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**Medications for alcohol and opioid use disorders and risk of suicidal behavior, accidental overdoses, and crime**

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**Contributors**

YM, SF and JZ conceived and designed the study with input from IAB, CH, and HL. YM and JZ analyzed the data. YM and SF wrote the first draft of the paper. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version. YM had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

**Declaration of interest**

Yasmina Molero, Johan Zetterqvist, Clara Hellner, and Seena Fazel declare that they have no conflict of interest. Henrik Larsson reports grants from Shire and has served as a speaker for Eli-Lilly and Shire outside of the submitted work. Ingrid A. Binswanger provides addiction treatment services for Colorado Permanente Medical Group and receives royalties from Uptodate.com on educational content related to providing health services to people who are incarcerated.

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**ABSTRACT**

**Objective:** To examine associations between medications for alcohol and opioid use disorders (acamprosate, naltrexone, methadone, and buprenorphine), and suicidal behavior, accidental overdoses, and crime. **Method:** In this total population cohort study, 21,281 individuals who had been treated with at least one of these medications between 2005 to 2013 were identified. Information on medication use and outcomes were collected from Swedish population-based registers. A within-individual design (using stratified Cox proportional hazards regression models) was used to compare rates of suicidal behavior, accidental overdoses, and crime in the same individuals when they were taking these medications compared to when they were not. **Results:** No significant associations with any of the primary outcomes were found for acamprosate. For naltrexone, there was a reduction in the Hazard Ratio (HR) of accidental overdoses when individuals were treated compared to when they were not (HR=0.82, 95% Confidence Interval [CI] 0.70-0.96). Buprenorphine was associated with reduced arrest rates for all crime categories (i.e. violent, non-violent, and substance-related crime), and a reduction of accidental overdoses (HR=0.75, 95%CI 0.60-0.93). For methadone, there were substantial reductions in the rate of suicidal behaviors (HR=0.60, 95%CI 0.40-0.88), and all crime categories. However, there was an increased risk for accidental overdoses for individuals on methadone (HR=1.25, 95%CI 1.13-1.38). **Conclusions:** The observed reductions in suicidality and crime with certain medications for alcohol and opioid use disorders need validation using other study designs.

## INTRODUCTION

Public health consequences of substance use disorders include premature mortality, infectious diseases, and chronic health problems (1), as well as criminality (2). In particular, deaths from prescription and illicit opioid overdoses have increased in many countries, contributing to substantially reduced life expectancy (3). Non-fatal overdoses are also common; studies show that 30-80% of those that inject or use illicit drugs regularly have experienced at least one non-fatal overdose (4). Furthermore, the non-medical use of prescription opioids has increased (5), and has been suggested as a risk factor for heroin use (6).

The most commonly prescribed medications to treat alcohol use disorders are acamprosate and naltrexone (7), which are associated with reductions in alcohol consumption (8). For opioid use disorder, the most commonly prescribed medications are naltrexone, buprenorphine, and methadone (9). Their efficacy in reducing illicit drug use has been shown to be stronger than for psychological treatments (10). Additionally, these medications improve psychosocial functioning (11). However, their impact on other adverse outcomes, such as suicidal behavior and crime, is uncertain. This is due in part to trials not having sufficient size or follow-up time to examine rare outcomes (10, 12). Furthermore, many randomized controlled trials have limited generalizability to real world practice as they often exclude patients with comorbid psychiatric disorders (13).

In this study, we have used a large population-based cohort of individuals who were prescribed medications for alcohol or opioid use disorders (i.e. acamprosate, naltrexone, methadone, and buprenorphine), and investigated their association with suicidal behavior, accidental overdoses, and crime. We used a within-individual design that compares rates of suicidal behavior, accidental overdoses, and crimes in

the same individuals when they were taking these medications, to when they were not. This design accounts for time-invariant factors, such as early environment and genetics, and confounding by indication - namely, that individuals who are prescribed these medications may have different background risks from those who do not.

## METHODS

### *Participants*

Individuals who had been treated with a medication for alcohol or opioid use disorders during 2005-2013 in Sweden.

### *Study design*

A within-individual design (a variant of self-controlled case series), using stratified Cox proportional hazards regression models, was used to examine associations between medications and outcomes, with each individual entering as a separate stratum in the analysis, and serving as their own control. The obtained hazard ratio is thus adjusted for (i.e. stratified on) all potential time-invariant confounders within each individual (e.g. genes, all factors prior to the start of follow-up, and all factors that do not change during follow-up). In this design, only individuals who change medication status during follow up contribute *directly* to the estimate. All other individuals contribute *indirectly* to the estimate through the effects of other covariates (e.g. age) on the estimate. Consequently, all individuals are included in the analyses, and contribute either directly (i.e. those who experience the outcome) or indirectly (i.e. the rest of the cohort) to the estimate. Since the covariates in this design are time-varying, we did not test for the proportional hazards assumption. This design is increasingly used in pharmaco-epidemiological studies in psychiatry (14), and more information is provided here (15).

### *Measures*

#### *Register linkage*

Information on all individuals was collected from Swedish population-based registers with national coverage, and were linked through each individual's unique identification number.

### *Medications*

We extracted information on medications approved in Sweden for treating alcohol use disorder (acamprosate [ATC: N07BB03] and oral naltrexone [ATC: N07BB04]), and opioid use disorder, mainly heroin (methadone [ATC: N07BC02], and buprenorphine and buprenorphine-naloxone combination [ATC: N07BC01, N07BC51]). Information was extracted from the Swedish Prescribed Drug Register, which identifies prescriptions collected (i.e. 'dispensed') from all pharmacies and addiction treatment centers in Sweden since July 2005 (for more details, see Supplemental Methods).

### *Suicidal behavior*

Suicidal behavior was defined as suicide attempts and/or completed suicides (ICD10: X60-X84). Information on attempts was collected from the Swedish Patient Register, which includes all admissions to all hospitals, and outpatient contacts with specialized secondary care. Information on completed suicides was collected from the Cause of Death Register (see Supplemental Methods).

### *Accidental overdoses*

Information on emergency visits and/or deaths due to accidental overdoses (ICD10:T36-T50, X40-X49, F10.0-F19.0) was collected from the Swedish Patient Register and the Cause of Death Register, respectively. This included accidental poisoning and acute intoxication by alcohol, illicit drugs, medicaments and biological substances, and excluded intentional self-poisoning (ICD10: X60-X69).

### *Crime*

Information on arrests was extracted from the Register of Persons Suspected of Offences, which includes all individuals arrested of a crime after a completed investigation by police, the customs authority, or the prosecution service (16).



Information on convictions was extracted from the National Crime Register, including all convictions in Swedish district courts (see Supplemental Methods).

#### *Other measures*

See Supplemental Methods.

#### *Treatment periods*

Reflecting clinical prescribing practice (17, 18), treatment periods with acamprosate and naltrexone were defined as a series of collected prescriptions with no more than 15 days between two collected prescriptions. A treatment period started on the date of the first collected (i.e. dispensed) medication, and ended on the same date as the last collected prescription in that series (i.e. the last collected prescription that was within 15 days of a prior prescription). If a prescription was collected more than 15 days after the prior prescription, a non-treatment period was considered to have started the day after the last collected prescription. A new treatment period started again on the day of the next collected prescription. Defining the end of a treatment period as the day of the last collected prescription, gives a more conservative estimate of medication exposure, which could result in lower sensitivity (i.e. individuals are classified as non-medicated when they may be on medication), and underestimate associations.

For methadone and buprenorphine, treatment periods were defined in the same manner, however, with no more than eight days between two collected prescriptions. For all medications, single prescriptions were excluded due to uncertainty over medication adherence (see Supplemental Methods).

The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed (Supplemental data).

## **Ethics**

The project was approved by the Regional Ethics Review Board in Stockholm, Sweden (2013/5:8).

## **Statistical analyses**

Follow-up started in September 1, 2005, or on the date of migration to Sweden, first release from prison, youth care, or hospital. Observations were censored in December 31, 2013 or in the event of death or permanent migration from Sweden. Follow-up was split into periods of treatment and non-treatment. In order to account for time at risk, we excluded time spent in prison, youth care, hospital or interim migration. First, we examined our four primary outcomes: suicidal behavior, accidental overdoses, any arrest, and arrest for violent crime. Second, we studied arrests for other crime categories: substance-related and non-violent crime. Third, we investigated convictions (rather than arrests). We adjusted for age by coding age as a categorical time-varying covariate, with one category for each whole year. We also used a quadratic function of age to allow for nonlinear effects.

### *Sensitivity analyses*

To account for the possibility of reverse causality (i.e. that an individual was prescribed the medication because of one of the examined outcomes), we performed sensitivity analyses excluding individuals who had initiated a treatment period within three months after experiencing the studied outcome (e.g. initiated a naltrexone treatment period within three months after being treated for an accidental overdose).

To further examine associations with suicidal behavior, we conducted analyses using the method of suicidal behavior (poisoning or other methods) as

outcome. We also adjusted for concurrent exposure to antidepressants (ATC: N06A) and benzodiazepines (ATC: N05B, N05C), separately, as time-varying covariates. We then excluded all medication periods with concurrent antidepressant or benzodiazepine use (e.g. co-occurring acamprosate and antidepressant treatment). We also examined the hazard of suicidal behavior within each cohort by using benzodiazepines as an exposure and suicidal behavior as an outcome in within-individual analyses (see Supplemental Methods).

To exclude the possibility of polypharmacy interactions among individuals treated with methadone or buprenorphine, we performed within-individual analyses where we excluded individuals who had also been treated with acamprosate during follow-up (naltrexone was not excluded as it is contraindicated for concurrent use with opioid medications).

We tested for non-specific treatment effects (e.g. contact with medical services) by using penicillin (ATC: JC01) and adrenergic inhalants (e.g. albuterol/salbutamol; ATC: R03A), respectively, as alternative exposures in the methadone and buprenorphine cohorts. The choice of medications was determined by theoretical reasons as not being associated with the tested outcomes (see Supplemental Methods).

## RESULTS

### *Descriptives*

In the total population of Sweden, we identified 21,281 individuals who were treated with medications for alcohol or opioid use disorders between 2005 and 2013. Of these, 10,309 individuals were treated with acamprosate, 4,389 with naltrexone, 3,320 with buprenorphine, and 5,449 with methadone. Between 61-73% of the participants were men. Background demographic factors are described in Table 1. Mean follow-up time for participants was 7.6 years (SD=1.9).

During follow-up, 14.3% (n=1,472) in the acamprosate cohort, 21.0% (n=916) in the naltrexone cohort, 19.3% (n=639) in the buprenorphine cohort, and 11.6% (n=629) in the methadone cohort were treated or died from suicidal behavior. Furthermore, 29.3% (n=3,025) in the acamprosate cohort, 37.1% (n=1,626) in the naltrexone cohort, 40.5% (n=1,343) in the buprenorphine, and 28.2% (n=1,536) in the methadone cohort received treatment or died from an accidental overdose. In addition, 37.3% (n=3,848) in the acamprosate cohort, 43.3% (n=1,900) in the naltrexone cohort, 82.5% (n=2,739) in the buprenorphine cohort, and 45.9% (n=2,504) in the methadone cohort were arrested at least once during follow-up (Figure 1).

*Associations with primary outcomes - suicidal behavior, accidental overdoses, any arrest, and arrests for violent crime*

### *Acamprosate*

No significant associations with any of the primary outcomes were found for acamprosate (Figure 2; Table 2).

### *Naltrexone*

The hazard ratio (HR) for accidental overdoses was reduced when individuals were taking naltrexone compared to periods when they were not (HR=0.82, 95% Confidence Interval [CI] 0.70-0.96). No other significant associations were found (Figure 2; Table 2).

#### *Buprenorphine*

Significant reductions were found for overall arrest rates (HR=0.77, 95%CI 0.72-0.84), and for arrests for violent crime (HR=0.65, 95%CI 0.50-0.84). There was a decreased hazard of 25% associated with accidental overdoses (HR=0.75, 95%CI 0.60-0.93) (Figure 2; Table 2).

#### *Methadone*

There was a reduction of 40% (HR=0.60, 95%CI 0.40-0.88) in suicidal behavior when individuals were treated with methadone compared to when they were not. Significant reductions were also associated with overall arrest rates (HR=0.87, 0.83-0.91), and arrest rates for violent crime (HR=0.84, 95%CI 0.73-0.96). A significant increase of 25% was associated with accidental overdoses (HR=1.25, 95%CI 1.13-1.38) (Figure 2; Table 2).

*Associations with secondary outcomes – arrests for non-violent and substance-related crime, and convictions.*

#### *Acamprosate*

Acamprosate was associated with reductions in substance-related convictions (HR=0.69, 95%CI 0.48-0.99), but not with other secondary outcomes (Table 3).

#### *Naltrexone*

Prescriptions of naltrexone were associated with reductions in substance-related convictions (HR=0.51, 95%CI 0.30-0.86) (Table 3).

*Buprenorphine*

Buprenorphine was associated with reductions in arrests for non-violent and substance-related crime, and with convictions of all crime categories (Table 3).

*Methadone*

Methadone was associated with reduced rates of arrests for non-violent and substance-related crime, and with lower conviction rates of any crime, and substance-related crime (Table 3).

*Sensitivity analyses*

To account for the potential of reverse causality, we excluded individuals who started the medication within three months after experiencing the studied outcome. When excluding individuals who had been treated with acamprosate within three months after experiencing an accidental overdose, a significant decreased hazard was shown (HR=0.88, 95%CI 0.80-0.99). Naltrexone was associated with a significant decrease in suicidal behaviors (HR=0.80, 95%CI 0.67-0.95), and overall arrests (HR=0.85, 95%CI 0.74-0.97). For buprenorphine, results remained similar to the primary analyses. For methadone, the increased risks of accidental overdoses no longer remained significant (Supplemental Table 1).

When examining suicidal behavior further, we first adjusted for concurrent use of antidepressants and then excluded all medication periods with co-occurring antidepressant treatment. Associations remained similar to the main analyses. When examining the method of suicidal behavior (i.e. poisoning or other) separately, reductions remained for methadone (Supplemental Table 2).

We then excluded individuals who had been prescribed acamprosate in order to account for the possibility of polypharmacy interactions among individuals taking methadone or buprenorphine. Results remained similar to the overall main analyses (Supplemental Table 3).

We used penicillin and adrenergic inhalants as negative controls to test for non-specific treatment effects. No significant associations were found for penicillin. For adrenergic inhalants, significant reductions were associated with any arrested crime (HR=0.71, 95%CI 0.65-0.78) (Supplemental Table 4).

We adjusted for concurrent benzodiazepine use. Associations remained similar to the main analyses - that is, methadone treatment was associated with significant reductions, and no other significant associations were found. When excluding all medication periods with co-occurring benzodiazepine treatment, reduced hazards were no longer significant for methadone, and no other significant associations were shown. We also examined the risk of suicidal behavior in each cohort by using benzodiazepines as exposure and suicidal behavior as outcome. Results showed that individuals in the acamprosate and naltrexone cohorts who took benzodiazepines had increased hazards of suicidal behavior (HR=1.54, 95%CI 1.34-1.76; HR=1.45 95%CI 1.28-1.64). Individuals in the methadone and buprenorphine cohorts showed no significant associations (Supplemental Table 5).

## DISCUSSION

In this population-based study of 21,281 individuals prescribed medications for alcohol or opioid use disorders, we found heterogeneity in the effect of these medications on suicidal behavior, accidental overdoses, and crimes. Using a within-individual design that accounted for factors that remain constant in an individual (e.g. genetic risks and early environment), we found substantial reductions in the rate of suicidal behavior when individuals were dispensed methadone compared to when they were not. We also found reductions in arrests for methadone and buprenorphine, although this was not specific to any particular arrest category. No significant reductions were found in suicidal behavior or arrests for acamprosate or naltrexone. When investigating accidental overdoses, naltrexone and buprenorphine were associated with reduced rates, but there was an increased risk associated with methadone, although this risk did not persist in our sensitivity analyses.

The reductions in a wide range of adverse outcomes for several of the medications could be seen as a proxy for their overall effectiveness in treating substance use disorders. There are three principal implications of these findings: First, they support the potential role of methadone in reducing suicidal behavior among individuals with opioid use disorder. Deaths from suicide and self-harming behavior are a public health priority, and various pharmacological approaches to address this have uncertain efficacy (19). However, the findings from the current study, which are consistent with a small body of trial evidence for naltrexone and buprenorphine (20, 21), suggest enhancing the timely and appropriate prescription of opioid medications as an important strategy to reduce adverse outcomes related to opioid use disorder.



Another potential implication is the use of such medications to reduce crime. There is a lack of consistency in the availability and policies over how these medications are used in the criminal justice system (22), even though opioid therapies have shown clear reductions in re-incarceration risk (23) and violent re-offending risk in individuals released from prison (24).

A final implication is the heterogeneity of the findings in relation to accidental overdoses, which may be explained by differences in the mechanisms of the medications. We found increased hazards for methadone, which is a full opioid agonist with no ceiling to its effects on respiratory depression and sedation. In addition, methadone blocks the opioid receptors that bind other opioids (25). However, lower doses may not be sufficient to prevent withdrawal symptoms and cravings, which could result in the use of supplementary illicit drugs, thus increasing the risk of accidental overdoses. It has been proposed that patients on lower methadone doses are at heightened risk of relapse (25), and that mortality is higher early on in methadone treatment (26). We found reduced associations with accidental overdoses for buprenorphine and naltrexone. Buprenorphine is a partial agonist with high affinity to the opioid receptor but weaker opioid effects than methadone, a plateau of effect at increased doses, and a lower risk of overdose (27). Naltrexone is an opioid antagonist that blocks opioid activity, and could thus decrease the risk of accidental overdoses from opioids. However, case reports have suggested an increased risk of opioid overdoses in patients who “break through” naltrexone’s opioid block with large doses of opioids (28).

In terms of clinical implications, these possible implications need to be interpreted in the context of the potential risks of these medications, such as accidental overdoses in methadone. In naltrexone, there is a potential risk of reduced

tolerance in opioid users. This could increase the risk of opioid overdose among individuals who terminate their naltrexone treatment and start using opioids again (29). Evidence is, however, conflicting (28, 30). Other clinical implications are ensuring that individuals are on the correct dose of methadone, and screening and treating co-occurring substance use disorders. In those at high risk of accidental overdose, buprenorphine could be considered as first line treatment (31). However, methadone has been shown to be superior to buprenorphine in retaining patients in treatment (32), and further corroborations that validate the increased risk of accidental overdoses reported here for methadone are required before changes to routine practice are recommended.

#### *Strengths and limitations*

The strengths of this observational study include its large size, testing for across multiple adverse outcomes, and a within-individual design that accounts for confounding by indication and other time-invariant confounders. A traditional Cox model (i.e. a between-individual design), would have been liable to confounding, particularly confounding by indication (15), even when adjusting for measured confounders.

A number of important limitations need to be considered. The findings are associations, and causal inferences should not be drawn. It was not possible to exclude the potential impact of contact with medical services, such as psychosocial interventions given at the same time as medications. This may be particularly relevant in relation to rates of lower suicidal behavior for methadone, as Swedish guidelines recommend monthly nursing appointments for opioid medications. However, the heterogeneity of the findings across different medications and outcomes would argue against healthcare contact entirely explaining these findings.

Swedish guidelines recommend supervision for suicidal behavior for patients treated with acamprosate, yet, we found no association between acamprosate and suicidal behavior. In addition, we found no significant associations for suicidal behavior or accidental overdoses when we used penicillin and adrenergic inhalants as negative controls. There were, however, reductions associated with any crime for adrenergic inhalants, which could suggest non-specific treatment effects for this outcome.

Differences in service provision may affect the generalizability of findings.

Rates of illicit opioid use are similar across the US and Sweden (1.5% of the population in the US, and 1.8% in Sweden) (33, 34). However, 15-20% of individuals with opioid use disorder are estimated to receive opioid treatment in the US (35), as compared to over 70% in Sweden (36). Results could be affected by a potential bias towards the null due to misclassification of exposures and/or outcomes. On the other hand, this should reduce the hazards reported, and would suggest that our estimates are underestimates. Furthermore, the hazard ratio takes into account the timing of an event rather than the number of events over time.

Even though we applied a more conservative estimate of medication exposure (defining periods of more than 8 or 15 days between collected prescriptions as non-treatment periods), we did not have data on medication adherence. This problem is similar to non-adherence in clinical trials, and the within-individual estimate is thus comparable to the intention-to-treat analysis. However, individuals on opioid medication receive their daily dose under medical supervision for at least the first six months of treatment, ensuring adherence. Furthermore, distinguishing suicidal behavior from accidental overdoses is challenging (37), and some suicides may have been classified as accidental overdoses due to uncertain evidence, overlapping risk

factors, or stigma (37). Thus, suicidal behavior could be underestimated, while accidental overdoses could be overestimated.

Suicide risks in the naltrexone cohort may have been diluted as our data does not distinguish whether the indication for treatment was alcohol or opiate use disorder. Naltrexone is only approved for treating alcohol use disorder in Sweden, however, a proportion of prescriptions may have been prescribed off-label. Furthermore, benzodiazepines are often prescribed to treat alcohol use disorder, and are associated with an increased risk of suicidal behavior in epidemiological studies (38). In our study, adjustment for the concurrent use of benzodiazepines did not change associations between medications and suicidal behavior. Benzodiazepines were, however, independently associated with increased hazards of suicidal behavior in the acamprosate and naltrexone cohorts. These findings require further examination in other settings, as we did not have information on the indication (e.g. alcohol use disorder or anxiety) for the prescription. Finally, the use of official registers may lead to underestimation of true outcome rates, and possibly involve selection effects.

### *Conclusions*

In this study of individuals prescribed medications for alcohol or opioid use disorders in Sweden, we found potentially interesting associations with reduced suicidal behavior and criminality. If validated using other designs, the application of these findings through treatment have the potential to reduce the substantial burden of morbidity in individuals with substance use disorders.

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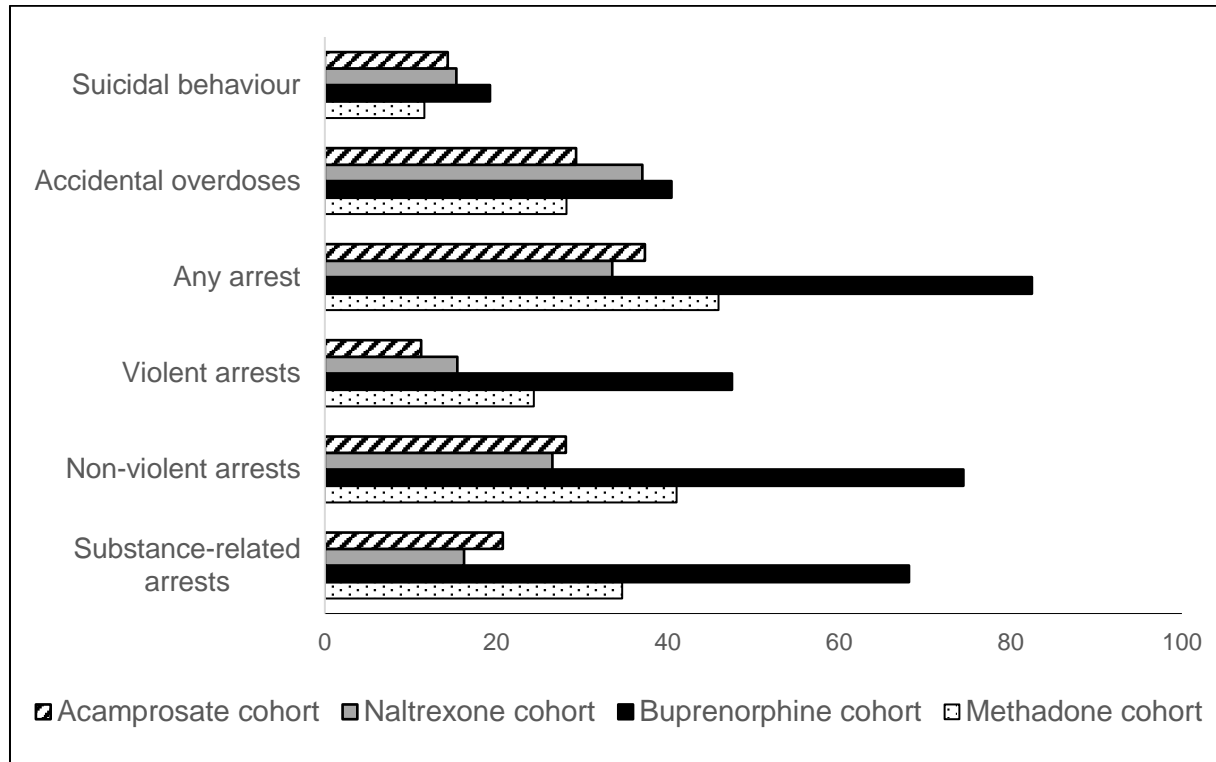
Table 1. Characteristics of participants at baseline 2005.

	Acamprosate cohort (n=10,309)		Naltrexone cohort (n=4,389)		Buprenorphine cohort (n=3,320)		Methadone cohort (n=5,449)	
	%	n	%	n	%	n	%	n
Sex								
Women	32.1	3,304	36.1	1,585	26.7	885	39.0	2,123
Men	67.9	7,005	63.9	2,804	73.3	2,435	61.0	3,326
Age distribution at baseline 2005								
<20	2.9	295	5.2	230	6.5	216	2.1	113
20-29	7.3	748	10.4	456	37.7	1,253	14.7	802
30-39	16.0	1,651	18.1	792	29.6	983	20.4	1,110
40-49	27.3	2,817	26.5	1,161	20.3	675	26.5	1,441
50-59	27.7	2,859	23.2	1,019	5.1	169	17.4	946
60-69	15.6	1,613	13.6	595	0.6	21	10.7	946
>69	3.2	326	3.1	136	0.1	3	8.3	453

Socio-demographic characteristics at baseline 2005								
Unmarried / Divorced	62.8	6,469	68.7	3,015	89.5	2,862	69.9	3,575
Employed	51.5	5,313	40.6	1,782	19.8	639	22.5	1,202
Social welfare	14.0	1,441	18.8	825	60.9	1,961	34.1	1,825
Disability pension	25.9	2,674	32.0	1,406	20.2	650	38.8	2,076
Lifetime psychiatric and substance use disorder diagnoses								
Alcohol use disorder	74.6	7,685	78.5	3,426	34.5	1,146	23.0	1,251
Substance use disorder*	22.9	2,359	33.7	1,478	99.2	3,293	61.4	3,343
Psychotic disorders	9.4	966	17.0	745	9.9	330	6.1	334
Bipolar disorder	8.7	896	13.3	583	4.8	160	3.5	188

\* Other than alcohol

Figure 1. Percentage of individuals in each cohort who experienced an adverse outcome during follow-up 2005-2013<sup>†</sup>.



<sup>†</sup> Average follow-up time: 7.6 years (SD=1.9)

Figure 2. Hazard rates of primary outcomes; suicidal behavior, accidental overdoses, overall arrests and arrests for violent crime, comparing treatment to non-treatment periods within the same person.

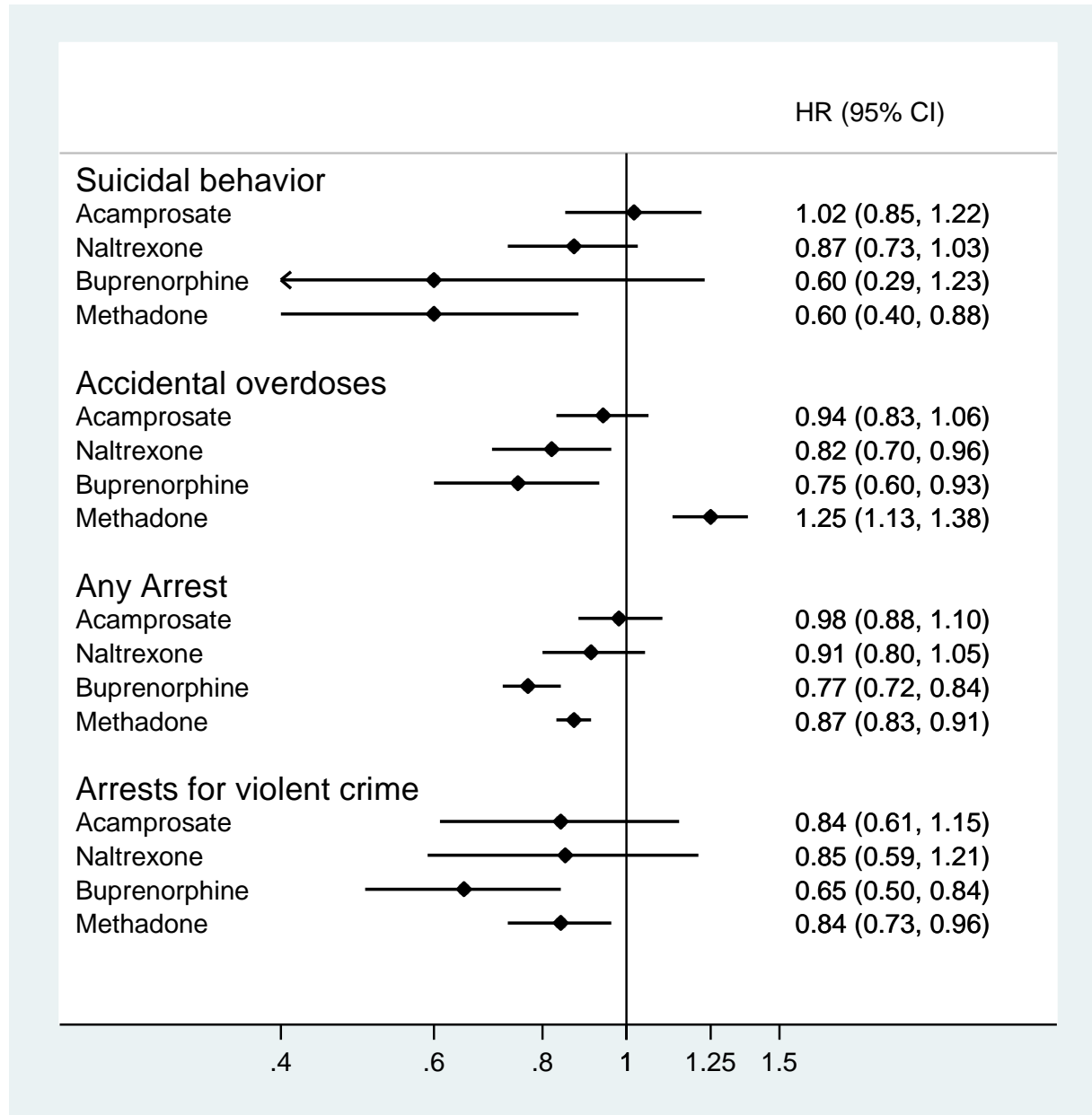


Table 2. Hazard rates of primary outcomes; suicidal behavior, accidental overdoses, overall arrests and arrests for violent crime, comparing treatment to non-treatment periods within the same person.

Outcome	Hazard ratio	95%CI	P-value	Number of events	Incidence rates per 1,000 person-years
ACAMPROSATE					
Suicidal behavior	1.02	0.85-1.22	0.826	3,940	48.5
Accidental overdoses	0.94	0.83-1.06	0.290	11,010	135.5
Any arrest	0.98	0.88-1.10	0.750	15,486	190.5
Arrests for violent crime	0.84	0.61-1.15	0.278	2,609	32.1
NALTREXONE					
Suicidal behavior	0.87	0.73-1.03	0.094	3,425	99.8
Accidental overdoses	0.82	0.70-0.96	0.011	6,724	195.9
Any arrest	0.91	0.80-1.05	0.202	9,182	267.5
Arrests for violent crime	0.85	0.59-1.21	0.365	1,529	44.5
BUPRENORPHINE					
Suicidal behavior	0.60	0.29-1.23	0.161	829	45.3

Accidental overdoses	0.75	0.60-0.93	0.009	2,869	156.9
Any arrest	0.77	0.72-0.84	<0.000	25,834	1412.8
Arrests for violent crime	0.65	0.50-0.84	0.001	3,923	214.5
METHADONE					
Suicidal behavior	0.60	0.40-0.88	0.009	882	27.9
Accidental overdoses	1.25	1.13-1.38	<0.000	4,305	135.9
Any arrest	0.87	0.83-0.91	<0.000	24,866	785.2
Arrests for violent crime	0.84	0.73-0.96	0.013	3,787	119.6

Table 3. Hazard rates of secondary outcomes, comparing treatment to non-treatment periods within the same person.

Outcome	Hazard ratio	95%CI	P-value	Number of events
<b>ACAMPROSATE</b>				
Arrests for non-violent crime	0.99	0.87-1.13	0.878	11,458
Arrests for substance-related crime	0.79	0.58-1.07	0.126	4,165
Conviction for any crime	0.93	0.80-1.08	0.367	9,247
Conviction for violent crime	1.05	0.69-1.60	0.811	1,615
Conviction for non-violent crime	1.03	0.85-1.24	0.767	5,468
Conviction for substance-related crime	0.69	0.48-0.99	0.041	3,467
<b>NALTREXONE</b>				
Arrests for non-violent crime	0.90	0.76-1.05	0.153	6,917
Arrests for substance-related crime	0.69	0.47-1.01	0.057	2,221
Conviction for any crime	0.86	0.70-1.07	0.174	5,325
Conviction for violent crime	0.70	0.39-1.26	0.234	986
Conviction for non-violent crime	0.88	0.67-1.16	0.364	3,273
Conviction for substance-related crime	0.51	0.30-0.86	0.011	1,754
<b>BUPRENORPHINE</b>				

Arrests for non-violent crime	0.78	0.71-0.86	<0.000	18,548
Arrests for substance-related crime	0.71	0.62-0.83	<0.000	9,789
Conviction for any crime	0.74	0.67-0.81	<0.000	18,562
Conviction for violent crime	0.44	0.23-0.83	0.012	1,106
Conviction for non-violent crime	0.75	0.66-0.84	<0.000	11,820
Conviction for substance-related crime	0.61	0.52-0.72	<0.000	8,470
METHADONE				
Arrests for non-violent crime	0.89	0.47-0.94	<0.000	18,070
Arrests for substance-related crime	0.77	0.70-0.84	<0.000	8,812
Conviction for any crime	0.89	0.84-0.94	<0.000	17,716
Conviction for violent crime	1.05	0.75-1.48	0.764	1,026
Conviction for non-violent crime	0.99	0.93-1.06	0.791	11,832
Conviction for substance-related crime	0.67	0.61-0.74	<0.000	7,359