

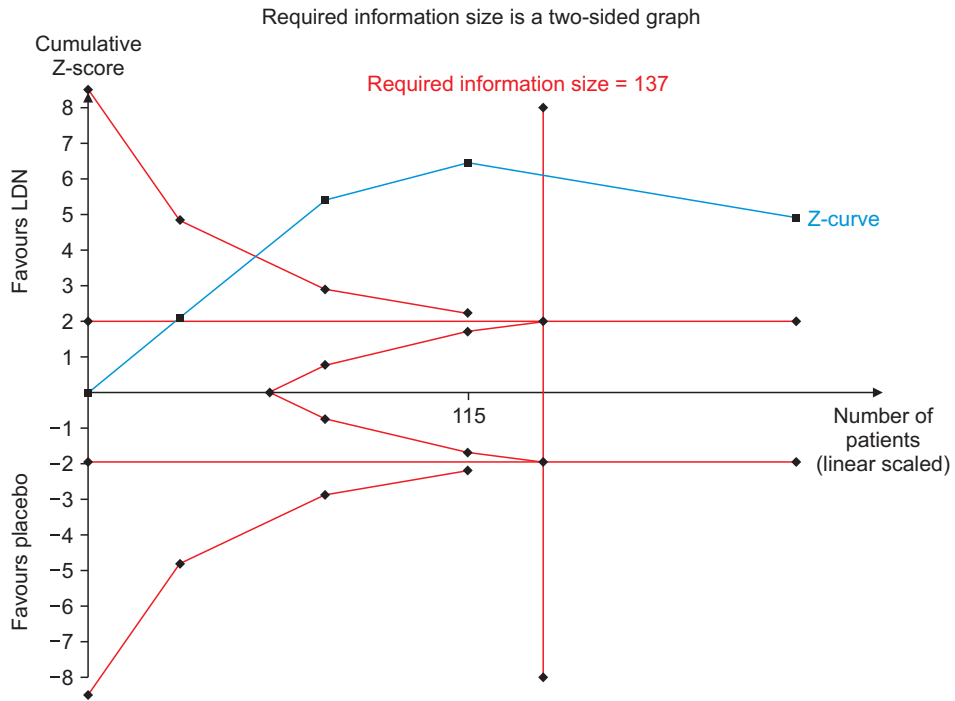
Supplementary Table 1. Literature search strategy

1A. PubMed search string:

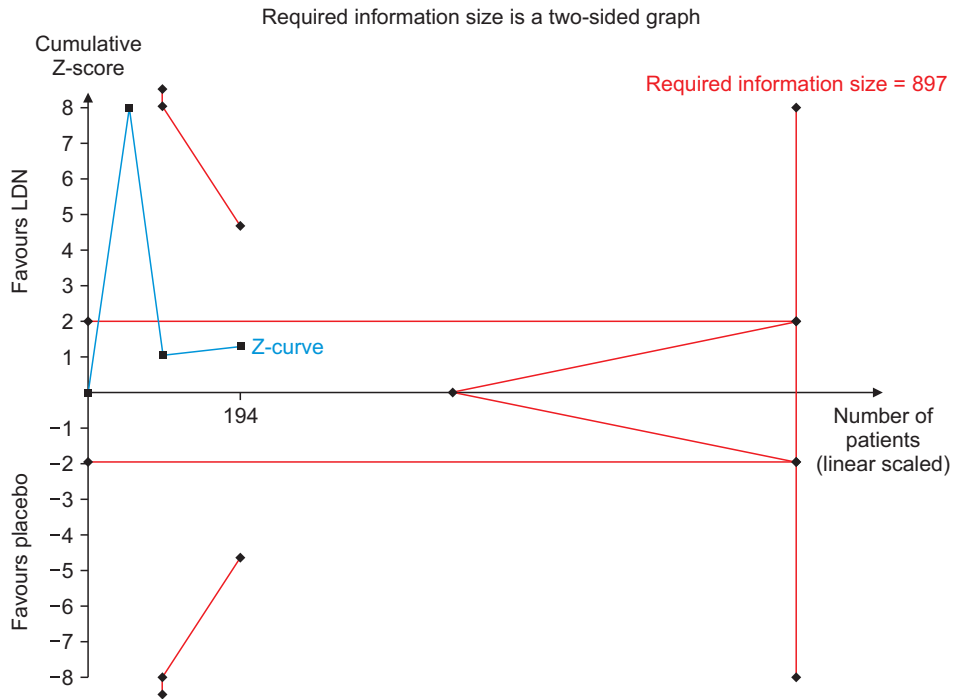
"(naltrexone OR low-dose naltrexone OR LDN) AND (fibromyalgia OR fibromyalgia syndrome OR fibromyositis OR fibrositis OR FM OR FMS)"

1B. Example Scopus, Cochrane Library, and ClinicalTrials.gov search strategy:

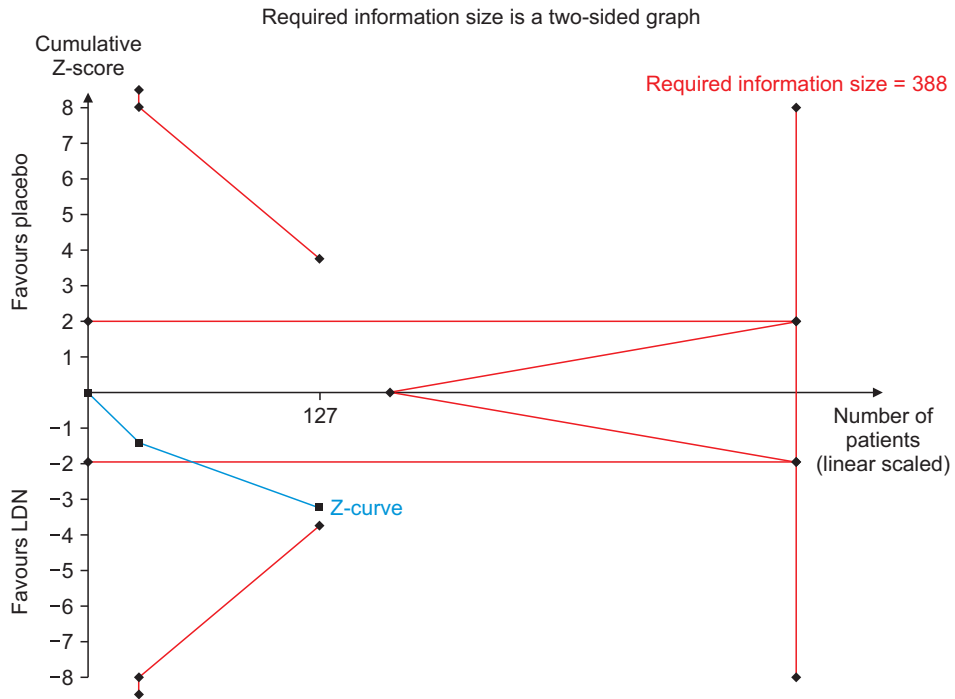
1. naltrexone
 2. low-dose naltrexone
 3. LDN
 4. fibromyalgia
 5. fibromyalgia syndrome
 6. fibromyositis
 7. fibrositis
 8. FM
 9. FMS
 10. 1 or 2 or 3
 11. 4 or 5 or 6 or 7 or 8 or 9
 12. 10 and 11
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Supplementary Fig. 1. Trial sequential analysis of low-dose naltrexone (LDN) versus placebo in the change of pain scores from baseline using power of 80% and 5% significance. The required sample size was 137 (vertical red line). The cumulative Z-curve (blue line with small black squares representing each trial) crossed both the traditional boundary (horizontal red line) and the superiority boundary (trial sequential monitoring boundary) (concave red line), indicating evidence is sufficient (true positive).



Supplementary Fig. 2. Trial sequential analysis of low-dose naltrexone (LDN) versus placebo in the change of fibromyalgia impact questionnaire revised scores from baseline using power of 80% and 5% significance. The required sample size was 897 (vertical red line). The cumulative Z-curve (blue line with small black squares representing each trial) did not cross both the traditional boundary (horizontal red line), the superiority boundary (trial sequential monitoring boundary) (concave red line), or the futility boundary (convex red line), indicating a lack of evidence (false negative).



Supplementary Fig. 3. Trial sequential analysis of low-dose naltrexone (LDN) versus placebo in at least 30% improvement in pain from baseline using power of 80% and 5% significance. The required sample size was 388 (vertical red line). The cumulative Z-curve (blue line with small black squares representing each trial) crossed the traditional boundary (horizontal red line), but did not cross both the superiority boundary (trial sequential monitoring boundary) (concave red line) and the futility boundary (convex red line), indicating a lack of evidence (false positive).