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# SERIOUS ADVERSE EVENTS REPORTED IN PLACEBO RANDOMISED CONTROLLED TRIAL OF ORAL NALTREXONE: REVIEW AND META-ANALYSIS

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**Abstract:**

*Naltrexone is actually an opioid antagonist applied in several conditions, either licensed or unlicensed. It is implemented at extensively different dosages from 3 to 250 mg. The objective of this analysis was to broadly examine the safeness of oral naltrexone by evaluating the potential risk of severe adverse events and negative events in random operated studies of naltrexone compared to placebo.*

*A thorough search of the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, different database sources and clinical studies registries was attempted up to May 2018. Parallel placebo-controlled random controlled studies lengthier as compared to 4 weeks released after 1 January 2001 of oral naltrexone at any dosage had been chosen. Any concern or population was incorporated, eliminating only reviews in opioid or ex-opioid individuals due to potential opioid/opioid antagonist relationships. The organized review utilized the direction of the Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-analyses damages variety all through. Numerical data had been separately drawn out by two individuals and cross-checked. Chance of bias was evaluated with the Cochrane risk of-bias tool. Meta-analyses had been carried out in R implementing random impacts brands throughout.*

*Eighty-nine random regulated studies with 11,194 individuals were discover, researching alcohol use disorders (n = 38), different psychiatric disorders (n = 13), impulse control disorders (n = 9), other harmful habits such as smoking (n = 18), obesity or eating disorders (n = 6), Crohn's disease (n = 2), fibromyalgia (n = 1) and cancers (n = 2). Twenty-six reviews (4,960 individuals) registered severe adverse events occurring by arm of study. There was no proof of enhanced threat of severe adverse events for naltrexone when compared with placebo (risk ratio 0.84, 95% confidence interval 0.66–1.06). Sensitivity examines combining risk variations recognized this realization (risk difference −0. 01, 95% confidence interval −0.02–0.00) and subgroup examines demonstrated that results were continuous across various dosages and disease groups. Secondary evaluation unveiled only 6 partially important adverse events for naltrexone in comparison to placebo, that were of moderate seriousness.*

*Naltrexone does not appear to increase the risk of serious adverse events over placebo. These findings confirm the safety of oral naltrexone when used in licensed indications and encourage investments to undertake efficacy studies in unlicensed indications.*

**Keywords:** *Naltrexone, Serious events, Review, Low dose naltrexone*

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## INTRODUCTION:

Naltrexone is the natural opioid antagonist along with exercise at several opioid and non-opioid human receptors. Its certified applications are as a possible assistance to counteract relapse in alcohol usage disorders (AUDs) and opioid craving just after withdrawal, and through the combination tablet naltrexone–bupropion for morbid obesity. These circumstances are typical leading global health issues, with increasing rates of impairment and death happening in many countries. Despite issue in regards to the impact of these illnesses along with the demand for cures, naltrexone is presently under-utilised across most states, especially for AUDs. At average or above doses (≥50 mg), naltrexone normally used off-label for many problems and impulse control ailments that already have no licensed medications, such as amphetamine and cocaine addiction, impulse control disorders, eating imbalance and autism spectrum imbalance. Subsequent experimental conclusions that low doses of naltrexone lead to tumour growth inhibition and immune modulation, it can be progressively used at doses of around 4.5 mg. This is called low dose naltrexone (LDN). Small-scale clinical studies of LDN have already been performed in, as an example, Crohn's disease, multiple sclerosis, fibromyalgia and HIV infection, in which the evidence has revealed effectiveness and/or low toxicity.

### Naltrexone and identified Safety Considerations

Naltrexone is contra-indicated in those presently utilizing opioids as a result of the probability of severe adverse events (SAEs) of either over-rapid opioid withdrawal or overdose of opioids, and this can be life-threatening. These SAEs are connected with a various nature from those happening in non-opioid consumers. Issues about naltrexone leading to the liver toxicity are derived from several high-dose researches (up to 300 mg) in the 1980s. Known side effects consist of nausea, vomiting, abdominal pain, lowered appetite, dizziness, lethargy, headaches and sleep disorders.

### Clinical Trials and Drug Safety

The quality of tracking and reporting of damage in clinical trials has traditionally been less demanding in contrast to efficacy. Development remains aided by the introduction of standard descriptions for adverse events; the necessity to maintain comprehensive details of adverse events (AEs) in clinical studies, introduced in 2001; the International Committee of Medical Journal Editors' recommendation of the reporting criteria recommended in the Consolidated Standards of Reporting Trials (CONSORT) extension for threats released in 2004, and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) threats listing released in 2016; and the necessity to record effects, such as AEs and SAEs, for RCTs licensed on clinical trials registries since 2014 in the European Union (EU) and 2017 in the USA.

### Review Purpose

The primary purpose of this analysis ended up being to analyze SAEs happening in clinical studies of oral naltrexone, provided for any concern aside from opioid or ex-opioid use, as compared to placebo. Authors' concentrate on SAEs accords with the recent importance on comprehending and controlling lasting or enduring patient problems (rather than examining every AE). Further objectives had been to look into possible confounders of risk of SAEs for naltrexone by subgroup critiques of disease group, measure and amount of research; to analyze particular SAEs (deaths, cardiovascular or cerebrovascular events and cancers); and to analyze withdrawals and withdrawals as a consequence of AEs in the equivalent clinical studies. An additional objective was to examine AEs for naltrexone compared to placebo.

## METHODS:

The review followed the Cochrane Handbook for guidance throughout and the PRISMA harms extension. The protocol was registered on the PROSPERO website in January 2017.

### Selection criteria

Any parallel-designed RCT longer than 4 weeks, in participants of any age and for any condition, in which oral naltrexone was compared to placebo was included. Studies in which opioid or ex-opioid use was specified in the protocol were excluded owing to the possibility of opioid/ opioid antagonist interactions occurring. Only studies published after 1 January 2001 were included, owing to the widespread introduction of regulations requiring the recording of AEs and reporting of SAEs in RCTs from that year.

### Outcomes

The primary outcome measure was the number of participants with an SAE recorded in the naltrexone arm compared to the placebo arm. The investigator's judgement as to whether an SAE had occurred and any causality was followed. The secondary outcome was the type of AEs reported in either treatment arm.

### Search Approaches for Identification of Studies

The following electronic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed MEDLINE, EMBASE (via

OVID), Web of Science Core Collection, PsycINFO (via OVID) and International Pharmaceutical Abstracts via OVID. There were no language restrictions. No terms for AE or side effects were included to avoid over-restrictive selection of studies with the potential risk of outcome reporting bias. The final date of searches was May 2018. Further sources were relevant systematic reviews containing clinical trials of naltrexone, and journal articles being assessed for inclusion in this review. The World Health Organization International Clinical Trials Registry, the US clinical trials registry, clinicaltrials.gov and the European Union Clinical Trials Registry EudraCT were searched online using the word "naltrexone". These are good sources of unpublished but completed clinical trials. Where a study appeared unpublished, the lead investigator was contacted to confirm this was so. Ongoing studies were recorded, to enable future updating of this systematic review.

**Data collection and management**

All testing and data retrieval had been performed by two researchers independently (MB and SB for screening and MB and AM for data extraction), and outcomes were in comparison with draw up an ultimate list. Any variations were fixed by discourse, with periodic feedback from a third reviewer (HvM, MP, SR or LR). Preliminary testing eliminated researches employing the title and abstract, with complete reports analyzed to choose the final incorporated studies.

Data had been registered on data extraction forms. Quantitative data for the primary and secondary outcomes, enrolment numbers and withdrawals (numbers and reasons), SAEs (both number of participants with an SAE and total number of SAEs, and descriptions) and AEs (total numbers per Medical Dictionary for Regulatory Activities (MedDRA) preferred term) were extracted onto an Excel spreadsheet. Website appendices, subsidiary studies and any published protocols were examined for relevant information. Results on clinicaltrials.gov and on EudraCT were cross-checked with the data available in the study report.

**Quality assessment**

The Cochrane risk-of-bias tool was adapted for the outcome measures in this review, highlighting eight areas of trial conduct and reporting. The CONSORT extension for harms was used to inform the choice of criteria. The areas chosen were:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel to randomisation (performance bias)
- Blinding of outcome assessment (detection bias)
- Adequate outcome data reporting (attrition bias)
- Adequate collection of AEs and SAEs (attrition bias)
- Adequate reporting of SAEs (reporting bias)
- Other bias (e.g. commercial sponsorship, placebo run-in periods)

**Studies with multiple treatment groups**

Studies trialling several medication or treatments (e.g. drug plus naltrexone compared to drug, or a four-arm factorial design) were incorporated when there had been a suitable placebo arm for review with naltrexone. Research which has a secured mixture of naltrexone and an additional drug where the comparator was a single placebo have not been incorporated. This ruled out the combination tablet of slow-release naltrexone–bupropion. In studies with several naltrexone arms and simply one placebo arm (e.g. if various dosages of naltrexone were trialled), data from the placebo arm were segregated on the lines of the naltrexone arms by the levels of individuals employed to every naltrexone arm. This prevented any double counting of the placebo arm. In trials with multiple psychotherapeutic interventions in different arms, the results of these could be combined, as long as the same interventions were in the placebo arms.

**Assessment of reporting biases**

This review pursued to scale back publication bias with the help of wide-ranging search techniques, by incorporating publications which were not in English, and through looking for unreported clinical studies on clinical trials registries. Reporting bias was evaluated confidently for each meta-analysis utilizing funnel plots and the appropriate statistical analyses.

## RESULTS:

Trial flow: flow diagram and numbers The electronic searches identified 7873 citations, and a further 995 records identified from clinical trials websites (821), systematic reviews (157) and references in other papers. Deleting duplicate references reduced this to 4738 records, of which 4390 were excluded on the basis of examining the abstracts. Full-text articles were obtained for 348 citations. From these, 96 citations were excluded and 163 were subsidiary papers. Thus, 89 primary studies were identified and the numbers identified at each stage through from initial searching to quantitative analyses, and the reasons for excluding studies, are given in a PRISMA 2009 flow diagram (Fig. 1).

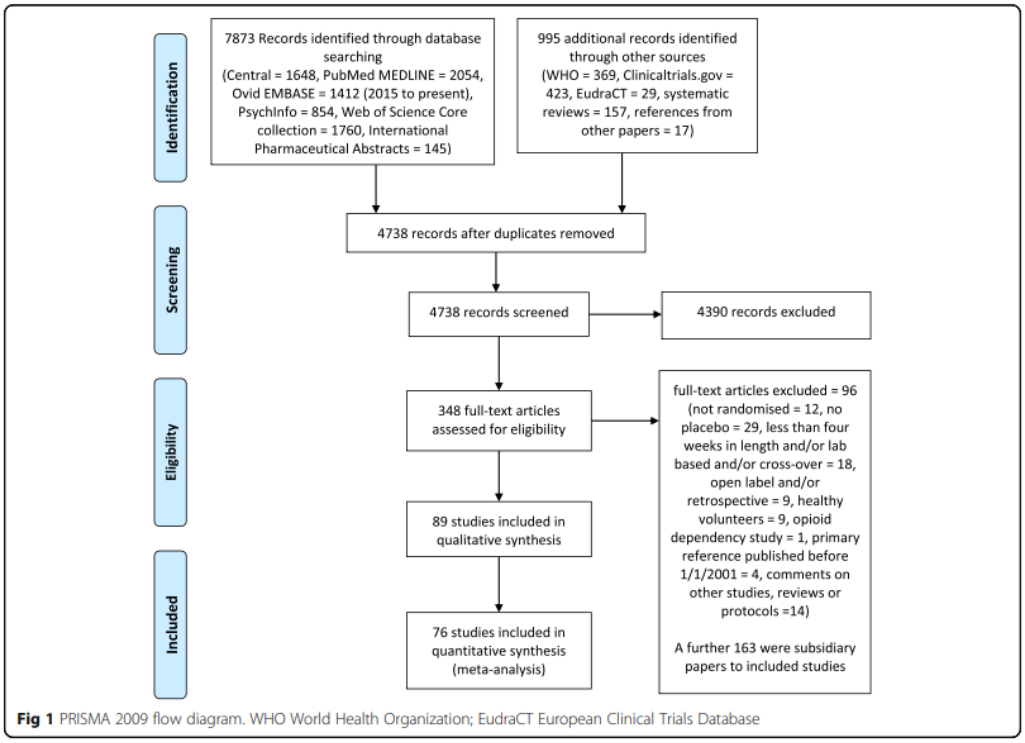


**Fig 1** PRISMA 2009 flow diagram. WHO World Health Organization; EudraCT European Clinical Trials Database

**Characteristics of included studies**

Eighty-nine studies (11,194 participants) were found that fulfilled the review criteria, including publication after 1 January 2001. Three studies were excluded because they only gave total participant numbers, leaving 86 studies (10,957 participants) from which data could potentially be extracted for analysis. Table 1 summarises the characteristics of included studies by broad categories;

**Table 1** Summary of characteristics of included studies

| Category | Characteristics of participants in study | Number of studies |
|---|---|---|
| Disease or condition | AUD | 38 |
| | Drug addiction or smoking ± AUD | 18 |
| | Psychiatric disorders ± AUD | 13 |
| | Impulse control disorders | 9 |
| | Obesity or eating disorders | 6 |
| | Inflammatory disorders | 3 |
| | malignancies | 2 |
| Target dose of naltrexone[a] (mg) | ≤4.5 | 5 |
| | 16–49 | 7 |
| | 50 | 61 |
| | 100 | 12 |
| | >100 | 8 |
| Mean age where given[b] (years) | 10 to <20 | 2 |
| | 20 to <30 | 2 |
| | 30 to <40 | 11 |
| | 40 to <50 | 62 |
| | 50 to <60 | 3 |
| | ≥60 | 2 |
| Length of study[c] (weeks) | 4–7 | 5 |
| | 8–11 | 17 |
| | 12–15 | 42 |
| | 16–25 | 18 |
| | 26–52 | 6 |

Below mentioned ***Table S1*** provides the details of each study. The target dose of naltrexone varied from 3 mg to 250 mg. The most frequent conditions were AUDs (36 studies). In a further 21 studies, including studies of HIV infection, psychiatric disorders, addictions and smoking, participants had a dual diagnosis including AUDs. Other studies were of various psychiatric disorders, impulse control disorders, other addictions, obesity, Crohn's disease, fibromyalgia and cancers.

Table S1: Characteristics of Included Studies

| Study | Conditions studied | Country | Final dose of naltrexone | Length of study | Other drugs & therapies trialled | Age mean/ median |
|---|---|---|---|---|---|---|
| Abou-Raya 2013 | fibromyalgia | Egypt | 4.5 mg | 24 weeks | | not stated |
| Ahmadi 2004 | alcohol | Iran | 50 mg | 36 weeks | counselling | 43 |
| Anton 2005 | alcohol | USA | 50 mg | 12 weeks | CBT or motivational enhancement therapy | 44 |
| Anton 2006 | alcohol | USA | 100 mg | 16 weeks | acamprosate, (4 arms, factorial) MM +/- CBI. (One arm CBI only, not included in analysis.) | median 44 |
| Anton 2011a | alcohol | USA | 50 mg | 16 weeks | 3 arms (gabapentin+NTX arm not included in this analysis), MM & CBI | 45 |
| Anton 2011b | alcohol | USA | 50 mg | 16 weeks | 3 arms (aripiprazole arm not included in analysis), MM | 48 |
| Anton 2018 | alcohol | USA | 50 mg | 16 weeks | MM | 49 |
| Balldin 2003 | alcohol | Sweden | 50 mg | 6 months | CBT or supportive therapy | 50 |
| Baltieri 2008 | alcohol | Brazil | 50 mg | 12 weeks | 3 arms (topiramate arm not included in analysis), relapse prevention counselling | 44 |
| Batki 2009 | alcohol and schizophrenia | USA | 50 mg averaged dose (directly observed intake 3 times weekly) | 12 weeks | motivational counselling | 42 |
| Brown 2009 | bipolar disorder & alcohol | USA | 50 mg | 12 weeks | CBT | 41 |
| Byars 2005 | smoking | USA | 50 mg | 12 weeks | NRT & psychosocial therapy | not stated – 18 to 65 |
| Castro 2004 | alcohol | Brazil | 50 mg | 12 weeks | brief intervention | 46 |
| Combine study research group 2003 | alcohol | USA | 100 mg | 16 weeks | acamprosate, (4 arm factorial), MM +/- CBI | 42 |
| Cook 2017 | alcohol and HIV | USA | 50 mg | 4 months | anti-retroviral treatment where appropriate clinically | 49 |
| Davidson 2004 | alcohol | USA | 50 mg | 10 weeks | brief counselling | 49 |

**Results of the quality assessment**

Twelve studies were judged to have a low risk of bias in all eight categories. These studies enrolled a total of 2,540 participants (28%). Eighteen studies (20%) were low risk for six or seven of the categories, and 14 studies (16%) were low risk in two or fewer categories.

**Prevalence and nature of serious adverse events**

In events ascribed to a particular study arm, naltrexone or placebo, a total of 315 SAEs were recorded among 260 participants. The number of participants having at least one SAE was 119 in the naltrexone arms and 141 in the placebo arms. Among the 315 SAEs, nine deaths were reported, three in the naltrexone arms and six in the placebo arms. Although examining the nature and causality of SAEs was beyond the scope of this study, wherever such data were provided, they were extracted. Our descriptive review of these limited data suggested that there were no differences between the two treatment arms in terms of the nature of SAEs. Among the included studies, AEs were reported across 20 independent comparisons. A total of 7,017 AEs (involving 188 MedDRA preferred-term events) were identified: 3,938 in the naltrexone arm and 3,079 in the placebo arm. All AEs were reported as being mild-moderate in nature.

**Statistical tests and results**

**Serious adverse events**

There was no evidence of any difference between naltrexone and placebo in the meta-analysis of RR of SAEs. A total of 31 comparisons from the 26 studies recording the number of SAEs by study arm were analysed. The pooled RR for the number of participants experiencing at least one SAE for naltrexone compared to placebo was not statistically significant (RR 0.84, 95% CI 0.66–1.06). Tests for heterogeneity showed low statistical heterogeneity (I2 = 0%). The forest plot for this result is shown in Fig. 2. The pooled RD for the number of participants experiencing at least one SAE for naltrexone compared to placebo was non-significant (RD −0.01, 95% CI −0.02–0.00). Heterogeneity was low (I2 = 7%). The forest plot for RR of death showed no increased risk of death for naltrexone over placebo (RR 0.79, 95% CI 0.33– 1.91). Although specified in the protocol, no meta-analysis of the specific SAEs due to cardiovascular or cerebrovascular events or cancers was undertaken owing to the low number of events recorded. Univariate and multivariate meta-regression analysis did not reveal any significance for any of the covariates.

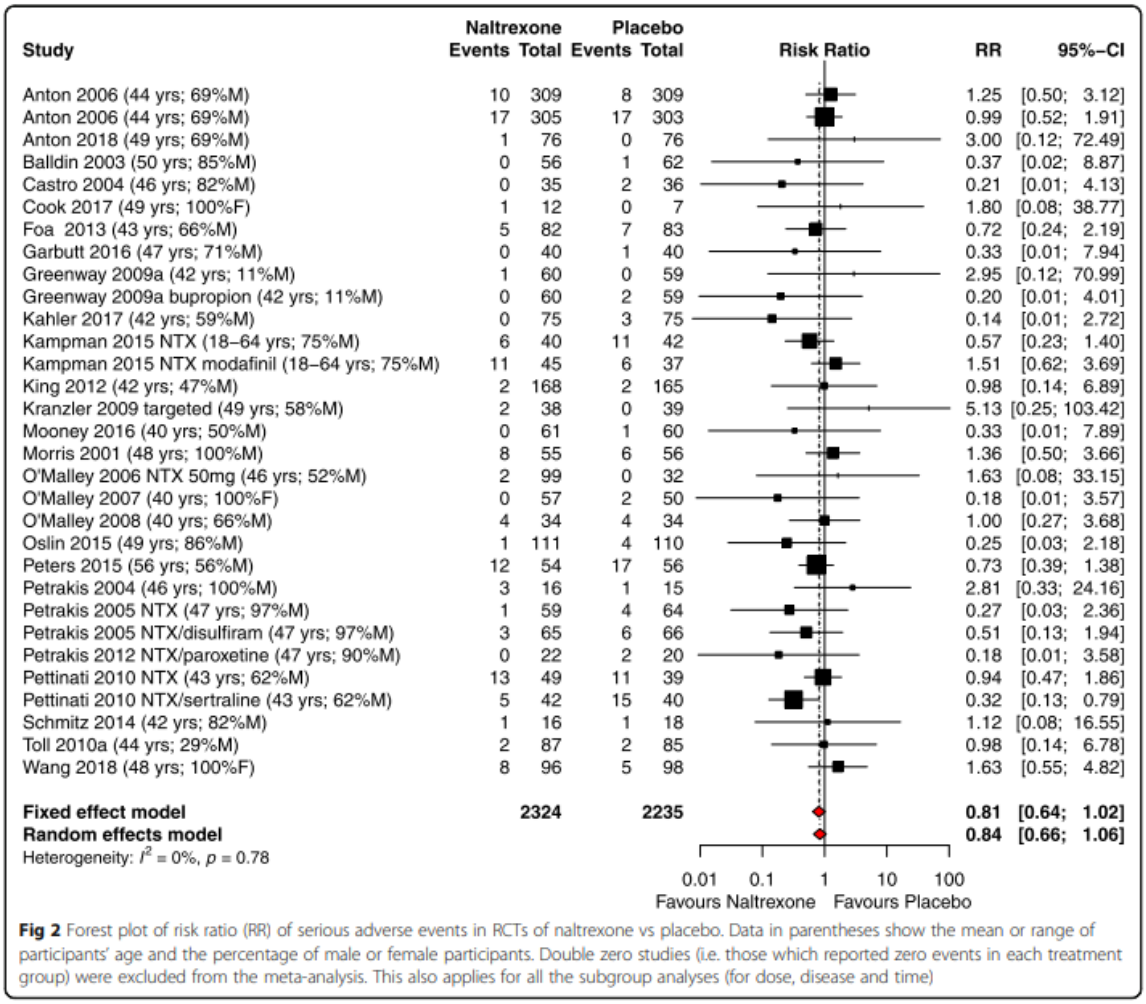


**Fig 2** Forest plot of risk ratio (RR) of serious adverse events in RCTs of naltrexone vs placebo. Data in parentheses show the mean or range of participants' age and the percentage of male or female participants. Double zero studies (i.e. those which reported zero events in each treatment group) were excluded from the meta-analysis. This also applies for all the subgroup analyses (for dose, disease and time)

**Adverse events**

A secondary analysis of 188 AEs revealed only six statistically significant MedDRA preferred-term AEs. These were decreased appetite (RR 1.44, 95% CI 1.09–1.91), dizziness (RR 1.45, 95% CI 1.15–1.83), nausea (RR 1.59, 95% CI 1.37–1.84), sleepiness (RR 1.45, 95% CI 1.07–1.97), sweating (RR 1.89, 95% CI 1.25–2.87) and vomiting (RR 1.91, 95% CI 1.51–2.42). However, sensitivity analysis revealed these to be of only mild nature and common among all patients.

**Withdrawals and withdrawals due to AEs**

There was no evidence of a difference between naltrexone and placebo in the meta-analysis of RR of withdrawals (RR 0.99, 95% CI 0.93–1.05, I 2 = 8%), whereas there was an increased risk of withdrawal due to AEs (RR 1.33, 95% CI 1.06–1.67, I 2 = 0%).

**Subgroup and sensitivity analyses**

In pre-specified subgroup analyses of RR of SAEs, there was no difference in results for different doses of naltrexone or for different disease groups/conditions. Because of the limited number of studies with dosages 15 weeks duration (RR 0.96, 95% CI 0.69–1.34, I 2 = 0%). Sensitivity analysis of the low risk of bias studies (RR 0.97, 95% CI 0.61–1.54, I 2 = 0%) showed no difference in risk compared with studies at higher risk of bias (RR 0.80, 95% CI 0.61–1.05, I 2 = 0%).

## DISCUSSION:

**Summary of main findings**

This meta-analysis of 89 RCTs based on 11,194 participants showed no evidence of an increased risk of SAEs occurring for naltrexone compared to placebo. These findings were consistent across trials with varying duration, dosages and index conditions, suggesting that naltrexone is safe to use across a wide variety of licensed and non-licensed indications. Author found that AEs such as dizziness, nausea and vomiting are potentially more common for naltrexone compared to placebo. However, this finding should be interpreted with caution because data reporting for

AEs was poor (fewer than 21 studies contributed to the AE analyses).

**Strengths and limitations**

There were several strengths of this review. One was the size, which was sufficiently large in both number of participants and number of studies that it would have enabled the detection of specific harms due to a drug. Papanikolaou and Ioannidis calculated the sample size of a systematic review needed to detect a rare event (0.25%) occurring in about 1% of subjects as 4000 subjects (80% power and $\alpha = 0.05$), and this systematic review contained over 10,000 subjects from 89 studies. In addition, this review included a broad range of studies from different countries, settings and disease groups, including patients with multiple morbidities or addictions. These latter complex scenarios more closely reflect clinical practice than the usual restrictive entry criteria of clinical trials. Hence, the relative effect size found is likely to be generalisable. Our methodology for examining the outcome measures which were not the primary outcome measures in any of the clinical trials but are now part of the standard reporting of clinical trials reduced the risk of reporting and publication bias, as did the use of clinical trials registries. It is likely that some studies inadequately reported and/or recorded SAEs.

Therefore, author checked and recorded any instances of discrepancies in data similar to previous reports. Author considers it unlikely that the missing or mis-recorded SAEs would have changed the conclusions of the meta-analysis, because there were no systematic differences between those studies adequately and inadequately reporting SAEs, and because the sensitivity analyses, particularly that including only studies with an overall low risk of bias, supported the main conclusion. There could have been under-recording of SAEs in studies with high attrition rates if follow-up was poor. Additionally, because adherence to the CONSORT extension for harms recommendations was poor in many studies, particularly in the use of standardised definitions and the descriptions of events, we were unable to undertake any qualitative analysis of results. This review was limited to studies of oral naltrexone, excluding studies involving current or prior opioid addiction or use. Our assessment of SAEs by disease group should only be considered as exploratory because classifying the populations into specific disease groups was not clear-cut owing to the predominance of AUDs even in studies of other disorders.

While the primary aim of this study was to examine SAE data from RCTs, author examined AEs in a secondary analysis, but this analysis was based on limited data identified in the journal publication and the registry report. Previous evidence has also shown that the assessment and reporting of AEs is often inconsistent and incomplete across the studies. For example, a large safety review of 44 studies of naltrexone for AUDs found that AEs were often not collected using standardised measures, that the methods for systematically capturing AEs were often not reported, and the reporting of AEs was highly selective. Recording of AEs can be hampered by the presence of nocebo (harmful) effects (i.e. worsening symptoms during placebo treatment), which can vary disease by disease. Particularly in alcohol and drug addiction, placebo and nocebo mechanisms could impact on the therapeutic outcomes and side effects of treatments. Although less likely in the recording of SAEs owing to their seriousness, this may have also impacted our results. Finally, a few refinements to the protocol were necessary, but these occurred as recommended before any data collection occurred. The main change was the exclusion of laboratory-based studies, studies of less than 4 weeks duration and cross-over studies from the review. The initial scoping exercise had not revealed the large numbers of such studies and attempting an analysis of all these would have exceeded available resources.

## CONCLUSIONS:

This systematic review and meta-analysis found no evidence of a difference in risk of SAEs for oral naltrexone compared to placebo. This evidence supports the use of naltrexone in its currently licensed form and provides solid support to contemporary efforts studying naltrexone where it is currently unlicensed.

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