month (risk reduction of 32%) and 12-month (risk reduction of 26%) follow-up intervals. (46) Also, the cohort study by Molero et al., which applied the within-individual design, showed that the use of buprenorphine is associated with a 25% reduced risk of accidental overdose compared with non-use of the medication. However, the use of methadone was associated with a 25% increased risk of overdose (defined as a visit to an emergency unit or death). (127) This could stem from the fact that methadone, unlike buprenorphine, has no ceiling effect. As a full agonist opioid, it may increase the risk for overdose when used at doses above the patient's tolerance. (43) Nevertheless, Molero et al. found significant reductions (40%) in the rate of suicidal

behaviour among persons using methadone. The results of Study II cannot fully be comprehensively compared to the results of the study by Molero et al., because the outcomes were defined differently. In Study II, the use of buprenorphine and methadone was associated with a significantly lower (61% and 60%, respectively) risk of mortality due to external causes (i.e., suicides and overdoses). However, the risk of mortality due to natural causes did not significantly decrease while an individual used either of these medications.

A recent systematic review and meta-analysis of 15 RCTs and 36 cohort studies by Santo et al. (2021) found that among cohort studies, OAT corresponded to a 53% lower all-cause mortality rate compared with time out of OAT. Nevertheless, the researchers found that the RCTs were underpowered to assess the mortality risk. (4) These results are in line with what was reported in Study II, more specifically both the use of buprenorphine and methadone were associated with a significantly lower adjusted risk of all-cause mortality (HR=0.45, 95%CI=0.34–0.59, and HR=0.51, 95%CI=0.41–0.63, respectively). Another systematic review and meta-analysis of cohort studies (N=138 716) reported remarkably higher pooled overdose mortality rates for individuals out of methadone treatment (12.7 per 1000 person years) or buprenorphine treatment (4.6 per 1000 person years), than in methadone or buprenorphine treatment (2.6 and 1.4 per 1000 person years, respectively). (3)

In Study II, the risk for all-cause mortality and OUD hospitalisation remained reduced when studied between-individual analyses by the duration of any OUD treatment (**Table 12**). The risk of all-cause mortality has previously been found to be higher in the first four weeks of methadone treatment than in the remainder of it (3). This phenomenon has been theorised to be a consequence of methadone accumulation exceeding the opioid tolerance level, as opioid tolerance does not necessarily completely protect against respiratory depression. (3) In Study II, no increased risk of mortality was found for any of the investigated categories concerning the duration of treatment with buprenorphine or methadone. However, the first 30 days of methadone treatment was not

associated with a reduced or increased risk of mortality. All of the other studied duration categories (31–180, 181–365 and >365 days) were associated with a reduced risk of all-cause mortality and hospitalisation due to OUD. (**Table 12**)

In study II, 14.7% of the cohort died during the follow-up period (median 7.3 years). This mortality rate seems higher than what has been reported in other studies regarding mortality among patients receiving OAT, with the proportion of all-cause mortality usually varying between 5–10% (4,150–152). However, it should be stated that previous studies have mainly been randomized controlled studies and other studies with mostly significantly shorter follow-up times, which may explain the lower mortality rate compared with Study II results.

Altogether, results of Study II suggest that the use of both buprenorphine and methadone for OUD is safe and effective, when considering the associations with reduced risk of OUD hospitalisation and death. In addition, the lack of any association between the studied medications and all-cause hospitalisation reported in Study II, may be indicative of the lack of severe adverse effects.

6.3 EFFECTIVENESS OF PHARMACOTHERAPY USED AMONG PERSONS WITH MAUD (STUDY III)

Study III investigated the effectiveness of 18 different medications or medication classes that are commonly used among persons with MAUD. The results showed that the ADHD medication lisdexamphetamine was the only medication that was significantly associated with a decreased risk for three studied outcomes, more specifically, a 18% lower risk of SUD hospitalisation, a 14% lower risk of any hospitalisation or death, and a 57% lower risk of all-cause mortality compared to the non-use of ADHD medication. Lisdexamphetamine is a pro-drug stimulant that has been approved for the treatment of ADHD. Lisdexamphetamine is biologically-inactive molecule which – following oral administration – enters the bloodstream almost entirely unchanged and then later converts into the

amino acid lysine and d-amphetamine (active drug) in the body. Lisdexamphetamine is long-acting and attempts to accelerate the conversion to the biologically active d-amphetamine by either intravenous injection or crushing for intranasal administration have been found to be unsuccessful, which reduces the attractiveness for abuse. (153,154) In addition to lisdexamphetamine, the use of the ADHD medication methylphenidate was associated with 44% lower all-cause mortality in Study III.

There is some previous evidence that treating MAUD with medications that exert similar effects to substance being abused (amphetamines) could be effective (58). This also involves some parallels, more specifically, the treatment of OUD with opioid agonists, or nicotine use disorder with nicotine replacement therapy; hence, psychostimulant substitution therapy for the treatment of MAUD may hold promise. The use of agonist-like medications in treatment of SUDs is based on the idea that using medications with similar properties to the abused drug, yet a lower abuse liability, will normalize an individual's neurochemistry and thus stabilise their behaviour to reduce drug use. (111) However, the results of previous studies that have investigated these "agonist-therapies" for MAUD have shown mixed results, and robust evidence is still lacking, partly due to small trials. The studies investigating agonist therapy of MAUD are mainly RCTs that include from a few dozen to up to a few hundred participants. In this way, observational cohort studies have mainly not been conducted. An RCT that included 53 patients showed that persons receiving methylphenidate had a significantly decreased risk of amphetamine-positive urine sample compared with placebo treatment (odds ratio 0.46). (116) Dexamphetamine, on the other hand, was associated with significantly lower amphetamine withdrawal symptoms and craving scores compared with placebo treatment in an RCT of 60 patients. (112) Moreover, a recent systematic review and meta-analysis of 10 RCTs (N=561) concluded that the prescription psychostimulants, such as methylphenidate and dextroamphetamine, may be more effective than the

tested placebo in diminishing amphetamine use, increasing retention in treatment and decreasing craving among individuals with MAUD. (155)

When considering the use of non-stimulants, naltrexone has been observed to reduce amphetamine use when taken as either oral or long-acting formulations (118,119). According to additional research, it may also have potential in reducing craving for amphetamines and improving retention (118). In their RCT of 403 patients, Trivedi et al. concluded that treatment with the extended-release injectable naltrexone, when combined with daily oral extended-release bupropion, over a period of 12 weeks resulted in a higher response (defined as at least three out of four methamphetamine-negative urine samples) than the placebo (120). In Study III, naltrexone showed no association with the outcomes of interest. As extended-release naltrexone was not available in Sweden during the study period, the results of Study III only concerned oral naltrexone. Furthermore, the use of bupropion was not associated with any of the outcomes of interest in Study III. Mirtazapine, when provided in combination with substance use counseling, was shown to decrease methamphetamine use in one RCT published in 2011 (121) and a replicated trial from 2020 (126). In Study III, the use of specific antidepressants (including mirtazapine) was not associated with a lower risk of hospitalisations or death. In fact, the use of antidepressants, when studied as a group, was shown to be associated with a statistically significant increase in the risk of hospitalisation due to SUD and any hospitalisation or death. The use of antipsychotics was also associated with an increased risk of hospitalisation and mortality. A previous study, in which aripiprazole, methylphenidate and a placebo were compared in the treatment of amphetamine dependence, found aripiprazole to not only be ineffective in reducing amphetamine use, but actually increased it (116). The poor results regarding antipsychotics reported in Study III, could be partly related to protopathic bias. In other words, the initiation of antipsychotics is a consequence of worsened clinical state, which is the actual reason for hospitalisation or death, rather than the medication. Nevertheless, it is important to state that the results remained unchanged when the analysis

omitted the 30 first days after medication was initiated to control protopathic bias. In Study III, the combination of different SUD medications was associated with a lower risk of SUD hospitalisation and all-cause hospitalisation or death. People affected by SUDs are more likely to have comorbidities to other SUDs (156), and treating different disorders with different medications may lead to better outcomes, which may explain the positive results in Study III. Despite previous, although scarce, evidence that topiramate could be effective in reducing methamphetamine use, Study III found no association between the use of any mood stabiliser and the outcomes.

It is possible that the beneficial effects associated with using lisdexamphetamine to treat MAUD reported in Study III are due to adequate treatment of undiagnosed ADHD, which is potentially the underlying reason for the use of amphetamines; this is plausible, as ADHD is highly comorbid with MAUD (157). A systematic review and meta-analysis by Tardelli et al., conducted in 2020, assessed, whether persons with stimulant use disorder and comorbid ADHD show a different response to prescribed psychostimulants, and found a significant benefit of psychostimulants in trials that did not report an ADHD diagnosis, whereas no benefit was observed in trials including persons with co-occuring ADHD (58). Furthermore, there is some evidence that particularly lisdexamphetamine is effective in the treatment of MAUD due to high efficacy and lower abuse potential than faster-acting stimulants (154,158). The most beneficial outcome in Study III was observed for doses ranging from 45–85 mg/day. When used to treat ADHD, the dosage of lisdexamphetamine usually ranges from 30–70 mg/day (158). However, there is some evidence that people with longterm, high-dose exposure to amphetamines may require higher doses of psychostimulants to generate a sufficient agonist effect to reduce amphetamine use (58,155). According to recent pilot study by Ezard et al., lisdexamphetamine – at a dose of up to 250 mg/day – is safe and well tolerated among patients with MAUD (158).

Altogether, there is limited evidence regarding the safe and effective pharmacological treatment of MAUD. However, the positive findings

concerning the use of lisdexamphetamine among persons with MAUD, offers encouragement for further RCT investigations regarding the efficacy of lisdexamphetamine. Currently, at least one trial concerning lisdexamphetamine in the treatment of methamphetamine use disorder is ongoing (114).

6.4 THE USE OF BENZODIAZEPINES AND RELATED DRUGS

The use of benzodiazepines and related drugs was associated with poor outcomes, such as increased mortality, in two of the studies included in this dissertation (Study I and Study III). Benzodiazepines are depressants of the central nervous system which mainly influence gamma-aminobutyric (GABA) A-receptors, an important part of the main inhibitory system of the brain. Benzodiazepine-related drugs, refered to as the called “z-drugs” (zolpidem, zopiclone and zaleplon), are predominantly prescribed as hypnotics. (159) Benzodiazepines reached the clinical practice in 1960s and are nowadays one of the most prescribed drugs on the market. The proportion of patients who have been prescribed benzodiazepines in primary care has slightly declined from 3.5% in 2000 to 2.6% in 2016. However, at the same time, the prescribing of z-drugs has increased. (160) Despite recommendations that benzodiazepines and related drugs are only appropriate for short-term use, typically a maximum of four weeks, the long-term use of benzodiazepines remains common, with an estimated prevalence rate of about 3% among the general population; the relative proportion of long-term users among adults ranging from 6% to 76% (mean value of 24%) (161). Benzodiazepines are used for example to relieve insomnia, anxiety and various withdrawal symptoms. All of these symptoms may occur during SUD and people with SUD are more likely to misuse benzodiazepines. The use of benzodiazepines is particularly common in persons with AUD, OUD (for the alleviation of withdrawal symptoms) and MAUD (for the reduction/termination of stimulatory effects). (159,162) This was also seen in the studies included in this dissertation, as 34.0% of persons with AUD and 43.7% of persons with

MAUD used these medications during the follow-up period. As sedative medications, benzodiazepines enhance the sedative effects of alcohol and potentiate the respiratory depressive effects of opioids, which increases the risk of death due to overdose. (163)

According to the results presented in Study I, the use of benzodiazepines is associated with an increased risk of hospitalisation due to AUD and all-cause mortality. In Study II, the use of benzodiazepines and related drugs were not analysed. Based on the results of Study III, the use of benzodiazepines and related drugs is associated with an increased risk of hospitalisation due to SUD and any cause and mortality in persons with MAUD. It is possible that the association between benzodiazepines and the increased risk of adverse outcomes could be affected by protopathic bias, meaning that the initiation of benzodiazepines is a consequence of a deterioration in the clinical state and benzodiazepines have been prescribed and initiated to relieve e.g., anxiety. In Study III, a sensitivity analysis which omitted the first 30 days of benzodiazepine use was performed to control for protopathic bias. The results of this analysis agreed with the findings of the main analysis. In fact, the risk of hospitalisations and death was even higher in omission-analysis compared to main analysis, indicating that increased risk of unfavourable outcomes associated with benzodiazepines cannot be explained by poor clinical state (e.g. anxiety), but rather the long-term use of benzodiazepines. Furthermore, the use of benzodiazepines was associated with poor outcomes in both the within- and between-individual models, which makes the results more generalisable. Thus, according to the results of the studies included in this dissertation, benzodiazepines are not associated with any beneficial outcomes in persons with SUD, but – on the contrary – can lead to highly detrimental consequences. The risks of benzodiazepine use among persons with SUD, have also been previously identified. (164) More specifically, benzodiazepine use may pose a risk for dependence, as well as overdose, and benzodiazepines are more likely to be misused among persons with SUD than the general population. (64,164) Moreover, benzodiazepines are not indicated in treatment of any SUD. If

benzodiazepines are used, this should be limited to situations that fall under the proper indication (such as the treatment of withdrawal symptoms) and last only until symptoms improve, after which benzodiazepine use should be tapered off (159,162,164).

6.5 METHODOLOGICAL CONSIDERATIONS

The strenghts of the studies presented in this dissertation include large, comprehensive and nationwide study cohorts and multiple years of follow up-time. With personal identification number information from different registers could be linked, and thus a broad array of outcomes could be studied. For these reasons, the results of the presented studies are generalisable to real-world patients with SUDs also in countries other than Sweden, which have relatively similar health-care systems. The majority of previous studies concerning pharmacotherapies of SUDs are randomized controlled studies (RCTs) that have assessed the effectiveness of a particular medication. However, RCTs are often characterized by the small and selected samples, along with rather short follow-up periods (usually 2–12 months) (35,57,66,72,74); as such, the results are not generalisable to the wider population (165). As register-based data often cover years or potentially decades of follow-up information, these resources enable the assessment of long-term events (such as mortality and hospitalisation), as thousands of patients, along with multiple years of follow-up, are needed to reach the statistical power necessary to compare these relatively rare outcomes across multiple medications. Hence, observational, register-based studies are pivotal to estimating the effects of interventions that cannot be tested using randomized designs. (166,167) However, observational studies bear the risk of being influenced by different biases. (166) In all three studies included in this dissertation, the selection bias has been strived to minimize with using within-individual analysis and conducting sensitivity analyses of the outcomes.

Thus, one of the main strengths of the research underlying this dissertation is the utilisation of within-individual models in statistical

analyses (141,168), as this approach minimises selection bias and thereby enhances the reliability and validity of the findings. The within-individual approach dictates, that each individual acts as his or her own control enabling automatical controlling of time-invariant covariates. In this way, the selection bias related to characteristics of individual, such as sex, genetics and initial severity of SUD, can be eliminated, and only time-varying factors (e.g., the temporal order of treatments, concomitant use of medications) need to be adjusted for. In addition to the within- individual design, analyses for the main outcomes were also conducted in between-individual design. Within-individual model directly considers persons who have experienced the outcome and have variation in exposure status (time periods with and without medication). The use of between-individual analyses ensured that the results represent all members of the study cohort. Between-individual model was also used in mortality analyses, as within-individual models can only be utilised for outcomes which can happen multiple times for the same individual. The results from the between-individual analyses were in line with the results of within-individual models; this increases the reliability and generalisability of the results. As register data on prescriptions dispensed are only available for outpatient care, periods of hospital care were excluded from the analyses.

Data derived from the Prescribed Drug Register was modelled into drug use periods (i.e., when drug use started and ended) by using a PRE2DUP-method. This method relies on calculating sliding averages of daily doses (measured in DDDs), the purchased amounts of medications, and individual patterns of medication use. As such, this approach considers variations in purchase histories due to events like stockpiling and periods of hospital care when drugs are supplied by the healthcare unit but not documented in the prescription register. (169) The PRE2DUP-method has demonstrated strong utility in generating precise estimates of drug use periods. The method describes drug use as well as data based on interviews (170) and has been stated to provide correct estimates of drug use periods based on the opinions of experts (171). In addition, PRE2DUP-

method has been demonstrated to perform relatively well when assessed in relation to forensic-toxicologial findings (172).

The studies presented in this dissertation were also affected by certain limitations. The studies, which were register-based and recorded only certain variables, were limited in scope regarding clinical information. For example, there were no data on the possible increase or decrease of substance use within the cohort because no information on possible illicit use of substances or levels in urine samples could be extracted. Thus, the effectiveness of a medication was evaluated based on secondary measures, such as the risk of hospitalisation, death, or work disability. However, these outcomes do represent significant and severe disadvantages for both the individual and society. In addition, it was impossible to know whether persons included in the cohort had received some form of psychosocial treatment during the follow-up period. Nevertheless, since the comparative effectiveness of the examined medications showed differences, the presence of potential psychosocial treatment alongside pharmacotherapy does not appear to be essential or crucial. Furthermore, there might also be some comorbidities, affecting both the use of studied medication and the expression of studied substance use disorder, that we are not aware of. For example, we do not know in Study III, whether the use of lisdexamphetamine was prescribed to treat ADHD or (off-label) MAUD. Furthermore, it is plausible that prescribing psychostimulants has required abstinence from substances, giving rise to the possibility of reverse causation, meaning that positive outcome may be attributed to abstinence rather than medication efficacy. However, comparative effectiveness of different psychostimulats showed differences and lisdexamphetamine was the only studied psychostimulant that was consistently associated with favourable outcomes in all of the analyses; this is an encouraging signal for further research.

Whereas within-individual design effectively eliminates selection bias, i.e, patient characteristics driving prescription choices also drive the outcomes, there is also a risk of protophatic bias in observational studies, possibly affecting the interpretation of results. Protopathic bias is defined

as a phenomenon, where medications are often discontinued once the clinical state has improved, and then started again when the clinical state gets worse. This kind of phenomenon may underestimate the putative beneficial effect of the studied treatment. Protopathic bias can be diminished by omitting initial days from exposure-analyses. (166) In studies included in this dissertation, we utilised 30 days omission, and the results remained similar.

7 CONCLUSIONS

1. Pharmacotherapies of AUD are underused.

2. The risk of alcohol-related hospitalisations is lower when patients with AUD are treated with naltrexone or with combinations including naltrexone, disulfiram or acamprosate compared to time periods when these medications are not used. Naltrexone and drug-combinations in particular could be effective in the treatment of AUD and are recommended to be used as part of treatment protocol.

3. Prescription benzodiazepine use was associated with poor outcomes in persons with AUD and MAUD indicating the increased risk of worsening of clinical state (e.g., possibly increased mental health issues or suicidality) when benzodiazepines are used. The use of benzodiazepines should be avoided other than in treatment of withdrawal symptoms. If benzodiazepines are used with proper indication, should treatment be short-term and gradually tapered.

4. Buprenorphine and methadone were both associated with a lower risk of OUD-hospitalisation and death due to all and external causes, when compared with no use of OUD-medication. Therefore, opioid agonists should be used in the treatment of OUD. The effectiveness of opioid agonist treatment appears to manifest within the first month of initiation and remains consistent during prolonged treatment, suggesting the possibility to continue treatment safely as long as needed.

5. Use of lisdexamphetamine was consistently associated with improved outcomes in persons with MAUD. As there are no pharmacotherapies approved by authorities for the treatment of MAUD due to scarce evidence, the result is encouraging. As a long-acting stimulant with minimal abuse potential, lisdexamphetamine could also be applicable to persons with SUD. However, further research in randomized controlled trials is needed to evaluate the efficacy of lisdexamphetamine in the treatment of MAUD.

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ORIGINAL PUBLICATIONS (I – III)

I

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

Heikkinen M, Taipale H, Tanskanen A, Mittendorfer-Rutz E, Lähteenvuo M, Tiihonen J

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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 psychotrophic 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

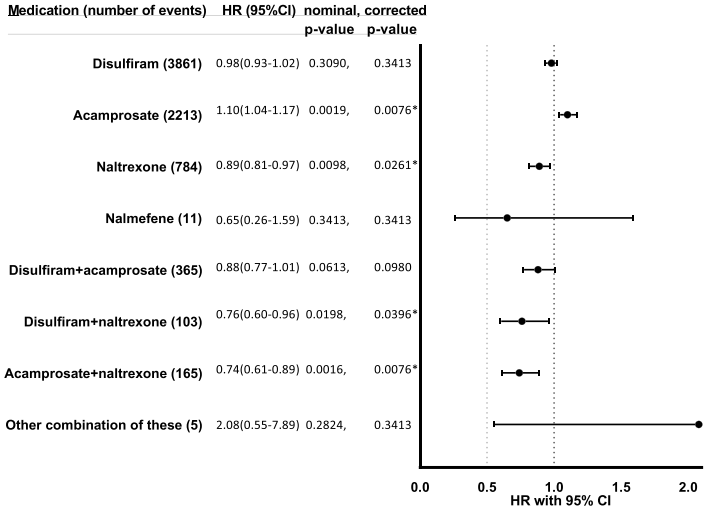

Figure 1 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of hospitalization due to alcohol use disorder (AUD) during pharmacotherapy compared with no use of medication in within-individual analyses. *Results significant after Benjamini–Hochberg false discovery rate correction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

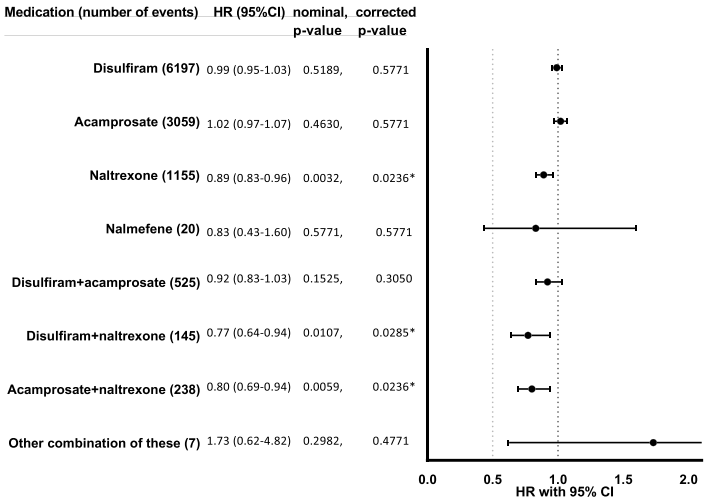

Figure 2 Risk of hospitalization due to any cause during follow-up. Within-individual model. *Results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold

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

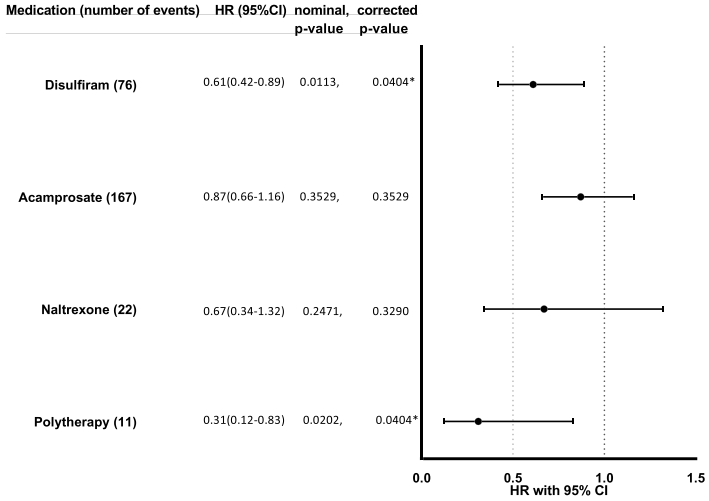

Figure 3 Risk of hospitalization due to alcohol-related somatic cause during exposure of studied medications (all drug-combinations grouped into 'polytherapy' category because the low rate of events). Nalmefene monotherapy was not analysed due to the small number of events. *Results significant after 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

J.T., H.T. and A.T. have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. H.T. reports personal fees from Janssen-Cilag. J.T. reports personal fees from the Finnish Medicines Agency (Fimea), the European Medicines Agency (EMA), Eli Lilly, Janssen-Cilag, Lundbeck and Otsuka, is a member of advisory board for Lundbeck and has received grants from the Stanley Foundation and Sigrid Jusélius Foundation. M.L. is a board member of Genomi Solutions Ltd and Nursie Health Ltd and has received honoraria from Sunovion Ltd and Orion Pharma Ltd. Janssen-Cilag and Otsuka Ltd and research funding from the Finnish Medical Foundation and Emil Aaltonen Foundation.

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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 Lähteenvuo:** 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 descripted 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 treshold.
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 treshold.
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.

II

Real-world effectiveness of pharmacological treatments of opioid use disorder in a national cohort

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RESEARCH REPORT

ADDICTION SSA

Real-world effectiveness of pharmacological treatments of opioid use disorder in a national cohort

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Abstract

Aim: To investigate the real-world effectiveness of pharmacological treatments (buprenorphine, methadone) of opioid use disorder (OUD).

Design: A nation-wide, register-based cohort study.

Setting: Sweden.

Participants: All residents aged 16–64 years living in Sweden using OUD medication from July 2005 to December 2016 (n = 5757, 71.8% men) were identified from registers of prescriptions, inpatient and specialized outpatient care, causes of death, sickness absence and disability pensions.

Measurements: Main outcome: hospitalization due to OUD. Secondary outcomes: hospitalization due to any cause; death due to all, natural and external causes. Mortality was analyzed with between-individual multivariate-adjusted Cox hazards regression model. Recurrent outcomes, such as hospitalizations, were analyzed with within-individual analyses to eliminate selection bias. OUD medication use versus non-use was modelled with PRE2DUP (from prescription drug purchases to drug use periods) method.

Findings: Buprenorphine [hazard ratio (HR) = 0.73, 95% confidence interval (CI) = 0.54–0.97] and methadone (HR = 0.74, 95% CI = 0.59–0.93) use were associated with significantly lower risk of OUD hospitalization, but not any-cause hospitalizations, compared with the time-periods when the same individual did not use OUD medication. The use of buprenorphine and methadone were both associated with significantly lower risk of all-cause mortality (HR = 0.45, 95% CI = 0.34–0.59; HR = 0.51, 95% CI = 0.41–0.63, respectively), compared with non-use of both medications. Similar results were found for risk of mortality due to external causes (HR = 0.39; 95% CI = 0.27–0.54; HR = 0.40; 95% CI = 0.29–0.53, respectively), but not for mortality due to natural causes. The risk of OUD hospitalization and all-cause mortality was decreased in all duration categories of studied medications (< 30, 31–180, 181–365 and >365 days), except for methadone use less than 30 days.

Conclusions: The use of buprenorphine and methadone are both associated with a significantly lower risk of hospitalization due to opioid use disorder and death due to all and external causes, when compared with non-use.

KEYWORDS
Buprenorphine, effectiveness, hospitalization, methadone, mortality, opioid use disorder

INTRODUCTION

Opioid use disorder (OUD) is an increasing cause of morbidity and mortality world-wide [1–4]. The use of opioids is associated with severe health consequences, such as mental health disorders, HIV infection, hepatitis-related liver cancer and cirrhosis, overdose and premature death [2, 5]. In 2017, the use of opioids accounted for two-thirds of the 167 000 deaths attributed to drug use disorders [2]. Mortality rates associated with OUD are 10-fold higher than in the general population [6, 7]. Thus, the prognosis of OUD without treatment is poor [8]. Unlike for many other drug use disorders, there are several medications for the treatment of OUD [9]. Methadone, buprenorphine and naltrexone are the primary evidence-based treatments for OUD [10], of which opioid agonists buprenorphine and methadone are used in Europe [11]. Treatment with methadone or buprenorphine improves physical and mental wellbeing and reduces mortality [12–14]. Longer treatment duration is associated with better outcomes [15] and the rate of recurrent opioid use is high, if OUD treatment is discontinued prematurely [4]. The periods associated with highest risk of mortality are the induction onto methadone treatment and the period immediately after leaving both treatments [13]. Despite the effectiveness of these medications, they still are underused [1, 12, 16], possibly due to deficient understanding of pharmacotherapy used in the treatment of OUD and regulated prescribing policies [12, 17]. It has also been claimed that access to competent treatment is restricted because of the lack of physicians willing and able to provide it [18].

Buprenorphine and methadone are well-established in recent reviews and meta-analyses in reducing especially mortality and opioid use in cohort studies and randomized, controlled trials (RCTs) [13, 14, 19]. However, patients included in RCTs are highly selected populations and according to Santo *et al.*'s recent systematic review and meta-analysis, RCTs of opioid agonist treatment are underpowered to assess mortality risk [14]. Thus, the effectiveness of treatments in non-selected patient populations in real-world treatment settings is less studied. Molero *et al.* concluded in their real-world study in 2018 that medications used to treat OUD appeared to reduce suicidality and crime [20]. Also, Wakeman *et al.* found in their study in 2020 that treatment with buprenorphine or methadone was associated with a lower risk of overdose and serious opioid-related acute care utilization when compared to other treatments [4]. Nevertheless, little is known about overall long-term health outcomes (such as risks of hospitalization and all-cause mortality) associated with specific treatments in real-world circumstances.

The aim of this study is to test the hypothesis that the pharmacological treatments of opioid dependence reduce the (1) risk of hospitalization due to OUD as a main outcome, and (2) hospitalization due to any cause and death due to all natural and external causes as secondary outcomes. In addition, the aim was to investigate the effect of duration of use of these medications on the outcomes.

METHODS

Nation-wide register-based data were used to conduct a prospective population-based cohort study of patients with OUD treatment. 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 pseudonymized data.

Study population

Data were gathered prospectively from nation-wide Swedish registers. People who purchased OUD pharmacotherapy were identified from the Prescribed Drug Register (PDR) from July 2005. Dates of death were obtained from the Causes of Death Register and demographic characteristics for the cohort were obtained from the LISA register (the Longitudinal Integration Database for Health Insurance and Labor Market Studies), National Patient Register (NPR) and the MiDAS register (Micro Data for Analyses of Social Insurance). Information regarding the employment and source of income was also received from the LISA register held by Statistics Sweden.

All residents aged 16–64 years living in Sweden with registered OUD medication purchased between 1 July 2005 and 31 December 2016 were included into this study. Individuals were chosen based on not having a previous diagnosis of schizophrenia or bipolar disorder (based on diagnoses recorded in NPR since 1996). All Swedish residents have been assigned a unique personal identification number which enabled linkage between various registers.

Exposures

Medication use data were gathered from the PDR. Medication use information in the PDR is categorized according to the anatomical therapeutic chemical (ATC) classification [21] and the purchased amount recorded as defined daily doses (DDD), together with information on medication package and formulation. Exposure to OUD medications was categorized as buprenorphine (ATC N07BC01, N07BC51) and methadone (N07BC02). For methadone, the analysis considered only oral solution as OUD therapy (tablet forms possibly used for cancer-related pain). In addition to monotherapies of these medications, concomitant use of studied medications was also modelled (probably representing mainly switches between these medications), but could not be reported due to the low number of events (fewer than five). Exposure to buprenorphine and methadone, as well

as non-use of both medications (as a reference), was followed in time and people could switch between treatments and contribute person-time to both exposures.

Medication use periods (i.e. when medication use started and ended) were constructed using the PRE2DUP-method. The method is based on the calculation of sliding averages of daily dose (in DDDs), the purchased amounts of medications and personal medication use patterns [22]. The method takes into account hospital stays (when medication use is not recorded in the register) and stockpiling of medications when constructing use periods.

Outcomes

The main outcome measure was hospitalization due to opioid use disorder [OUD hospitalization, International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code F11, as a main diagnosis]. Hospitalizations were derived from the NPR and defined as an inpatient stay of at least overnight (so that the date of admission is different than the date of discharge). The secondary outcomes were hospitalization due to any cause, all-cause mortality and death due to natural and external causes. Natural cause of death was defined as ICD-10 codes A00–R99 and external cause of death as ICD-10 code V01–Y98.

Covariates

Within-individual analyses were adjusted for temporal order of treatments, time since cohort entry (i.e. time since first dispensing of OUD pharmacotherapy) and use of psychotrophic medications; antidepressants, benzodiazepines and related medications, mood stabilizers and antipsychotics (Supporting information, Table S1). Between-individual analyses were additionally adjusted for baseline covariates age, gender, education, granted disability pension, long-term sickness absence during previous year (> 90 days) and time-varying covariates (i) medication-related: temporal order of treatment, concomitant use of psychotrophic medications, other medication use (opioid and non-opioid analgesics, cardiovascular medications, alimentary tract and metabolism medications, anti-epileptic medications and naltrexone; and (ii) comorbidities: the number of previous hospitalizations due to OUD, cardiovascular disease, diabetes, asthma/chronic obstructive pulmonary disorder (COPD), previous cancer, renal disease, previous suicide attempt, previous infections and other SUD than OUD (Supporting information, Table S1).

Statistical analysis

Hospitalizations were treated as recurrent events and analyzed using the within-individual Cox regression model [23, 24] (Supporting information, Figure S1). The within-individual model is a stratified Cox regression model in which each individual forms his or her own stratum. This reduces selection bias of different treatments. The follow-up time is reset to zero after each outcome event to allow comparison of treatment periods within each individual. Mortality was analyzed 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 OUD hospitalization and all-cause mortality. Only people having an event and variation in exposure status (on-medication/off-medication) over time contribute to the model in within-individual analysis, whereas all individuals contribute to the between-individual models. Dependence among repeated observations was corrected with robust sandwich estimator in between-individual analyses. The follow-up started at the first dispensing of OUD pharmacotherapy. The follow-up ended at death, emigration, diagnosis of schizophrenia or bipolar disorder, or end of study follow-up (31 December 2016). Subgroup analysis for the main outcome was performed by tightening the inclusion criteria by restricting analysis to people without any other substance use disorder (SUD) than OUD. Sensitivity analysis for the main outcome was conducted by including only incident cases ('first-time use'). 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 results are reported as adjusted hazard ratios (HR) with 95% confidence intervals (CIs), with non-use of buprenorphine and methadone as a reference. The primary research question and analysis plan were not pre-registered on a publicly available platform; thus, the results should be considered exploratory.

RESULTS

Cohort characteristics

In the total cohort, including 5757 people, 4136 (71.8%) were men; the mean age was 37.7 [standard deviation (SD) 10.1] years. The median follow-up time was 7.3 [interquartile range (IQR) 3.5–11.0] years. The follow-up started from the first purchase of OUD medication; however, according to the NPR, 4822 (83.8%) of the patients had a recorded diagnosis of OUD prior to or at the start of OUD medication. During the follow-up, 3766 (65.4%) of the patients used buprenorphine and 3245 (56.4%) used methadone. A total of 1017 (17.7%) patients had work income during the calendar year before cohort entry. Altogether, 791 (13.7%) of the patients were unemployed for 1–180 days and 213 (3.7%) for more than 180 days during the previous calendar year before cohort entry. Overall, 1857 (32.3%) of the patients were on disability pension at the time of cohort entry. A total of 4826 (83.8%) patients had no sickness absence during a year before cohort entry, 315 (5.5%) had sickness absence for 1–90 days and 616 (10.7%) for more than 90 days. The clinical and socio-demographic characteristics of the cohort are described in Supporting information, Table S2. Overall, 522 (9.1%) of the patients were diagnosed with schizophrenia or bipolar disorder after cohort entry and were censored at that point.

Outcomes

Table 1 shows the numbers of events for each exposure and outcome analyzed.

Primary outcome

During the follow-up, 798 (13.9%) patients had an OUD hospitalization. Buprenorphine (HR = 0.73, 95% CI = 0.54–0.97) and methadone (HR = 0.74, 95% CI = 0.59–0.93) were associated with significantly lower risk of OUD hospitalization compared to those time-periods when the same individual did not use any OUD medication (Figure 1). In between-individual analyses, the results were similar concerning buprenorphine, but methadone was not associated with lower risk of OUD hospitalization (buprenorphine HR = 0.53, 95% CI = 0.42–0.66, methadone HR = 1.09, 95% CI = 0.86–1.38, Table 2). When between-individual analyses were stratified according to duration of use, the risk of hospitalization due to OUD was significantly lower in all analyzed categories of treatment duration (< 30, 31–180, 181–365 and > 365 days) when the exposure was buprenorphine or any OUD medication compared to non-use of all OUD medication. The use of methadone during the first 30 days did not significantly reduce the risk of hospitalization due to OUD. The lowest risk of OUD hospitalization was associated with use of buprenorphine (HR = 0.38, 95% CI = 0.26–0.57), methadone (HR = 0.66, 95% CI = 0.50–0.88) or any OUD medication (HR = 0.55, 95% CI = 0.43–0.71) which had lasted for 181–365 days (Table 2).

Altogether, 2222 (38.6%%) patients with diagnosis of OUD were also diagnosed with some other SUD during the follow-up. The risk of OUD hospitalization did not significantly decrease with the use of buprenorphine or methadone in patients diagnosed with only OUD, but no other substance use disorders (HR = 0.62, 95% CI = 0.36–1.07; HR = 0.65, 95% CI = 0.42–1.01, respectively). The results were similar in sensitivity analyses, where only incident users were included. The risk of OUD hospitalization did not significantly decrease with the use of buprenorphine (HR = 0.97, 95% CI = 0.67–1.39) or methadone (HR = 0.81, 95% CI = 0.60–1.09) (Table 1).

Secondary outcomes

The risk of hospitalization due to any cause did not significantly decrease during use of either of the studied medications (Table 1). Overall, 843 (14.7%) of the patients died during the follow-up time. The use of buprenorphine and methadone were both associated with significantly lower adjusted risk of all-cause mortality (HR = 0.45, 95% CI = 0.34–0.59, HR = 0.51, 95% CI = 0.41–0.63, respectively) (Figure 2). The results were similar when the outcome was analyzed by duration of use of the studied medications. The risk of all-cause mortality was significantly lower in all analyzed categories of duration of use (> 30, 31–180, 181–365 and > 365 days) for all exposures (the risk of all-cause mortality reduced 28–78%). The lowest risk of all-cause mortality was associated with use of buprenorphine, methadone or any OUD medication, which lasted 181–365 days (a reduction 65, 78 and 74%, respectively) (Table 3). The use of buprenorphine (HR = 0.39, 95% CI = 0.27–0.54) and methadone (HR = 0.40, 95% CI = 0.29–0.53) was also associated with significantly lower risk of mortality due to external causes (i.e. suicides and overdoses). The risk of mortality due to natural causes did not significantly decrease during use of buprenorphine or methadone (HR = 0.73, 95% CI = 0.44–1.21, HR = 1.03, 95% CI = 0.72–1.48, respectively) (Figure 2).

TABLE 1 The numbers of events for each exposure and for each outcome analyzed

	Exposure					
	Buprenorphine			Methadone		
Outcome (*n* = individuals having this outcome at least once)	Events	HR (95% CI)	*P*-value (*)	Events	HR (95% CI)	*P*-value (*)
OUD hospitalization (*n* = 798)	275	**0.73 (0.54–0.97)**	**0.0328***	651	**0.74 (0.59–0.93)**	**0.0092***
Any hospitalization (*n* = 1236)	721	0.87 (0.74–1.02)	0.0838	1854	0.89 (0.78–1.01)	0.0644
All-cause mortality (*n* = 843)	76	**0.45 (0.34–0.59)**	**< 0.0001***	191	**0.51 (0.41–0.63)**	**< 0.0001***
Mortality, external cause (*n* = 466)	54	**0.39 (0.27–0.54)**	**< 0.0001***	97	**0.40 (0.29–0.53)**	**< 0.0001***
Mortality, natural cause (*n* = 377)	22	0.73 (0.44–1.21)	0.2194	94	1.03 (0.72–1.48)	0.8625
Sensitivity analysis OUD only (*n* = 681)	183	0.62 (0.36–1.07)	0.0854	361	0.65 (0.42–1.01)	0.0555
Sensitivity analysis incidents only	163	0.97 (0.67–1.39)	0.97	439	0.81 (0.60–1.09)	0.16

*Bold type denotes *P*-values significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hazard ratios (HRs) with 95% confidence intervals (CIs), with non-use of both opioid use disorder (OUD) medications as a reference. OUD hospitalization: ICD-10 code F11 as a main diagnosis;
any hospitalization: ICD-10 code other than F11 as a main diagnosis;
mortality, external cause: the cause of death ICD-10 code V01–Y98;
mortality, natural cause: the cause of death ICD-10 code A00–R99;
sensitivity analysis OUD only: no other substance use disorder than OUD;
sensitivity analysis incidents only: first-time users of OUD medication since 1 July 2006.

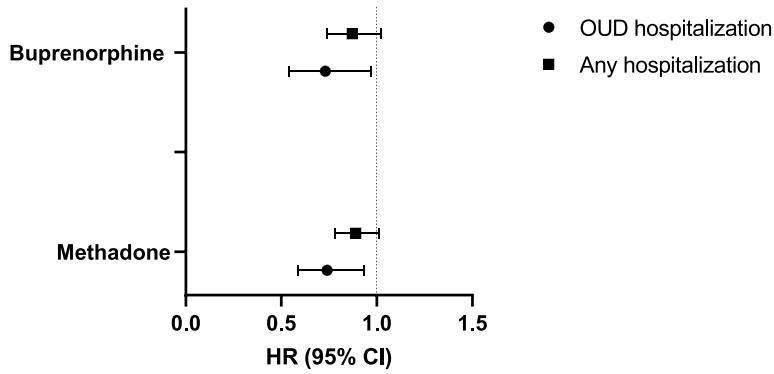

FIGURE 1 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of hospitalization due to opioid use disorder (OUD) or any cause during pharmacotherapy compared with no use of medication in within-individual analyses

TABLE 2 The risk of OUD hospitalization in between-individual model and by duration of use for buprenorphine, methadone and any OUD medication. Dose stratified by the number of relapses experienced during the follow-up

The risk of OUD hospitalization	HR (95% CI)	*P*-value	*n* events
Buprenorphine	**0.53 (0.42–0.66)**	**< 0.0001***	275
Methadone	1.09 (0.86–1.38)	0.4995	651
Duration of medication use (days)	**HR (95%CI)**	***P*-value**	***n* events**
Buprenorphine			
≤ 30	**0.55 (0.43–0.71)**	**< 0.0001***	90
31–180	**0.46 (0.36–0.58)**	**< 0.0001***	122
181–365	**0.38 (0.26–0.57)**	**< 0.0001***	37
> 365	**0.36 (0.23–0.57)**	**< 0.0001***	26
Methadone			
≤ 30	0.93 (0.78–1.12)	0.4566	237
31–180	**0.77 (0.65–0.92)**	**0.0033***	279
181–365	**0.66 (0.50–0.88)**	**0.0041***	69
> 365	**0.70 (0.51–0.95)**	**0.0218***	66
Any OUD medication			
≤ 30	**0.79 (0.67–0.94)**	**0.0073***	327
31–180	**0.65 (0.55–0.76)**	**< 0.0001***	401
181–365	**0.55 (0.43–0.71)**	**< 0.0001***	106
> 365	**0.57 (0.43–0.74)**	**< 0.0001***	92

*Bold type denotes results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hazard ratios (HRs) with 95% confidence intervals (CIs), with non-use of both opioid use disorder (OUD) medications as a reference.

DISCUSSION

In this nation-wide cohort and with median follow-up of > 7 years, we found that use of either buprenorphine or methadone was associated with a reduced risk of hospitalization due to OUD and mortality due to any cause and external causes, in comparison to non-use periods of any OUD medications. To the best of our knowledge, no other prospective cohort study has investigated the long-term health outcomes (such as hospitalizations and all-cause mortality) associated with these medications in real-world circumstances. Using a within-individual design, we were able to reduce selection bias and study the effectiveness of medications in a non-selected patient population. A similar design was used in a study by Molero *et al*. 2018, in which the use of buprenorphine and methadone appeared to reduce suicidality and crime during treatment [20].

In this study, the use of either buprenorphine or methadone was associated with a significantly reduced risk of hospitalization due to OUD. To our knowledge, this risk has not been assessed previously. However, these results are in line with previous studies which have found buprenorphine and methadone to be effective in the treatment of OUD, especially in reducing overdose and serious opioid-related acute care use [4]. Buprenorphine has also been shown to reduce

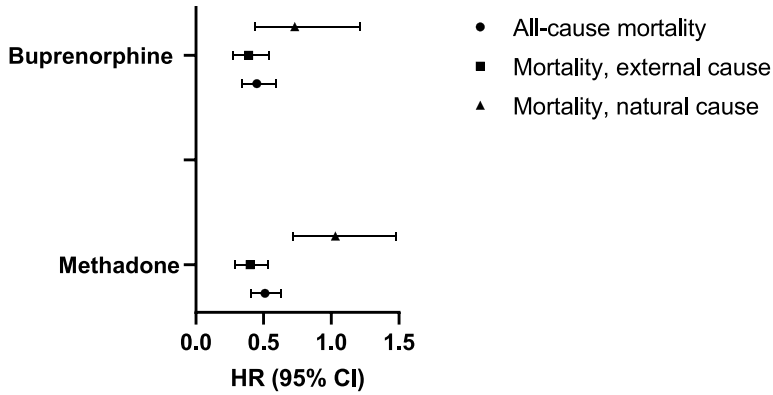

FIGURE 2 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of mortality (all, external and natural causes). Between-individual model, adjusted for baseline covariates (age, gender, education, granted disability pension, long-term sickness absence) and time-varying covariates: (i) medication-related: temporal order of treatment, concomitant use of psychotrophic drugs, other medication use (opioid and non-opioid analgesics, cardiovascular medications, alimentary tract and metabolism medications, anti-epileptic drugs) and naltrexone, (ii) comorbidities: the number of previous hospitalizations due to opioid use disorder (OUD), cardiovascular disease, diabetes, asthma/chronic obstructive pulmonary disease (COPD), previous cancer, renal disease, previous suicide attempt, previous infections and other substance use disorders than OUD

TABLE 3 The risk of all-cause mortality in between-individual model and by duration of use for buprenorphine, methadone and any OUD medication. Dose stratified by the number of relapses experienced during the follow-up

The risk of all-cause mortality	HR (95% CI)	*P*-value	*n* events
Buprenorphine	**0.45 (0.34–0.59)**	**< 0.0001***	**76**
Methadone	**0.51 (0.41–0.63)**	**< 0.0001***	**191**
Duration of medication use (days)	**HR (95% CI)**	***P*-value**	***n* events**
Buprenorphine			
≤ 30	**0.50 (0.32–0.81)**	**0.0043***	20
31–180	**0.38 (0.25–0.56)**	**< 0.0001***	28
181–365	**0.35 (0.19–0.67)**	**0.0014***	10
> 365	**0.61 (0.37–1.00)**	**0.0479***	18
Methadone			
≤ 30	0.83 (0.62–1.11)	0.2114	68
31–180	**0.45 (0.33–0.60)**	**< 0.0001***	69
181–365	**0.22 (0.13–0.38)**	**< 0.0001***	15
> 365	**0.48 (0.33–0.69)**	**< 0.0001***	39
Any OUD medication			
≤ 30	**0.72 (0.55–0.95)**	**0.0177***	88
31–180	**0.42 (0.33–0.55)**	**< 0.0001***	97
181–365	**0.26 (0.17–0.40)**	**< 0.0001***	25
> 365	**0.51 (0.37–0.70)**	**< 0.0001***	57

*Bold type denotes results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hazard ratios (HRs) with 95% confidence intervals (CIs), with non-use of both opioid use disorder (OUD) medications as a reference.

accidental overdoses [20]. Buprenorphine is usually well tolerated and, because of its high receptor affinity and only partial agonism, it protects against both overdose and reinforcing effects of full agonist opioids [8]. Conversely, as a full agonist, methadone has no ceiling effect compared to buprenorphine, which increases the risk for overdose when used at doses above the patient's tolerance [17].

However, our results suggest that the use of either of the studied medications seems safe and effective, considering their association with reduced risk of OUD hospitalization and as no association was found between studied medications and any-cause hospitalization (indicator of possible severe adverse effects).

Overall, 843 (14.7%) of the patients died during the follow-up time. The mortality rate in our study seems somewhat high compared to other studies regarding mortality among patients receiving opioid agonist treatment [14, 25, 26]. However, there is a limited number of studies within a similar setting. Studies are mainly RCTs or studies with a somewhat short follow-up time, which may explain the lower mortality rate compared with our results. The use of either buprenorphine or methadone was associated with a significantly reduced risk of mortality due to all and external causes. This association has also been previously reviewed [13], although the use of methadone has been linked to increased risk of accidental overdoses [20], which can cause death due to external causes. However, in this study methadone was also associated with a reduced risk of mortality due to external causes. No association with the risk of mortality were found due to natural causes and studied medications. This may be because the most commonly found causes of death among opioid users are overdose- or trauma and suicide-related (external causes), and disease-specific deaths (here presented as death due to natural cause) are far less common [27].

The risk for all-cause mortality and OUD hospitalization remained reduced when studied between analyses by the duration of any OUD treatment. The association of retention in OUD treatment and reduced mortality has also been observed in recent systematic reviews and meta-analyses [10, 14]. According to Sordo *et al*., the induction phase of methadone treatment and the time immediately after leaving treatment with both methadone and buprenorphine are periods of particularly increased mortality risk [13]. However, we did not find an increased risk of mortality or OUD hospitalization associated with any categorized duration of treatment, although methadone treatment during the first 30 days was not associated with a reduced risk of OUD hospitalization or mortality, unlike other duration categories. Evans *et al*. found in their cohort study in 2015 that exposure to detoxification and maintenance treatment (versus being out of treatment) was associated with lower risk of all-cause and cause specific mortality risk [25]. However, the median observation time was 2.6 years, and researchers assumed that observation over a longer time-period may reinforce knowledge of the cumulative protective effect of methadone maintenance treatment. Our results, with more than 7 years of follow-up, shows that the risk of all-cause mortality was significantly lower in all analyzed categories of duration of use for all exposures (the risk of all-cause mortality reduced from 28 to 78%). Thus, our findings extend knowledge of the effectiveness of OUD treatment during a longer period and offers valuable information to reduce the high mortality risk of OUD patients.

In Sweden, OUD treatment is basically available for all citizens at no or insignificant costs. However, an entry for maintenance treatment for OUD requires a diagnosis of OUD for at least 12 months. This inclusion criterion is stricter than in other Nordic countries [28] and may lead to a lower rate of pharmacological treatment for OUD. Low utilization rates of OUD pharmacotherapies have also been observed in other studies [1, 12, 16]. Despite Sweden's stricter inclusion criteria, entry for maintenance treatment does not require failed attempts of detoxification prior to opioid agonist treatment [28]. This seems reasonable, concerning the results of a large American cohort study reporting poor outcomes and decreasing odds of success in repeated attempts at detoxification [29]. The follow-up of this study started when a person purchased OUD medication for the first time, and thus we cannot make any conclusions regarding possible undertreatment of OUD in our study. However, only 83.8% of the patients had an OUD diagnosis, possibly indicating deficient diagnosing or recording of diagnoses of OUD.

Strengths and limitations

The main strength of this study is the data linkage of different registers and the nation-wide coverage of all actual OUD medication purchases (instead of data on prescriptions given to the patients) providing exceptionally wide data concerning medication use in real-world circumstances. Also, the follow-up time of up to 7 years was extensive. We analyzed the risk of hospitalization-based outcomes using within-individual design where each individual acts as his or her own control, which eliminates selection bias by accounting for factors remaining constant for an individual. Medication use was modelled with the PRE2DUP-method, which describes actual medication use well when compared with interview-reported use [30]. Even though the medical treatment of opioid use disorder is well established, our study provided new, pivotal information of the real-world effectiveness of buprenorphine and methadone on long-term health outcomes.

One of the limitations of this study is that some of the OUD medications are provided by the treatment centres and not dispensed through pharmacies; thus we could not acquire information on these treatments. However, in 2012 the number of opioid substitution treatment patients in Sweden was a little over 5000 [31], possibly indicating that the majority of patients using opioid substitution treatment is included in the cohort. Another limitation of this study is that we do not know whether people actually took medications they purchased. However, the medication use data take into account actually dispensed medications (from the pharmacy), not prescriptions for the medications. This provides more reliable information about the actual medication use.

In addition, there was no information on possible levels of illicit opioid use, so the effectiveness of studied medications was evaluated with secondary measures such as risk of hospitalization and death. However, these outcomes represent severe and significant consequences for both the individual and society. Another limitation is that we did not know whether an individual had psychosocial treatments during the use of medication. However, the effectiveness of non-pharmacological treatment is shown to be inferior to pharmacological treatment [4].

CONCLUSION

Buprenorphine and methadone were both associated with a significantly lower risk of hospitalization due to OUD and death due to all and external causes, when compared with no use of OUD medication. Thus, the results of our study imply the effectiveness of these pharmacological treatments of OUD. Regarding the analysis of the duration of medications, effectiveness seems to begin within the first month after initiation and remain similar during long-term treatment. Thereby, long-term use seems feasible, even for more than a year. Hospitalizations and mortality of individuals with OUD cause remarkable harm and costs for both individuals and society and, according to our findings, buprenorphine and methadone seem to reduce these outcomes. Increasing knowledge of the effectiveness of medications for OUD can encourage clinicians to steer their patients towards medical treatment of OUD and possibly strive societies for re-evaluating inclusion criteria for OUD treatment. Due to the increasing awareness of OUD medications being associated with favourable outcomes, societies may consider offering more low-threshold treatment to high-risk OUD patients.

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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 Lähteenvuo:** 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 in the online version of the article at the publisher's website.

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III

Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients

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JAMA Psychiatry | Original Investigation

Association of Pharmacological Treatments and Hospitalization and Death in Individuals With Amphetamine Use Disorders in a Swedish Nationwide Cohort of 13 965 Patients

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IMPORTANCE There are no medications approved by authorities for the treatment of amphetamine or methamphetamine dependence, and studies investigating the effectiveness of pharmacological treatments in hard outcomes, such as hospitalization and death, are lacking.

OBJECTIVE To investigate the association between pharmacotherapies and hospitalization and mortality outcomes in persons with amphetamine or methamphetamine use disorder.

DESIGN, SETTING, AND PARTICIPANTS This nationwide register-based cohort study was conducted from July 2006 to December 2018 with a median (IQR) follow-up time of 3.9 (1.0-6.1) years. Data were analyzed from December 1, 2021, to May 24, 2022. All residents aged 16 to 64 years living in Sweden with a registered first-time diagnosis of amphetamine or methamphetamine use disorder and without previous diagnoses of schizophrenia or bipolar disorder were identified from nationwide registers of inpatient care, specialized outpatient care, sickness absence, and disability pension.

EXPOSURES Medications for substance use disorders (SUDs) or for attention-deficit/hyperactive disorder, mood stabilizers, antidepressants, benzodiazepines and related drugs, and antipsychotics. Medication use vs nonuse was modeled with the PRE2DUP (from prescription drug purchases to drug use periods) method.

MAIN OUTCOMES AND MEASURES Primary outcomes were hospitalization due to SUD and any hospitalization or death, which were analyzed using within-individual models by comparing use and nonuse periods of 17 specific medications or medication classes in the same individual to minimize selection bias. The secondary outcome was all-cause mortality, studied using between-individual analysis as traditional Cox models.

RESULTS There were 13 965 individuals in the cohort (9671 [69.3%] male; mean [SD] age, 34.4 [13.0] years). During follow-up, 7543 individuals (54.0%) were taking antidepressants, 6101 (43.7%) benzodiazepines, 5067 (36.3%) antipsychotics, 3941 (28.2%) ADHD medications (1511 [10.8%] were taking lisdexamphetamine), 2856 (20.5%) SUD medications, and 1706 (12.2%) mood stabilizers. A total of 10 341 patients (74.0%) were hospitalized due to SUDs, 11 492 patients (82.3%) were hospitalized due to any cause or died, and 1321 patients (9.5%) died of any cause. Lisdexamphetamine was the only medication in this study that was significantly associated with a decrease in risk of 3 outcomes (adjusted hazard ratio [aHR], 0.82; 95% CI, 0.72-0.94 for SUD hospitalization; aHR, 0.86; 95% CI, 0.78-0.95 for any hospitalization or death; aHR, 0.43; 95% CI, 0.24-0.77 for all-cause mortality). Methylphenidate use also was associated with lower all-cause mortality (aHR, 0.56; 95% CI, 0.43-0.74). Use of benzodiazepines was associated with a significantly higher risk of SUD hospitalization (aHR, 1.17; 95% CI, 1.12-1.22), any hospitalization or death (aHR, 1.20; 95% CI, 1.17-1.24), and all-cause mortality (aHR, 1.39; 95% CI, 1.20-1.60). Use of antidepressants or antipsychotics was associated with a slight increase in risk of SUD hospitalization (aHR, 1.07; 95% CI, 1.03-1.11 and aHR, 1.05; 95% CI, 1.01-1.09) as well as any hospitalization or death (aHR, 1.10; 95% CI, 1.06-1.14 and aHR, 1.06; 95% CI, 1.03-1.10, respectively).

CONCLUSIONS AND RELEVANCE In this study, use of lisdexamphetamine was associated with improved outcomes in persons with amphetamine or methamphetamine use disorders, encouraging the conduct of randomized clinical trials. Prescription benzodiazepine use was associated with poor outcomes.

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Multimedia

Supplemental content

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Amphetamines are the second most used illicit drugs worldwide and amphetamine-related hospitalizations are increasing substantially.[1,2] There is an elevated risk of infections and mental disorders associated with methamphetamine or amphetamine use disorders (MAUD).[1,3] People with MAUD are also at higher risk of mortality compared with the general population, mainly from directly drug-related deaths, but also due to suicide, homicide, cardiovascular disease, and injuries.[4,5] Amphetamine use is associated with aggressive behavior and criminality, which also indirectly lead to morbidity and mortality.[6] Mortality related to amphetamine or methamphetamine use is increasing[7,8] and has doubled over the past decade, possibly indicating the next substance use crisis.[9] According to the European Monitoring Centre for Drugs and Drug Addiction Sweden Country Drug Report 2019,[10] amphetamines were the third most commonly used illicit drugs, and 1.2% of young adults aged 17 to 34 years were taking them. Concerning all the harm and costs that MAUD cause for the individual and society, effective treatments seem essential.[11] However, there are currently no approved pharmacological interventions available for treating MAUD.[6] Recent meta-analyses have investigated the effectiveness of antidepressants, antipsychotics, psychostimulants, anticonvulsants, and opioid agonists and antagonists[3,6] and suggest that there are some promising candidates for the treatment of MAUD, yet convincing evidence is lacking.[3] Treatment with the combination of extended-release injectable naltrexone and daily oral extended-release bupropion resulted in a low, but higher than placebo, response for methamphetamine-negative urine samples.[12] In addition, the antidepressant mirtazapine has been reported to reduce methamphetamine use when combined with substance use counseling.[13] The most consistent positive findings have been demonstrated with stimulant agonists (dexamphetamine[14,15] and methylphenidate[16-18]), naltrexone,[19,20] and topiramate,[21] whereas antidepressants have shown less consistent results in reducing amphetamine use.[3] A recent systematic review and meta-analysis[22] evaluated agonist-based pharmacological interventions (similarly as used in opioid and tobacco use disorders) and found that prescription psychostimulants had a beneficial effect to promote abstinence in persons with stimulant use disorders. Dexamphetamine has similar neurochemical and behavioral effects to methamphetamine,[23] and it has been used as an off-label treatment for MAUD. Lisdexamphetamine is a pharmacologically inactive prodrug of dexamphetamine. It presents a candidate pharmacotherapy for MAUD and seems relatively safe and well tolerated.[24] However, studies tend to be limited by small sample sizes in defined populations and by low treatment retention or completion rates.[3]

To our knowledge, no studies have investigated the effectiveness of pharmacological treatments concerning hard outcomes, such as hospitalization and death. We aimed to investigate the association of various pharmacotherapies in persons with MAUD with hospitalization due to substance use disorder (SUD) and any hospitalization or death as main outcomes and mortality due to all causes as the secondary outcome.

Key Points

Question What is the association between pharmacological treatments and hospitalization and mortality outcomes in individuals with amphetamine use disorders?

Findings In this Swedish nationwide cohort study of 13 965 individuals, lisdexamphetamine was significantly associated with a decrease in risk of hospitalization due to substance use disorder, any hospitalization or death, and all-cause mortality.

Meaning In this study, lisdexamphetamine was consistently associated with improved outcomes in individuals with amphetamine use disorders, while other pharmacological treatments were not, encouraging the conduct of randomized clinical trials.

Methods

Nationwide register-based data were used to conduct a population-based cohort study of patients with MAUD. 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 nationwide Swedish registers, including the National Patient Register, the Causes of Death Register, the Longitudinal Integration Database for Health Insurance and Labor Market Studies register, and the Micro Data for Analyses of Social Insurance (MiDAS) register. Drug use data were gathered from the Prescribed Drug Register (PDR) from July 2005 to December 2018. The data analysis was conducted from December 1, 2021, to May 24, 2022.

All residents aged 16 to 64 years living in Sweden with a registered first-time treatment contact due to MAUD (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes F15.0-15.9, other stimulant use, including amphetamine and methamphetamine) between July 1, 2006, and December 31, 2018, were included in this study. They were identified from inpatient, specialized outpatient, sickness absence, and disability pension (MiDAS) registers. Individuals were chosen based on not having a previous diagnosis of schizophrenia or bipolar disorder. All Swedish residents have been assigned a unique personal identification number, which enabled linkage between various registers.

Exposures

Medication use information in the PDR is categorized according to the Anatomical Therapeutic Chemical classification.[25] Drugs were categorized as medications for SUDs, medications for attention-deficit/hyperactive disorder (ADHD), mood stabilizers, antidepressants, benzodiazepines and related drugs, and antipsychotics (eMethods in the Supplement). Each medication class was compared with nonuse of that class unless otherwise stated. Medication use periods (ie, when medication use started and ended) were constructed using the

PRE2DUP (from prescription drug purchases to drug use periods) method[26] (eMethods in the Supplement).

Outcomes

The main outcome measures were hospitalization due to SUD (*ICD-10* codes F10-F19 as a main diagnosis) and hospitalization due to any cause or death. The secondary outcome was all-cause mortality.

Covariates

Within-individual analyses were adjusted for temporal order of treatments and time since cohort entry (eTable 1 in the Supplement). Between-individual analyses were additionally adjusted for baseline covariates age, sex, education, granted disability pension, long-term sickness absence during previous year (more than 90 days), and time-varying covariates, including medication-related comorbidities (eTable 1 in the Supplement).

Statistical Analysis

Main outcomes were treated as recurrent events and analyzed with the within-individual Cox regression model[27,28] (eMethods in the Supplement). A within-individual model was also used in sensitivity analysis on lisdexamphetamine dose categories[29] (as time-varying dose, measured in defined daily dose [DDD]) (eMethods in the Supplement) and in the analysis, where the first 30 days after medication use started were omitted (omission analysis). The within-individual model is a stratified Cox regression model in which each individual formed his or her own stratum, which reduces selection bias. All-cause mortality was analyzed with traditional multivariate-adjusted Cox regression model as between-individual analysis (eMethods in the Supplement). Follow-up started at the first diagnosis of MAUD and ended at death, emigration, diagnosis of schizophrenia or bipolar disorder, or end of study follow-up (December 31, 2018). Statistical significance was set at .05 using Benjamini-Hochberg false discovery rate method on a per graph basis. The results are reported as adjusted hazard ratios (aHRs) with 95% CIs.

Results

Cohort Characteristics

In the total cohort, including 13 965 persons with a diagnosis of MAUD, 9671 individuals (69.3%) were men, and the mean (SD) age was 34.4 (13.0) years. The median (IQR) follow-up time was 3.9 (1.0-6.1) years. During follow-up, 7543 individuals (54.0%) were taking antidepressants, 6101 (43.7%) benzodiazepines, 5067 (36.3%) antipsychotics, 3941 (28.2%) ADHD medications (1511 [10.8%] were taking lisdexamphetamine) 2856 (20.5%) SUD medications, and 1706 (12.2%) mood stabilizers. The number of individuals taking each studied drug are shown in eTable 2 in the Supplement. A total of 4059 patients (29.1%) had work income during the calendar year before cohort entry, 3292 (23.6%) were unemployed for 1 to 180 days, 890 (6.4%) for more than 180 days, 889 (6.4%) for more than 90 days sickness absence, and 2082 (14.9%) were receiving a disability pension at cohort entry. Overall, 4075 participants (29.2%) were diagnosed with alcohol use disorder, 1791 (12.8%) with sedative use disorder, 1623 (11.6%) with opioid use disorder, and 4728 (33.9%) with other psychoactive multiuse disorder. Altogether, 2690 (19.3%) had anxiety disorder, 1843 (13.2%) depression, and 1657 (11.9%) ADHD at baseline. At the end of follow-up, 3160 individuals (22.6%) were diagnosed with ADHD.

Outcomes

Risk of SUD Hospitalization

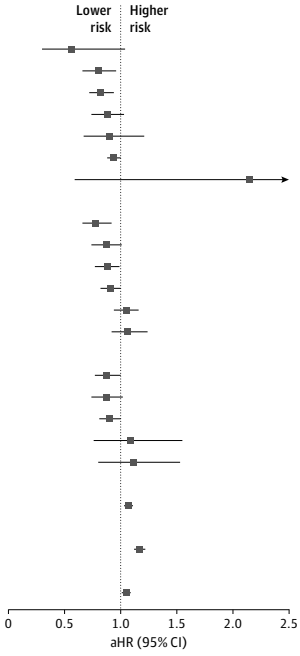
During follow-up, 10 341 patients (74.0%) were hospitalized due to SUDs. The use of lisdexamphetamine (aHR, 0.82; 95% CI, 0.72-0.94, compared with ADHD medication nonuse), as well as polytherapy of SUD medications (aHR, 0.78; 95% CI, 0.66-0.92, compared with nonuse of SUD medications) were associated with significantly lower risk of SUD hospitalization in within-individual analysis (**Figure 1**). The results were similar in the 30-day omission analysis and, in addition to lisdexamphetamine, the use of valproic acid was associated with a 13% lower risk of SUD hospitalization (eTable 3 in the Supplement). In between-individual analyses, the use of lisdexamphetamine (aHR, 0.75; 95% CI, 0.66-0.85), combination of ADHD medications (aHR, 0.82; 95% CI, 0.70-0.95), and methylphenidate (HR, 0.90; 95% CI, 0.86-0.95) were associated with reduced risk of SUD hospitalization compared with nonuse of ADHD medications (**Table 1**). The use of antidepressants (aHR, 1.07; 95% CI, 1.03-1.11) and benzodiazepines (aHR, 1.17; 95% CI, 1.12-1.22) were associated with a significantly increase in risk of SUD hospitalization (Figure 1) and the results remained similar in the omission-analysis (eTable 3 in the Supplement) and in the between-individual analysis (Table 1). In between-individual analysis, also the use of methadone (aHR, 1.25; 95% CI, 1.15-1.36) and antipsychotics (aHR, 1.19; 95% CI, 1.15-1.23) were associated with an increase in risk of SUD hospitalization, and the result was similar for antipsychotics in the omission analysis. Of specific antidepressants, the use of mirtazapine (aHR, 1.08; 95% CI, 1.00-1.15), venlafaxine (aHR, 1.13; 95% CI, 1.02-1.25), and citalopram (HR, 1.14; 95% CI, 1.00-1.29) were associated with an increase in risk of SUD hospitalization, and none of the most used antidepressants were associated with reduced risk (eTable 4 in the Supplement).

Risk of Any Hospitalization or Death

During follow-up, 11 492 patients (82.3%) were hospitalized due to any cause or died. The use of a combination of 2 or more SUD medications (aHR, 0.77; 95% CI, 0.66-0.90), lisdexamphetamine (aHR, 0.86; 95% CI, 0.78-0.95), and buprenorphine (aHR, 0.89; 95% CI, 0.81-0.97) were associated with significantly lower risk of any hospitalization or death compared with periods when the same individual was not taking the studied medication class (**Figure 2**). In the omission analyses, the use of lisdexamphetamine and the combination of 2 or more ADHD medications were associated with a lower risk of any hospitalization or death (eTable 3 in the Supplement). In between-individual analyses, the use of lisdexamphetamine (aHR, 0.86; 95% CI, 0.78-0.94) and methylphenidate (aHR, 0.94; 95% CI, 0.90-0.99) were associated with a lower risk of any hospitalization or death compared with ADHD medication nonuse (Table 1). The use of an-

Figure 1. Adjusted Hazard Ratios (aHRs) and 95% CIs for the Risk of Hospitalization Due to Substance Use Disorder (SUD) During Pharmacotherapy Compared With Nonuse of the Medication Class in Within-Individual Analyses

Medication	No. of events	aHR (95% CI)	Corrected *P* value
Modafinil	20	0.56 (0.30-1.04)	.12
Combination ADHD medication[a]	223	0.80 (0.66-0.96)	.06
Lisdexamphetamine	472	0.82 (0.72-0.94)	.03[b]
Atomoxetine	249	0.88 (0.74-1.03)	.16
Dexamphetamine	103	0.90 (0.67-1.21)	.54
Methylphenidate	2484	0.94 (0.88-1.00)	.11
Amphetamine	11	2.15 (0.59-7.85)	.33
Combination SUD medication[a]	224	0.78 (0.66-0.92)	.02[b]
Acamprosate	263	0.87 (0.74-1.01)	.12
Disulfiram	443	0.88 (0.77-0.99)	.10
Buprenorphine	1127	0.91 (0.82-1.00)	.11
Methadone	1516	1.05 (0.94-1.16)	.49
Naltrexone	325	1.06 (0.92-1.24)	.49
Valproic acid	560	0.87 (0.77-1.00)	.10
Lamotrigine	389	0.87 (0.74-1.02)	.13
Carbamazepine	787	0.90 (0.81-1.00)	.10
Combination mood stabilizer[a]	59	1.09 (0.76-1.55)	.65
Topiramate	76	1.11 (0.80-1.53)	.56
Antidepressants	8843	1.07 (1.03-1.11)	.02[b]
Benzodiazepines	8674	1.17 (1.12-1.22)	.002[b]
Antipsychotics	7920	1.05 (1.01-1.09)	.09



ADHD indicates attention-deficit/hyperactive disorder.

[a] Refers to the concomitant use of 2 or more medications.

[b] Results significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons at a .05 threshold.

tidepressants (aHR, 1.10; 95% CI, 1.06-1.14), benzodiazepines (aHR, 1.20; 95% CI, 1.17-1.24), and antipsychotics (aHR, 1.06; 95% CI, 1.03-1.10) were associated with an increase in risk of any hospitalization or death (Figure 2), and the results were similar in the omission analysis (eTable 3 in the Supplement) and in between-individual analysis (Table 1). In between-individual analysis, the use of methadone (aHR, 1.28; 95% CI, 1.18-1.40) and carbamazepine (HR, 1.14; 95% CI, 1.05-1.23) were associated with a significant increase in risk of any hospitalization or death. In the sensitivity analysis for the most used antidepressants, none of the studied antidepressants were associated with favorable outcomes. The use of mirtazapine (aHR, 1.09; 95% CI, 1.02-1.15), venlafaxine (aHR, 1.17; 95% CI, 1.07-1.26), citalopram (aHR, 1.15; 95% CI, 1.05-1.27), fluoxetine (aHR, 1.13; 95% CI, 1.02-1.24), and paroxetine (aHR, 1.19; 95% CI, 1.00-1.43) were associated with an increase in risk of death or hospitalization due to any cause, and none of antidepressants was associated with a lower risk (eTable 4 in the Supplement). The results for the specific combinations of ADHD and SUD medications are shown in eTable 5 in the Supplement.

As a sensitivity analysis for the main outcomes, we performed subgroup analyses, where the use of lisdexamphetamine was stratified by dose categories (<45 mg/d, 45-<65 mg/d, 65-<85 mg/d, and ≥85 mg/d). The risk of SUD hospitalization and the risk of any hospitalization or death were lower in the dose categories 45 to less than 65 mg/d (a reduction of 30% and 23%, respectively) and 65 to less than 85 mg/d (a reduction of 25% and 21%, respectively) compared with nonuse of lisdexamphetamine (**Table 2**).

Risk of All-Cause Mortality

During follow-up, 1321 patients (9.5%) died of any cause. The use of lisdexamphetamine (aHR, 0.43; 95% CI, 0.24-0.77) and methylphenidate (HR, 0.56; 95% CI, 0.43-0.74) were associated with a significantly lower risk of death due to any cause. The use of benzodiazepines (aHR, 1.39; 95% CI, 1.21-1.60) was associated with a significant increase in risk of death (**Figure 3**). The results were similar in the analysis where the outcome was death due to overdose. In addition to lisdexamphetamine (aHR 0.34, 95% CI, 0.14-0.82) and methylphenidate (HR, 0.60; 95% CI, 0.42-0.85), the use of buprenorphine (aHR, 0.32; 95% CI, 0.14-0.73) and methadone (aHR, 0.44; 95% CI, 0.21-0.93) were also associated with a lower risk of death due to overdose. The use of benzodiazepines (aHR, 1.74; 95% CI, 1.40-2.17) and antipsychotics (aHR, 1.29; 95% CI, 1.02-1.64) were associated with an increase in risk of death due to overdose (eTable 6 in the Supplement).

Discussion

To the best of our knowledge, no other cohort study has investigated the association of pharmacological treatments and

Table 1. Adjusted Risk of Hospitalization Due to Substance Use Disorder (SUD) and Any Hospitalization or Death in Traditional Between-Individual Cox Model Associated With Use of Medication vs Nonuse of Medication Class

Medication	SUD hospitalization			Any hospitalization or death		
	Events, No.	aHR[a] (95% CI)	Nominal *P* value	Events, No.	aHR[a] (95% CI)	Nominal *P* value
SUD medications						
Disulfiram	443	0.90 (0.80-1.01)	.08	649	0.95 (0.86-1.06)	.36
Acamprosate	263	1.00 (0.85-1.17)	.99	344	0.96 (0.84-1.10)	.55
Naltrexone	325	1.14 (0.98-1.33)	.10	406	1.07 (0.92-1.25)	.38
Buprenorphine	1127	1.02 (0.93-1.11)	.75	1332	0.98 (0.90-1.06)	.57
Methadone	1516	1.25 (1.15-1.36)	<.001[b]	1807	1.28 (1.18-1.40)	<.001[b]
≥2 SUD medications	224	0.89 (0.77-1.04)	.13	270	0.91 (0.79-1.05)	.19
Mood stabilizers						
Carbamazepine	787	1.11 (1.01-1.22)	.03	1140	1.14 (1.05-1.23)	.001[b]
Valproic acid	560	0.96 (0.85-1.07)	.44	954	1.08 (0.99-1.18)	.09
Lamotrigine	389	0.92 (0.82-1.03)	.14	787	1.11 (1.00-1.24)	.05
Topiramate	76	0.97 (0.78-1.21)	.81	161	1.14 (0.89-1.46)	.31
≥2 Mood stabilizers	59	1.16 (0.87-1.57)	.32	110	1.18 (0.94-1.50)	.16
ADHD medication						
Amphetamine	11	0.72 (0.44-1.17)	.18	26	0.91 (0.64-1.30)	.61
Dexamphetamine	103	0.83 (0.57-1.21)	.33	222	0.88 (0.72-1.08)	.23
Methylphenidate	2484	0.90 (0.86-0.95)	<.001[b]	4198	0.94 (0.90-0.99)	.01[b]
Modafinil	20	0.72 (0.52-0.99)	.046	49	0.92 (0.72-1.18)	.51
Atomoxetine	249	0.90 (0.78-1.04)	.15	372	0.90 (0.80-1.01)	.06
Lisdexamphetamine	472	0.75 (0.66-0.85)	<.001[b]	909	0.86 (0.78-0.94)	<.001[b]
≥2 ADHD medications	223	0.82 (0.70-0.95)	.007[b]	428	0.89 (0.81-0.99)	.04
Benzodiazepines	8674	1.15 (1.11-1.19)	<.001[b]	15 118	1.23 (1.19-1.26)	<.001[b]
Antipsychotics	7920	1.19 (1.15-1.23)	<.001[b]	11 977	1.23 (1.20-1.27)	<.001[b]
Antidepressants	8843	1.06 (1.02-1.10)	<.001[b]	14 551	1.10 (1.07-1.13)	<.001[b]

Abbreviations: ADHD, attention-deficit/hyperactive disorder; aHR, adjusted hazard ratio.

[a] Adjusted for other medication use (opioid and nonopioid analgesics, cardiovascular medications, alimentary tract and metabolism medications, and antiepileptic drugs), number of previous hospitalizations due to methamphetamine use disorders, comorbidities (cardiovascular disease, diabetes, asthma or chronic obstructive pulmonary disease, previous cancer, kidney disease, previous suicide attempt, SUD other than methamphetamine use disorders, depression, anxiety disorder, ADHD), and sociodemographic factors (age, sex, and education) with nonuse of medications as a reference.

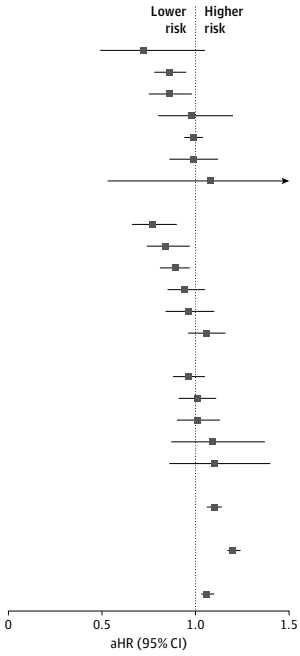
[b] Results significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons at a .05 threshold.

outcomes in patients with MAUD during a long-term follow-up period. This study provides insight concerning the association of different medications, generally used in persons with MAUD, with long-term health outcomes, such as risk of hospitalization and death. We found that, compared with personal nonuse periods, lisdexamphetamine was the only medication studied that was associated with a statistically significant beneficial finding in all 3 outcomes (SUD hospitalization, any hospitalization or death, and all-cause mortality). Benzodiazepines, antidepressants, and antipsychotics were associated with an increase in risk of any hospitalization or death. Benzodiazepines and antidepressants were also associated with an increase in risk of SUD hospitalization and the use of benzodiazepines was associated with a higher risk of death.

Currently there are no officially approved pharmacotherapies for MAUD and, despite promising medication candidates, studies are often limited by small and selected cohorts as well as low treatment retention or completion rates. The most consistent positive findings have been demonstrated with stimulant-agonist treatments as well as naltrexone and topiramate, and less consistent benefits have been observed for antidepressants bupropion and mirtazapine.[3] SUDs and mental disorders have high comorbidity, and the combination of SUD and ADHD is associated with an increase in risk of other psychiatric comorbidities, such as mood, anxiety and personality disorders.[30] In this study, lisdexamphetamine was associated with beneficial outcomes. Also, the combination of ADHD medications showed a trend toward positive outcomes, although the results were not statistically significant. The use of methylphenidate was associated with the lowest observed mortality. Lisdexamphetamine is licensed for doses ranging from 30 to 70 mg/d in the treatment of ADHD and binge eating disorder in non–stimulant-dependent populations, although there is available safety data from the use of lisdexamphetamine up to 250 mg/d.[24] In this study, 1511 persons (10.8%) were taking lisdexamphetamine. The most beneficial outcome was observed with doses from 45 to 85 mg/d. Overall, 1657 individuals (11.9%) were diagnosed with ADHD at baseline (n = 3160; 22.6% at the end of study), and the use of lisdexamphetamine might have been indicated for its treatment. However, the use of lisdexamphetamine was associated with positive outcomes in between-analyses also, indi-

Figure 2. Risk of Hospitalization Due to Any Cause or Death During Use of Pharmacotherapy Compared With Nonuse of the Medication Class in Within-Individual Analyses

Medication	No. of events	aHR (95% CI)	Corrected *P* value
Modafinil	49	0.72 (0.49-1.05)	.20
Lisdexamphetamine	909	0.86 (0.78-0.95)	.01[b]
Combination ADHD medication[a]	428	0.86 (0.75-0.98)	.06
Dexamphetamine	222	0.98 (0.80-1.20)	.92
Methylphenidate	4198	0.99 (0.94-1.04)	.87
Atomoxetine	372	0.99 (0.86-1.12)	.92
Amphetamine	26	1.08 (0.53-2.21)	.92
Combination SUD medication[a]	270	0.77 (0.66-0.90)	.007[b]
Acamprosate	344	0.84 (0.74-0.97)	.05
Buprenorphine	1332	0.89 (0.81-0.97)	.04[b]
Disulfiram	649	0.94 (0.85-1.05)	.54
Naltrexone	406	0.96 (0.84-1.10)	.76
Methadone	1807	1.06 (0.96-1.16)	.53
Carbamazepine	1140	0.96 (0.88-1.05)	.61
Valproic acid	954	1.01 (0.91-1.11)	.92
Lamotrigine	787	1.01 (0.90-1.13)	.92
Topiramate	161	1.09 (0.87-1.37)	.69
Combination mood stabilizer[a]	110	1.10 (0.86-1.40)	.69
Antidepressants	14 551	1.10 (1.06-1.14)	.001[b]
Benzodiazepines	15 118	1.20 (1.17-1.24)	.001[b]
Antipsychotics	11 977	1.06 (1.03-1.10)	.005[b]



ADHD indicates attention-deficit/hyperactive disorder; aHR, adjusted hazard ratio; SUD, substance use disorder.

[a] Refers to the concomitant use of 2 or more medications.

[b] Results significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons at a .05 threshold.

Table 2. Risk of Outcomes Associated With Use of Lisdexamphetamine Compared With Nonuse of Lisdexamphetamine in Within-Individual Model Stratified by Dose Categories in Defined Daily Doses (DDDs)

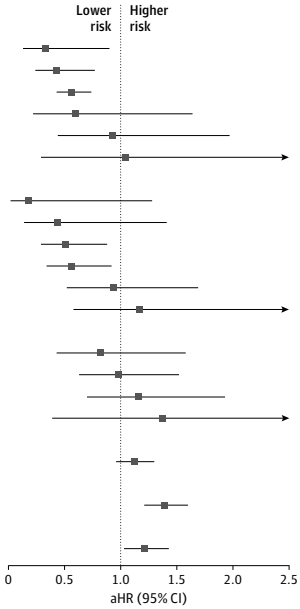
	DDD/d	Events, No.	Individuals, No.	Person-years	aHR (95% CI)
Risk of hospitalization due to substance use disorder					
Lisdexamphetamine by dose categories					
<45 mg/d	<1.50	72	457	185	1.10 (0.80-1.52)
45 to <65 mg/d	1.50 to <2.17	86	425	308	0.70 (0.52-0.93)
65 to <85 mg/d	2.17 to <2.83	117	399	394	0.75 (0.57-0.99)
≥85 mg/d	≥2.83	197	525	546	0.83 (0.67-1.03)
Risk of hospitalization due to any cause or death					
Lisdexamphetamine by dose categories					
<45 mg/d	<1.50	124	455	185	1.02 (0.80-1.30)
45 to <65 mg/d	1.50 to <2.17	167	423	308	0.77 (0.62-0.95)
65 to <85 mg/d	2.17 to <2.83	246	398	392	0.79 (0.64-0.96)
≥85 mg/d	≥2.83	372	517	542	0.92 (0.78-1.07)

Abbreviation: aHR, adjusted hazard ratio.

cating that it may have potential for improving outcomes in individuals who use methamphetamine in general. Concerning the positive results in treating MAUD with stimulant analogs, it may signalize the possibility to treat MAUD parallel to opioid and tobacco use disorders, in which treatment with agonistlike medication has been successfully implemented.[22] Naltrexone has been a promising candidate in treating amphetamine use disorder,[3,12,20] and therefore we analyzed various pharmacological treatments of different SUDs. However, naltrexone had no association with the outcomes of interest in our study. To exclude the impact of possible poor adherence to continue oral naltrexone soon after it is started, we performed a sensitivity analysis for the main outcomes by omitting the first 30 first days of medication use. Still, the use of naltrexone was not associated with a lower risk of hospitalizations or death. It should be noted that this concerned only

Figure 3. Adjusted Risk of All-Cause Mortality Associated With Medication Use vs Medication Class Nonuse in Between-Individual Analyses (Traditional Cox Model)

Medication	No. of events	aHR (95% CI)	Corrected *P* value
Combination ADHD medication[a]	4	0.33 (0.13-0.90)	.08
Lisdexamphetamine	12	0.43 (0.24-0.77)	.03[b]
Methylphenidate	61	0.56 (0.43-0.74)	.001[b]
Dexamphetamine	4	0.60 (0.22-1.64)	.55
Atomoxetine	7	0.93 (0.44-1.97)	.95
Modafinil	2	1.04 (0.29-3.70)	.96
Combination SUD medication[a]	1	0.18 (0.02-1.28)	.20
Naltrexone	3	0.44 (0.14-1.41)	.32
Buprenorphine	14	0.51 (0.29-0.88)	.07
Methadone	20	0.56 (0.34-0.92)	.08
Disulfiram	12	0.94 (0.52-1.69)	.95
Acamprosate	8	1.17 (0.58-2.37)	.84
Lamotrigine	10	0.82 (0.43-1.58)	.84
Carbamazepine	20	0.98 (0.63-1.52)	.96
Valproic acid	16	1.16 (0.70-1.93)	.84
Topiramate	3	1.37 (0.39-4.80)	.84
Antidepressants	301	1.12 (0.96-1.30)	.31
Benzodiazepines	415	1.39 (1.21-1.60)	.001[b]
Antipsychotics	213	1.21 (1.03-1.43)	.07



The use of amphetamine and combination of mood stabilizers were not analyzed due to zero events. ADHD indicates attention-deficit/hyperactive disorder; aHR, adjusted hazard ratio; SUD, substance use disorder.

[a] Refers to the concomitant use of 2 or more medications.

[b] Results significant after Benjamini-Hochberg false discovery rate correction for multiple comparisons at a .05 threshold.

oral naltrexone, as extended-release injectable naltrexone was not available during the study period. However, the combination of different SUD medications was associated with a lower risk of hospitalization due to SUD and of any hospitalization or death. The finding may be explained by the fact that people with SUDs tend to have comorbidities to other SUDs, and treating different disorders with different medications may lead to better outcomes. The use of buprenorphine was associated with a significantly lower risk of any hospitalization or death and showed a positive trend in reducing SUD hospitalization and all-cause mortality, although the associations were not statistically significant. This result is in line with a recent finding where the use of buprenorphine was associated with a reduction in hospitalizations due to opioid use disorder and all-cause mortality.[31] Methadone, also used in the treatment of opioid use disorder, was not clearly associated with beneficial outcomes. This may be due to the fact that methadone is associated with more severe adverse effects and a greater risk for sublethal intoxication, which buprenorphine does not have due to its ceiling effect. However, when the outcome was death due to overdose, both buprenorphine and methadone were associated with a lower risk. The mood stabilizer topiramate has been suggested to be beneficial in treating MAUD.[21,32] In our study, the use of any of the studied mood stabilizers were not associated with a decrease or increase in risk of studied outcomes. In addition, the use of specific antidepressants was not associated with lower risk of hospitalizations or death, which is in line with previous studies,[3,6] and only the use of mirtazapine in combination with counseling and bupropion in combination with with naltrexone have shown previously positive signals in treating MAUD.[12,13] In fact, in this study, the use of antidepressants as a group was associated with a statistically significant increase in risk of SUD hospitalization and any hospitalization or death, and the use of mirtazapine and bupropion was not associated with any of the outcomes of interest in our study. Overall, the use of benzodiazepines and antipsychotics was associated with an increase in risk of hospitalizations as well as mortality. Poor outcomes associated with use of benzodiazepines in other SUDs have been recently demonstrated.[31,33] The antipsychotic aripiprazole has been previously studied in the treatment of amphetamine or methamphetamine dependence and has been found not only ineffective in reducing methamphetamine use, but in fact increasing it.[34,35]

The main strengths of this study are large population size of almost 14 000 persons with nationwide coverage of people with diagnosed MAUD. Previous studies concerning the effectiveness of medications for MAUD are mostly randomized clinical trials limited by small sample sizes, low participant retention, and low treatment adherence rates. The median follow-up time in this study was 3.9 years. Overall, the results are generalizable for real-world patients and offer new and useful information on the association of medications widely used in persons with MAUD with long-term health outcomes. We analyzed the main outcomes by using within-individual design where each individual acts as his or her own control. The method eliminates selection bias by accounting for factors remaining constant for an individual. In addition, we used data on actu-

ally purchased medications instead of data on prescriptions given to patients. Drug use was modeled with the PRE2DUP method, which is known to estimate drug use-periods with high accuracy.[36] We analyzed various medications from different medication groups and performed sensitivity analyses for the most consistent findings, which increases the reliability of the results.

Limitations

Although within-individual analyses eliminate selection bias, they do not eliminate protopathic bias. In other words, pharmacological treatments are often discontinued when clinical state has improved and are started when clinical state deteriorates. Therefore, the results may underestimate the putative beneficial effect with treatments, and this may partly explain the poor results for antidepressants, benzodiazepines, and antipsychotics. To control for this bias, we conducted sensitivity analyses by omitting the first 30 days of use, and the results were in line with main analyses. One of the limitations of this study is that we had no information on possibly reduced amphetamine or methamphetamine consumption or total abstinence. In addition, there was no information on the possible effects of withdrawal symptoms or craving of amphetamine or methamphetamine. Thus, we evaluated the effectiveness of different medications by estimating the risk for unfavorable outcomes (hospitalizations or death), as these outcomes represent significant disadvantages and costs for both the individual and society. Another limitation of this study is that we did not know how many of the studied medications were indicated for some specific comorbidity. For example, we do not know whether lisdexamphetamine was used to treat ADHD or (off-label) MAUD. However, the positive findings with lisdexamphetamine were consistent in all studied outcomes, encouraging the conducting of randomized clinical trials in the future.

Conclusions

In this Swedish nationwide cohort study, use of lisdexamphetamine was consistently associated with a reduction in risk of death and hospitalization in persons with amphetamine or methamphetamine. Use of antidepressants were associated with an increase in risk of hospitalization due to SUD and any hospitalization or death. Benzodiazepine use was associated with poor outcomes.

ARTICLE INFORMATION

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MILJA HARTIKAINEN

Substance use disorders are associated with health and societal challenges, elevating the likelihood of morbidities and premature mortality. Despite the potential for improvement through pharmacotherapy, it remains underutilised, largely attributed to a deficient knowledge of comparative effectiveness of different medications. This thesis aimed to investigate the real-world effectiveness of medications for alcohol, opioid and amphetamine use disorders by analysing the data from Swedish nationwide registers.

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