Harms associated with taking nalmefene for substance use and impulse control disorders: A systematic review and meta-analysis of randomised controlled trials

Karina Glies Vincents Johansen[1]*, Simon Tarp[1], Arne Astrup[2], Hans Lund[3,4], Anne K. Pagsberg[5], Robin Christensen[1]

1 Musculoskeletal Statistics Unit, The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, 2 Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark, 3 Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, 4 Centre for Evidence-based Practice, Bergen University College, Bergen, Norway, 5 Child and Adolescent Mental Health Centre, Mental Health Services Capital Region of Denmark & Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark

* k_vincents@hotmail.com

Abstract

Importance

Nalmefene is a newly approved drug for alcohol use disorder, but the risk of harms has not been evaluated from empirical trial evidence.

Objective

To assess the harm of nalmefene administered to individuals diagnosed with substance use or impulse control disorders by performing a systematic review and meta-analysis of randomised controlled trials.

Data sources

A search was performed in Cochrane Central Register of Controlled Trials (CENTRAL, 2014), MEDLINE via PubMed (1950), EMBASE via Ovid (1974), and Clinicaltrials.gov through December 2014.

Study selection

This study included only randomised controlled trials with placebo or active controls that administered nalmefene to adult individuals for treating impulse control and/or substance use disorders. Both published and unpublished randomised controlled trials were eligible for inclusion.

Data extraction and synthesis

Internal validity was assessed using the Cochrane risk-of-bias tool. Published information from the trials was supplemented by contact between reviewers and industry sponsor. Data

pathological gambling. Am J Psychiatry 2006 Feb;163(2):303-12. van den Brink W, Sorensen P, Torup L, Mann K, Gual A. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. J Psychopharmacol 2014 Mar 26;28(8):733-44. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry 1999 Aug;56(8):719-24. Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, et al. A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcohol Clin Exp Res 1994 Oct;18(5):1162-7. Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol 2004 Aug;24(4):421-8. Mann K, Bladstrom A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomised controlled study of as-needed nalmefene. Biol Psychiatry 2013 Apr 15;73 (8):706-13. Gual A, He Y, Torup L, van den Brink W, Mann K. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol 2013 Nov;23(11):1432-42. whose authors may be contacted by email.

were combined using two meta-approaches in fixed effects models; Peto Odds Ratios and risk differences were reported with 95% confidence intervals (95%CIs).

Main outcomes and measures

Number of patients with serious adverse events, including specific psychiatric serious adverse events and withdrawals due to adverse events.

Results

Of 20 potentially relevant studies, 15 randomised controlled trials met the inclusion criteria, and 8 of these provided data enabling the meta-analysis. Overall, serious adverse events did not occur more often in the nalmefene group than in the placebo group (Peto Odds Ratio = 0.97 [95% CI 0.64–1.44]; P = 0.86). Risk of psychiatric serious adverse events was slightly elevated, albeit not at a statistically significant level (Peto Odds Ratio = 1.32 [95% CI 0.62, 2.83]; P = 0.47). Withdrawals due to adverse events were significantly more likely to occur with nalmefene compared to placebo (Peto Odds Ratio = 3.22 [95% CI 2.46–4.22]; P<0.001)

Conclusions and relevance

The three-fold increased risk of withdrawal from treatment on nalmefene due to adverse events is a matter of safety concern. The nature of these adverse events cannot be elucidated further without access to individual patients data.

Introduction

Impulse control and substance use disorders are diagnostically separate mental illnesses that, however, share similar features of pathological behaviours [1]. Impulse control disorder (which include kleptomania, pathological gambling, pyromania, and intermittent explosive disorder) are "behavioural addictions" characterized by behaviours and urges that are harmful to oneself and impair social and occupational function as well as incur legal and financial difficulties [2,3]. Substance use disorder is an addiction characterized by a craving or a strong desire or urge to use a substance (e.g., drug, alcohol, or nicotine), which leads to clinically significant impairment or distress [4]. DSM-5 regards impulse control and substance use problems as disorders [4], and pharmacological intervention (e.g., with opioid antagonists) is one of the suggested opportunities for treatment [4].

Because adverse reactions from prescription drugs are so frequent, leading to 4.7% hospital admissions in the US, pharmacological treatment of impulse control and substance use disorders may lead one to infer adverse or serious adverse events (SAEs). An adverse event is considered serious by the investigator and sponsor of the trial if any of the following outcomes occur: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect [5]. In 1998, 2.7 million hospitalized Americans experienced SAEs from prescription drugs [6]. Furthermore, mortality from adverse drug reactions is 0.32%, constituting the fourth leading cause of death in US hospitals [7,8]. Nalmefene hydrochloride dehydrate (nalmefene) is an opioid antagonist and was approved by the European Medicines Agency (EMA) in 2012 to reduce alcohol consumption in patients with alcohol dependence. To date, no systematic review and meta-

analysis has been performed regarding harm (SAEs psychiatric SAE or withdrawal due to adverse events (WD d/t AE) associated with use of nalmefene for substance use and impulse control disorders. Most of the systematic reviews investigate the effect of treating alcohol dependence with different drugs [9–16] without addressing the potential harm (e.g., SAEs and WD d/t AE). According to the EMA's nalmefene assessment report, oral nalmefene 18 mg/day is a well-tolerated and efficacious dose and overall, there were no SAEs causing major safety concern [17]. The report emphasizes that individuals with depressive or psychotic comorbidities were excluded from the different clinical trials investigating nalmefene; estimates of the potential psychiatric SAEs of the drug, therefore, are likely conservative [17–20].

In light of the likely increase in drug prescriptions and after approval of nalmefene by EMA (currently no marketing authorization request to the US Food and Drug Administration), we performed a systematic review and meta-analysis of RCTs comparing nalmefene with placebo or active controls to assess nalmefene's potential for causing harms.

Methods

The definition of harm is "the totality of possible adverse consequences of an intervention or therapy; they are the direct opposite of benefits, against which they must be compared"[5]. Harms in the present study refer to SAEs, psychiatric SAEs or WD d/t AE.

An event refers to the overall number of SAE, psychiatric SAE or WD d/t AE, in the studies and is thus not necessarily an expression of any pathological causality between nalmefene and a specific effect.

The systematic review and the meta-analysis were performed according to the '*Preferred Reporting Items for Systematic reviews and Meta-Analyses*' (PRISMA) guidelines for reporting systematic reviews and meta-analyses [21]. The protocol is registered and available on PROS-PERO (CRD42014015279).

Selection criteria and search strategy

This study included RCTs with placebo or active controls that administered nalmefene to individuals for treating impulse control and/or substance use disorders. We sought all placebo- and active-controls RCTs of nalmefene at any dose for any duration in humans. Both published and unpublished RCTs were eligible for inclusion in the systematic review. If the RCTs had data on harms, the RCTs were eligible for inclusion in the meta-analysis.

Online clinical registries and four bibliographic databases—Cochrane Central Register of Controlled Trials (CENTRAL, (2014); MEDLINE via PubMed (1950); EMBASE via Ovid (1974); and Clinicaltrials.gov—were searched through December 2014 for RCTs investigating the effect and safety of nalmefene compared to any control group. The search strategy is available from the protocol **S1 File**.

Online documents available from EMA regarding nalmefene were identified and scrutinized for data not available in scientific publications. All RCTs relating nalmefene to substance use or impulse control disorders were identified. Furthermore, the reference lists of all apparently relevant review articles and included studies were manually searched to identify other potentially relevant RCTs. One reviewer (KGVJ) screened all references by titles and abstracts according to the eligibility criteria. Full text papers were retrieved for further assessment if the abstract information suggested that the study compared nalmefene with placebo or an active comparator and included participants with impulse control or substance use disorders. Two reviewers (KGVJ, ST) assessed full-text papers for the systematic review.

Data collection, data items, and risk-of-bias assessment

Data were extracted by one reviewer (KGVJ) and confirmed by a second reviewer (ST). Primary outcome measures were extracted as the overall number of nonspecific SAEs, defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use events [5], both in the nalmefene and in the control groups. Secondary outcomes are specific SAEs (e.g. all cause mortality) and specific psychiatric SAEs emphasizing depression, anxiety, suicidal attempts, suicidal ideation, and suicide. Furthermore, data were extracted on WD d/t AE. For exploratory qualitative purposes, all types of SAEs reported in the different trials were also extracted. We included all the aforementioned outcomes regardless of whether or not we believed that SAEs, psychiatric SAEs or WD d/t AE were related or not to drug treatment.

The Cochrane risk-of-bias tool was used to assess whether there was high, low, or unclear risk of bias in the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting [22]. KGVJ and ST assessed the risk of bias independently for all included studies. Discrepancies were resolved by referring to the original publications and discussing with a third reviewer (RC). Study characteristics based on condition, trial duration, and number of participants (including doses and the percentage of males participating) were abstracted from the eligible trials.

Statistical analyses

We described study characteristics according to sample size and characteristics of study participants, including mental illness condition (e.g. substance use disorder or impulse control disorder) and trial duration. Review Manager (5.3) was used to conduct all the meta-analyses. Because our outcomes of interest are rare, we followed recommendations of Bradburn and colleagues [23] and used Peto odds ratios (PORs) under fixed effects models to compare nalmefene and placebo/active comparator groups. We also undertook meta-analyses using Mantel-Haenszel risk differences (RD) under fixed effects models. We present results using both a relative measure as PORs and an absolute measure as RD. We reported results using 95% confidence intervals (95%CIs) and forest plots for both measures so that findings can be compared. Statistical heterogeneity was assessed with the I-squared statistic [24]; we assigned adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively [25]. A relevant study-level covariate was defined a priori as one that was able to decrease the between-study variance (tau-squared, and thus the I-squared statistic)[24]. Risk of bias across RCTs was assessed by using stratified analyses for each of the domains included in the risk-of-bias tool [22].

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study and there are no plans to involve the patients in the dissemination of the results.

Results

The bibliographic searches identified 795 references, and after removal of 323 duplicates across the different data sources, 472 titles and abstracts were screened (**Fig 1**). From these, 441 records were excluded based on abstract and title (93%). Of the remaining 31 records **S2 File**, a further 11 full-text articles were excluded based on the eligibility criteria. Thus, 20 records were identified as potentially eligible RCTs retrieved for further scrutiny **S2 File**. Two of the 20 records [26,26,27] were spinoff papers of two already included RCTs [19,28]. One record that
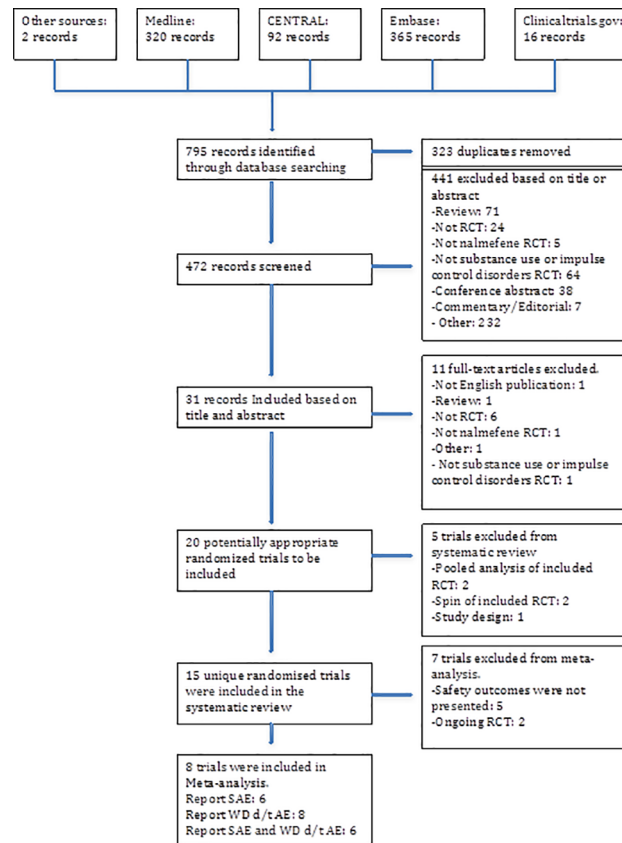
Fig 1. Flow chart showing selection of randomized controlled trials for inclusion in systematic review of nalmefene.

https://doi.org/10.1371/journal.pone.0183821.g001

was simply excluded from the study since the record wasn't an RCT [29,29], and two other RCTs were pooled analyses of included RCTs [30,31].

Ultimately, eight studies were used as the basis of the statistics on harms from nalmefene [19,20,32–37]. 15 fulfilled eligibility requirements [18–20,28,32–38,38–41] but were further whittled down to 8 because of missing data on harms.

Table 1 illustrates the study characteristics and the risk-of-bias assessment of the 15 RCTs included in the systematic review. From these 15 RCTs, two were ongoing studies [39,41].

The remaining 13 completed RCTs, undertaken between 1994 and 2014, were multicenter studies, with a total of 3,793 participants (based on the intention-to-treat populations) assessed. The mean age for participants in the included studies ranged from 30.3 to 51.6 years. In the included studies, most of the participants were male; the majority ranged from 58 to 81%. Trial durations varied from one day to 52 weeks, and the participants received either 5–100 mg/day nalmefene or 25–50 mg/day of naltrexone, or placebo. Of the 15 completed RCTs, five did not report on SAEs or WD d/t AE [17,18,28,38,38,40]. Eight RCTs were included in the meta-analysis [19,20,32–37]. All eight RCTs reported WD d/t AE. Six RCTs, reported both on SAEs and WD d/t AE [19,32–34,36,37]. Two of these eight RCTs did not report on SAEs, and data could not be identified through other sources; hence we deemed these two RCTs [20,35] a high risk of selective-outcome-reporting bias. Three of the eight RCTs used as-treated data instead of intention-to-treat data and therefore were considered high risk of incomplete-data bias [32,36,37].

Table 1. Study characteristics including the risk of bias assessment of randomised controlled trials of nalmefene included in the systematic review.

Author, Year, (Ref) Included in the meta-analysis*	Outcomes Included in meta-analysis	Condition	Trial duration (Weeks)	No. of patients randomised	Male (%)	Mean age year	Risk of bias Δ	Opioid antagonist	Daily dose (mg)	No. of patients
Anton et al 2004	WD d/t AE	Alcohol Use Disorder	12	270	210	45.0	U/U/U/U/I	Nalmefene	40	68
CPH-101-0299					(78)			Nalmefene	20	66
[35](*)								Nalmefene	5	68
								Placebo	0	68
Grant et al 2006	WD d/t AE	Gambling Disorder	16	207	116	45.9	A/U/U/U/I	Nalmefene	100	52
[20](*)					(56)			Nalmefene	50	52
								Nalmefene	25	52
								Placebo	0	51
Gual et al 2013	SAE	Alcohol Use Disorder	24	718	503	44.8	A/A/A/I/A	Nalmefene	18	358
NCT 00812461	Anxiety				(70)			Placebo	0	360
(ESENSE 2)	Depression									
[37](*)	WD d/t AE									
Karhuvaara et al 2007	SAE	Alcohol Use Disorder	28	403	326	49.2	A/A/A/A/U	Nalmefene	10–40	242
CPH-101-0801	WD d/t AE				(81)			Placebo	0	161
[19](*)										
Mann et al 2013	SAE	Alcohol Use Disorder	24	604	405	51.6	A/A/A/I/A	Nalmefene	18	306
NCT00811720	Anxiety				(67)			Placebo	0	298
(ESENSE 1	Depression									
[36](*)	WD d/t AE									
Mason et al.1994	SAE	Alcohol Use Disorder	12	21	15	42.0	U/A/U/U/A	Nalmefene	40	7
[34](*)	WD d/t AE				(71)			Nalmefene	10	7
								Placebo	0	7
Mason et al 1999	SAE	Alcohol Use Disorder	12	105	70	41.8	U/A/U/A/A	Nalmefene	20–80	70
[33](*)	WD d/t AE				(67)			Placebo	0	35
Van den brink et al 2014	SAE	Alcohol Use Disorder	52	675	506	44.3	A/A/A/I/A	Nalmefene	18	499
(SENSE)	Anxiety				(75)			Placebo	0	163
NCT00811941	Depression									
[32](*)	WD d/t AE									
Grant et al 2010	NA	Gambling Disorder	10	233	135	46.5	A/U/U/U/I	Nalmefene	40	82
[18]					(58)			Nalmefene	20	77
								Placebo	0	74
Drobes et al.2000	NA	Alcohol Use Disorder	1	25	20	35.1	U/U/U/U/I	Naltrexone	NA	NA
[40]					(80)			Nalmefene	NA	NA
								Placebo	0	NA

(*Continued*)

Table 1. (*Continued*)

Author, Year, (Ref)	Outcomes Included	Condition	Trial duration	No. of patients	Male	Mean age	Risk of bias	Opioid antagonist	Daily dose	No. of patients
Included in the meta-analysis*	in meta-analysis		(Weeks)	randomised	(%)	year	Δ		(mg)	
Drobes et al.2003	NA	Group a)	1	125	NA	30.3	A/U/U/U/I	Naltrexone	25–50	39
[28]		Alcohol Use Disorder						Nalmefene	20–40	36
								Placebo	0	50
		Group b)	1	90	NA	32.0	A/U/U/U/I	Nalmefene	25–50	29
		social drinkers						Nalmefene	20–40	31
								Placebo	0	30
Somaxon pharmaceuticals	NA/on	Smoking Use Disorder	5	NA	NA	NA	NA	Nalmefene	80	NA
[39]								Nalmefene	40	NA
								Placebo	0	NA
Lundbeck A/S 2014	NA/on	Alcohol Use Disorder	1+1day	100	NA	NA	NA	Nalmefene	18	NA
[41]								Placebo	0	NA
Biotie	NA	Alcohol Use Disorder	28	167	NA	NA	NA	Nalmefene	40	82/3
CPH-101-0701								Nalmefene	20	NA
[38]								Nalmefene	10	NA
								Placebo	NA	85
Biotie	NA	Alcohol Use Disorder	16	150	NA	NA	NA	Nalmefene	40	50
CPH-101-0399								Nalmefene	10	50
[38]								Placebo	0	50

ΔRisk of bias: sequence generation/concealment of allocation/blinding of participants and investigators/incomplete outcome data/selective outcome data. A = Adequate (low risk of bias); U = Unclear (unclear risk of bias); I = Inadequate (high risk of bias). NA = data not available. DSM-5 = Diagnostic and Statistical Manual of Mental Disorders. SAE = serious adverse event. WD d/t AE = withdrawal due to adverse event.

* Included in the meta-analysis.

The objectives of the available studies in the meta-analysis were to examine the safety and efficacy of nalmefene for reducing alcohol consumption in alcohol-dependent patients [33–37], to evaluate the long-term efficacy and safety of nalmefene in reducing alcohol consumption [32], to determine the effect and safety of nalmefene in reducing heavy drinking [19], and to examine the efficacy and tolerability/safety of nalmefene in reducing of pathological gambling [20].

Harms observed

Six of the ultimately eight RCTs that were used as the basis of the statistics on harms from nalmefene reported SAEs (**Fig 2**). Forest plot of odds (Peto odds ratio) and risk (Mantel-Haenszel risk difference) of serious adverse event associated with nalmefene use compared to placebo. Every square represents the individual study's serious adverse events estimates with 95% CI indicated by horizontal line. We found no evidence of increased odds of SAEs in the nalmefene group compared with the placebo group. The Peto Odds (POR) for nalmefene versus placebo was POR 0.97 (95% CI 0.64 to 1.44; P = 0.86; I^2 = 18%), and the Risk difference (RD) was -0.00 (-0.02 to 0.01; P = 0.84; I^2 = 0%). There was no reason to suspect a rejection of the hypothesis of homogeneity based on the P value in the POR method Q = 3.65; P = 0.30.
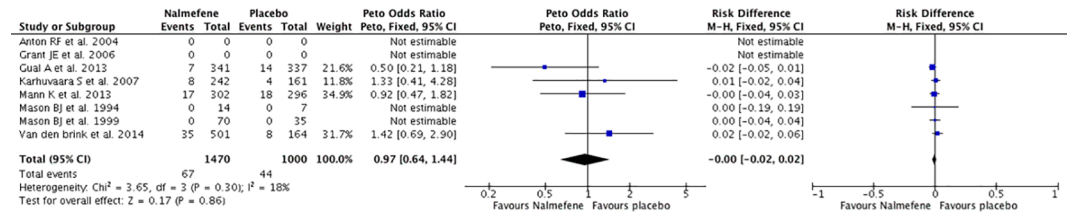
Fig 2. Serious adverse events of nalmefene compared to placebo in patients with substance use or/and impulse control disorder.

https://doi.org/10.1371/journal.pone.0183821.g002

Three out of the six RCTs that reported SAEs categorized SAEs into different sub-disorders such as psychiatric disorders or death. To analyse secondary harm outcomes, we used the overall number of psychiatric SAEs **S1 Fig**; the POR for nalmefene versus placebo was POR 1.32 (95% CI 0.62 to 2.83; P = 0.47, I^2 = 40%). The RD was 0.00 (-0.01 to 0.01; P = 0.40, I^2 = 72%). In other words, we found no evidence of increased odds of overall psychiatric SAEs in the nalmefene group compared with the placebo group. Based on the Cochrane Q statistic test, homogeneity among the studies was present according to the p-value in the POR method Q = 3.33, P = 0.19. However, the analysis showed a moderate degree of inconsistency among the study findings according to their I^2 values.

After we have analysed the overall number of psychiatric SAEs we subcategorized psychiatric SAEs into depression, anxiety, and mortality (including completed suicide and sudden death). Of the six studies mentioned above, three reported depression; the POR was 5.48 (95% CI 0.28 to 106.79; P = 0.26, I^2 = 0%). The RD was 0.00 (-0.01 to 0.01; P = 0.60, I^2 = 0%). For anxiety; the POR was 3.77 (95% CI 0.04 to 355.81; P = 0.57, I^2 = Not applicable. Hence, only one study reported events on anxiety). The RD was 0.00 (-0.00 to 0.00; P = 0.87, I^2 = 0%). Mortality, including suicide and sudden death, was reported in three RCTs (total 1/1144) in the nalmefene group and 2/797 in the placebo group). The POR for mortality was 0.50 (95% CI 0.05 to 4.85; p = 0.55, I^2; = 63%) and the RD was -0.00 (-0.01 to 0.01; P = 0.93, I^2 = 0%). Based on the Cochrane Q statistic test, homogeneity among the studies was present Q = 2.68; P = 0.10. We found no evidence of an increased risk of depression, anxiety, or death in the nalmefene group compared with the placebo group. A list of all different reported SAEs in the included studies is presented in **S1 Table.**

Eight RCTs in the meta-analysis reported WD d/t AE (**Fig 3**)**.** Forest plot of odds (Peto odds ratio) and risk (Mantel-Haenszel risk difference) of withdrawals due to adverse events associated with nalmefene use compared to placebo. Every square represents the individual study's withdrawals due to adverse events estimates with 95% CI indicated by horizontal line; the POR was 3.22 (95% CI 2.46 to 4.22; P<0.00 I^2; = 0%). The RD was 0.09 (0.08 to 0.11; P = 0.00, I^2 = 86%). Based on the Cochrane Q statistic test, homogeneity among the studies was present according to the p-value in the POR method Q = 3.69; P = 0.81.
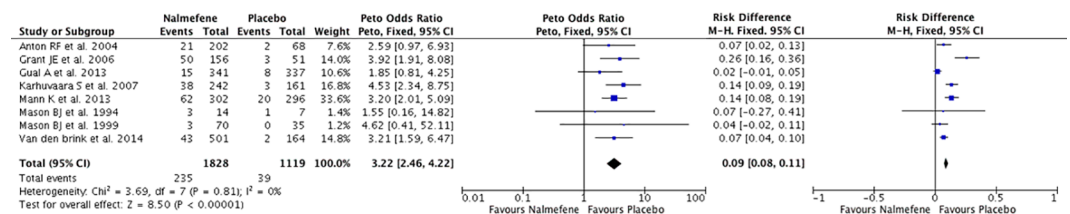

Fig 3. Withdrawals due to adverse events of nalmefene compared to placebo in patients with substance use or/and impulse control.

https://doi.org/10.1371/journal.pone.0183821.g003

Additional analyses

The risk of bias across RCTs according to the major outcome (SAE) was assessed by using subgroup analyses for each of the five domains: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting stated in the Cochrane risk-of-bias tool, including if the RCTs were using the as-treated or intention-to-treat principle **S2 Table**. The subgroups' differences for sequence generation, allocation concealment, and blinding were not applicable because all the included studies provide data only in the adequate categorizations in the above mention domains. For Intention to treat (P = 0.57), incomplete outcome data (P = 0.57), and selective outcome reporting (P = 0.57), the differences among the groups were not significant.

Even if there are similarities as indicated in the diagnostics, the abuse of alcohol can very well have changed or modulated biology so that response to a drug and also potential WD t/t AE. Since the risk of WD d/t AE was more than 3 times likely for the patient in the nalmefene group than for the placebo group, a subgroup analysis stratified in two groups, substance use disorder and impulse control disorder was made **S2 Fig**. The subgroup differences for the two groups were P = 0.57; I^2 = 0%, the differences between the two groups were not significant.

Discussion

This meta-analysis of eight RCTs involving 1,828 patients with substance use or impulse control disorder who were prescribed nalmefene and 1,119 patients who were prescribed placebo found no increased risk of SAEs compared to placebo. However, patients taking nalmefene were 3.22 times more likely to discontinue therapy due to side effects compared to placebo. In the WD d/t AE stratified analysis, no statistical differences among the two groups were observed.

Treatment with nalmefene did not increase risk of death when compared to placebo. The overall psychiatric SAEs apparently occurred more frequently, but not statistically significantly in the nalmefene group compared to placebo. In the risk-of-bias stratified analyses, no statistical differences among the different groups in the risk-of-bias tool were observed.

Comparison with other studies

Currently there is no systematic review and meta-analysis report on SAEs associated with use of nalmefene for substance use or impulse control disorders. Two meta-analyses by Jones et al. and Rösner et al. reported on the effect of different pharmaceutical treatments for alcohol dependence and included an analysis of WD d/t AE [10,15]. Jonas et al. included 135 studies, seven of which compared nalmefene with placebo [10,11]. Compared with placebo, participants treated with nalmefene or naltrexone had a higher risk of WD d/t AE. In one study two participants in placebo group committed suicide. In another trial one patient allocated to the placebo group died of hepatocellular carcinoma and one patient randomised to nalmefene died suddenly for unknown causes. In studies comparing nalmefene with placebo, four cases of suicide attempts or suicidal ideation in nalmefene group and 9 in placebo group were reported. Rösner et al. included 50 RCTs, including three studies comparing nalmefene to placebo (13). Compared to the placebo group, patients in the nalmefene group had a 43% higher risk of WD d/t AE. The dropout rates were not statistically significant [15]. SAEs were not reported as an outcome or calculated in that meta-analysis. Our meta-analysis has shown a similar trend according to withdrawals due to adverse events in the nalmefene group compared to placebo group.

Strengths and limitations

To the best of our knowledge, ours is the most comprehensive systematic review and meta-analysis of harm associated with using nalmefene to treat impulse control and substance use disorders.

Our systematic review was rigorously performed and reported according to the PRISMA statement [21]. A highly sensitive search strategy was used in order to identify as many relevant studies as possible and to reduce potential publication bias. An extensive range of resources was searched, including electronic databases, guidelines, and references listed in other systematic reviews. Both published and unpublished RCTs were eligible for inclusion in the systematic review and if the RCTs had data on harms, the RCTs were eligible for inclusion in the meta-analysis. We present results using both a relative measure as Peto Odds Ratio and an absolute measure as Risk Difference with a fixed effect model. We used the Cochrane risk-of-bias tool to assess the internal validity in all the included studies.

Our results were limited by a lack of access to all available sources reporting safety data, including unpublished RCTs and RCTs in progress, as well an absence in several trials of consistent reporting of psychiatric SAEs. Additionally, the secondary endpoints reported in the studies were depression, anxiety, suicidal attempts, suicidal ideation, and suicide and mortality; some of these phenomena had very different severity and clinical implications. In all the studies, the enrolled patient populations were highly selected, as patients with a history of comorbid psychiatric disorder were excluded from the studies. For these reasons, our estimates of psychiatric SAEs are probably conservative, and our results cannot be extended to populations of patients with substance use or impulse control disorders and other psychiatric comorbidity.

Many of the RCTs included in the meta-analysis were relatively small and short-term, resulting in few events; our study, therefore, was not able to effectively discuss the risk for further SAEs in larger studies. The limited number of events resulted in PORs that could be affected by small changes in the classification of events and may have caused problems concerning heterogeneity in the meta-analysis. The confidence intervals for the PORs for SAEs, WD d/t AE, and deaths were wide, resulting in considerable uncertainty about the magnitude of the observed odds.

We did not have full access to all original source data, and we based the meta-analysis on available data from publications. However, we found two RCTs in the Selincro assessment report [17] and in the Biotie Therapies Corp. update [38]. These RCTs had not yet been published; hence, we weren't able to include them in the meta-analysis together with the risk-of-bias analysis. Two RCTs had not been completed—one for using nalmefene for smoking cessation and one for using nalmefene to treat alcohol dependence [39,41]. Ongoing RCTs may provide useful data, which could have increased the probability for significance within our primary and/or secondary results had it been possible to include them [39,41].

According to our objective, the two domains—*selective outcome reporting* and *incomplete outcome data*—were both considered as important domains in the risk-of-bias tool. Based on these tools, five RCTs had high risk of bias from selective outcome reporting and an unclear risk of bias from incomplete outcome data. Another three RCTs had a high risk of bias from incomplete outcome data, resulting in as-treated data's being used. The proportion of information from RCTs at high risk of bias in the key domains was sufficient to affect the interpretation and validity of the result. Some of the results were not applicable because some outcomes were not estimable in some of the groups, which decreased the reliability of our study's results.

The manufacturers' and authors' public disclosure of safety results for nalmefene RCTs were not sufficient to enable a robust assessment of specifically the risk of SAEs from

nalmefene. The manufacturers and authors have available all source data for completed RCTs and should make these data available due to ethical considerations. If more manufacturers and authors chose to strictly follow good clinical practice (GCP), harmonization of technical requirements for registration of pharmaceuticals for Human Use (ICH) and the CONSORT Statement for better reporting of harm in randomised trials [5], then market transparency will increase, resulting in greater chances for improved validity.

Conclusions and clinical implications

Based on our systematic review of published RCTs, there is no evidence of an increased risk of SAEs including psychiatric SAEs and death from any cause associated with treatment with nalmefene for substance use and impulse control disorders. Nalmefene users, however, have an increased risk of WD d/t AE, which are consistent with findings from other systematic reviews. However, this conclusion is based upon a highly selected group of patients; a more representative selection procedure may not rule out the possibility of more adverse events. This risk seems to be supported by an "increased risk of WD d/t AE," which likely reflects the ultimate decision of the participant and physician to quit the intervention due to side effects.

The findings of our meta-analysis suggest a risk of WD d/t AE associated with use of nalmefene compared to placebo, but the risk of SAEs remains unclear until more precise estimates of SAEs associated with nalmefene treatment in patients suffering from substance use or impulse control disorder has become available. Further studies are needed to enable a more robust assessment of the harm of nalmefene. Large RCTs with more participants in both groups and a balance in the number of participants in the groups, comparing placebo with nalmefene, reporting on both SAEs and WD d/t AE, with use of Intention-to-treat data are strongly recommended to strengthen the evidence base for treatment with nalmefene.

Supporting information

S1 File. Trial protocol—Harms associated with use of nalmefene for substance use and impulse control disorder: Protocol for a systematic review and meta-analysis of randomised trials.
(PDF)

S2 File. Reference list of all 31 full text papers included based on title and abstract.
(DOCX)

S3 File. PRISMA-Checklist.
(DOC)

S1 Table. Exploratory table of all serious adverse events reported in all the selective studies.
(DOCX)

S2 Table. Results of risk-of-bias stratified meta-analyses for serious adverse event(s) (Peto Odds Ratio). * NE = not estimable. NA = Not applicable.
(DOCX)

S3 Table. Available data set *NA = Not applicable.
(DOCX)

S1 Fig. Psychiatric serious adverse events on nalmefene compared to placebo in patients with substance use or/and impulse control disorder.
(TIF)

S2 Fig. Subgroup analysis of withdrawal due to adverse events.
(PNG)

Author Contributions

Conceptualization: KGVJ RC HL.

Data curation: KGVJ ST RC.

Formal analysis: KGVJ ST.

Investigation: KGVJ ST.

Methodology: KGVJ RC.

Supervision: AKP AS HL.

Writing – original draft: KGVJ.

Writing – review & editing: ST AS HL AKP.

References

1. World Health Organization (2014) ICD-10 Version:2014.

2. Grant JE, Potenza MN (2004) Impulse control disorders: clinical characteristics and pharmacological management. Ann Clin Psychiatry 16: 27–34. PMID: 15147110

3. Schreiber L, Odlaug BL, Grant JE (2011) Impulse control disorders: updated review of clinical characteristics and pharmacological management. Front Psychiatry 2: 1. https://doi.org/10.3389/fpsyt.2011.00001 PMID: 21556272

4. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5. 947 p.

5. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D (2004) Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 141: 781–788. PMID: 15545678

6. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279: 1200–1205. PMID: 9555760

7. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329: 15–19. https://doi.org/10.1136/bmj.329.7456.15 PMID: 15231615

8. van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH, Sturkenboom MC (2008) Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf 17: 365–371. https://doi.org/10.1002/pds.1565 PMID: 18302300

9. Gowing L, Ali R, White JM (2010) Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database Syst Rev CD002022. https://doi.org/10.1002/14651858.CD002022.pub3 PMID: 20091529

10. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC (2014) Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings. AHRQ. NBK208590 [bookaccession].

11. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC (2014) Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 311: 1889–1900. https://doi.org/10.1001/jama.2014.3628 PMID: 24825644

12. Keating GM (2013) Nalmefene: a review of its use in the treatment of alcohol dependence. CNS Drugs 27: 761–772. https://doi.org/10.1007/s40263-013-0101-y PMID: 23949908

13. Kjellberg F, Tramer MR (2001) Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaesthesiol 18: 346–357. PMID: 11412287

14. Mann K (2004) Pharmacotherapy of alcohol dependence: a review of the clinical data. CNS Drugs 18: 485–504. 1882.

15. Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M (2010) Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev CD001867. https://doi.org/10.1002/14651858.CD001867.pub2 PMID: 21154349

16. Srisurapanont M, Jarusuraisin N (2005) Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev CD001867. https://doi.org/10.1002/14651858.CD001867.pub2 PMID: 15674887

17. European Medicines Agency (2012) Assessement report Selincro. 1–73.

18. Grant JE, Odlaug BL, Potenza MN, Hollander E, Kim SW (2010) Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. Br J Psychiatry 197: 330–331. https://doi.org/10.1192/bjp.bp.110.078105 PMID: 20884959

19. Karhuvaara S, Simojoki K, Virta A, Rosberg M, Loyttyniemi E, Nurminen T, Kallio A, Makela R (2007) Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin Exp Res 31: 1179–1187. https://doi.org/10.1111/j.1530-0277.2007.00401.x PMID: 17451401

20. Grant JE, Potenza MN, Hollander E, Cunningham-Williams R, Nurminen T, Smits G, Kallio A (2006) Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. Am J Psychiatry 163: 303–312. https://doi.org/10.1176/appi.ajp.163.2.303 PMID: 16449486

21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62: e1–34. https://doi.org/10.1016/j.jclinepi.2009.06.006 PMID: 19631507

22. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928. https://doi.org/10.1136/bmj.d5928 PMID: 22008217

23. Bradburn MJ, Deeks JJ, Berlin JA, Russell LA (2007) Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 26: 53–77. https://doi.org/10.1002/sim.2528 PMID: 16596572

24. Thompson SG, Higgins JP (2002) How should meta-regression analyses be undertaken and interpreted? Stat Med 21: 1559–1573. https://doi.org/10.1002/sim.1187 PMID: 12111920

25. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–560. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

26. Drobes DJ, Anton RF, Thomas SE, Voronin K (2004) Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. Alcohol Clin Exp Res 28: 1362–1370. PMID: 15365307

27. Arias AJ, Armeli S, Gelernter J, Covault J, Kallio A, Karhuvaara S, Koivisto T, Makela R, Kranzler HR (2008) Effects of opioid receptor gene variation on targeted nalmefene treatment in heavy drinkers. Alcohol Clin Exp Res 32: 1159–1166. https://doi.org/10.1111/j.1530-0277.2008.00735.x PMID: 18537939

28. Drobes DJ, Anton RF, Thomas SE, Voronin K (2003) A clinical laboratory paradigm for evaluating medication effects on alcohol consumption: naltrexone and nalmefene. Neuropsychopharmacology 28: 755–764. https://doi.org/10.1038/sj.npp.1300101 PMID: 12655322

29. Jones HE, Johnson RE, Fudala PJ, Henningfield JE, Heishman SJ (2000) Nalmefene: blockade of intravenous morphine challenge effects in opioid abusing humans. Drug Alcohol Depend 60: 29–37. PMID: 10821987

30. Grant JE, Kim SW, Hollander E, Potenza MN (2008) Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. Psychopharmacology (Berl) 200: 521–527. https://doi.org/10.1007/s00213-008-1235-3 PMID: 18581096

31. van den Brink W, Aubin HJ, Bladstrom A, Torup L, Gual A, Mann K (2013) Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. Alcohol Alcohol 48: 570–578. https://doi.org/10.1093/alcalc/agt061 PMID: 23873853

32. van den Brink W, Sorensen P, Torup L, Mann K, Gual A (2014) Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. J Psychopharmacol 28: 733–744. https://doi.org/10.1177/0269881114527362 PMID: 24671340

33. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB (1999) A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry 56: 719–724. PMID: 10435606

34. Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, Mantero-Atienza E (1994) A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcohol Clin Exp Res 18: 1162–1167. PMID: 7847600

35. Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, McCaul ME, Anthenelli R, Salloum I, Galloway G, Garbutt J, Swift R, Gastfriend D, Kallio A, Karhuvaara S (2004) A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol 24: 421–428. PMID: 15232334

36. Mann K, Bladstrom A, Torup L, Gual A, van den Brink W (2013) Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry 73: 706–713. https://doi.org/10.1016/j.biopsych.2012.10.020 PMID: 23237314

37. Gual A, He Y, Torup L, van den Brink W, Mann K (2013) A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol 23: 1432–1442. https://doi.org/10.1016/j.euroneuro.2013.02.006 PMID: 23562264

38. Edison Investment Research (2011) Biotie Therapies Corp. Update 21 June 2011.

39. Somaxon Pharmaceuticals I (2015) Somaxon Pharmaceuticals Reports Positive Results From a Pilot Phase 2 Study of Oral Nalmefene in Smoking Cessation.

40. Drobes DJ, Anton RF (2000) Drinking in alcoholics following an alcohol challenge research protocol. J Stud Alcohol 61: 220–224. PMID: 10757131

41. H.Lundbeck A/S (2015) Effects of Nalmefene After Single Dose on the Blood Oxygen Level Dependent (BOLD) fMRI Signal in the Ventral Striatum to Reward Responding in the Monetary Incentive Delay Task (MIDT), in Non-treatment Seeking Subjects With Alcohol Dependence Following Alcohol Challenge.