# The use of naltrexone in low doses beyond the approved indication

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English

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Systematic review

kunnskapssenteret

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We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, April 2015

# Key messages (English)

In Norway, naltrexone is approved as supportive treatment of alcohol dependence. The recommended dose is 50 mg, equivalent to the marketed tablet. Naltrexone in much lower doses than 50 mg has been used in Norway for the treatment of a variety of diseases, such as multiple sclerosis (MS), Crohn's disease, fibromyalgia, cancer, inflammatory bowel disease, chronic fatigue syndrome, and amyotrophic lateral sclerosis. Doses of 3 to 5 mg per day have often been termed low dose naltrexone. This use is beyond the approved indication. The purpose of this report is to examine whether there is a documented effect of the use of naltrexone in low doses.

We summarized data from a systematic review and several randomized controlled and prospective controlled studies in order to investigate the effect of using naltrexone in low doses on illness, and on functioning in daily life and to examine the risk of side effects.

We identified studies for people with:
- Crohn's disease (one systematic review, two studies)
- multiple sclerosis (two studies)
- fibromyalgia (two studies)
- cancer (one study)
- HIV (one study)
- various pain conditions (three studies)
- opioid dependence (six studies)

All studies were either small, of short duration, or had other methodological limitations. We considered the documentation to have very low quality. That means that we can not conclude whether the use of naltrexone in low doses is effective or safe.

**Title:**
The use of naltrexone in low doses beyond the approved indication

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## Doesn't answer everything:

Doesn't cover use of naltrexone in higher than 5 mg/day doses. Doesn't cover resutls from studies without a control group.

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## Peer review:

Lillebeth Larun, researcher, The Norwegian Knowledge Centre for the Health Service (NOKC)
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# Executive summary (English)

## Background

In Norway, naltrexone (Naltrexone POA Pharma) is approved as supportive treatment of alcohol dependence. The recommended dose is 50 mg, equivalent to the marketed tablet. Naltrexone in much lower doses than 50 mg has been used in Norway for the treatment of a variety of diseases, such as multiple sclerosis (MS), Crohn's disease, fibromyalgia, cancer, inflammatory bowel disease, chronic fatigue syndrome, and amyotrophic lateral sclerosis. Doses of 3 to 5 mg per day have often been termed low dose naltrexone. This use is beyond the approved indication. The purpose of this report is to examine whether there is a documented effect of the use of naltrexone in low doses.

## Objective

Our objective was to examine efficacy and safety of any use of naltrexone in doses of 5 mg/day or lower.

## Method

We searched systematically for systematic reviews and randomized controlled or prospective controlled trials on the efficacy and safety of naltrexone in low doses. Two researcher working independently screened all titles and abstracts according to inclusion and exclusion criteria. The quality of the included publications was assessed in the same way. We summarized the results in text and tables and used GRADE to establish our confidence in the effect estimates.

## Results

We identified studies that met our inclusion criteria for people with Crohn's disease, multiple sclerosis, fibromyalgia, cancer, HIV, various pain disorders, and opioid dependence.

We included a systematic review on patients with inflammatory bowel disease, two studies on patients with MS, two studies on patients with fibromyalgia, a study on patients with cancer, a study on patients with HIV, three studies of patients with pain conditions and six studies of patients with opioid dependence.

All studies were either small, of short duration or had other methodological limitations. We considered the documentation to have very low quality. Studies had unclear or high risk of bias, the results had unclear reproducibility, few events, wide confidence intervals or distribution of the results was not provided. That means that we can not conclude whether the use of naltrexone in low doses is effective or safe.

## Discussion

We summarized data from a systematic review and several randomized controlled and prospective controlled studies in order to investigate the effect of using naltrexone in low doses on illness and, functioning in daily life, and to examine the risk of side effects. We were not able to conclude whether such use is effective and safe.

The studies that included people with Crohn's disease, fibromyalgia, multiple sclerosis, cancer and HIV used naltrexone in daily doses of between 3 and 5 mg. The treatment time was usually between 8 and 12 weeks. These studies describe themselves as pilot studies, the first controlled study, or similar, and are accordingly of short duration. However, the choice of treatment duration is important. It must be long enough to allow a change to occur and be measured. The studies in question are not able to answer questions about the efficacy and safety of long term use.

The studies that examined naltrexone in low doses for patients with chronic pain and opioid dependence had shorter treatment duration and / or lower doses than in studies related to other conditions. Doses ranged from 0.0001 mg to 1 mg. We did not investigate potential dose-findings studies, so we have no evidence to estimate the dose interval where naltrexone could have an effect. It may therefore be that the doses used creates uncertainty about whether not an effect could be expected.

The included studies investigated several outcomes that could potentially be measured after a short time, such as daily pain, "craving for substance" or withdrawal symptoms. Because of the short treatment duration, the studies could not give answers relating to efficacy and safety of long term use.

The included studies were generally small. It is unlikely that the studies included in this section could have shown a difference between treatment groups with certainty, even if there was a difference. Moreover, it is extremely uncertain whether low-dose naltrexone has been investigated in a sufficient number of patients to identify rare side effects, and to determine whether there may be relative differences in the frequency of rare adverse events between different treatment options.

## Conclusion

Based on current the evidence, it is not possible to determine whether low-dose naltrexone is effective and safe. Neither is it possible to determine whether there are differences in efficacy between different patient groups.

We identified studies that included people with Crohn's disease, multiple sclerosis, fibromyalgia, cancer, HIV, addiction problems and various chronic pain disorders and opioid dependence. The studies were small, of short duration, had uncertain estimates for effect and safety and other methodological limitations that overall made it impossible to draw any conclusions.

There is a need for well-planned and well-conducted RCTs of long enough duration to reliably capture any effects, to investigate whether effects persists over time, and if side effects occur during long-term use.