Supplemental Methods

Treatment periods

In line with clinical prescribing practice, acamprosate and naltrexone treatment periods were defined as a series of collected prescriptions (i.e. dispensed) with no more than 15 days between two consecutive collected prescriptions (1). For opioid medications, treatment periods were defined as a series of collected prescriptions with no more than 8 days between two consecutive collected prescriptions. This definition was used as individuals are not allowed to personally collect more than seven daily doses of opioid medications during one week (2). To ensure that guidelines were applied in real life practice, we examined treatment patterns by assessing the median number of days between two consecutive opioid prescriptions among all individuals who collected at least two prescriptions within six months (Mdn=6.7 IQR=4.9-7.8).

In Sweden, methadone is predominately prescribed to individuals with opioid use disorder, although it is also approved for the treatment of severe pain. Buprenorphine is approved only for treating opioid use disorder. For both methadone and buprenorphine, pharmacological treatment is combined with psychosocial interventions (3). Swedish guidelines for methadone and buprenorphine treatment are similar to international guidelines; supervised administration through approved programs is required, there is no time-limit on treatment duration, and treatment is initiated on an outpatient-basis in most cases (4).

Individuals receive their daily dose of methadone or buprenorphine under medical supervision at an addiction treatment center for at least six months before personally collecting the medication at a pharmacy (5). During this time, their prescriptions are collected by the center and dispensed to them at the center. All of

these prescriptions are still registered to the individual patient in the Swedish Prescribed Drug Register, and are thus traceable through this register. However, between 13% (in 2009) and 32% (in 2013) of methadone and buprenorphine prescriptions dispensed at the addiction treatment centers were clinic-based acquisitions, with no individual patient links to the Swedish Prescribed Drug Register (6).

Measures

Alcohol and opioid use disorder medications

In this study, we examined associations for five medications approved in Sweden for the treatment of alcohol or opioid use disorder; acamprosate, naltrexone, methadone, and buprenorphine/buprenorphine-naloxone combination. We did not include disulfiram in our analysis as we could not establish a clear definition of exposure due to inconsistent prescription patterns in our data. Clinical prescription practices for disulfiram vary - it is recommended to be dispensed three times per week at a clinic. However, because some individuals may have difficulties to attend frequent appointments, disulfiram may be dispensed at other time intervals, through company health services, or directly to the individual at the pharmacy. Nalmefen was not approved for use in Europe until 2013, and therefore not included in our analyses.

Suicidal behavior

Information on treatment for suicidal behavior was collected from the Swedish Patient Register, which includes the primary diagnoses listed in 99% of all cases (7).

Information on death for suicidal behavior was collected from the Cause of Death Register (8). This register had a 98.9% coverage on causes of death in 2013 (9).

For treatment of suicidal behavior, only diagnoses received during unplanned (i.e. emergency) visits were used in our analyses, and diagnoses received during planned visits (i.e. booked appointments, follow-ups, and referrals) were excluded. Although this is a more conservative approach, we used it to avoid overestimation of diagnoses, as the diagnosis that is the reason for treatment initiation is also coded during follow-ups and referrals, regardless of current symptoms.

Crimes

For crimes, we used arrests, rather than convictions, as our primary outcome. The reason for this is that a large number of investigations tend to be dropped by the prosecution, such as when an individual has committed several crimes or when they are already serving a sentence for another crime. This includes mainly substance-related crimes, thefts, and assaults (10), which were common in our cohorts. Furthermore, the decision to discontinue criminal proceedings may or may not be influenced by the charged person being treated for their substance use disorder. Both arrests and convictions were divided into three crime categories: 1) Violent crime, defined as crimes against the person, and included attempted or completed homicide or manslaughter, assault resulting in death, unlawful threats, harassment, gross violation of integrity, gross violation of woman's integrity, kidnapping, unlawful deprivation of liberty, unlawful coercion, attempted or completed rape and aggravated rape, sexual assault, sexual molestation, indecent exposure, procurement, purchase of a sexual act from a minor, exploitation of a minor for sexual posing, sexual coercion, incest, sexual abuse against minor, grooming,

robbery and aggravated robbery, arson and aggravated arson, child pornography crimes, assault and aggravated assault, and assault on an official; 2) Substance-related crime, defined as manufacturing alcohol, driving under the influence of alcohol or illicit substances, smuggling illicit substances, manufacturing illicit substances, supplying illicit substances, possession of illicit substances, and personal use of illicit substances; 3) Non-violent crime, defined as all offences other than violent crimes and substance-related crimes.

Demographic measures

Information on age, sex, civil status, employment, disability pension, and social welfare payments was extracted from the Longitudinal Integration Database for Health Insurance and Labour Market Studies. This register provides annual data for all individuals aged 16 years and older residing in Sweden (11). Information on migration was collected from the Migration Register (12), and information on periods in prison or youth care was identified in the Prison Register (13).

Lifetime psychiatric and substance use disorders

Lifetime rates of psychiatric and substance use disorders were identified from the Patient Register as a lifetime inpatient or outpatient hospital or specialized secondary care visit coded with a substance use disorder diagnosis, including alcohol, opioids, cannabinoids, sedatives or hypnotics, cocaine, other stimulants, hallucinogens, other psychoactive substances or multiple drug use (ICD-8: 291, 303, 304; ICD-9: 291, 303, 304, 305A, 305X; ICD-10: F10-16, F19), or psychotic disorders (ICD-8: 295, 297, 298, 299; ICD-9: 295, 297, 298, 301.2; ICD-10: F20-29), or bipolar disorder (ICD-8: 296; ICD-9: 296; ICD-10: F30-31).

Sensitivity analyses

Suicidal behavior

To examine if accidental overdoses were miss-classified as suicidal behavior, suicidal behavior was divided into suicidal behavior by poisoning (ICD10: X60-X69), and suicidal behavior by other methods (ICD10: X70-X8) in sensitivity analyses.

Antidepressants and benzodiazepines

In sensitivity analyses of suicidal behavior, adjustments were made for concurrent use of antidepressants (ATC: N06A) and benzodiazepines (ATC: N05B, N05C), respectively. This was done as the prescription of these medications may affect associations with suicidal behavior (14, 15). Antidepressant and benzodiazepine prescriptions are typically restricted to three months at a time (16). For both medications, treatment periods were thus defined as a series of collected prescriptions with no more than six months between two consecutive collected prescriptions (17). The start of a treatment period was defined as the first date of a collected prescription, and the end of a treatment period was defined as the date of the last collected prescription in that treatment period. Periods of more than six months between collected prescriptions were considered as non-treatment periods. A new treatment period was considered to have started at the first date of the next series of consecutive collected prescriptions.

Negative controls

In further sensitivity analyses, we tested for long-term (i.e. penicillin) and short-term (i.e. adrenergic inhalants) non-specific treatment effects by using penicillin (ATC: JC01) and adrenergic inhalants such as albuterol/salbutamol (ATC: R03A) as separate exposures among individuals treated with methadone and/or buprenorphine. For penicillin, treatment periods were defined as a series of collected prescriptions with no more than 8 days between two consecutive collections. For adrenergic inhalants, treatment periods were defined as a series of collected prescriptions with no more than 6 months between two consecutive collections (as per previous work (18)).

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Supplemental Table 1. Sensitivity analyses: Hazard rates of primary outcomes, excluding individuals who started treatment within three months after experiencing the studied outcome.

Outcome	Hazard ratio	95% CI	P-value	Number of individuals left in the analyses
ACAMPROSATE				
Suicidal behavior	0.98	0.82-1.17	0.784	9,872
Accidental overdoses	0.88	0.80-0.99	0.038	9,410
Any arrest	0.95	0.85-1.06	0.317	9,503
Arrests for violent crimes	0.81	0.59-1.12	0.201	10,149
NALTREXONE				
Suicidal behavior	0.80	0.67-0.95	0.009	4,128
Accidental overdoses	0.74	0.64-0.87	0.000	3,913
Any arrest	0.85	0.74-0.97	0.018	3,978
Arrests for violent crimes	0.74	0.52-1.07	0.109	4,301
BUPRENORPHINE				
Suicidal behavior	0.63	0.30-1.28	0.2010	3,252
Accidental overdoses	0.65	0.52-0.81	0.000	3,044
Any arrest	0.78	0.72-0.84	<0.000	2,189
Arrests for violent crimes	0.71	0.55-0.92	0.009	3,004
METHADONE				
Suicidal behavior	0.57	0.38-0.85	0.006	5,276
Accidental overdoses	1.05	0.95-1.16	0.3518	4,796

Any arrest	0.87	0.83-0.92	<0.000	3,991
Arrests for violent crimes	0.91	0.79-1.06	0.2252	4,935

Supplemental Table 2. Sensitivity analyses: Hazard rates of suicidal behavior adjusted for, or excluding, concurrent antidepressant use, and suicidal behavior by poisoning or by other methods.

Outcome	Hazard ratio	95% CI	P-value	Number of events
ACAMPROSATE				
Suicidal behavior, adj. for concurrent treatment with antidepressants	1.06	0.89-1.27	0.278	3,940
Suicidal behavior, excl. individuals treated with antidepressants	1.36	0.87-2.12	0.174	1,581
Suicidal behavior by poisoning	1.02	0.83-1.24	0.883	3,233
Suicidal behavior by other methods	1.02	0.65-1.59	0.946	745
NALTREXONE				
Suicidal behavior, adj. for concurrent treatment with antidepressants	0.89	0.76-1.06	0.184	3,425
Suicidal behavior, excl. individuals treated with antidepressants	0.79	0.44-1.43	0.436	1,327
Suicidal behavior by poisoning	0.84	0.66-1.06	0.141	2,298
Suicidal behavior by other methods	0.93	0.72-1.19	0.563	1,179
BUPRENORPHINE				
Suicidal behavior, adj. for concurrent treatment with antidepressants	0.58	0.28-1.17	0.129	829

Suicidal behavior, excl. individuals treated with antidepressants	1.06	0.40-2.86	0.905	625
Suicidal behavior by poisoning	0.46	0.21-1.03	0.059	665
Suicidal behavior by other methods	0.58	0.11-3.02	0.514	172
METHADONE				
Suicidal behavior, adj. for concurrent treatment with antidepressants	0.62	0.57-0.68	<0.000	882
Suicidal behavior, excl. individuals treated with antidepressants	0.55	0.49-0.63	<0.000	116
Suicidal behavior by poisoning	0.66	0.60-0.73	<0.000	747
Suicidal behavior by other methods	0.14	0.09-0.23	<0.000	144

Supplemental Table 3. Sensitivity analyses: Hazard rates of primary outcomes in individuals treated with buprenorphine or methadone, excluding individuals who had also been treated with acamprosate.

Outcome	Hazard ratio	95% CI	P-value	Number of events
BUPRENORPHINE†				
Suicidal behavior	0.60	0.30-1.23	0.166	794
Accidental overdoses	0.76	0.61-0.94	0.014	2,804
Any arrest	0.78	0.72-0.85	<0.000	25,384
Arrests for violent crimes	0.66	0.51-0.86	0.002	3,852
METHADONE††				
Suicidal behavior	0.60	0.41-0.89	0.011	850
Accidental overdoses	1.25	1.13-1.38	<0.000	4,105
Any arrest	0.86	0.82-0.90	<0.000	24,485
Arrests for violent crimes	0.82	0.71-0.94	0.006	3,701

† Excluding 65 individuals who were also treated with acamprosate

†† Excluding 63 individuals who were also treated with acamprosate

Supplemental Table 4. Sensitivity analysis: Hazard rates of primary outcomes during penicillin or adrenergic inhalant treatment periods among individuals with any opioid treatment (i.e. methadone and/or buprenorphine).

Outcome	Hazard ratio	95% CI	P-value	Number of events
PENICILLIN				
Suicidal behavior	0.83	0.04-16.42	0.902	146
Accidental overdoses	0.67	0.19-2.38	0.538	713
Any arrest	0.94	0.55-1.61	0.833	4,451
Arrests for violent crimes	0.51	0.06-4.60	0.548	667
ADRENERGIC INHALANTS				
Suicidal behavior	1.16	0.73-1.84	0.521	304
Accidental overdoses	1.01	0.80-1.26	0.968	1,074
Any arrest	0.71	0.65-0.78	<0.000	5,985
Arrests for violent crimes	0.84	0.65-1.08	0.178	937

Supplemental Table 5. Sensitivity analyses: Hazard rates of suicidal behavior adjusted for, or excluding, concurrent benzodiapzepine use, and benzodiazepine use as exposure.

Outcome	Hazard ratio	95% CI	P-value	Number of events
ACAMPROSATE				
Benzodiazepines as exposure	1.54	1.34-1.76	<0.000	3,940
Suicidal behavior, adj. for concurrent treatment with benzodiazepines	1.09	0.92-1.30	0.314	3,940
Suicidal behavior, excl. individuals treated with benzodiazepines	1.06	0.66-1.70	0.813	1,456
NALTREXONE				
Benzodiazepines as exposure	1.45	1.28-1.64	<0.000	3,425
Suicidal behavior, adj. for concurrent treatment with benzodiazepines	0.92	0.78-1.09	0.321	3,425
Suicidal behavior, excl. individuals treated with benzodiazepines	0.92	0.59-1.43	0.706	1,207
BUPRENORPHINE				
Benzodiazepines as exposure	1.24	0.97-1.60	0.085	829
Suicidal behavior, adj. for concurrent treatment with benzodiazepines	0.64	0.32-1.26	0.197	829
Suicidal behavior, excl. individuals treated with benzodiazepines	1.00	0.37-2.65	0.993	532

METHADONE				
Benzodiazepines as exposure	0.89	0.66-1.19	0.426	882
Suicidal behavior, adj. for concurrent treatment with benzodiazepines	0.62	0.43-0.91	0.014	882
Suicidal behavior, excl. individuals treated with benzodiazepines	0.78	0.44-1.38	0.387	551

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Methods section of the Abstract, page 1]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Results section of Abstract, page 1]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Introduction page 1]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[pages 1-2]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Methods page 2]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Methods pages 2-3]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Methods pages 2-3]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Methods pages 2-3 and Suppl. Methods]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Methods pages 2-3 and Suppl. Methods]**
Bias	9	Describe any efforts to address potential sources of bias **[Statistical analyses pages 3-4]**
Study size	10	Explain how the study size was arrived at **[N/A – Cohort study]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Statistical analyses pages 3-4 and Suppl. Methods]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Statistical analyses pages 3-4]**
		(*b*) Describe any methods used to examine subgroups and interactions **[Statistical analyses pages 3-4 and Suppl. Methods]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) If applicable, explain how loss to follow-up was addressed **[Statistical analyses page 3]**
		(*e*) Describe any sensitivity analyses **[Sensitivity analyses pages 3-4 and Suppl. Methods]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Results page 3]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Results page 4 and Figure 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) Summarise follow-up time (eg, average and total amount) **[Results page 4]**

Outcome data	15*	Report numbers of outcome events or summary measures over time **[Tables 2-3, Suppl. Tables 1-5]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Results pages 4-6, Tables 2-3, Suppl. Tables 1-5]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[Results pages 5-6, Suppl. Tables 1-5]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Discussion page 6]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Discussion pages 7-8]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Discussion pages 6-8]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Discussion page 8]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Page 8]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.