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Low dose naltrexone for induction of remission in Crohn's disease (Review)

Parker CE, Nguyen TM, Segal D, MacDonald JK, Chande N

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TABLE OF CONTENTS

[Intervention Review]

Low dose naltrexone for induction of remission in Crohn's disease

Claire E Parker[1], Tran M Nguyen[2], Dan Segal[3], John K MacDonald[2], Nilesh Chande[4]

[1]Robarts Clinical Trials, London, Canada. [2]Cochrane IBD Group, Robarts Clinical Trials, London, Canada. [3]London Health Sciences Centre - University Hospital, London, Canada. [4]London Health Sciences Centre - Victoria Hospital, London, Canada

Contact address: Claire E Parker, Robarts Clinical Trials, 100 Dundas Street, Suite 200, London, ON, N6A 5B6, Canada. claire.parker@robartsinc.com.

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ABSTRACT

Background

Crohn's disease is a transmural, relapsing inflammatory condition afflicting the digestive tract. Opioid signalling, long known to affect secretion and motility in the gut, has been implicated in the inflammatory cascade of Crohn's disease. Low dose naltrexone, an opioid antagonist, has garnered interest as a potential therapy.

Objectives

The primary objective was to evaluate the efficacy and safety of low dose naltrexone for induction of remission in Crohn's disease.

Search methods

A systematic search of MEDLINE, Embase, PubMed, CENTRAL, and the Cochrane IBD Group Specialized Register was performed from inception to 15 January 2018 to identify relevant studies. Abstracts from major gastroenterology conferences including Digestive Disease Week and United European Gastroenterology Week and reference lists from retrieved articles were also screened.

Selection criteria

Randomized controlled trials of low dose naltrexone (LDN) for treatment of active Crohn's disease were included.

Data collection and analysis

Data were analyzed on an intention-to-treat basis using Review Manager (RevMan 5.3.5). The primary outcome was induction of clinical remission defined by a Crohn's disease activity index (CDAI) of ¡ 150 or a pediatric Crohn's disease activity index (PCDAI) of ¡ 10. Secondary outcomes included clinical response (70- or 100-point decrease in CDAI from baseline), endoscopic remission or response, quality of life, and adverse events as defined by the included studies. Risk ratios (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. The methodological quality of included studies was evaluated using the Cochrane risk of bias tool. The overall quality of the evidence supporting the primary outcome and selected secondary outcomes was assessed using the GRADE criteria.

Main results

Two studies were identified (46 participants). One study assessed the efficacy and safety of 12 weeks of LDN (4.5 mg/day) treatment compared to placebo in adult patients (N = 34). The other study assessed eight weeks of LDN (0.1 mg/kg, maximum 4.5 mg/day) treatment compared to placebo in pediatric patients (N = 12). The primary purpose of the pediatric study was to assess safety and tolerability. Both studies were rated as having a low risk of bias. The study in adult patients reported that 30% (5/18) of LDN treated patients achieved clinical remission at 12 weeks compared to 18% (3/16) of placebo patients, a difference that was not statistically significant (RR 1.48, 95% CI 0.42 to 5.24). The study in children reported that 25% of LDN treated patients achieved clinical remission (PCDAI ¡ 10) compared to none of the patients in the placebo group, although it was unclear if this result was for the randomized placebo-controlled trial or for the open label extension study. In the adult study 70-point clinical response rates were significantly higher in those treated with LDN than placebo. Eighty-three per cent (15/18) of LDN patients had a 70-point clinical response at week 12 compared to 38% (6/16) of placebo patients (RR 2.22, 95% CI 1.14 to 4.32). The effect of LDN on the proportion of adult patients who achieved a 100-point clinical response was uncertain. Sixty-one per cent (11/18) of LDN patients achieved a 100-point clinical response compared to 31% (5/16) of placebo patients (RR 1.96, 95% CI 0.87 to 4.42). The proportion of patients who achieved endoscopic response (CDEIS decline ¿ 5 from baseline) was significantly higher in the LDN group compared to placebo. Seventy-two per cent (13/18) of LDN patients achieved an endoscopic response compared to 25% (4/16) of placebo patients (RR 2.89; 95% CI 1.18 to 7.08). However, there was no statistically significant difference in the proportion of patients who achieved endoscopic remission. Endoscopic remission (CDEIS ¡ 3) was achieved in 22% (4/18) of the LDN group compared to 0% (0/16) of the placebo group (RR 8.05; 95% CI 0.47 to 138.87). Pooled data from both studies show no statistically significant differences in withdrawals due to adverse events or specific adverse events including sleep disturbance, unusual dreams, headache, decreased appetite, nausea and fatigue. No serious adverse events were reported in either study. GRADE analyses rated the overall quality of the evidence for the primary and secondary outcomes (i.e. clinical remission, clinical response, endoscopic response, and adverse events) as low due to serious imprecision (sparse data).

Authors' conclusions

Currently, there is insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN used to treat patients with active Crohn's disease. Data from one small study suggests that LDN may provide a benefit in terms of clinical and endoscopic response in adult patients with active Crohn's disease. Data from two small studies suggest that LDN does not increase the rate of specific adverse events relative to placebo. However, these results need to be interpreted with caution as they are based on very small numbers of patients and the overall quality of the evidence was rated as low due to serious imprecision. Further randomized controlled trials are required to assess the efficacy and safety of LDN therapy in active Crohn's disease in both adults and children.

PLAIN LANGUAGE SUMMARY

Low dose naltrexone for treatment of active Crohn's disease

What is Crohn's disease?

Crohn's disease is a chronic inflammatory condition of the gut, which can affect people anywhere from the mouth to anus. Common symptoms include abdominal pain, diarrhea and weight loss. People with Crohn's disease who are experiencing symptoms have 'active' disease. When the symptoms stop, it is called 'remission'.

What is naltrexone?

Naltrexone is a long-acting opioid antagonist. It is a drug that counteracts the effects of opoid drugs. This drug is commonly used for the treatment of alcohol and opioid abuse and is taken by mouth. Specific hormones (proteins that transmit instructions in the body) that are known to be involved in pain response may be involved in the inflammation that underlies Crohn's disease. Perhaps by giving people a low dose of naltrexone Crohn's disease can be improved.

What did the researchers investigate?

The researchers studied the effectiveness and safety (i.e. side effects) of low dose naltrexone therapy for inducing remission in people with active Crohn's disease.

What did the researchers find?

This review identified two small randomized controlled trials that included a total of 46 participants. One study compared 12 weeks of treatment with low dose naltrexone (4.5 mg/day) to a placebo (i.e. a fake drug such as a sugar pill) in 34 adult patients with active Crohn's disease. The other study compared eight weeks of treatment with low dose naltrexone (0.1 mg/kg up to a maximum 4.5 mg/day) to a placebo in 12 children with active Crohn's disease. The results from both studies were imprecise with regard to the proportion of patients who achieved clinical remission. The results of the study in adult patients suggest that low dose naltrexone may provide a benefit in terms of clinical response (i.e. an improvement in disease symptoms) and endoscopic response (i.e. a reduction in inflammation of the gut as shown by examining the gut with a scope). We could not tell whether low dose naltrexone led to specific side effects including sleep disturbance, unusual dreams, headache, decreased appetite, nausea and fatigue due to the low number of people who experienced these problems in the studies. The results of this review need to be interpreted with caution as they are based on small numbers of patients and the overall quality of the evidence was rated as low due to lack of precision of the results. Thus no firm conclusions can be made regarding the effectiveness and side effect profile of low dose naltrexone treatment for patients with active Crohn's disease. Further randomized controlled trials are required to assess the effectiveness and side effects of low dose naltrexone therapy in active Crohn's disease in both adults and children.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Low dose naltrexone versus placebo for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease
Settings: Outpatient
Intervention: Low dose naltrexone versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Low dose naltrexone versus placebo				
Induction of clinical remission CDAI ¡ 150	**Study population**		**RR 1.48** (0.42 to 5.24)	34 (1 study)	⊕⊕◯◯ **low**[2,3]	
	188 per 1000[1]	**278 per 1000** (79 to 985)				
Induction of 70-point clinical response CDAI	**Study population**		**RR 2.22** (1.14 to 4.32)	34 (1 study)	⊕⊕◯◯ **low**[3,4]	
	375 per 1000[1]	**832 per 1000** (427 to 1000)				
Induction of 5-point endoscopic response CDEIS	**Study population**		**RR 2.89** (1.18 to 7.08)	34 (1 study)	⊕⊕◯◯ **low**[3,5]	
	250 per 1000[1]	**722 per 1000** (295 to 1000)				
Sleep disturbance (adverse event)	**Study population**		**RR 0.92** (0.38 to 2.2)	46 (2 studies)	⊕⊕◯◯ **low**[3,7]	
	318 per 1000[6]	**293 per 1000** (121 to 700)				

Withdrawals due to adverse outcomes	**Study population**		**RR 1.57** (0.23 to 10.71)	46 (2 studies)	⊕⊕◯◯ **low**[3,8]
	45 per 1000[6]	**71 per 1000** (10 to 487)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The control group risk estimate comes from the control arm of the included study on adult patients.
[2] Sparse data (8 events).
[3] Wide confidence intervals.
[4] Sparse data (21 events).
[5] Sparse data (17 events).
[6] The control group estimate comes from the control arm of the two included studies.
[7] Sparse data (14 events).
[8] Sparse data (3 events).

BACKGROUND

Description of the condition

Crohn's disease is a transmural, relapsing inflammatory condition afflicting the gastrointestinal system. It can involve any portion of the digestive tract and numerous extra-intestinal sites. Complications include large and small bowel obstructions, fistulas and intra-abdominal abscesses, and perianal disease (Baumgart 2007). Furthermore patients experience major impacts in employment, relationships, and general well being (Hommes 2012). The pathogenesis of Crohn's disease remains unclear. In those patients with certain genetic and environmental factors there may be a loss of balance between immune tolerance and pathogenic response towards the vast luminal microbe environment (Abraham 2009).
The burden of Crohn's disease is growing in both developing and developed nations. The highest annual incidence of disease is 20.2 per one hundred thousand person-years in North America (Molodecky 2012). Current medical therapies include corticosteroids, immunosuppressives (e.g. azathioprine, 6-mercaptopurine, or methotrexate), and tumour necrosis factor-alpha antagonists and other biologics (Burger 2011). Upwards of 30% of patients require major abdominal surgery within five years of diagnosis (Bouguen 2011). However, surgery is not curative and the endoscopic recurrence rate may be as high as 90% within one year of surgery and the clinical recurrence rate may be 30% within two years of surgery (Rutgeerts 1984; Tytgat 1988; Olaison 1992).

Description of the intervention

Naltrexone is a long-acting opioid antagonist (Preston 1993). Its use has been well described for the treatment of alcohol and opioid abuse (Anton 2006; Minozzi 2011). In the gut, opioids affect secretion and motility by interacting with δ-, κ-, and μ- opioid receptors (Holzer 2009). Naltrexone is a potent inhibitor of the μ-opioid receptor (MOR) (Preston 1993), present in the gut as well as the central nervous system, which interacts with endogenous opioid peptides β-endorphin, met-enkephalin, and leu-enkephalin (Holzer 2009). The finding that MOR is overexpressed by $CD4^+$ and $CD8^+$ T lymphocytes in inflamed bowel led to the hypothesis that regulation of the innate opioid axis may be an effective treatment for Crohn's disease (Philippe 2006).

How the intervention might work

MOR activation by opioid agonists reduces inflammation in mouse models of colitis with a concomitant reduction in $CD4^+$ T lymphocytes and cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) (Philippe 2003). The mechanism of action may involve a decrease in inflammatory cell proliferation via tonic inhibition through the opioid axis (Zagon 2011). Naltrexone, a MOR antagonist, when administered in low doses temporarily increases proliferation by blocking the opioid receptor, but up-regulates both ligands and receptors providing a longer period of decreased proliferation once it falls off (Zagon 1989). A small (N = 17), uncontrolled, open label, pilot study found that low dose naltrexone (LDN) may improve quality of life and induce remission in patients with moderate to severely active Crohn's disease (Smith 2007). Opiod antagonists are also thought to stimulate peristalsis and increase transit and LDN has been studied in a randomized trial of treatment for constipation-predominant irritable bowel syndrome (Foxx-Orenstein 2007).

Why it is important to do this review

Crohn's disease patients still have suboptimal rates of remission and maintenance of remission with contemporary therapies including biologics (Peyrin-Biroulet 2011). Low dose naltrexone has gained attention from the public as a possible treatment for Crohn's disease despite limited data (Smith 2007; Smith 2011; Smith 2013). This review aims to systematically evaluate the effectiveness of LDN in order to inform the developing debate. This systematic review is an update of a previously published Cochrane review (Segal 2014).

OBJECTIVES

The primary objective was to evaluate the efficacy and safety of low dose naltrexone for induction of remission in Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) were considered for inclusion.

Types of participants

Participants of any age with active Crohn's disease defined by a combination of clinical (e.g. Crohn's disease activity index, CDAI ¿ 150), radiographic, endoscopic, and histological criteria were considered for inclusion.

Types of interventions

RCTs where low dose naltrexone was given by any route versus placebo or an active comparator were considered for inclusion.

Types of outcome measures

Primary outcomes

The primary outcome was the proportion of patients achieving clinical remission (e.g. CDAI ¡ 150) as defined by the included studies, and expressed as a percentage of the patients randomized (intention-to-treat analysis).

Secondary outcomes

Secondary outcome measures included the proportion of patients with:
A. Clinical response (as defined by the included studies);
B. Endoscopic response or remission (as defined by the included studies);
C. Improvement in quality of life (as defined by the included studies);
D. Adverse events;
E. Withdrawal due to adverse events; and
F. Serious adverse events.

Search methods for identification of studies

Electronic searches

Embase, MEDLINE, the Cochrane Library (CENTRAL), PubMed, the Cochrane IBD Group Specialized Register and clinicaltrials.gov were searched from inception until 15 January 2018. The search strategies are listed in Appendix 1.

Searching other resources

We performed a manual review of conference proceedings including Digestive Disease Week (DDW) and United European Gastroenterology Week (UEGW). Reference lists from retrieved articles were scanned to identify additional citations that may have been overlooked by the electronic searches.

Data collection and analysis

Selection of studies

All studies identified by the search strategy were independently assessed by two authors (TMN and CP) for inclusion, according to pre-specified criteria listed above. Studies in abstract form were only included if the authors could be contacted for further information. Any disagreements were resolved by consensus. If necessary a third party (NC) was engaged to resolve any ongoing disagreements.

Data extraction and management

A standardized form was used to extract relevant data from the included studies. The form was based on the Cochrane checklist of items to consider for data extraction (Higgins 2011a). Two authors (TMN and CP) independently extracted and recorded the data. Any disagreements were resolved by consensus with possible input from a third author (NC). The following data were extracted:
A. Methods (methods of randomization, allocation concealment, and blinding; inclusion and exclusion criteria, definition of outcomes);
B. Participants (number, age, gender, disease activity, co-medication);
C. Interventions (formulation, dose, frequency, duration); and
D. Outcomes (clinical remission and response rates, endoscopic remission and response rates, quality of life, adverse events, withdrawals due to adverse events, and serious adverse events).

Assessment of risk of bias in included studies

Two authors (TMN and CP) independently assessed the methodological quality of the included studies using the Cochrane risk of bias tool (Higgins 2011b). Any disagreements were resolved by consensus with possible input from a third author (NC). Factors that were assessed included:
A. Sequence generation;
B. Allocation concealment;
C. Blinding of participants and personnel;
D. Blinding of outcome assessment;
E. Completeness of outcome data;
F. Selective reporting; and
G. Other sources of bias.
Studies were assigned a low risk of bias, high risk of bias, or unclear risk of bias for each category.
The quality of the total body of evidence supporting the primary outcome and selected secondary outcomes was assessed using the GRADE criteria (Guyatt 2008; Schünemann 2011). Randomized trials are considered high quality and were downgraded if the following factors were present: within-study risk of bias, indirectness of evidence, heterogeneity, imprecision of effect estimates, and risk of publication bias. The quality of the body of evidence for a particular outcome was then graded as:
A. High: Further research is very unlikely to change our confidence in estimate of effect;
B. Moderate: Further research is likely to have an important impact on our confidence in estimate of effect and may change estimate;

C. Low: Further research is very likely to have an important impact on our confidence in estimate of effect and likely may change estimate; or
D. Very low: Any estimate of effect is very uncertain.

Measures of treatment effect

Data were analyzed using Review Manager (RevMan 5.3.5). All data were analyzed on an intention-to-treat basis. For dichotomous outcomes, we calculated the risk ratio and 95% confidence intervals (95% CI). For continuous outcomes with uniform units, we planned to calculate the mean difference (MD) and corresponding 95% CI. We planned to calculate the standardized mean difference (SMD) and 95% CI when different scales were used to measure the same outcome.

Unit of analysis issues

The primary analysis combined data from the trial-defined primary observation time-point. For studies that reported outcomes at fixed intervals, outcomes were combined at those time points as well. For a parallel group design a single measurement for each outcome per participant was collected. For crossover trials, data from the first part of the trial (prior to crossover) were extracted. For cluster-randomized trials, we planned to extract data at the level of the individual. When more than one efficacy or safety event was reported per subject, we used the proportion of subjects with at least one event as the outcome. If studies allocated subjects to different active treatment arms we planned to combine the active treatment arms (e.g. different dose groups) for the primary analysis. In this case, a subgroup analysis was planned to assess outcomes among different doses of naltrexone. Separate analyses were planned for LDN versus placebo, and LDN versus active comparator.

Dealing with missing data

As the primary analysis was carried out on an intention-to-treat basis, missing data were assumed to be negative (i.e. treatment failure). Whenever possible, study authors were contacted to request missing data, or to ascertain the reason for data loss. When data were missing, we planned a sensitivity analysis to assess the impact of the treatment failure assumption on the effect estimate.

Assessment of heterogeneity

Heterogeneity in included studies was evaluated using the Chi ^{2} test (a P value of 0.10 was considered statistically significant) and the I^2 statistic. Sensitivity analysis were used as indicated to investigate potential sources of heterogeneity.

Assessment of reporting biases

If there were a sufficient number of studies (i.e. ¿ 10), we planned to assess publication bias by constructing funnel plots (Egger 1997).

Data synthesis

Studies were pooled for meta-analyses when the studies were similar in terms of treatments, comparators, and outcomes (determined by consensus). Data were not pooled for analysis if there was a high degree of heterogeneity (I^2 ¿ 75%). A fixed-effect model was used in the absence of statistically significant heterogeneity; while a random-effects model was used if there was statistically significant heterogeneity (P ¡ 0.10).

Subgroup analysis and investigation of heterogeneity

The following pre-specified subgroup analysis were planned:
A. LDN dose;
B. Disease activity;
C. Duration of treatment;
D. Age; and
E. Gender.

Sensitivity analysis

The following sensitivity analyses were planned:
A. Exclusion of low quality studies;
B. Worst case versus best case assumptions for missing data; and
C. Exclusion of outlier studies to investigate potential explanations for heterogeneity.

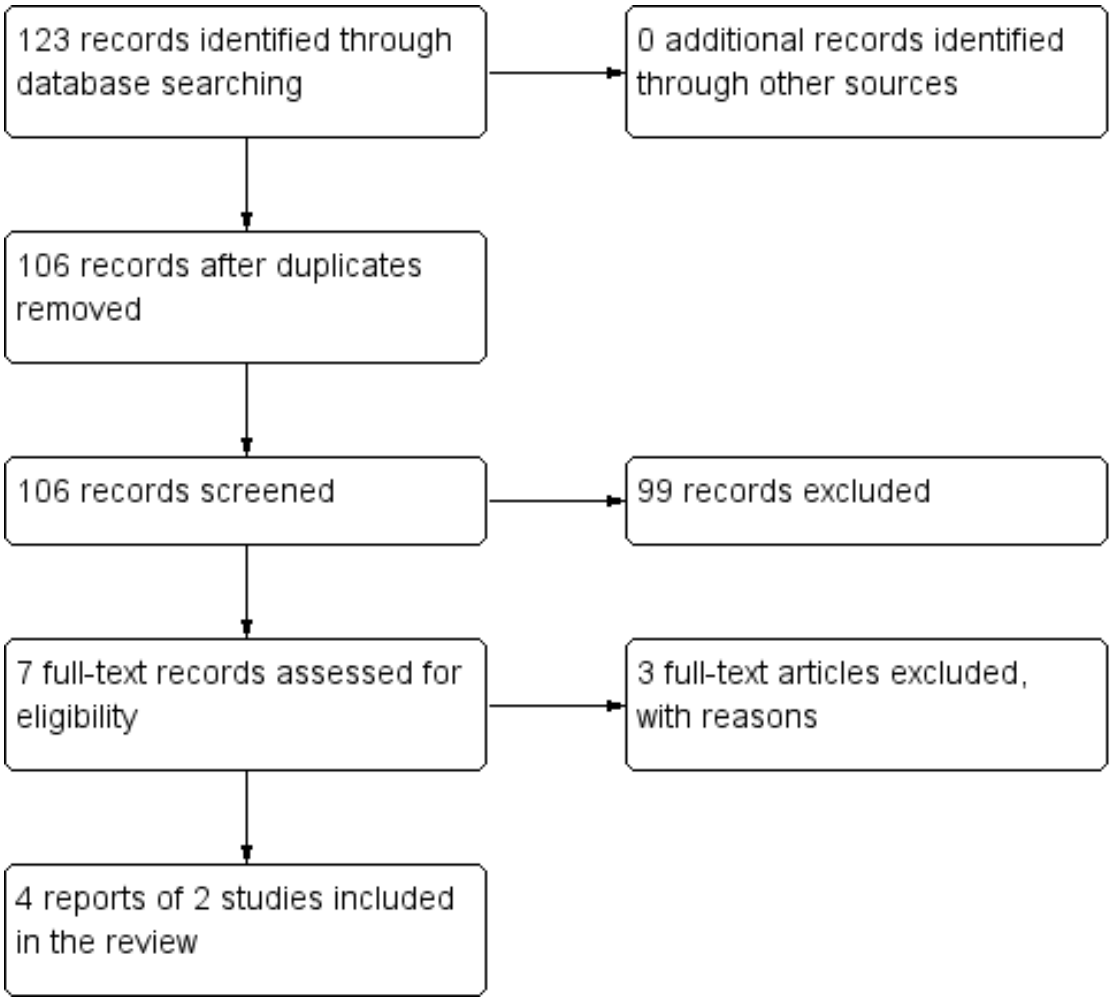
RESULTS

Description of studies

Results of the search

A literature search conducted on 15 January 2018 identified 123 records. No additional studies were identified through searching of conference abstracts or references. After duplicates were removed, a total of 106 trials remained for review of titles and abstracts. Two authors (TMN and CP) independently reviewed the titles and abstracts see (Figure 1), and seven studies were selected for full-text review. Three of these studies were excluded with reasons (Jackson 2013; Ploesser 2010; Smith 2007). Four reports of two trials met the pre-defined inclusion criteria and were included in the review (Smith 2011; Smith 2013).

Figure 1. Flow diagram.



Included studies

Smith 2011 conducted a single centre, randomized, double-blind, placebo-controlled trial allocating patients with moderate to severe Crohn's disease (CDAI ¿ 220) to either 4.5 mg/day of naltrexone (n = 18) or identical placebo (n = 16) for twelve weeks of treatment. Patients were randomized in blocks of four stratified by C-reactive protein (CRP) and disease location. After twelve weeks all patients received naltrexone in an open-label extension study for a further three months. Data from the open-label extension study were not utilized for this systematic review. The primary outcome was the proportion of patients with a 70-point decline in CDAI from baseline. Secondary outcomes included the proportion of subjects with a 100-point decline in CDAI from baseline, endoscopic improvement (five point decline in the Crohn's disease endoscopic index of severity, CDEIS), endoscopic remission (CDEIS ¡ 6 or ¡ 3) and clinical remission (CDAI ¡ 150). Other secondary outcomes include a histological inflammation score, measures of quality of life (IBDQ and SF36), and adverse events. All outcomes for the randomized component of the trial including endoscopy were measured at entry and twelve weeks. Patients were evaluated clinically every four weeks with CDAI scores, laboratory tests, and a physical exam. Patients had to be on stable doses of steroids or aminosalicylates for 4 weeks and thiopurines for 12 weeks prior to randomization. Exclusion criteria included use of tTNF-α antagonists within eight weeks of entry; use of lomotil, pregnancy or breastfeeding, or ostomy or ileoanal anastomosis, short bowel syndrome, or abnormal liver enzymes. Data were analyzed on an intention-to-treat basis.

Smith 2013 conducted a single centre, randomized, double-blind,

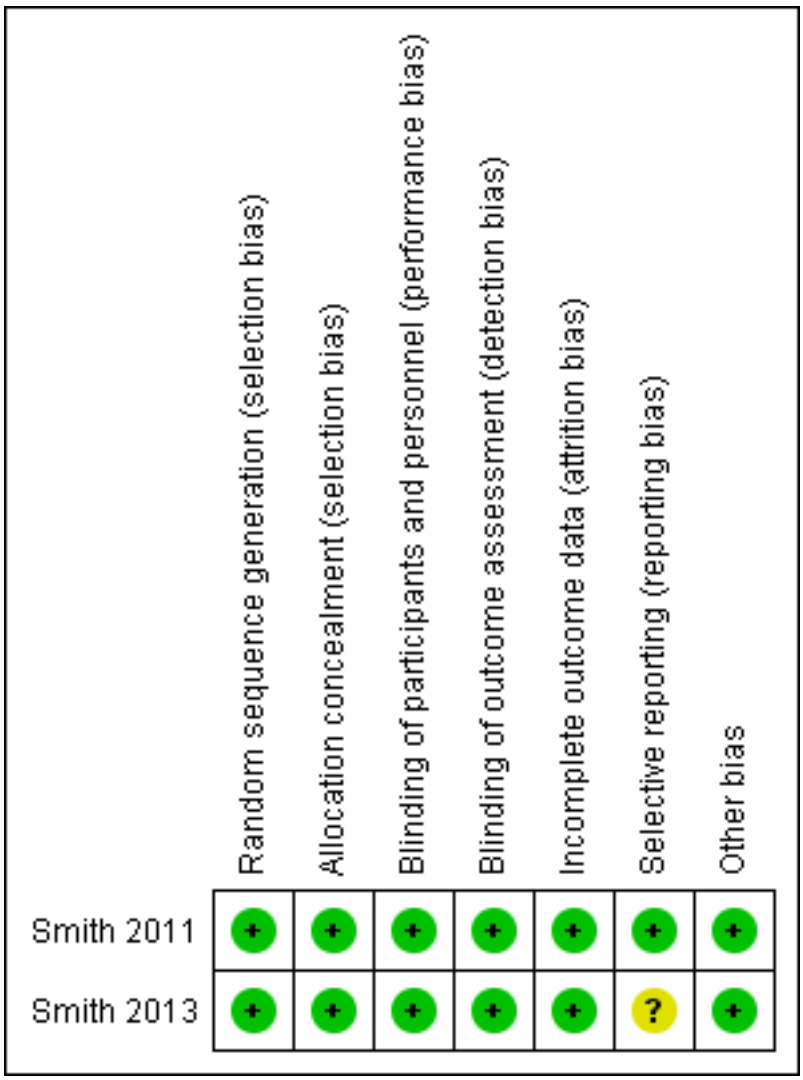
placebo-controlled trial allocating children, aged six to seventeen years, with moderate to severe Crohn's disease (pediatric Crohn's disease activity index, PCDAI ¿ 30), diagnosed at least six months prior to entry, to naltrexone 0.1 mg/kg up to a maximum of 4.5 mg/day (n = 6) or placebo (n = 6) for eight weeks of treatment. Patients were randomized in blocks of four based upon disease location and CRP. After eight weeks all patients were treated with open-label naltrexone for two months. Data from the open-label extension study were not utilized for this systematic review. The primary outcome was the safety and tolerability of naltrexone treatment. Secondary outcomes include clinical response (¿ 10 point decline in PCDAI), Harvey-Bradshaw index, clinical remission (PCDAI ¡ 10), and a quality of life assessment (Impact III survey). All outcomes for the randomized component of the study were evaluated at entry and eight weeks, although the Impact III survey was also evaluated at four weeks. Patients had to be on stable doses of steroids or aminosalicylates for 4 weeks and thiopurines for 12 weeks prior to randomization. Exclusion criteria included the use of steroid doses greater than 10 mg/day, or TNF-α antagonists within 8 weeks prior to entry; use of lomotil or diphenoxylate hydrochloride, pregnancy; or ostomy, ileoanal anastomosis, or abnormal liver enzymes. Any patient who flared (PCDAI increase of 12.5) was rescued with steroids and the data were analyzed on an intention-to-treat basis.

See the Characteristics of included studies tables for further information on the included studies.

Risk of bias in included studies

The risk of bias for the two included studies is summarized in Figure 2. Smith 2011 was rated as low risk for all domains. Smith 2013 was rated as low risk for six of seven domains assessed. Although the primary purpose of the study was to assess safety and tolerability, complete data for predefined secondary outcomes, specifically comparisons between LDN and placebo groups, were not explicitly reported in the text so the study was rated as unclear risk of bias for selective reporting.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

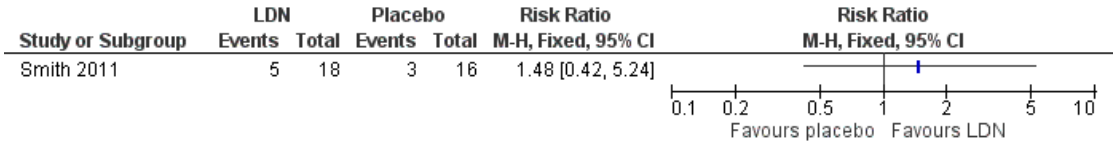


Effects of interventions

See: **Summary of findings for the main comparison** Low dose naltrexone versus placebo for induction of remission in Crohn's disease

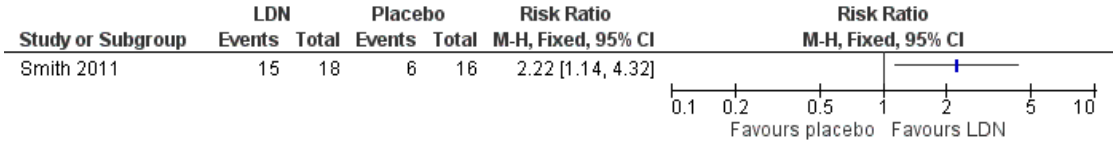
There was no statistically significant difference in the proportion of adult patients who achieved clinical remission (Figure 3). Smith 2011 reported that 30% (5/18) of LDN treated patients achieved clinical remission (CDAI ¡ 150) compared to 18% (3/16) placebo patients (RR 1.48, 95% CI 0.42 to 5.24). Smith 2013 reported that 25% of LDN treated patients achieved clinical remission (PCDAI ¡ 10) compared to none of the placebo treated patients, although it was unclear if this result was for the randomized placebo-controlled trial or for the open label extension study.

Figure 3. Forest plot of comparison: 1 Low dose naltrexone versus placebo, outcome: 1.1 Clinical remission (CDAI ¡ 150).



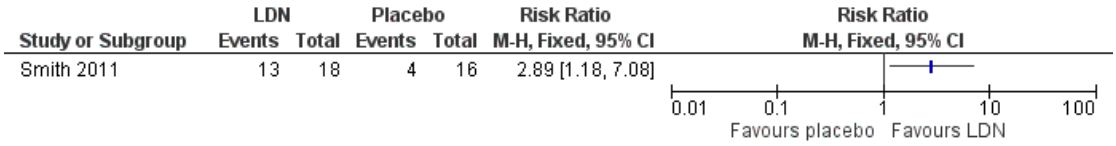
While both studies reported data on clinical response (decrease in CDAI ¿ 70 or PCDAI ¿ 10), only Smith 2011 clearly reported the proportion of patients that achieved a 70-point clinical response for both groups prior to the open label extension study. Seventy-point clinical response rates were significantly higher in those treated with LDN than placebo (See Figure 4). Eighty-three per cent (15/18) of LDN patients had a 70-point clinical response at week 12 compared to 38% (6/16) of placebo patients (RR 2.22; 95% CI 1.14 to 4.32). There was no statistically significant difference in the proportion of patients who achieved a 100-point clinical response (CDAI decline ¿ 100 from baseline). Sixty-one per cent (11/18) of LDN patients achieved a 100-point clinical response compared to 31% (5/16) of placebo patients (RR 1.96; 95% CI 0.87 to 4.42).

Figure 4. Forest plot of comparison: 1 Low dose naltrexone versus placebo, outcome: 1.2 Clinical response (CDAI change of 70 or greater).



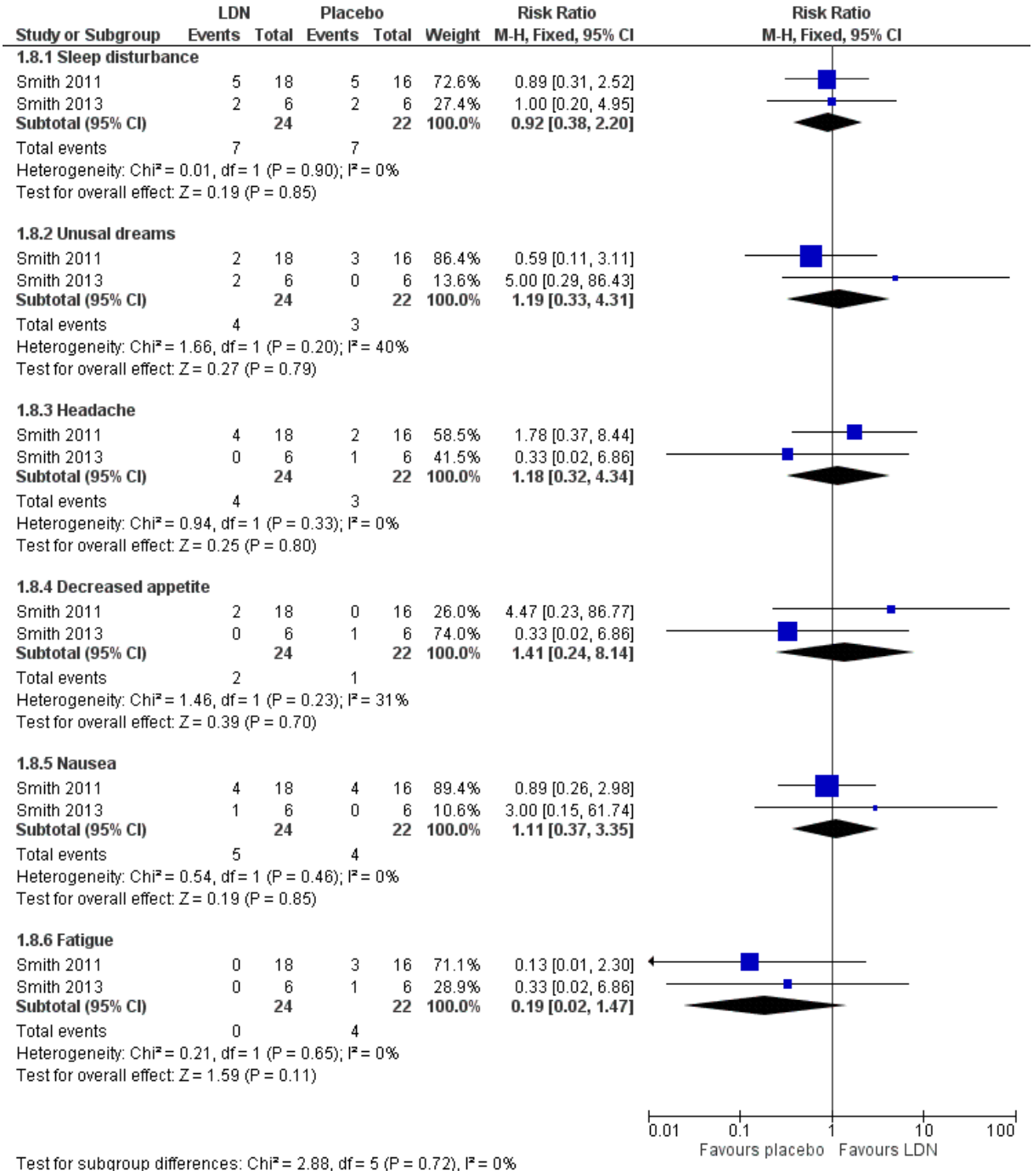
Smith 2011 reported endoscopic outcomes including remission and response. The proportion of patients who achieved endoscopic response (CDEIS decline ¿ 5 from baseline, see Figure 5) was significantly higher in the LDN group compared to placebo. Seventy-two per cent (13/18) of LDN patients achieved an endoscopic response compared to 25% (4/16) of placebo patients (RR 2.89; 95% CI 1.18 to 7.08). There was no statistically significant difference in the proportion of patients who achieved endoscopic remission. Endoscopic remission (CDEIS ¡ 3) was achieved in 22% (4/18) of the LDN group compared to 0% (0/16) of the placebo group (RR 8.05; 95% CI 0.47 to 138.87). When less stringent criteria were employed to define endoscopic remission (CDEIS ¡ 6), 33% (6/18) of LDN patients achieved endoscopic remission compared to 6% (1/16) of placebo patients (RR 5.33; 95% CI 0.72 to 39.69). Neither study reported quality of life results in a manner that allowed the pooling of outcomes for meta-analysis. Smith 2011 reported the mean change in IBDQ and SF36 scores for LDN and placebo treated patients in a graph. Smith 2011 reported that there was no statistically significant difference between LDN and placebo for both quality of life outcomes. Smith 2013 only reported the results of the Impact III survey at the completion of the open label extension study indicating that systemic and social quality of life were significantly improved in naltrexone patients (P = 0.035).

Figure 5. Forest plot of comparison: 1 Low dose naltrexone versus placebo, outcome: 1.6 Endoscopic response.



Smith 2011 and Smith 2013 reported on the proportion of subjects who experienced specific adverse events. Neither study reported the proportion of patients who experienced any adverse event. The most commonly reported adverse event was sleep disturbance or insomnia. There was no statistically significant difference between the groups in sleep disturbance (see Figure 6). Twenty-nine per cent (7/24) of LDN patients reported sleep disturbance compared to 32% (7/22) of placebo patients (RR 0.92; 95% CI 0.38 to 2.20). No heterogeneity was detected for this comparison (P = .92, I^2 = 0%). There was no statistically significant difference in the proportion of patients who experienced other specific adverse events including unusual dreams, headache, decreased appetite, nausea, and fatigue. There were no serious adverse events reported in either study. There was no statistically significant difference in withdrawals due to adverse events, (e.g. a Crohn's flare). Eight per cent of LDN patients (2/24) withdrew due to an adverse event compared to 4% (1/22) of placebo patients (RR 1.57; 95% CI 0.23 to 10.84). While Smith 2011 did not report criteria for a flare, Smith 2013 defined a flare as an increase in the PCDAI by 12.5.

Figure 6. Forest plot of comparison: 1 Low dose naltrexone versus placebo, outcome: 1.8 Specific adverse events.



The small number of patients and studies did not allow for pre-specified subgroup, sensitivity analyses, or assessment of reporting biases (i.e. funnel plot).

DISCUSSION

This systematic review confirms the results of the previous version of this systematic review. The 2014 version of this review included 2 studies and 46 participants (Segal 2014) . This updated review includes an additional secondary publication of the Smith 2013 study, however, this publication only contributed minimal quality of life data to the final analysis. The only outcomes of interest for this systematic review that were clearly reported by Smith 2013 were specific adverse events and withdrawals due to adverse events; whereas Smith 2011 reported on clinical and endoscopic outcomes as well as specific adverse events. Neither study reported quality of life data in a manner amenable to meta-analysis.

Smith 2011 (n = 34) found no statistically significant difference in the proportion of patients who achieved clinical remission. However, the LDN group had a statistically significant clinical response (CDAI decrease ¿ 70) compared to placebo. These results were clinically relevant with an absolute risk reduction (ARR) of 46% that translates to a number needed to treat (NNT) of approximately two for inducing a clinical response. When a more stringent measure of clinical response was used (CDAI decrease ¿ 100) there was no statistically significant difference between LDN and placebo. The same study found a statistically significant difference in endoscopic response (¿ 5 point drop in CDEIS) between LDN and placebo. This difference amounts to an ARR of 47% with a NNT of two for this outcome. However, there was no statistically significant difference in endoscopic remission between patients treated with LDN and placebo (CDEIS ¡ 3 or CDEIS ¡ 6).

While both studies reported the rates of specific adverse events, neither study reported on the proportion of patients who experienced at least one adverse event. There were no statistically significant differences between LDN and placebo in the proportion of patients that experienced specific adverse events, including sleep disturbance or insomnia, unusual dreams, headache, decreased appetite, and constipation. There was no statistically significant difference between LDN and placebo in withdrawals due to a Crohn's flare.

The results of this systematic review should be interpreted with caution due to several limitations. Both included studies were by the same author who was the principal investigator for both studies and this author holds a patent for the use of naltrexone in IBD. No other research group has published data on the use of naltrexone for the treatment of IBD. All the patients were recruited from one tertiary care facility, which limits the applicability of any conclusions. Both of the included studies were small in size and subsequently event numbers for outcomes were low leading to extremely sparse data. The confidence intervals for all outcomes were wide, in some instances ranging from appreciable harm to benefit. For the majority of outcomes, data could only be extracted from one trial. The GRADE rating for the body of evidence supporting the these outcomes was low due to serious imprecision.

The review process for both studies required decisions that could have led to varying results. For Smith 2011 the outcomes were reported as percentages, so the proportion of patients experiencing an event had to be extrapolated based on sample sizes described in the paper. For Smith 2013 clinical outcome data for the placebo group were only reported in the discussion. Furthermore, it was unclear if the clinical outcome data for the treatment group related to the primary study or the open label extension component so these data were not incorporated into the meta-analysis. It was difficult to compare the results of this systematic review to other systematic reviews as there are minimal published data.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN used to treat patients with active Crohn's disease. Data from one small study suggests that low dose naltrexone may provide a benefit in terms of clinical and endoscopic response in adult patients with active Crohn's disease. Data from two small studies suggest that LDN does not increase the rate of specific adverse events relative to placebo. However, these results need to be interpreted with caution as they are based on small numbers of patients and the overall quality of the evidence was rated as low due to serious imprecision.

Implications for research

Further randomized control trials are required to assess the efficacy and safety of LDN therapy for induction of remission in Crohn's disease in adult and pediatric patients. To date all completed studies have occurred at one North American tertiary centre under the auspices of one research group. One trial was registered on March 13, 2013 (NCT01810185), however it was later withdrawn on November 20, 2014 due to low patient enrollment.

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The authors would like to thank Dr Jill P Smith for providing additional information on the two studies that were included in this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Smith 2011

Methods	Randomized, double-blinded, placebo-controlled, single centre trial Centralized pharmacy allocation with block randomization
Participants	34 adult patients with moderate to severe Crohn's disease (CDAI greater than or equal to 220) Concomitant medications were allowed if patients received stable doses of steroids or aminosalicylates for 4 weeks and thiopurines for 12 weeks prior to entry Exclusion criteria: use of TNF-alpha antagonists within 8 weeks of entry, on lomotil, pregnant or breastfeeding, ostomy or ileoanal anastomosis, short bowel syndrome, abnormal liver enzymes
Interventions	Naltrexone 4.5 mg or placebo for 12 weeks
Outcomes	The primary outcome was the proportion of subjects with a 70-point or more decline in CDAI from baseline Secondary outcomes included the proportion of subjects with a 100 point decline in CDAI, endoscopic improvement (5 point decline in CDEIS), endoscopic remission (CDEIS less than 6 or less than 3) and clinical remission (CDAI ¡ 150) Other secondary outcomes included a histological inflammation score, measures of quality of life (IBDQ and SF36), and adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The method of randomization was not described in the paper The contact author was able to confirm that randomization was computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization "Assignments were made by the investigational pharmacy department"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded with identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endoscopist was blinded

Smith 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient from each group dropped out do to flare
Selective reporting (reporting bias)	Low risk	In the manuscript the proportion of patients with clinical remission was only reported for patients in the LDN group The contact author provided the proportion of placebo patients who achieved clinical remission
Other bias	Low risk	The study appears to be free of other sources of bias

Smith 2013

Methods	Randomized, double-blinded, placebo-controlled, single centre trial Centralized pharmacy allocation with block randomization
Participants	12 children, ages 6 to 17, with moderate to severe Crohn's disease (PCDAI greater than or equal to 30) for a minimum of six months Concomitant medications were allowed if patients received stable doses of steroids or aminosalicylates for 4 weeks and thiopurines for 12 weeks prior to entry Exclusion criteria: use of TNF-alpha antagonists within 8 weeks of entry, on lomotil or diphenoxylate hydrochloride, pregnancy, ostomy or ileoanal anastomosis, abnormal liver enzymes
Interventions	Naltrexone 0.1 mg/kg (maximum 4.5 mg) versus placebo for 8 weeks
Outcomes	The primary outcome was the safety and tolerability of treatment Secondary outcomes included clinical response (greater than or equal to a 10 point decline in PCDAI) and clinical remission (PCDAI = or ¡10) Other outcomes included two quality of life assessments (Impact III survey, Harvey-Bradshaw index)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The method of randomization was not described in the paper The contact author was able to confirm that randomization was computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization "Randomized by the investigational pharmacy department"

Smith 2013 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded with identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endoscopist was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients appear to have completed the study
Selective reporting (reporting bias)	Unclear risk	Although the primary aim of the trial was to assess safety and tolerability secondary outcomes were incompletely reported The contact author provided the proportion of placebo patients who achieved clinical remission
Other bias	Low risk	The study appears to be free of other sources of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Jackson 2013	Open label study. Does not meet inclusion criteria
Ploesser 2010	Not an RCT. A retrospective postal survey investigating adverse events and efficacy of low dose naltrexone in patients with inflammatory bowel disease and irritable bowel syndrome
Smith 2007	Not an RCT

Characteristics of ongoing studies *[ordered by study ID]*

NCT01810185

Trial name or title	Low dose naltrexone in symptomatic inflammatory bowel disease
Methods	Randomized, double-blind, placebo-controlled, parallel group trial
Participants	Confirmed active Crohn's disease or ulcerative colitis through radiographic, endoscopic or histologic criteria
Interventions	Low dose naltrexone (4.5 mg) daily for 12 weeks or placebo daily for 12 weeks

NCT01810185 (*Continued*)

Outcomes	IBDQ
Starting date	Estimated starting date was March 2013
Contact information	Erick J Imbertson, M.D., Santa Barbara Cottage Hospital, Santa Barbara, California, United States, 93105
Notes	This trial was withdrawn on November 20, 2014 due to low patient enrollment

DATA AND ANALYSES

Comparison 1. Low dose naltrexone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission (CDAI ¡ 150)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical response (CDAI change of 70 or greater)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Clinical response (CDAI change of 100 or greater)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Endoscopic remission (CDEIS less than 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Endoscopic remission (CDEIS less than 6)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Endoscopic response	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Withdrawals due to adverse events	2	46	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.23, 10.71]
8 Specific adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Sleep disturbance	2	46	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.38, 2.20]
8.2 Unusal dreams	2	46	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.33, 4.31]
8.3 Headache	2	46	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.32, 4.34]
8.4 Decreased appetite	2	46	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.24, 8.14]
8.5 Nausea	2	46	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.37, 3.35]
8.6 Fatigue	2	46	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.47]

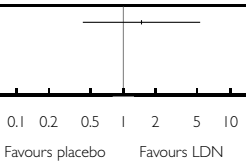
Analysis 1.1. Comparison 1 Low dose naltrexone versus placebo, Outcome 1 Clinical remission (CDAI ¡ 150).

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 1 Clinical remission (CDAI < 150)

Study or subgroup	LDN n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Smith 2011	5/18	3/16		1.48 [0.42, 5.24]

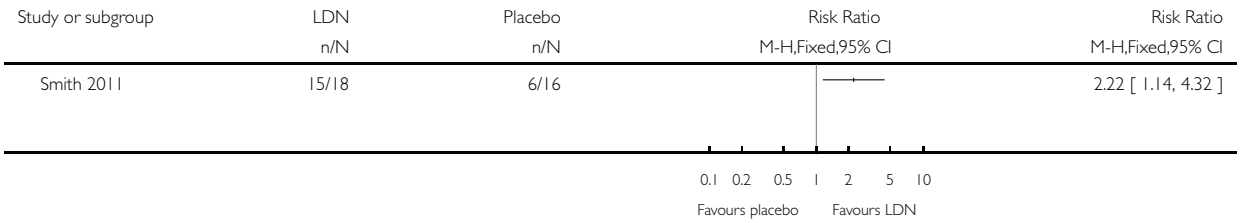


Analysis 1.2. Comparison 1 Low dose naltrexone versus placebo, Outcome 2 Clinical response (CDAI change of 70 or greater).

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 2 Clinical response (CDAI change of 70 or greater)

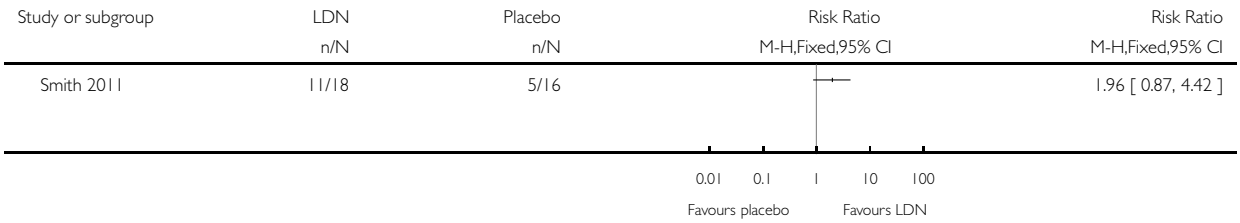


Analysis 1.3. Comparison 1 Low dose naltrexone versus placebo, Outcome 3 Clinical response (CDAI change of 100 or greater).

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 3 Clinical response (CDAI change of 100 or greater)



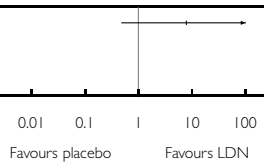
Analysis 1.4. Comparison 1 Low dose naltrexone versus placebo, Outcome 4 Endoscopic remission (CDEIS less than 3).

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 4 Endoscopic remission (CDEIS less than 3)

Study or subgroup	LDN n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Smith 2011	4/18	0/16		8.05 [0.47, 138.87]



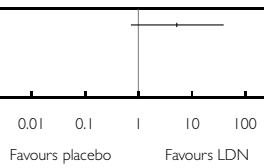
Analysis 1.5. Comparison 1 Low dose naltrexone versus placebo, Outcome 5 Endoscopic remission (CDEIS less than 6).

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 5 Endoscopic remission (CDEIS less than 6)

Study or subgroup	LDN n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Smith 2011	6/18	1/16		5.33 [0.72, 39.69]

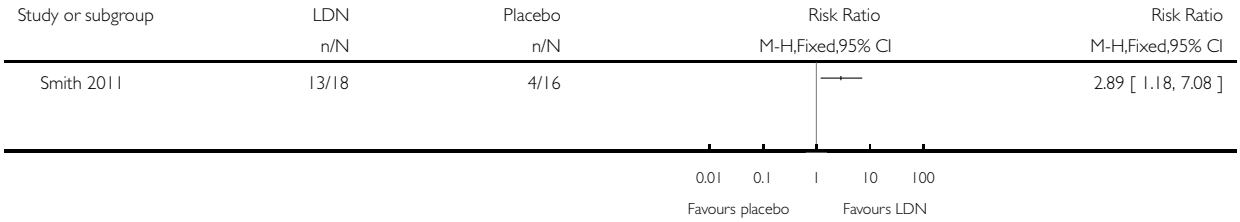


Analysis 1.6. Comparison 1 Low dose naltrexone versus placebo, Outcome 6 Endoscopic response.

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 6 Endoscopic response

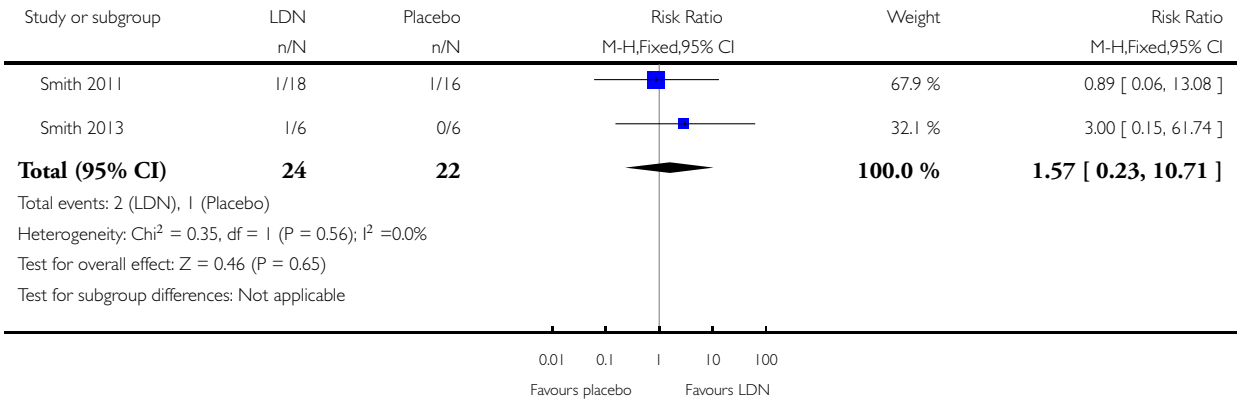


Analysis 1.7. Comparison 1 Low dose naltrexone versus placebo, Outcome 7 Withdrawals due to adverse events.

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 7 Withdrawals due to adverse events

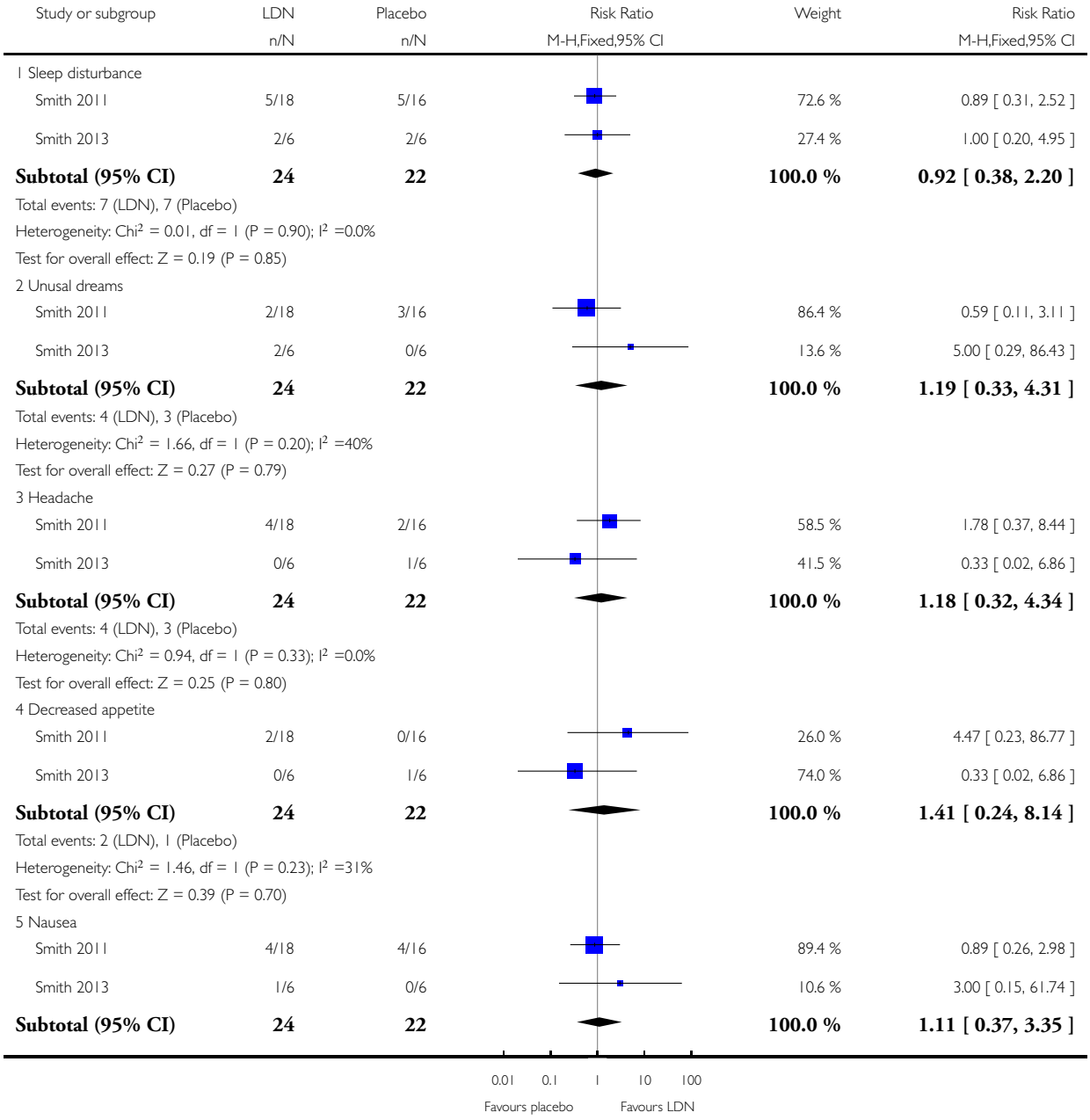


Analysis 1.8. Comparison 1 Low dose naltrexone versus placebo, Outcome 8 Specific adverse events.

Review: Low dose naltrexone for induction of remission in Crohn's disease

Comparison: 1 Low dose naltrexone versus placebo

Outcome: 8 Specific adverse events



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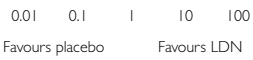
Study or subgroup	LDN n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 5 (LDN), 4 (Placebo)					
Heterogeneity: Chi^2 = 0.54, df = 1 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 0.19 (P = 0.85)					
6 Fatigue					
Smith 2011	0/18	3/16		71.1 %	0.13 [0.01, 2.30]
Smith 2013	0/6	1/6		28.9 %	0.33 [0.02, 6.86]
Subtotal (95% CI)	**24**	**22**		**100.0 %**	**0.19 [0.02, 1.47]**
Total events: 0 (LDN), 4 (Placebo)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 1.59 (P = 0.11)					
Test for subgroup differences: Chi^2 = 2.88, df = 5 (P = 0.72), I^2 =0.0%					



APPENDICES

Appendix 1. Search strategies

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. Exp Crohn disease/
16. Crohn*.mp.
17. IBD.mp.
18. Inflammatory bowel disease*.mp.
19. Or/15-18
20. Exp Naltrexone/
21. Naltrexone.mp.

22. Exp naloxone/
23. Naloxone.mp.
24. Naloxone benzoylhydrazone.mp.
25. Revia.mp.
26. Vivitrol.mp.
27. Or/20-26
28. 14 and 19 and 27

EMBASE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. Exp Crohn disease/
20. Crohn*.mp.
21. IBD.mp.
22. Inflammatory bowel disease*.mp.
23. Or/19-22
24. Exp Naltrexone/
25. Naltrexone.mp.
26. Exp naloxone/
27. Naloxone.mp.
28. Naloxone benzoylhydrazone.mp.
29. Revia.mp.
30. Vivitrol.mp.
31. Exp Naltrexone derivative/
32. Exp naloxone 6 spirohydantoin/
33. Or/24-32
34. 18 and 23 and 33

Cochrane Library

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 Crohn Disease
#3 Crohn
#4 IBD
#5 #1 or #2 or #3 or #4
#6 MeSH: [Naltrexone] explode all trees
#7 Naltrexone
#8 MeSH: [Naloxone] explode all trees
#9 Naloxone*
#10 Revia

#11 Vivitrol
#12 #6 or #7 or #8 or #9 or #10 or #11
#13 #5 and #12

Pubmed

Ti/ab((Naltrexone OR Naloxone* OR Revia OR Vivitrol)) AND ti/ab((Crohn Disease OR Inflammatory Bowel Disease OR CD))

SR-IBD

naltrexone OR naloxone

Clinical trials. Gov

1. Crohn Disease and Naltrexone
2. Crohn Disease and Naloxone
3. Inflammatory bowel disease and Naltrexone

WHAT'S NEW

Last assessed as up-to-date: 15 January 2018.

Date	Event	Description
26 April 2018	Amended	Correction of a minor error in PLS and in Characteristics of included studies table

HISTORY

Protocol first published: Issue 2, 2013

Review first published: Issue 2, 2014

Date	Event	Description
27 October 2017	New search has been performed	New literature search was run on 15 January 2018. One new secondary publication was added to the review
27 October 2017	New citation required but conclusions have not changed	Updated review with new authors

DECLARATIONS OF INTEREST

Claire Parker: None known

Tran Nguyen: None known

Dan Segal has received consulting fees from Abbvie.

John MacDonald: None known

Nilesh Chande has received fees for consultancy from AbbVie, Ferring, Janssen, Takeda, Lupin, Shire, Allergan and speakers's fees from AbbVie, Takeda, Shire, Allergan. All of these financial activities are outside the submitted work.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage; adverse effects]; Crohn Disease [*drug therapy]; Induction Chemotherapy [*methods]; Intention to Treat Analysis; Naltrexone [*administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans