Retrospective Study of Naltrexone

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Serious adverse events reported in placebo randomised controlled trials of oral naltrexone: a systematic review and meta-analysis.

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Abstract

BACKGROUND: Naltrexone is an opioid antagonist used in many different conditions, both licensed and unlicensed. It is used at widely varying doses from 3 to 250 mg. The aim of this review was to extensively evaluate the safety of oral naltrexone by examining the risk of serious adverse events and adverse events in randomised controlled trials of naltrexone compared to placebo.

METHODS: A systematic search of the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, other databases and clinical trials registries was undertaken up to May 2018. Parallel placebo-controlled randomised controlled trials longer than 4 weeks published after 1 January 2001 of oral naltrexone at any dose were selected. Any condition or age group was included, excluding only studies in opioid or ex-opioid users owing to possible opioid/opioid antagonist interactions. The systematic review used the guidance of the Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-analyses harms checklist throughout. Numerical data were independently extracted by two people and cross-checked. Risk of bias was assessed with the Cochrane risk-of-bias tool. Meta-analyses were performed in R using random effects models throughout.

RESULTS: Eighty-nine randomised controlled trials with 11,194 participants were found, studying alcohol use disorders (n = 38), various psychiatric disorders (n = 13), impulse control disorders (n = 9), other addictions including smoking (n = 18), obesity or eating disorders (n = 6), Crohn's disease (n = 2), fibromyalgia (n = 1) and cancers (n = 2). Twenty-six studies (4,960 participants) recorded serious adverse events occurring by arm of study. There was no evidence of increased risk of serious adverse events for naltrexone compared to placebo (risk ratio 0.84, 95% confidence interval 0.66-1.06). Sensitivity analyses pooling risk differences supported this conclusion (risk difference -0.01, 95% confidence interval -0.02-0.00) and subgroup analyses showed that results were consistent across different doses and disease groups. Secondary analysis revealed only six marginally significant adverse events for naltrexone compared to placebo, which were of mild severity.

CONCLUSIONS: 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.

TRIAL REGISTRATION: PROSPERO 2017 CRD42017054421 .

KEYWORDS: LDN; Low dose naltrexone; Naltrexone; Serious adverse events; Systematic review; alcohol use disorder

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