Medications for Alcohol and Opioid Use Disorders and Risk of Suicidal Behavior, Accidental Overdoses, and Crime

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Objective: The authors examined 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 received treatment with at least one of the four medications between 2005 and 2013 were identified. Data 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 for the same individuals during the period when they were receiving the medication compared with the period 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 for accidental overdoses during periods when individuals received treatment compared with periods when they did not (hazard ratio=0.82, 95% CI=0.70, 0.96). Buprenorphine was associated with reduced arrest rates for all crime categories (i.e., violent, nonviolent, and substance-related) as well as reduction in accidental overdoses (hazard ratio=0.75, 95% CI=0.60, 0.93). For methadone, there were significant reductions in the rate of suicidal behaviors (hazard ratio=0.60, 95% CI=0.40–0.88) as well as reductions in all crime categories. However, there was an increased risk for accidental overdoses among individuals taking methadone (hazard ratio=1.25, 95% CI=1.13, 1.38).

Conclusions: Medications currently used to treat alcohol and opioid use disorders also appear to reduce suicidality and crime during treatment.

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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 overdoses of prescription and illicit opioids have increased in many countries, contributing to substantially reduced life expectancy (3). Additionally, nonfatal overdoses are common. Studies have shown that 30%−80% of persons who use illicit drugs regularly, by injection or by other methods of consumption, have experienced at least one nonfatal overdose (4). Furthermore, the nonmedical 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 disorder 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). The efficacy of these medications in reducing illicit drug use has been shown to be stronger than the efficacy of psychological treatments (10). Additionally, these medications improve psychosocial functioning (11). However, their effect 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, because they often exclude patients who have comorbid psychiatric disorders (13).

Here, we used a large population-based cohort of individuals who received prescriptions for medications for an alcohol or opioid use disorder (i.e., acamprosate, naltrexone, methadone, and buprenorphine), and we investigated the association of these medications with suicidal behavior, accidental overdoses, and crime. We used a within-individual design that compared rates of suicidal behavior, accidental overdoses, and crimes for the same individuals during the

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period when they were taking these medications with the period 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 receive prescriptions for these medications may have background risks that differ from those of persons who do not.

METHOD

Participants

We examined data for individuals in Sweden who were treated with a medication for an alcohol or opioid use disorder (acamprosate, naltrexone, methadone, or buprenorphine) during the period 2005–2013.

Study Design

A within-individual design (a variant of self-controlled case series), with stratified Cox proportional hazards regression models, was used to examine associations between medications and outcomes, with each individual entered as a separate stratum in the analysis and serving as his or her own control. Therefore, the obtained hazard ratio was adjusted for (i.e., stratified on) all potential time-invariant confounders for each individual (e.g., genes, all factors before the start of the follow-up period, and all factors that did not change during follow-up). In this design, only individuals who changed medication status during the follow-up period contributed directly to the estimate. All other individuals contributed indirectly to the estimate through the effects of other covariates (e.g., age) on the estimate. Consequently, all individuals were included in the analyses and contributed either directly (i.e., individuals who experienced the outcome) or indirectly (i.e., the remaining individuals in the cohort) to the estimate. Because the covariates in this design are time-varying, we did not test for the proportional hazards assumption. This design is increasingly used in pharmacoepidemiological studies in psychiatry (14), and further details are provided elsewhere (15).

Measures

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

Medications. We extracted information on medications approved in Sweden for treating alcohol use disorder (acamprosate: Anatomical Therapeutic Chemical [ATC] classification system code N07BB03 and oral naltrexone: ATC code N07BB04) and for treating opioid use disorder, mainly heroin use (methadone [ATC code N07BC02], buprenorphine [ATC code N07BC01] and buprenorphine-naloxone combination [ATC code 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 further details, see the online supplement).

Suicidal behavior. Suicidal behavior was defined as suicide attempts or deaths by suicide (ICD-10 codes X60–X84). Information on suicide attempts was collected from the Swedish National Patient Register, which includes all admissions to all hospitals as well as outpatient contacts with specialized secondary care. Information on deaths by suicide was collected from the Swedish Cause of Death Register (for further details, see the Methods section in the online supplement).

Accidental overdoses. Information on emergency department visits or deaths due to accidental overdoses (ICD-10 codes T36–T50, X40–X49, F10.0–F19.0) was collected from the Swedish National Patient Register and Cause of Death Register, respectively. This included accidental poisoning and acute intoxication by alcohol, by illicit drugs, by medications, or by biological substances and excluded intentional self-poisoning (ICD-10 codes X60–X69).

Crime. Information on arrests was extracted from the Swedish Register of Persons Suspected of Offenses, which includes all individuals arrested for a crime after a complete investigation by police, the customs authority, or the prosecution service (16). Information on convictions was extracted from the Swedish National Crime Register, including all convictions in Swedish district courts (for further details, see the Methods section in the online supplement).

Other measures. Detailed information pertaining to other measures is summarized in the Methods section in the online supplement.

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 previous prescription). If a prescription was collected more than 15 days after the previous prescription, a nontreatment period was considered to have started on the day after the last collected prescription. A new treatment period was considered to have 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 allows for a more conservative estimate of medication exposure, which could result in lower sensitivity (i.e., individuals are classified as nonmedicated when they may be taking a medication) and underestimation of associations.

For methadone and buprenorphine, treatment periods were defined in the same manner but with no more than 8 days between two collected prescriptions. For all medications, single prescriptions were excluded due to

TABLE 1. Baseline Characteristics of Participants Treated for Alcohol or Opioid Use Disorder by Medication Prescribed (2005)

	Acamprosate Cohort (N=10,309)		Naltrexone Cohort (N=4,389)		Buprenorphine Cohort (N=3,320)		Methadone Cohort (N=5,449)	
Characteristic	N	%	N	%	N	%	N	%
Sex								
Women	3,304	32.1	1,585	36.1	885	26.7	2,123	39.0
Men	7,005	67.9	2,804	63.9	2,435	73.3	3,326	61.0
Age (years)								
<20	295	2.9	230	5.2	216	6.5	113	2.1
20–29	748	7.3	456	10.4	1,253	37.7	802	14.7
30–39	1,651	16.0	792	18.1	983	29.6	1,110	20.4
40–49	2,817	27.3	1,161	26.5	675	20.3	1,441	26.5
50–59	2,859	27.7	1,019	23.2	169	5.1	946	17.4
60–69	1,613	15.6	595	13.6	21	0.6	946	10.7
>69	326	3.2	136	3.1	3	0.1	453	8.3
Sociodemographic variables								
Unmarried or divorced	6,469	62.8	3,015	68.7	2,862	89.5	3,575	69.9
Employed	5,313	51.5	1,782	40.6	639	19.8	1,202	22.5
Receiving social welfare	1,441	14.0	825	18.8	1,961	60.9	1,825	34.1
Receiving disability pension	2,674	25.9	1,406	32.0	650	20.2	2,076	38.8
Lifetime psychiatric and substance use disorder diagnoses								
Alcohol use disorder	7,685	74.6	3,426	78.5	1,146	34.5	1,251	23.0
Substance use disorder[a]	2,359	22.9	1,478	33.7	3,293	99.2	3,343	61.4
Psychotic disorders	966	9.4	745	17.0	330	9.9	334	6.1
Bipolar disorder	896	8.7	583	13.3	160	4.8	188	3.5

[a] In this category, we report substance use disorders other than alcohol use disorder.

uncertainty of medication adherence (for further details, see the Methods section in the online supplement).

We followed the Strengthening the Reporting of Observational studies in Epidemiology guidelines (see the online supplement).

The study was approved by the Regional Ethical Review Board in Stockholm.

Statistical Analyses

Follow-up started on September 1, 2005, or on the date of migration to Sweden, the first day of release from prison, the first day of secure residential homes for juveniles, or the first day of hospitalization. Observations were censored on December 31, 2013, or in the event of death or permanent migration from Sweden. Follow-up was divided into periods of treatment and nontreatment. To account for time at risk, we excluded time spent in prison, secure residential homes for juveniles, hospitals, or interim migration. First, we examined the four primary outcomes: suicidal behavior, accidental overdoses, any arrests, and arrests for violent crimes. Second, we examined arrests for other crime categories: substance-related and nonviolent crimes. 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. Additionally, we used a quadratic function for age to allow for nonlinear effects.

Sensitivity analyses. To account for the possibility of reverse causality (i.e., that an individual was prescribed medication because of one of the examined outcomes), we performed sensitivity analyses excluding individuals who initiated a treatment period within 3 months after experiencing the studied outcome (e.g., individuals who initiated a naltrexone treatment period within 3 months after being treated for an accidental overdose).

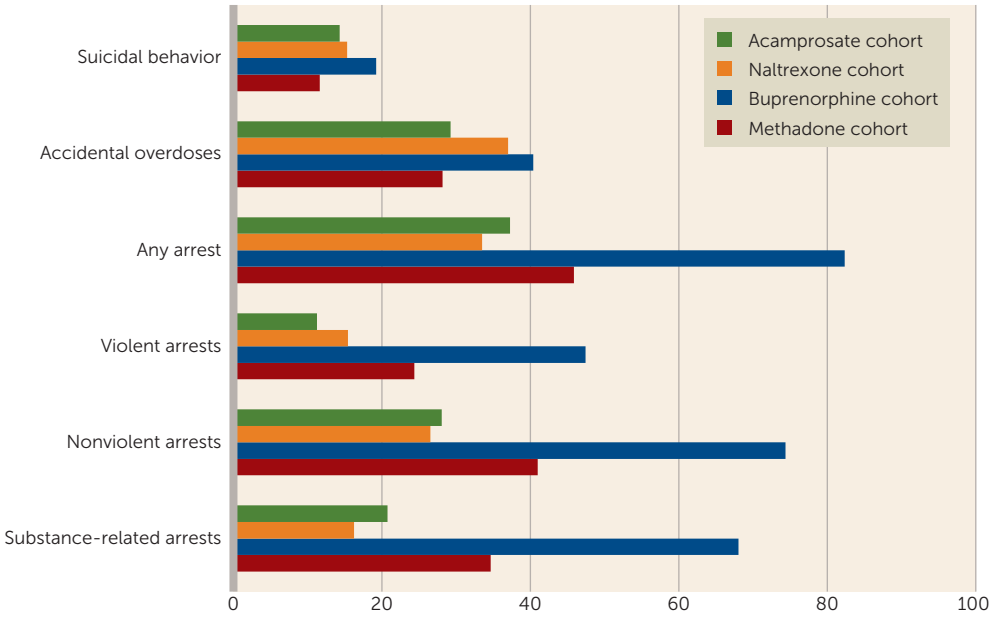
To further examine associations with suicidal behavior, we conducted analyses using the method of suicidal behavior (poisoning or other methods) as outcome. Additionally, we adjusted for concurrent exposure to antidepressants (ATC code N06A) and benzodiazepines (ATC codes N05B and N05C), separately, as time-varying covariates. We then excluded all medication periods with concurrent antidepressant or benzodiazepine treatment (e.g., co-occurring acamprosate and antidepressant treatment). Furthermore, we examined the hazard of suicidal behavior in each cohort by using benzodiazepines as an exposure and suicidal behavior as an outcome in within-individual analyses (for further details, see the Methods section in the online supplement).

To exclude the possibility of polypharmacologic interactions among individuals treated with methadone or buprenorphine, we performed within-individual analyses in which we excluded individuals who were also treated with acamprosate during follow-up assessment (naltrexone was not excluded, because it is contraindicated for concurrent use with opioid medications).

We tested for nonspecific treatment effects (e.g., contact with medical services) by using penicillin (ATC code JC01) and adrenergic inhalants (e.g., albuterol/salbutamol [ATC code R03A]), respectively, as alternative exposures in the

methadone and buprenorphine cohorts. The choice of these alternative medications was determined on the basis of theoretical reasons for not being associated with the tested outcomes (for further details, see the Methods section in the online supplement).

FIGURE 1. Percentage of Individuals Who Experienced an Adverse Outcome During Follow-Up by Medication Cohort (2005–2013)[a]



[a] The mean follow-up time was 7.6 years (SD=1.9).

RESULTS

In the total population of Sweden, we identified 21,281 individuals who were treated with medications for alcohol or opioid use disorder 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% and 73% of these subgroups were men. The demographic characteristics of the study population are summarized in Table 1. The mean follow-up time for participants was 7.6 years (SD=1.9).

During the follow-up period, 14.3% (N=1,472) of individuals 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 for or died as a result of suicidal behavior. Furthermore, 29.3% (N=3,025) of individuals in the acamprosate cohort, 37.1% (N=1,626) in the naltrexone cohort, 40.5% (N=1,343) in the buprenorphine cohort, and 28.2% (N=1,536) in the methadone cohort received treatment for or died as a result of an accidental overdose. Additionally, 37.3% (N=3,848) of individuals 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 the follow-up period (Figure 1).

Associations With Primary Outcomes (Suicidal Behavior, Accidental Overdoses, Any Arrests, and Arrests for Violent Crime)

Acamprosate. No associations of statistical significance were observed with any of the primary outcomes for acamprosate (Table 2, Figure 2).

Naltrexone. Among individuals who received prescriptions for naltrexone, the hazard ratio for accidental overdoses was reduced during periods when they were taking the medication compared with periods when they were not (hazard ratio=0.82, 95% CI=0.70, 0.96). No other significant associations were found for this medication (Table 2, Figure 2).

Buprenorphine. Significant reductions were found for overall arrest rates with use of buprenorphine (hazard ratio=0.77, 95% CI=0.72, 0.84) as well as for arrests for violent crime (hazard ratio=0.65, 95% CI=0.50, 0.84). A decreased hazard ratio was associated with accidental overdoses (hazard ratio=0.75, 95% CI=0.60, 0.93) (Table 2, Figure 2).

Methadone. Among individuals who received prescriptions for methadone, there was a 40% reduction in suicidal behavior during periods when they were taking the medication compared with when they were not (hazard ratio=0.60, 95% CI=0.40, 0.88). Additionally, significant reductions were associated with overall arrest rates (hazard ratio=0.87, 95% CI=0.83, 0.91) as well as arrest rates for violent crime (hazard ratio=0.84, 95% CI=0.73, 0.96). A significant increased hazard of 25% was associated with accidental overdoses (hazard ratio=1.25, 95% CI=1.13, 1.38) (Table 2, Figure 2).

Associations With Secondary Outcomes (Arrests for Nonviolent and Substance-Related Crime and Convictions)

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

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

TABLE 2. Hazard Ratios and Incidence Rates of the Primary Outcomes for Treatment Periods Compared With Nontreatment Periods for the Same Person[a]

Medication and Outcome	Hazard Ratio	95% CI	p	Number of Events	Incidence (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	<0.001	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	<0.001	4,305	135.9
Any arrest	0.87	0.83, 0.91	<0.001	24,866	785.2
Arrests for violent crime	0.84	0.73, 0.96	0.013	3,787	119.6

[a] The primary outcomes are suicidal behavior, accidental overdoses, overall arrests, and arrests for violent crime.

Buprenorphine. Buprenorphine was associated with reductions in arrests for nonviolent and substance-related crimes as well as convictions for all crime categories (Table 3).

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

Sensitivity analyses. To account for the possibility of reverse causality, we excluded individuals who started taking their prescribed medication within 3 months after experiencing the studied outcome. When we excluded individuals who were treated with acamprosate within 3 months after experiencing an accidental overdose, we observed a significant decreased hazard ratio (hazard ratio=0.88, 95% CI=0.80, 0.99). In these subanalyses, naltrexone was associated with a significant decrease in suicidal behaviors (hazard ratio=0.80, 95% CI=0.67, 0.95) and overall arrests (hazard ratio=0.85, 95% CI=0.74, 0.97). For buprenorphine, results in the sensitivity analyses were similar to those in the primary analyses. For methadone, the increased risks of accidental overdoses were no longer statistically significant (for further details, see Table S1 in the online supplement).

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 those observed in the main analyses. When examining the method of suicidal behavior (i.e., poisoning or other) separately, reductions in suicidal behavior remained significant for methadone (for further details, see Table S2 in the online supplement).

We then excluded individuals who were prescribed acamprosate in order to account for the possibility of polypharmacologic interactions among individuals taking methadone or buprenorphine. Results remained similar to those of the overall main analyses (for further details, see Table S3 in the online supplement).

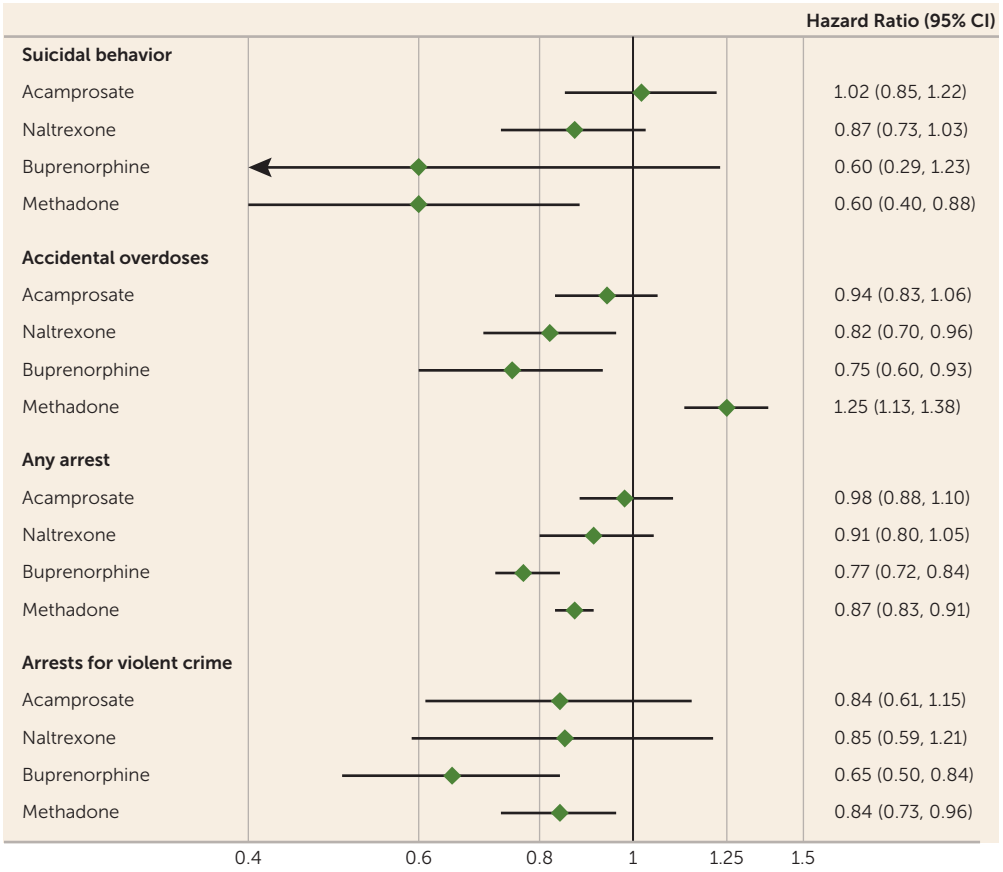
We used penicillin and adrenergic inhalants as negative controls to test for nonspecific treatment effects. No significant associations were found for penicillin. For adrenergic inhalants, significant reductions were associated with any crime that resulted in an arrest (hazard ratio=0.71, 95% CI=0.65, 0.78) (for further details, see Table S4 in the online supplement).

We adjusted for concurrent benzodiazepine treatment. Associations remained similar to those observed in the main analyses—that is, methadone treatment was associated with significant reductions, and no other significant associations were found. When all medication periods with co-occurring benzodiazepine treatment were excluded, reduced hazard ratios were no longer significant for methadone treatment, and no other significant associations were observed. We also examined the risk of suicidal behavior in each cohort by using benzodiazepines as exposure and suicidal behavior as outcome. Results showed increased hazard ratios for suicidal behavior among individuals in the acamprosate and naltrexone cohorts who were taking benzodiazepines (acamprosate cohort, hazard ratio=1.54, 95% CI=1.34, 1.76; naltrexone cohort, hazard ratio=1.45, 95% CI=1.28, 1.64). Individuals in the methadone and buprenorphine cohorts showed no significant associations (for further details, see Table S5 in the online supplement).

DISCUSSION

In this population-based study of 21,281 individuals who were prescribed medications for an alcohol or opioid use disorder, we found heterogeneity with regard to the effect of these medications on suicidal behavior, accidental overdoses, and crime. Using a within-individual design that accounted for factors that remain constant for an individual (e.g., genetic risks and early environment), we found significant reductions in the rate of suicidal behavior when individuals were dispensed methadone compared with when they were not. Additionally, we observed reductions in arrests in the methadone and buprenorphine cohorts, and a similar pattern was found for violent and substance-related arrests. No significant reductions in suicidal behavior or arrests were found in the acamprosate and naltrexone cohorts. When investigating accidental overdoses, we found that naltrexone and buprenorphine were associated with reduced rates; however, there was an increased risk associated with methadone treatment.

FIGURE 2. Risk Hazard Ratios of Adverse Primary Outcomes for Treatment Periods Compared With Nontreatment Periods for the Same Person Dispensed Medication for Alcohol or Opioid Use Disorder[a]



[a] The primary outcomes are suicidal behavior, accidental overdoses, overall arrests, and arrests for violent crime.

The reductions in a wide range of adverse outcomes associated with 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 by suicide and self-harming behavior are a public health priority, and the efficacy of various pharmacological approaches to address these concerns remains uncertain (19). However, our findings here, which are consistent with a small body of trial evidence regarding the use of 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.

The second implication is the potential for use of such medications to reduce crime. There is a lack of consistency in the availability and policies regarding how these medications are used in the criminal justice system (22), even though opioid therapies have demonstrated clear reductions in reincarceration risk (23) and violent reoffending risk among individuals released from prison (24).

The third implication lies in 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 hazard ratios for methadone, which is a full opioid agonist with no ceiling to its effects on respiratory depression and sedation. Furthermore, 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 receiving lower methadone doses are at heightened risk for relapse (25) and that mortality is higher in the early phases of methadone treatment (26). We found reduced associations with accidental overdoses in the buprenorphine and naltrexone cohorts. Buprenorphine is a partial agonist with high affinity to the opioid receptor but weaker opioid effects compared with methadone, and it has a plateau of effect at increased doses and a lower risk of overdose (27). Naltrexone is an opioid antagonist that blocks opioid activity and thus could decrease the risk of accidental overdoses

TABLE 3. Hazard Ratios of the Secondary Crime Outcomes for the Treatment Periods Compared With the Nontreatment Periods for the Same Person

Medication and Outcome	Hazard Ratio	95% CI	p	Number of Events
Acamprosate				
Arrests for nonviolent 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 nonviolent 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
Naltrexone				
Arrests for nonviolent 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 nonviolent 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
Buprenorphine				
Arrests for nonviolent crime	0.78	0.71, 0.86	<0.001	18,548
Arrests for substance-related crime	0.71	0.62, 0.83	<0.001	9,789
Conviction for any crime	0.74	0.67, 0.81	<0.001	18,562
Conviction for violent crime	0.44	0.23, 0.83	0.012	1,106
Conviction for nonviolent crime	0.75	0.66, 0.84	<0.001	11,820
Conviction for substance-related crime	0.61	0.52, 0.72	<0.001	8,470
Methadone				
Arrests for nonviolent crime	0.89	0.47, 0.94	<0.001	18,070
Arrests for substance-related crime	0.77	0.70, 0.84	<0.001	8,812
Conviction for any crime	0.89	0.84, 0.94	<0.001	17,716
Conviction for violent crime	1.05	0.75, 1.48	0.764	1,026
Conviction for nonviolent crime	0.99	0.93, 1.06	0.791	11,832
Conviction for substance-related crime	0.67	0.61, 0.74	<0.001	7,359

from opioids. However, case reports have suggested an increased risk of opioid overdoses among patients who "break through" naltrexone's opioid block with large doses of opioids (28).

In terms of clinical implications, the possible implications above need to be interpreted in the context of the potential risks of these medications, such as accidental overdoses with methadone. For naltrexone, there is a potential risk of reduced tolerance in opioid users. This could increase the risk of opioid overdose among individuals who discontinue naltrexone treatment and restart opioid use (29). However, the evidence is inconsistent (28, 30). Other clinical implications are the need to ensure that individuals are taking the correct dose of methadone and the importance of screening and treating co-occurring substance use disorders. Among individuals at high risk of accidental overdose, buprenorphine could be considered as a first-line treatment (31). However, methadone has been shown to be superior to buprenorphine in retaining patients in treatment (32), and replications of our reported finding of increased accidental overdose risk associated with methadone are required before changes to routine practice are recommended.

Strengths and Limitations

The strengths of this observational study include its large sample size, testing across multiple adverse outcomes, and a within-individual design that accounted 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 effect of contact with medical services, such as psychosocial interventions provided at the same time the medications were taken. This may be particularly relevant in relation to lower rates of suicidal behavior in the methadone cohort, since Swedish guidelines recommend monthly nursing appointments for opioid medications. However, the heterogeneity of the findings across different medications and outcomes would argue against health care 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. Additionally, we found no significant associations for suicidal behavior or accidental overdoses when we used penicillin and adrenergic inhalants as negative controls. However, there were reductions associated with any crime with adrenergic inhalants, which could suggest nonspecific treatment effects for this outcome.

Differences in service provision may affect the generalizability of our findings. The rates of illicit opioid use are similar across the United States and Sweden (1.5% of the population in the United States, and 1.8% in Sweden) (33, 34). However, only 15%–20% of individuals with opioid use disorder are estimated to receive opioid treatment in the United States (35) compared with more than 70% in Sweden (36). Results could be affected by a potential bias toward the null due to misclassification of exposures or outcomes. On the other hand, this should reduce the hazard ratios

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 nontreatment periods), we did not have data on medication adherence. This problem is similar to nonadherence in clinical trials, and thus the within-individual estimate is comparable to an intention-to-treat analysis. However, individuals who take opioid medication receive their daily dose under medical supervision for at least the first 6 months of treatment, ensuring adherence. Furthermore, distinguishing suicidal behavior from accidental overdoses is challenging (37), and some deaths by suicide 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 may be overestimated.

Suicide risks in the naltrexone cohort may have been diluted because our data did not distinguish whether the indication for treatment was alcohol or opioid use disorder. In Sweden, naltrexone is only approved for treating alcohol use disorder, although a proportion may have been prescribed off-label. Moreover, 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, however, were independently associated with increased hazard ratios for suicidal behavior in the acamprosate and naltrexone cohorts. These findings require further examination in other settings, because 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 have led to underestimation of true outcome rates and possibly involved selection effects.

CONCLUSIONS

In this study of individuals prescribed medications for alcohol or opioid use disorder in Sweden, we found potentially important associations with reduced suicidal behavior and criminality. If validated using other designs, evidence-based pharmacologic treatment has the potential to reduce the substantial burden of morbidity among individuals with substance use disorders.

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REFERENCES

1. Degenhardt L, Hall W: Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet 2012; 379:55–70
2. Bennett T, Holloway K, Farrington D: The statistical association between drug misuse and crime: a meta-analysis. Aggress Violent Behav 2008; 13:107–118
3. Dowell D, Arias E, Kochanek K, et al: Contribution of opioid-involved poisoning to the change in life expectancy in the United States, 2000–2015. JAMA 2017; 318:1065–1067
4. United Nations Office on Drugs and Crime: World Drug Report 2015 (United Nations publication sales number E.15.XI.6). New York, United Nations
5. Brady KT, McCauley JL, Back SE: Prescription opioid misuse, abuse, and treatment in the United States: an update. Am J Psychiatry 2016; 173:18–26
6. Guy GP Jr, Zhang K, Bohm MK, et al: Vital signs: changes in opioid prescribing in the United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017; 66:697–704
7. World Health Organization: Atlas on Substance Use: Resources for the Prevention and Treatment of Substance Use Disorders. Geneva, World Health Organization, 2010
8. Jonas DE, Amick HR, Feltner C, et al: Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 2014; 311:1889–1900
9. Woody GE: Current progress in opioid treatment. Am J Psychiatry 2017; 174:414–416
10. Mattick RP, Breen C, Kimber J, et al: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2009; (3):CD002209
11. Metrebian N, Groshkova T, Hellier J, et al: Drug use, health and social outcomes of hard-to-treat heroin addicts receiving supervised injectable opiate treatment: secondary outcomes from the Randomized Injectable Opioid Treatment Trial (RIOTT). Addiction 2015; 110:479–490
12. Perry AE, Neilson M, Martyn-St James M, et al: Pharmacological interventions for drug-using offenders. Cochrane Database Syst Rev 2015; (6):CD010862
13. Dennis BB, Roshanov PS, Naji L, et al: Opioid substitution and antagonist therapy trials exclude the common addiction patient: a systematic review and analysis of eligibility criteria. Trials 2015; 16:475
14. Viktorin A, Lichtenstein P, Thase ME, et al: The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry 2014; 171:1067–1073
15. Allison PD: Fixed Effects Regression Models. Washington, DC, Sage, 2009

16. National Council for Crime Prevention [Brottsförebyggande Rådet]: Criminal statistics, Official Statistics of Sweden 2014 [Kriminalstatistik 2014]. Stockholm, BRÅ Rapport 2015:16 ISSN 1100-667; 2015
17. Takanen M: Treatment of patients with alcohol use disorder–local instruction 2012-11-19. Edited by Szabó I. The Stockholm Centre for Dependency Disorders, Stockholm County Council, 2012. [Behandling av patienter med alkoholberoende–lokal instruktion 2012-11-19] ([Beroendecentrum, Stockholms Läns Landsting])
18. Uppström D: Pharmacological treatment of opioid dependence–local instruction 2013-02-06. Edited by Eriksson N. The Stockholm Centre for Dependency Disorders, Stockholm County Council, 2013. [Läkemedelsassisterad behandling vid opiatberoende–okal instruktion 2013-02-06] ([Beroendecentrum, Stockholms Läns Landsting])
19. Zalsman G, Hawton K, Wasserman D, et al: Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry 2016; 3:646–659
20. Yovell Y, Bar G, Mashiah M, et al: Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. Am J Psychiatry 2016; 173:491–498
21. Turner BJ, Austin SB, Chapman AL: Treating nonsuicidal self-injury: a systematic review of psychological and pharmacological interventions. Can J Psychiatry 2014; 59:576–585
22. Michel L, Lions C, Van Malderen S, et al: Insufficient access to harm reduction measures in prisons in 5 countries (PRIDE Europe): a shared European public health concern. BMC Public Health 2015; 15:1093
23. Hedrich D, Alves P, Farrell M, et al: The effectiveness of opioid maintenance treatment in prison settings: a systematic review. Addiction 2012; 107:501–517
24. Chang Z, Lichtenstein P, Långström N, et al: Association between prescription of major psychotropic medications and violent reoffending after prison release. JAMA 2016; 316:1798–1807
25. Kleber HD: Pharmacologic treatments for opioid dependence: detoxification and maintenance options. Dialogues Clin Neurosci 2007; 9:455–470
26. Bakker A, Fazey C: Methadone tolerance testing in drug misusers. BMJ 2006; 333:1056–1059
27. Lutfy K, Cowan A: Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol 2004; 2:395–402
28. Kunøe N, Lobmaier P, Ngo H, et al: Injectable and implantable sustained release naltrexone in the treatment of opioid addiction. Br J Clin Pharmacol 2014; 77:264–271
29. Ritter AJ: Naltrexone in the treatment of heroin dependence: relationship with depression and risk of overdose. Aust N Z J Psychiatry 2002; 36:224–228
30. Lee JD, Friedmann PD, Kinlock TW, et al: Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. N Engl J Med 2016; 374:1232–1242
31. Kimber J, Larney S, Hickman M, et al: Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. Lancet Psychiatry 2015; 2:901–908
32. Mattick RP, Breen C, Kimber J, et al: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014; (2):CD002207
33. Degenhardt L, Bucello C, Calabria B, et al: What data are available on the extent of illicit drug use and dependence globally? results of four systematic reviews. Drug Alcohol Depend 2011; 117:85–101
34. The Public Health Agency of Sweden (Folhälsomyndigheten): The 2013 National Report (2012 data) to the EMCDDA by the Reitox National Focal Point Sweden: New Development and Trends. Statens Folkhälsoinst A 2013; 02:2013
35. Saloner B, Karthikeyan S: Changes in substance abuse treatment use among individuals with opioid use disorders in the United States, 2004–2013. JAMA 2015; 314:1515–1517
36. National Board of Health and Welfare [Socialstyrelsen]: An investigation of opioid replacement therapy. [Kartläggning av läkemedelsassisterad behandling vid opiatberoende]. National Board of Health and Welfare [Socialstyrelsen] ISBN 978-91-87169-88-52012
37. Stone DM, Holland KM, Bartholow B, et al: Deciphering suicide and other manners of death associated with drug intoxication: a Centers for Disease Control and Prevention consultation meeting summary. Am J Public Health 2017; 107:1233–1239
38. McCall WV, Benca RM, Rosenquist PB, et al: Hypnotic medications and suicide: risk, mechanisms, mitigation, and the FDA. Am J Psychiatry 2017; 174:18–25