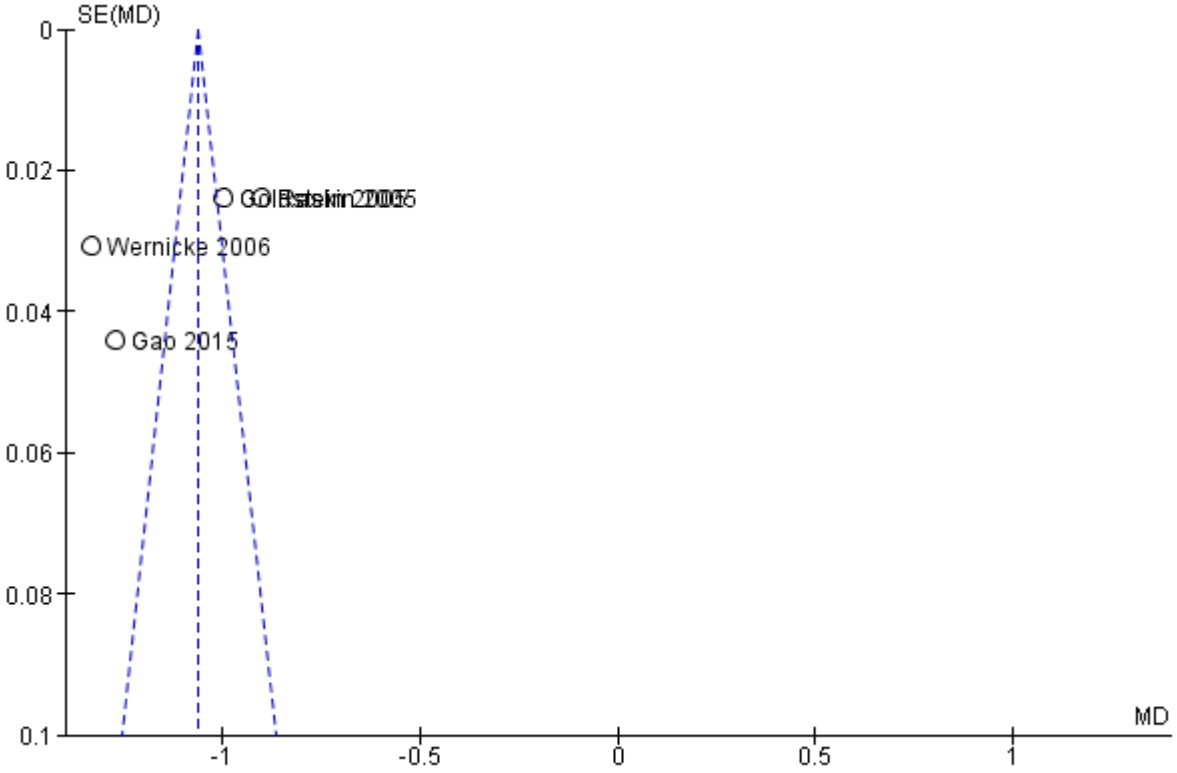
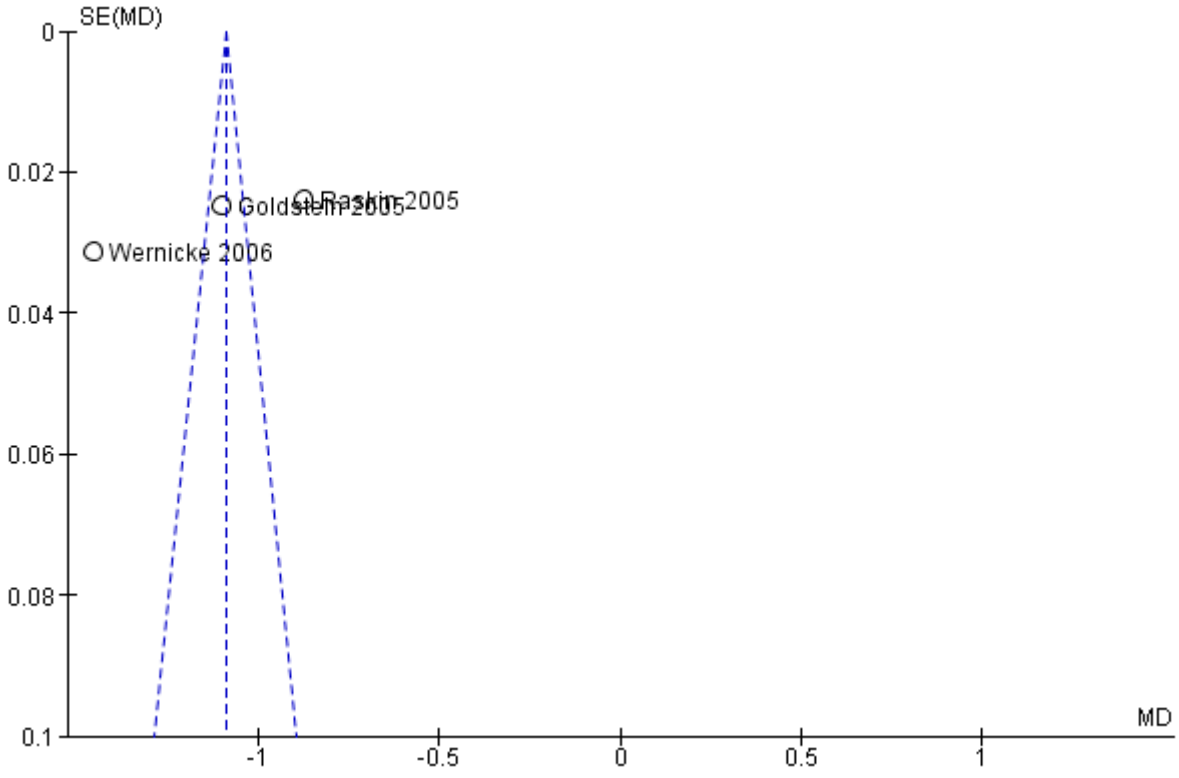
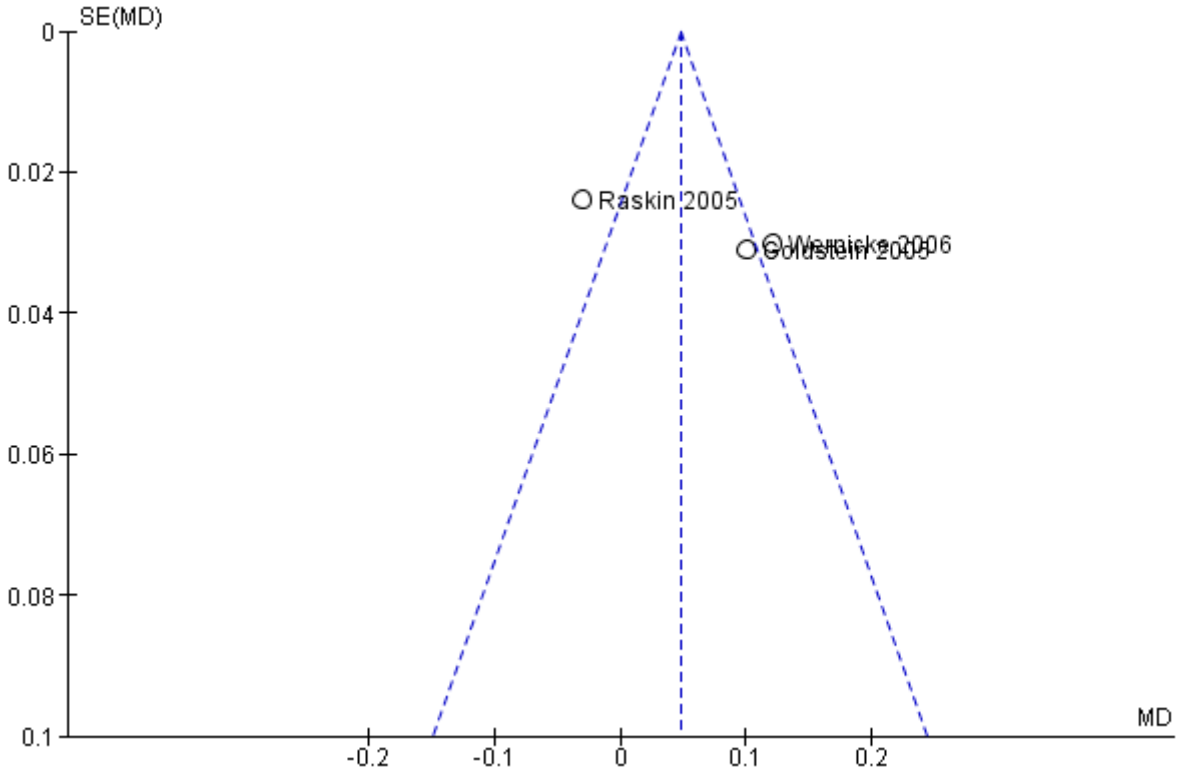


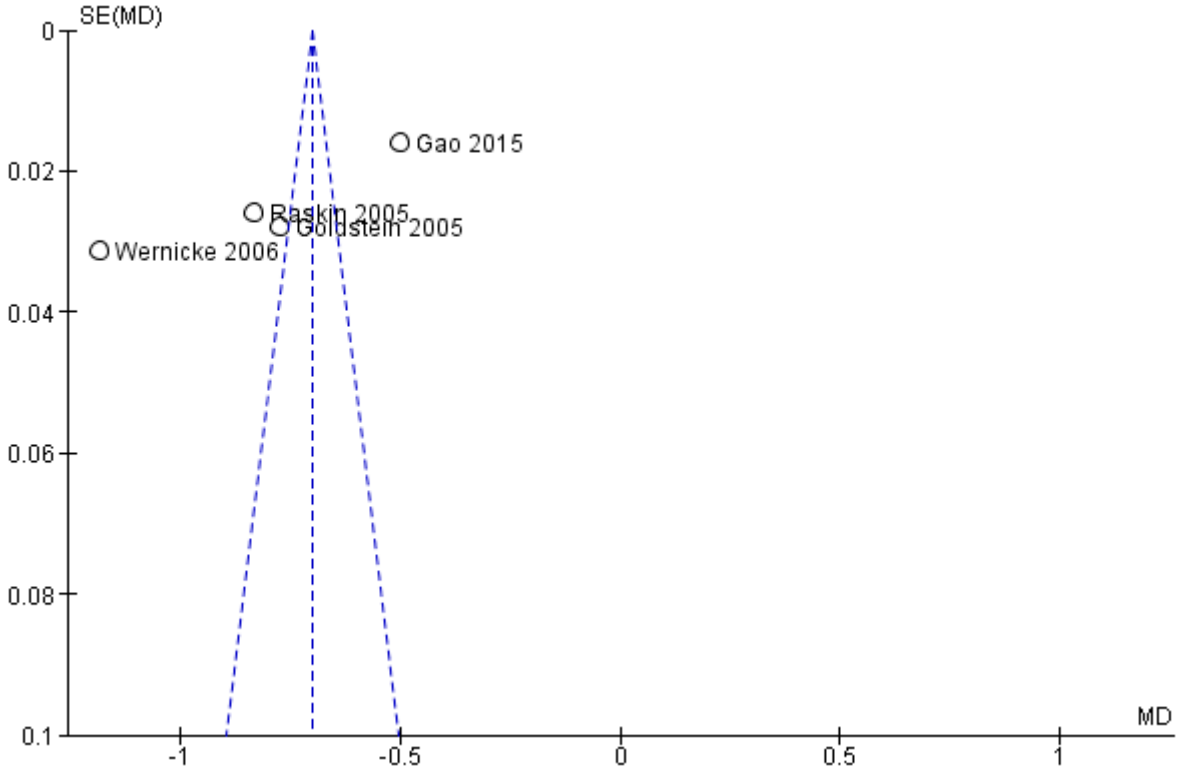
Supplementary Figure S1. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on 24-hour Average Pain Severity Score.



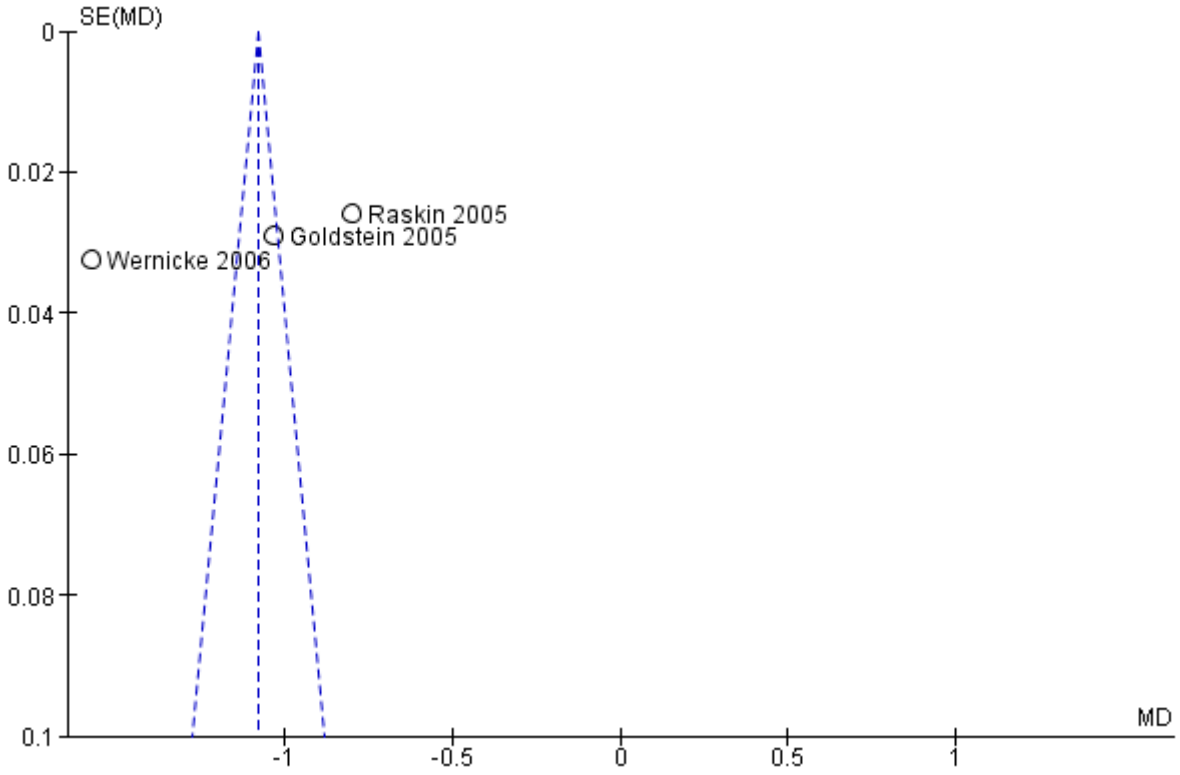
Supplementary Figure S2. Funnel plot of the effect of 120 mg/d dose of duloxetine compared to placebo on 24-hour Average Pain Severity Score.



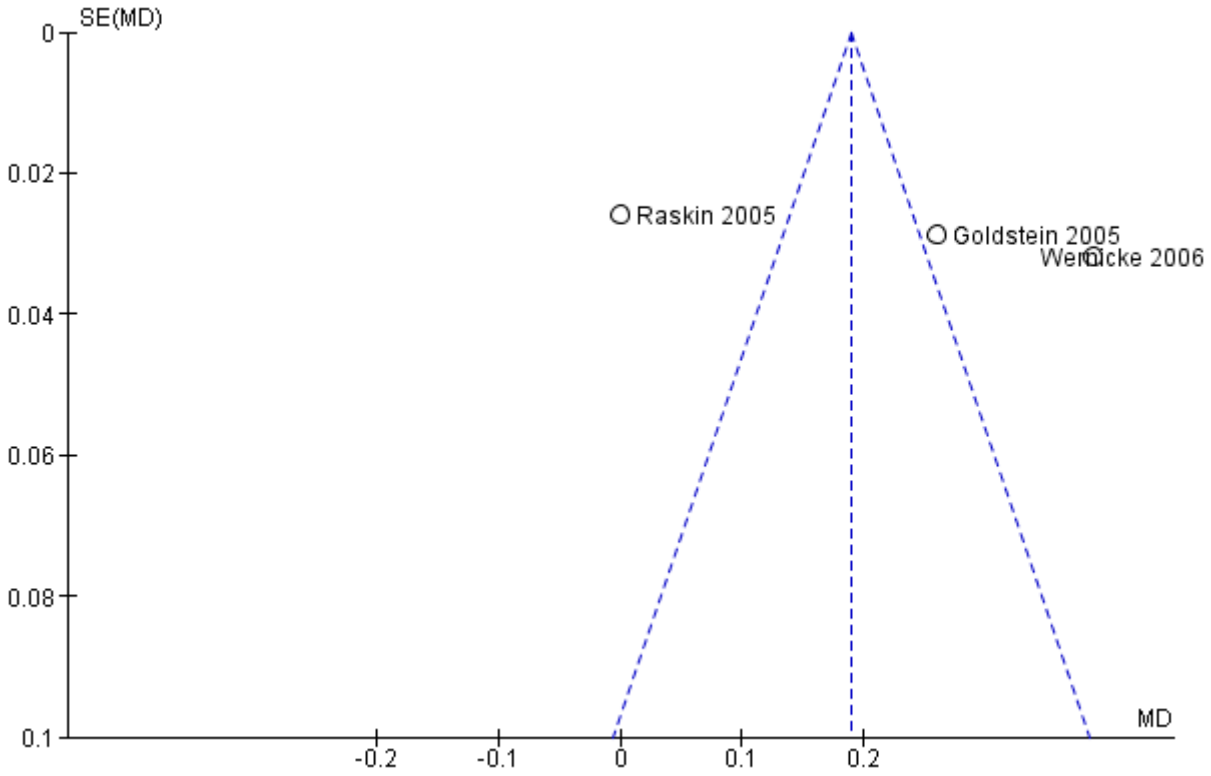
Supplementary Figure S3. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on 24-hour Average Pain Severity Score.



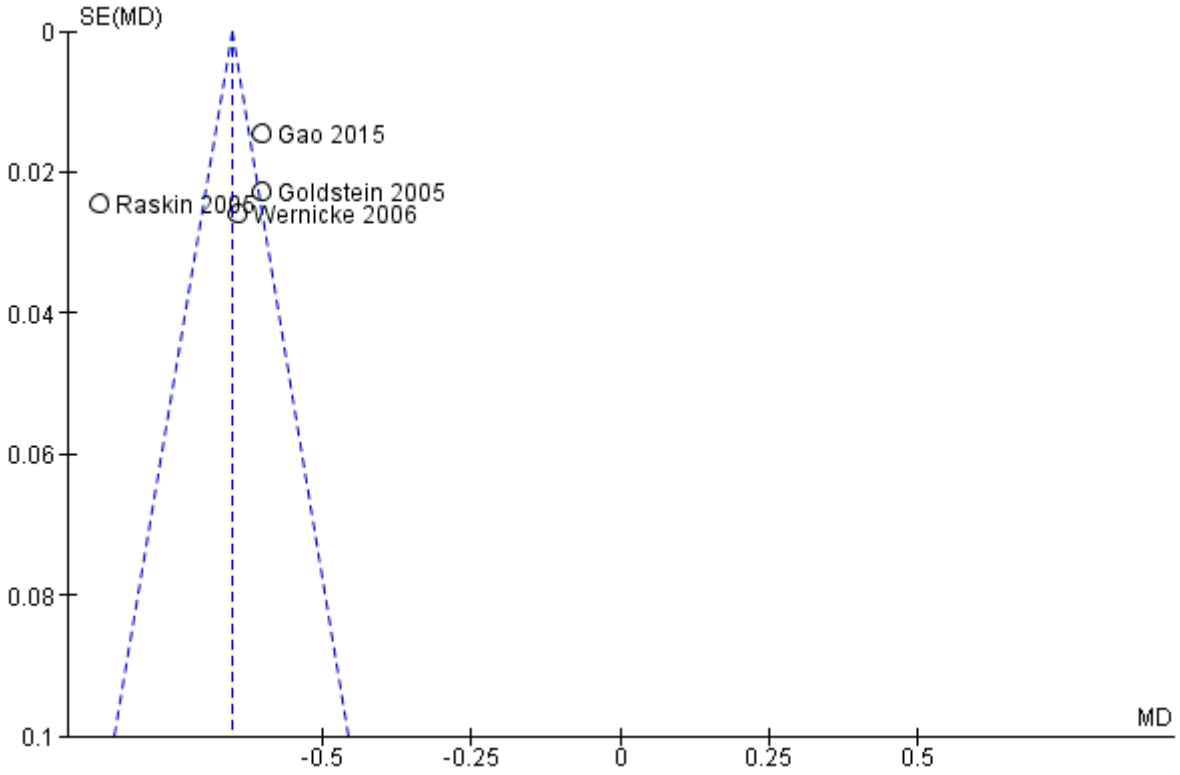
Supplementary Figure S4. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on BPI Severity.



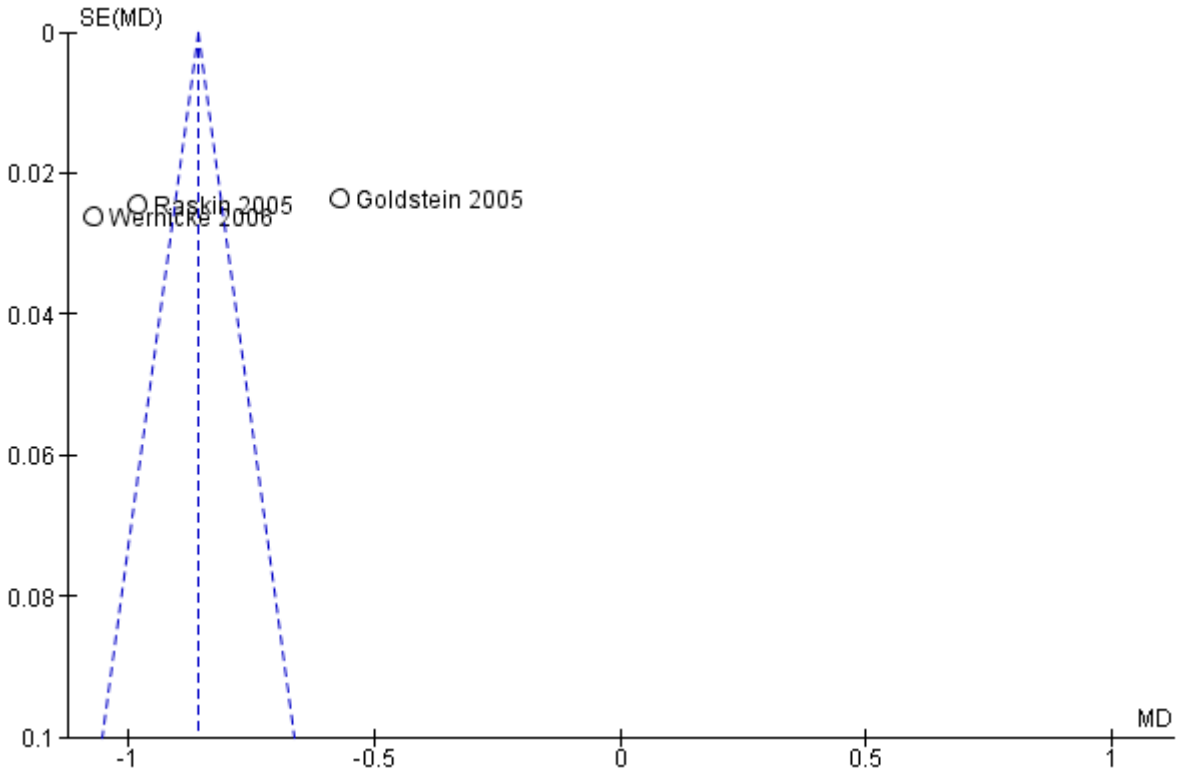
Supplementary Figure S5. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on BPI Severity.



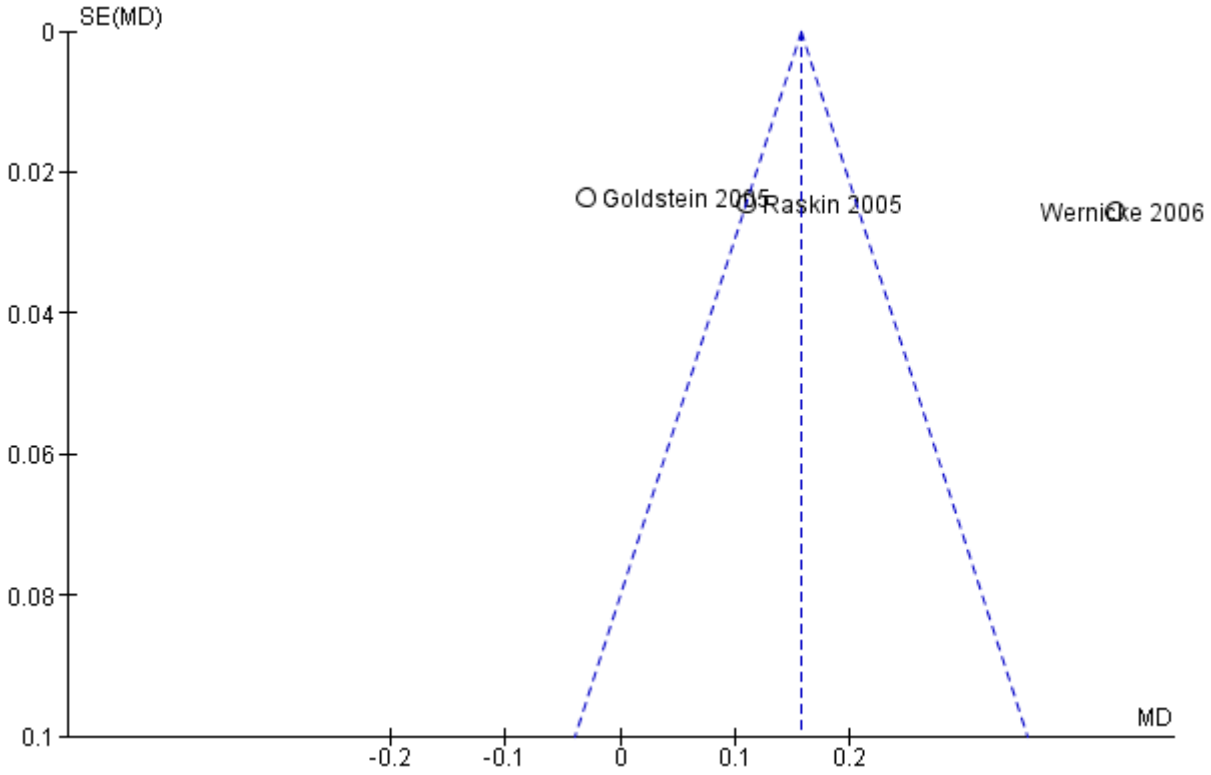
Supplementary Figure S6. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on BPI Severity.



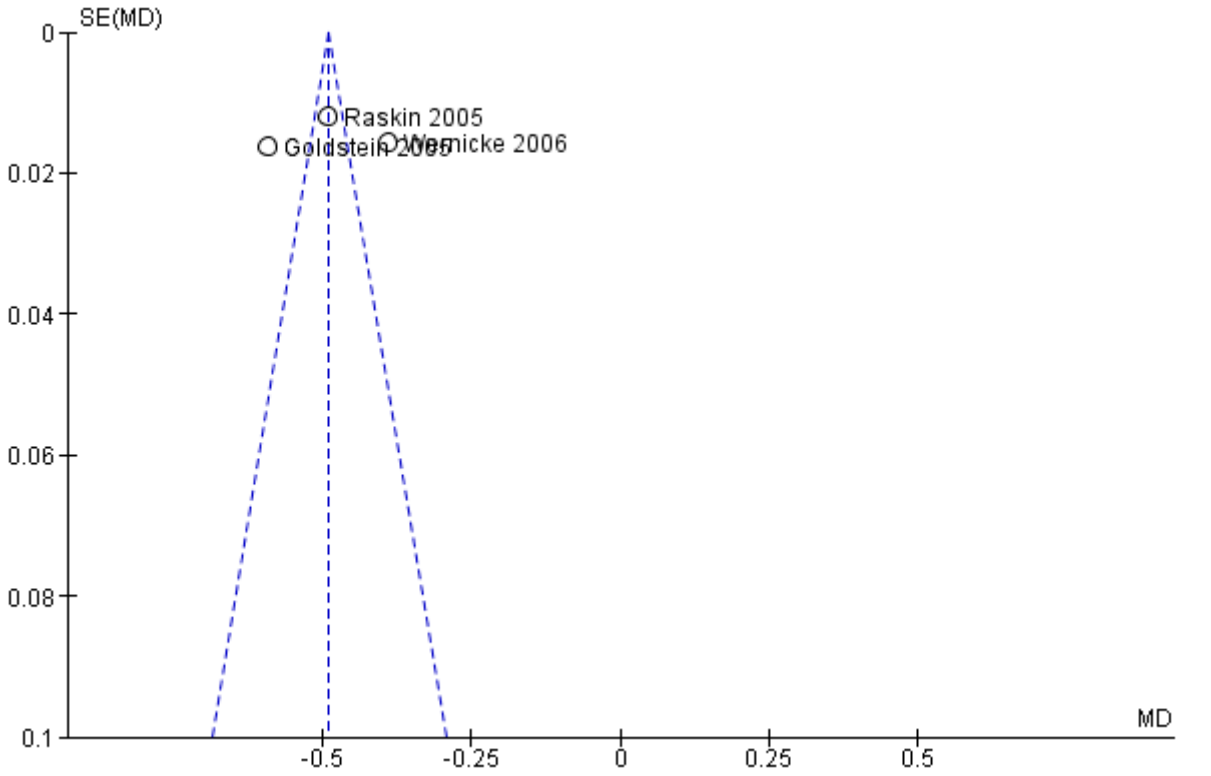
Supplementary Figure S7. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on BPI Interference.



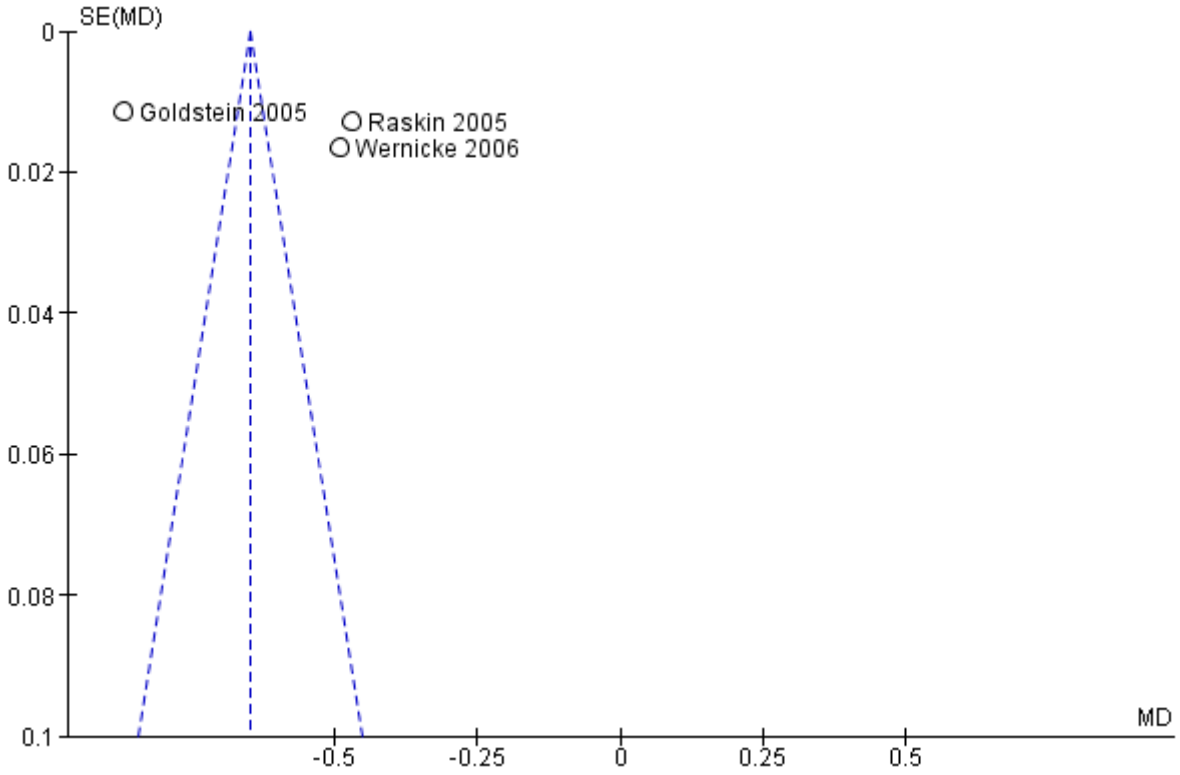
Supplementary Figure S8. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on BPI Interference.



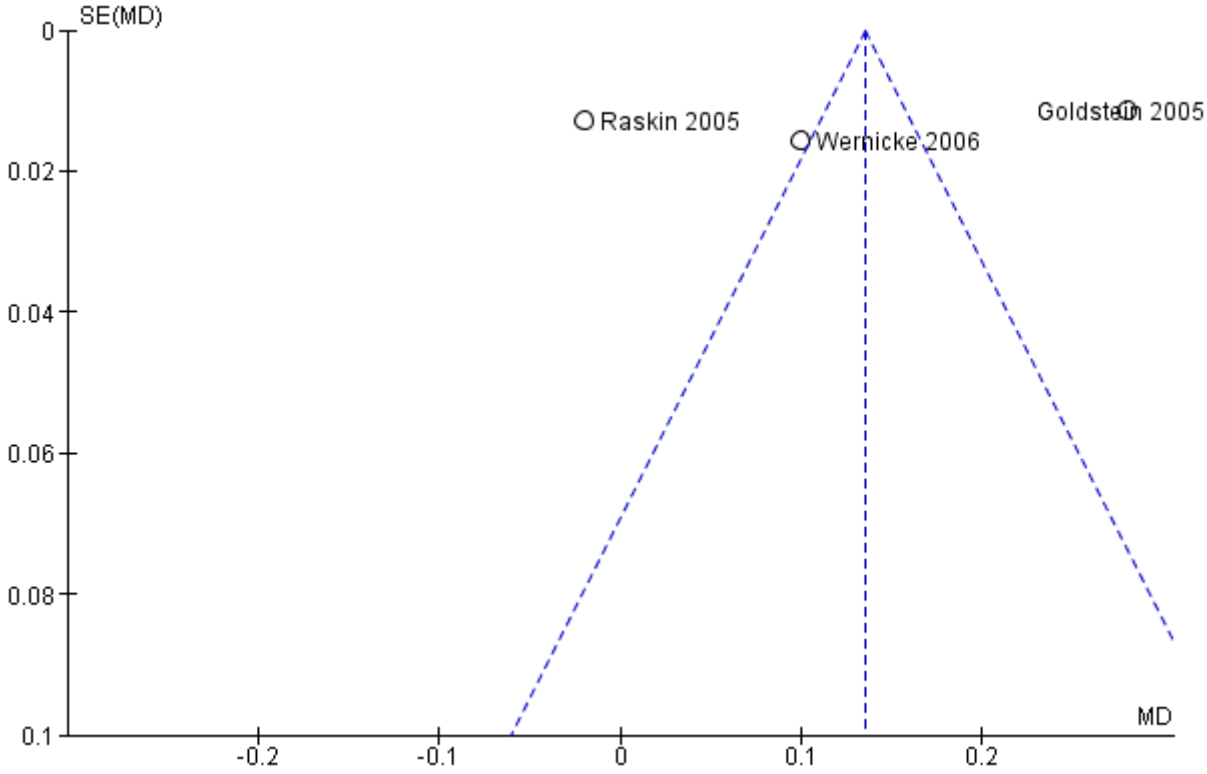
Supplementary Figure S9. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on BPI Interference.



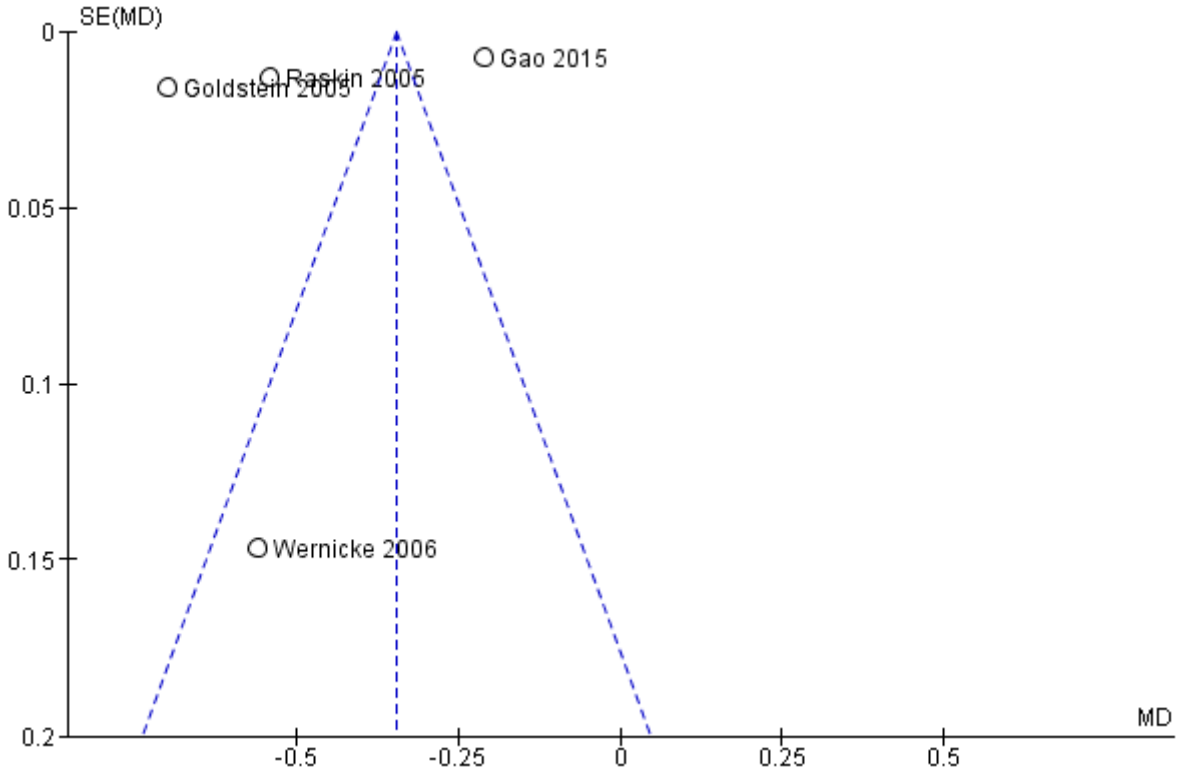
Supplementary Figure S10. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on CGI Severity.



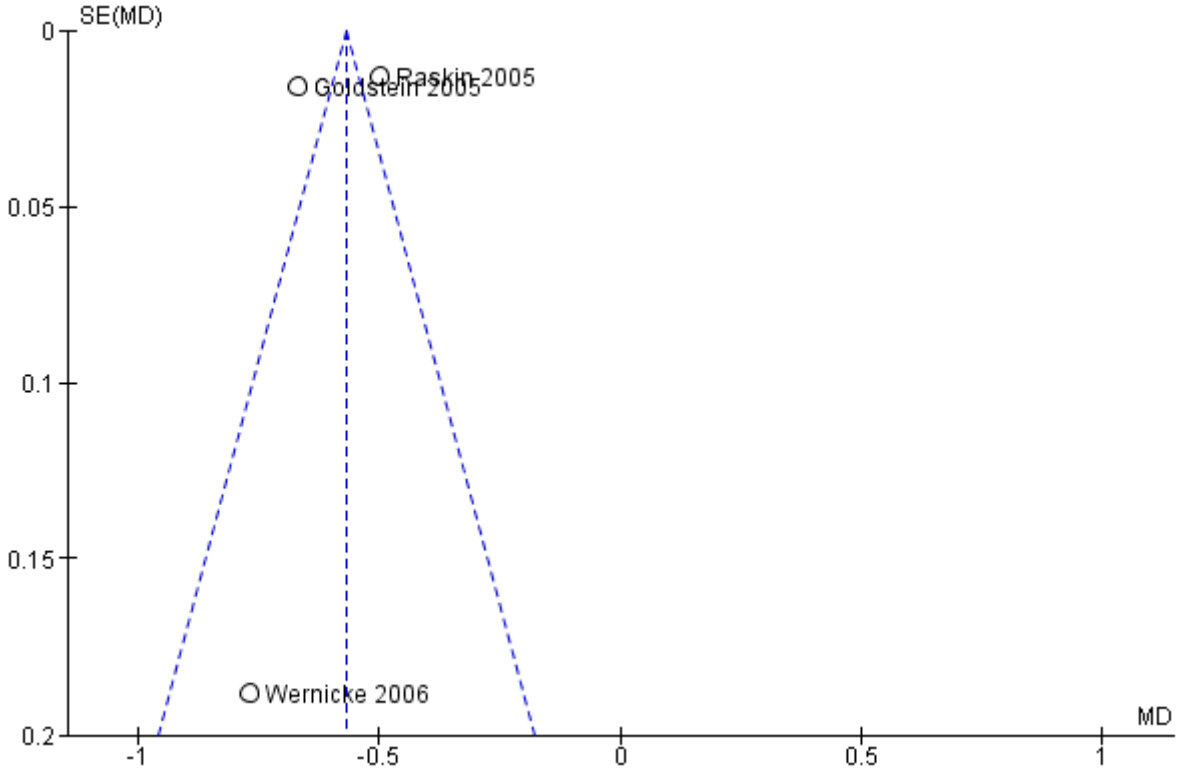
Supplementary Figure S11. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on CGI Severity.



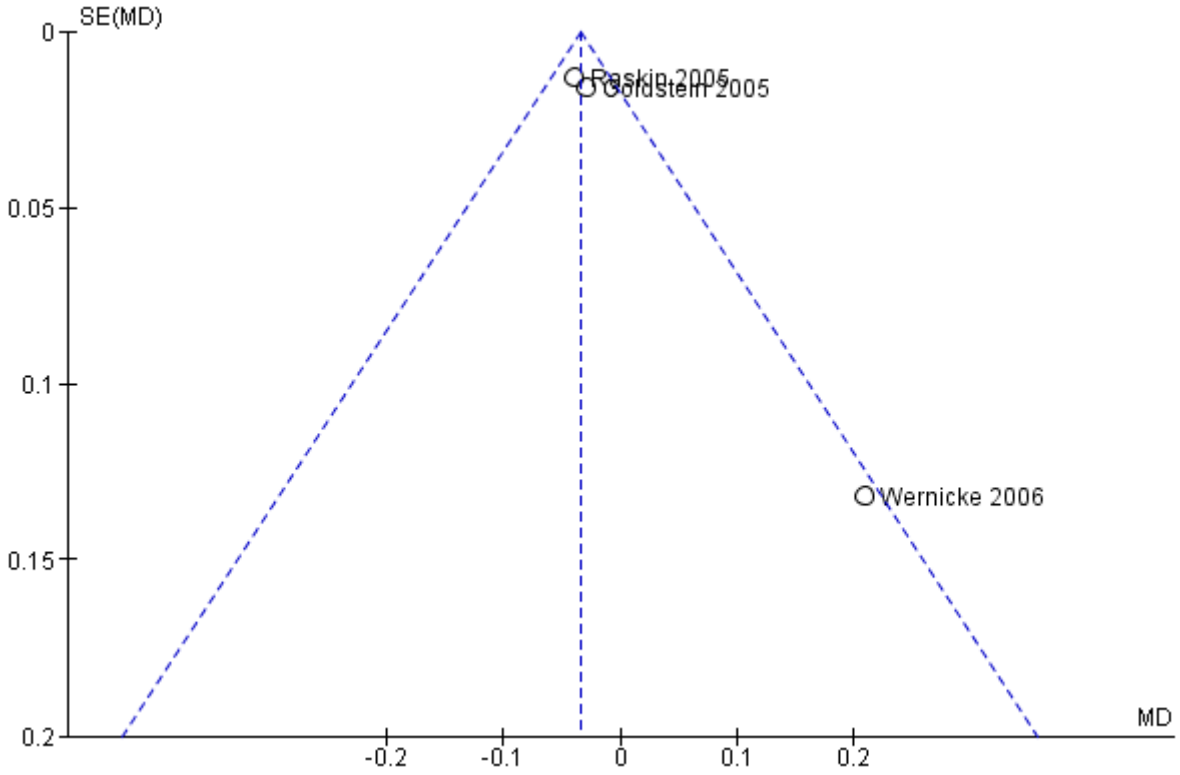
Supplementary Figure S12. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on CGI Severity.



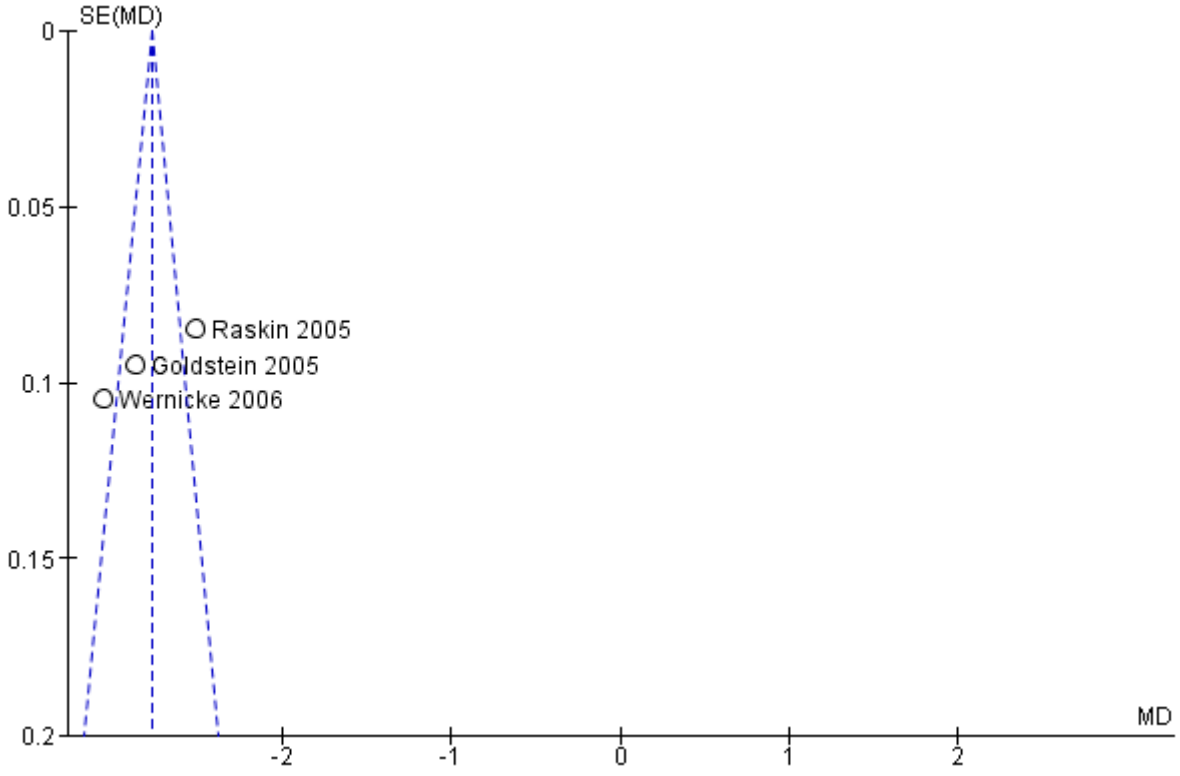
Supplementary Figure S13. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on PGI Improvement.



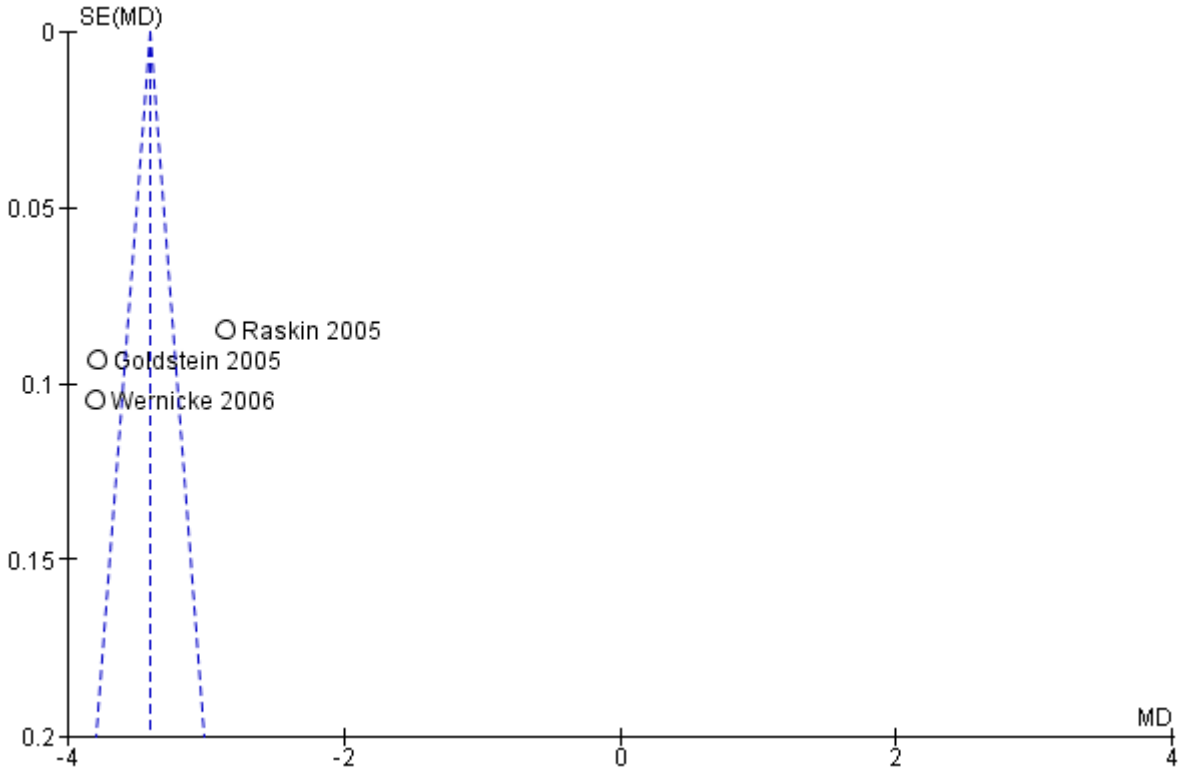
Supplementary Figure S14. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on PGI Improvement.



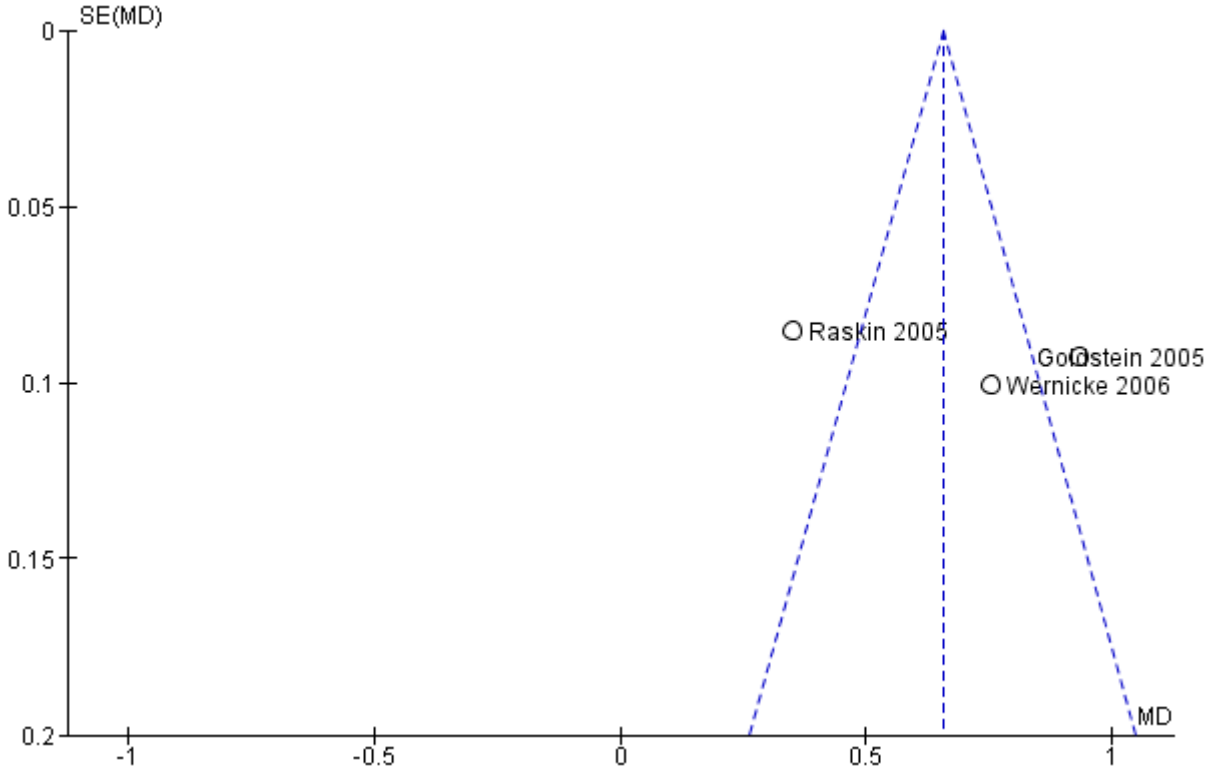
Supplementary Figure S15. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on PGI Improvement.



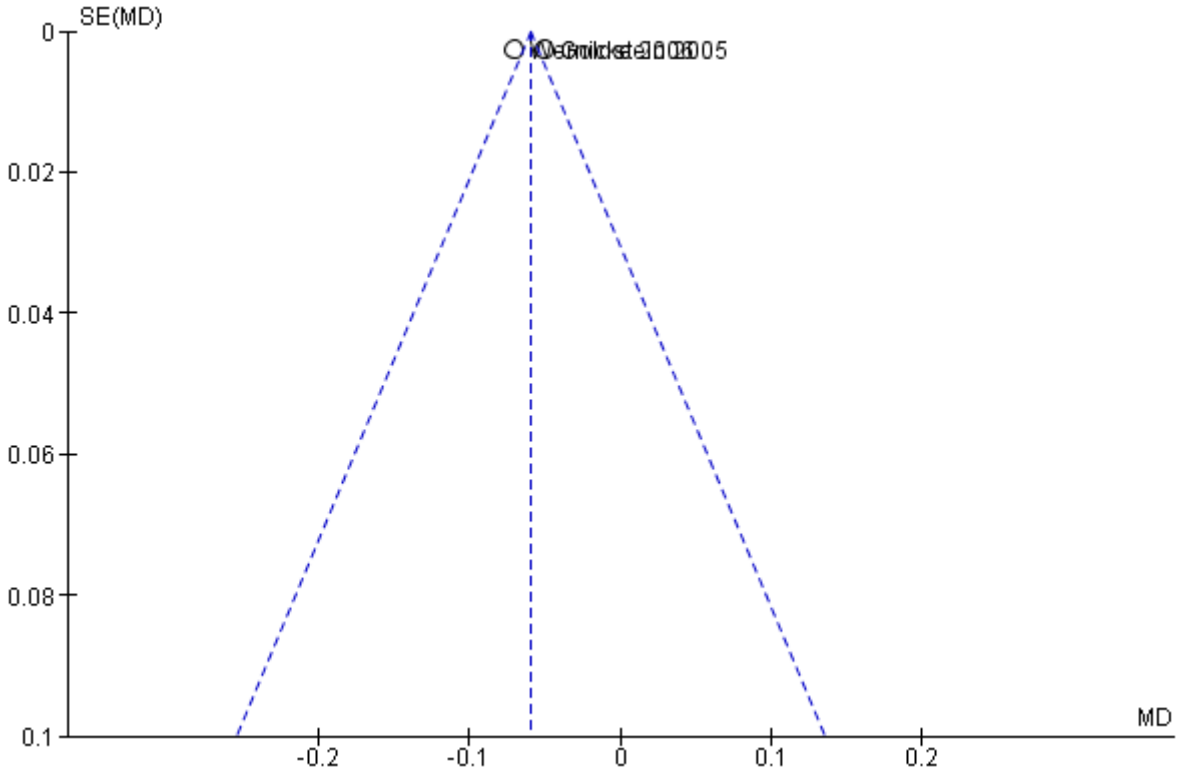
Supplementary Figure S16. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on SF-MPQ Total Score.



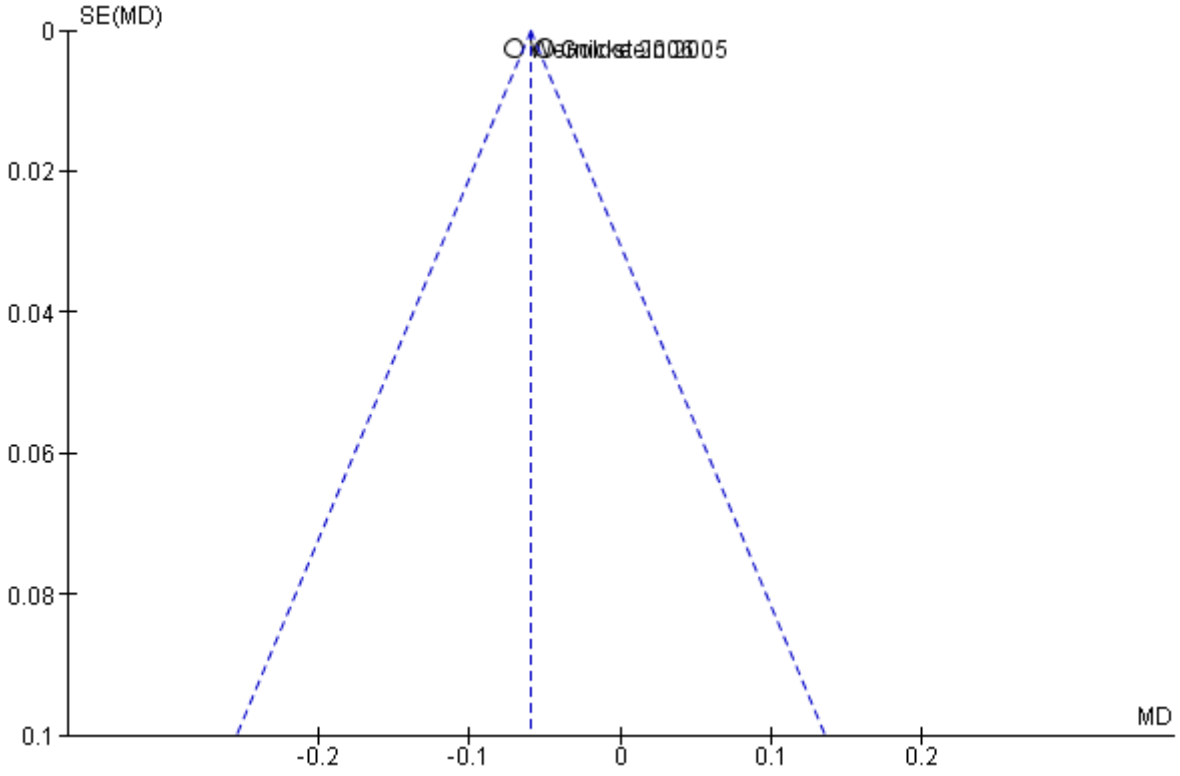
Supplementary Figure S17. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on SF-MPQ Total Score.



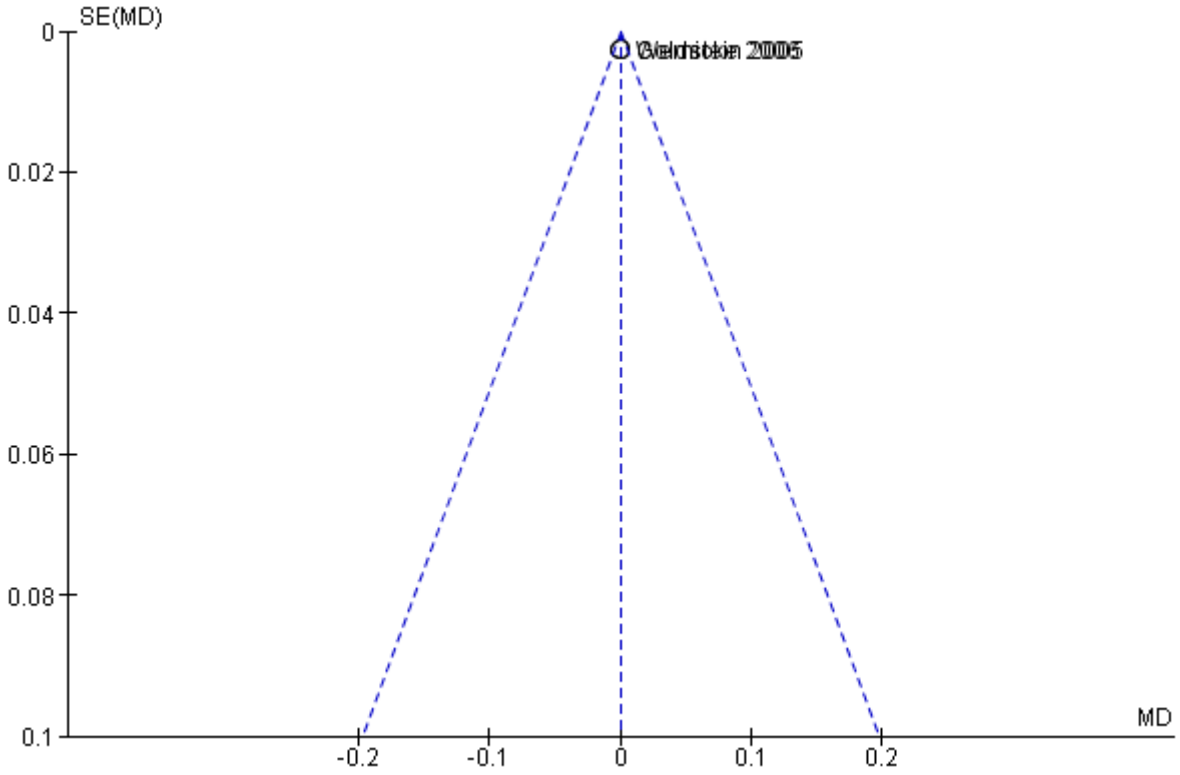
Supplementary Figure S18. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on SF-MPQ Total Score.



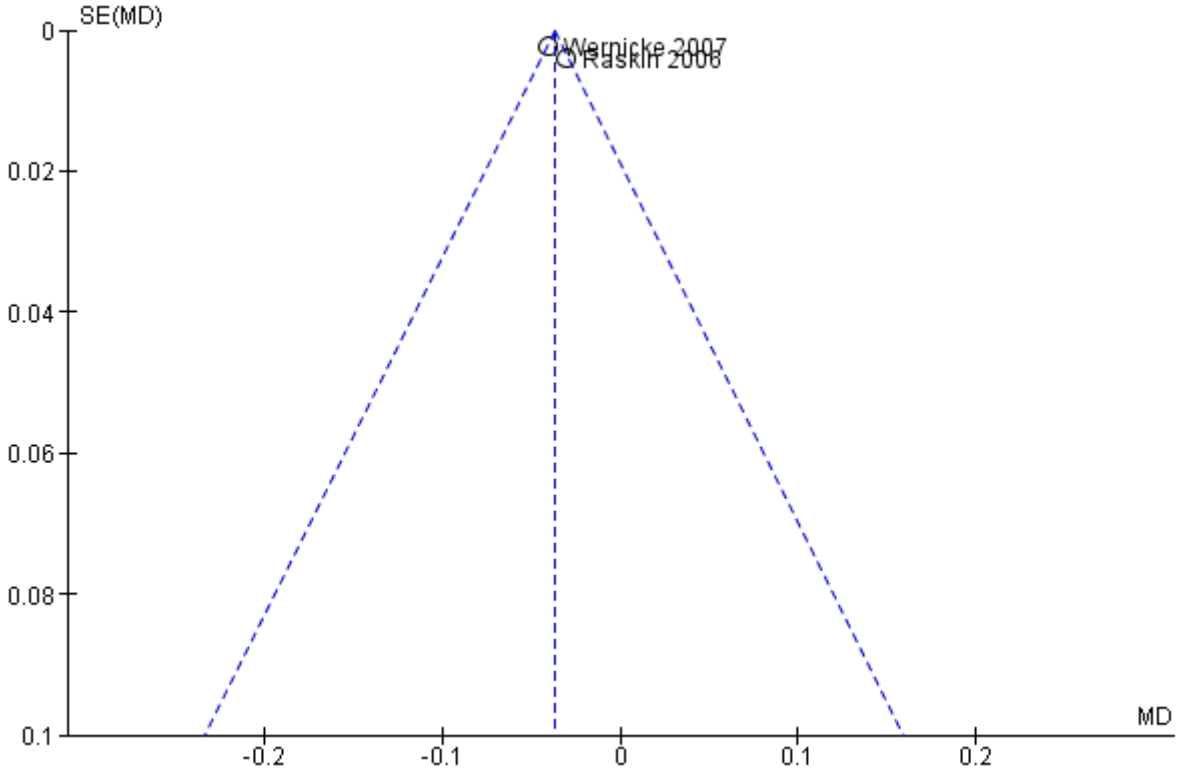
Supplementary Figure S19. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on Euro Quality of Life Questionnaire.



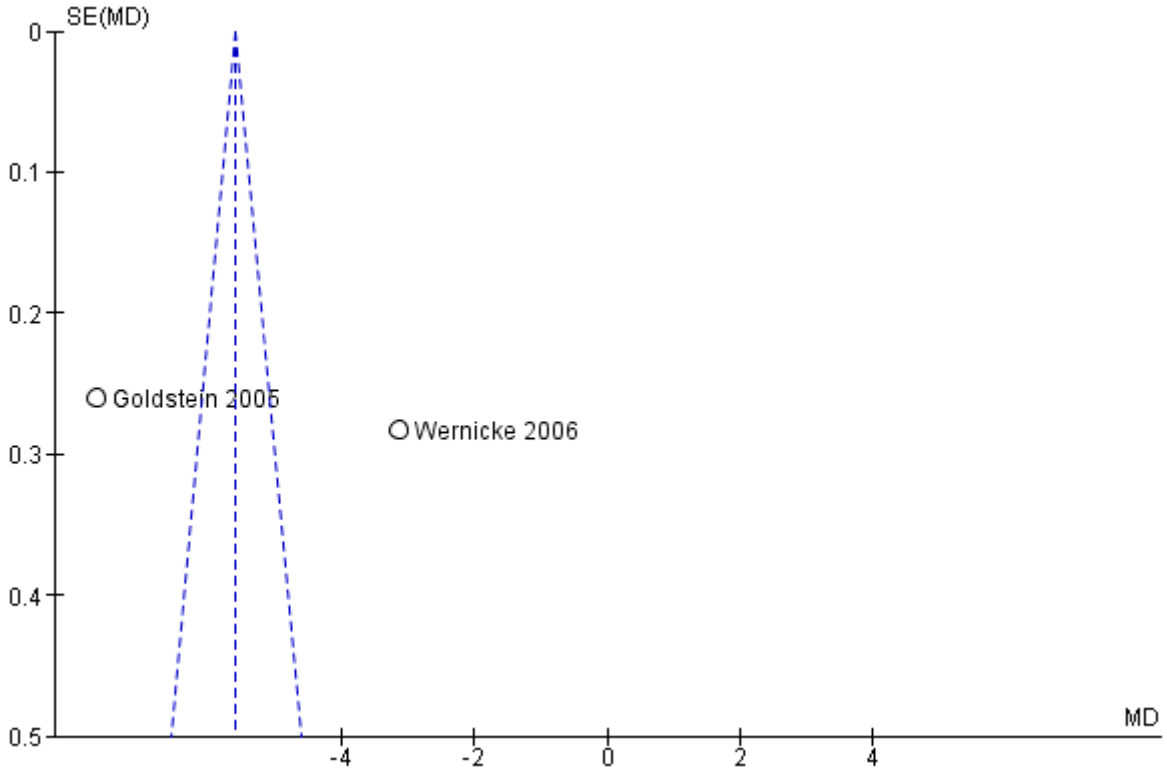
Supplementary Figure S20. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on Euro Quality of Life Questionnaire.



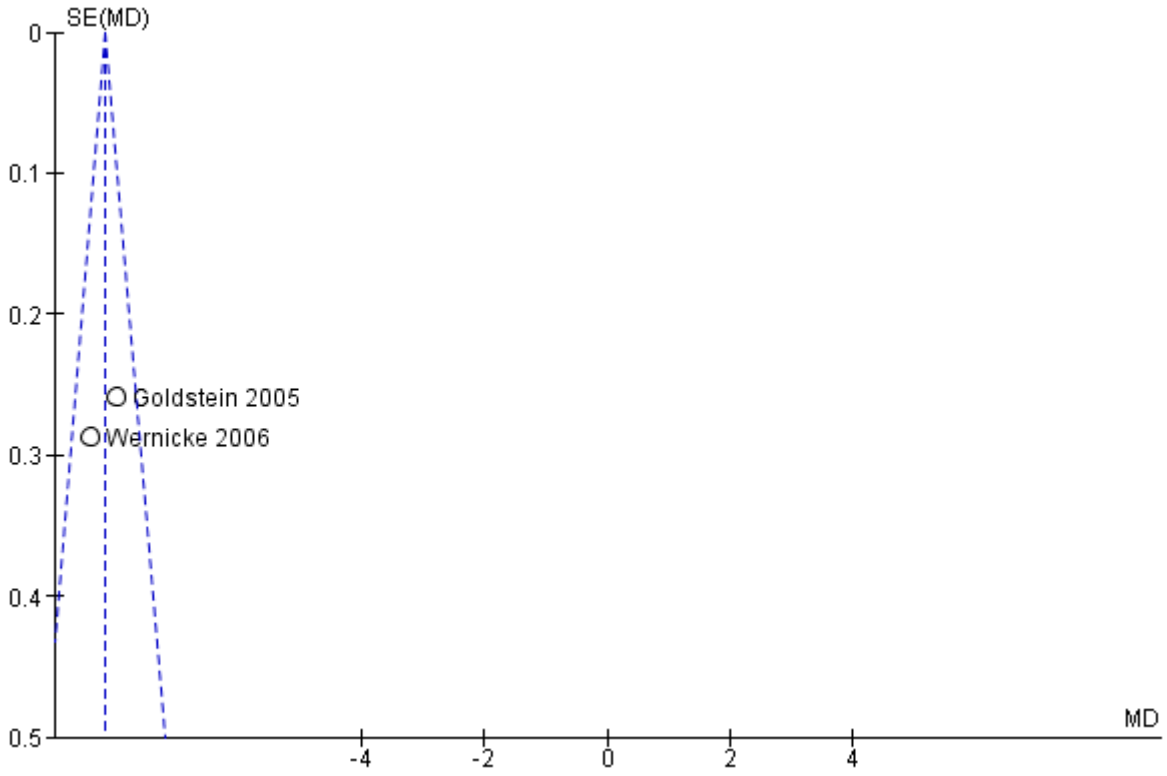
Supplementary Figure S21. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other on Euro Quality of Life Questionnaire.



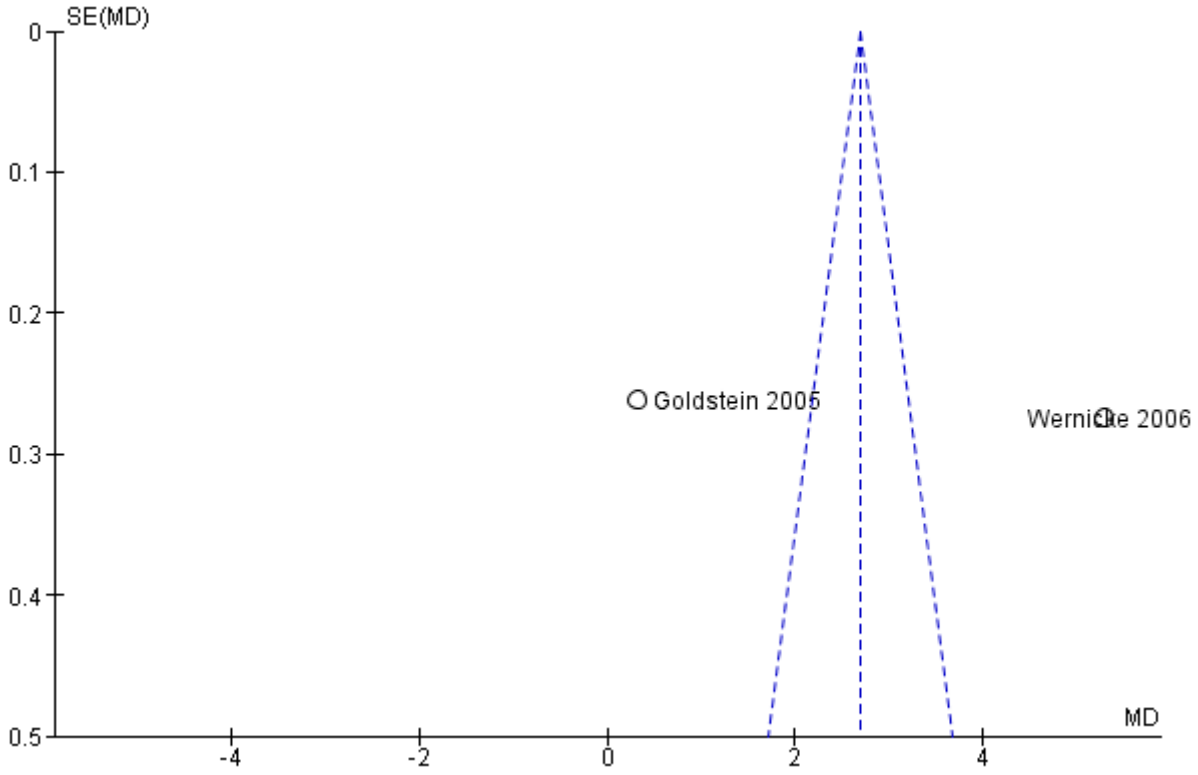
Supplementary Figure S22. Funnel plot of the effect of 120 mg/d dose of duloxetine compared to routine care on Euro Quality of Life Questionnaire.



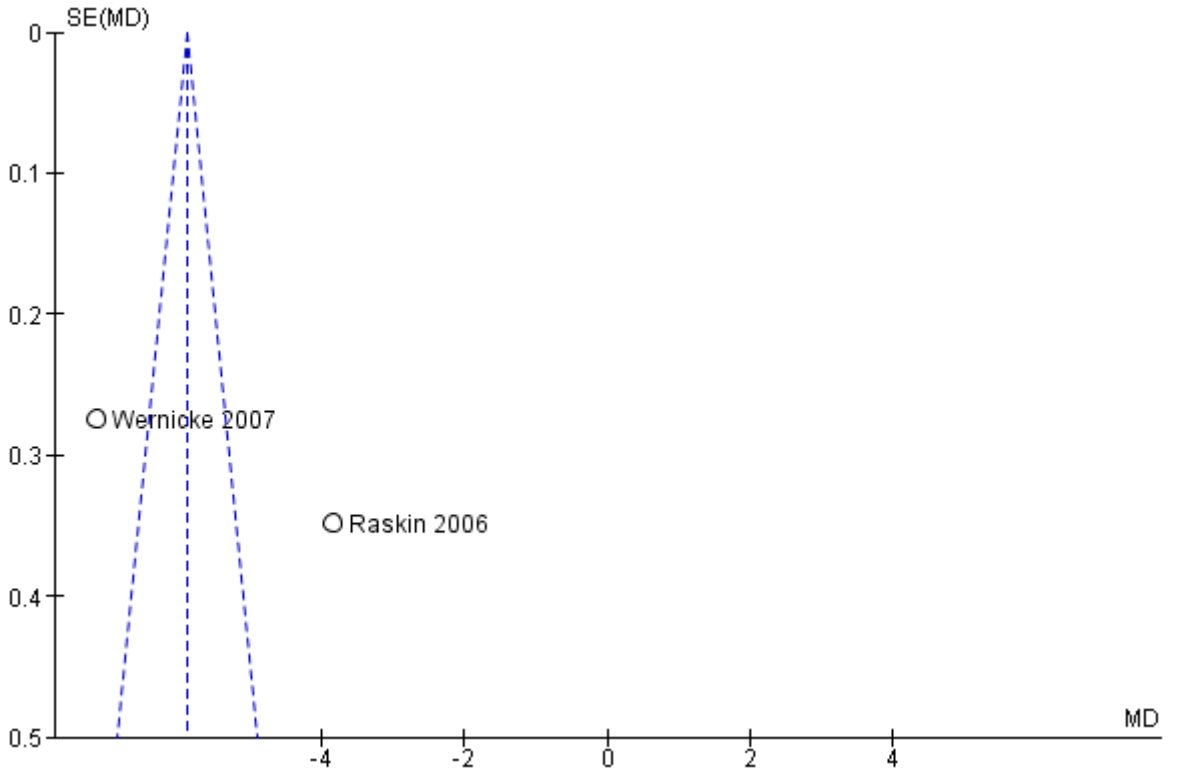
Supplementary Figure S23. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with placebo on SF-36 Survey Bodily Pain.



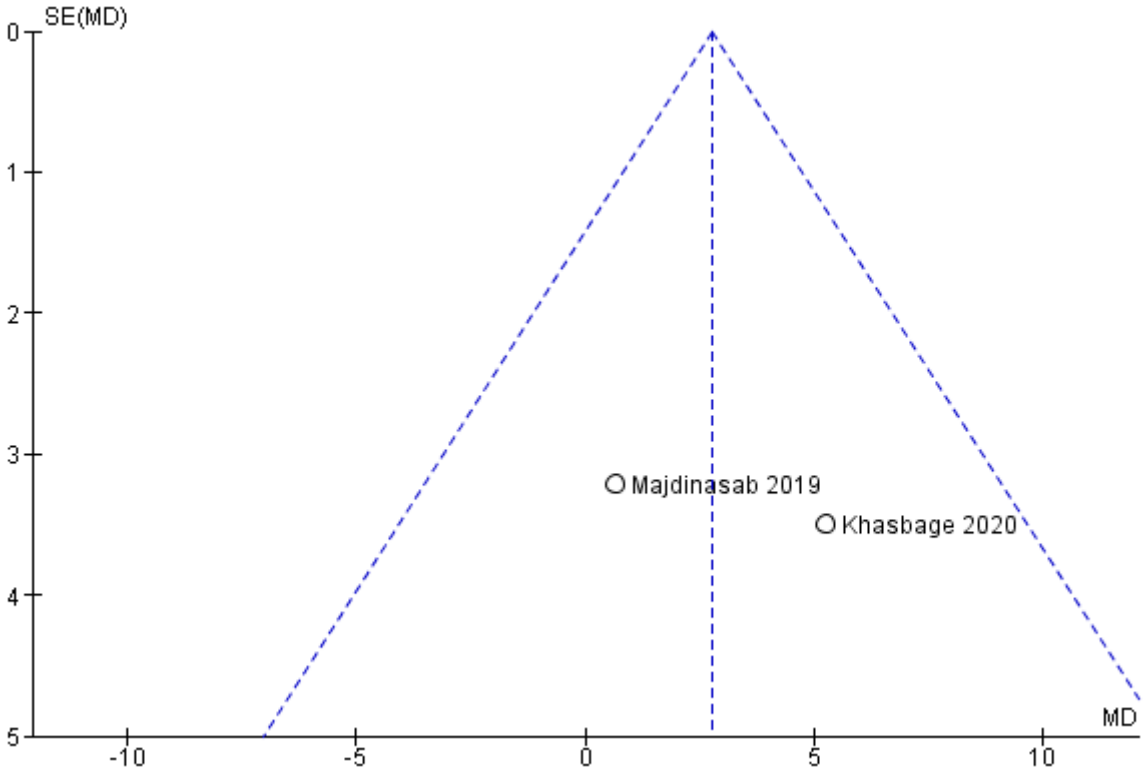
Supplementary Figure S24. Funnel plot of the effect of 120 mg/d dose of duloxetine compared with placebo on SF-36 Survey Bodily Pain.



Supplementary Figure S25. Funnel plot of the effect of both doses of duloxetine (60 mg/d and 120 mg/d) compared with each other, on SF-36 Survey Bodily Pain.



Supplementary Figure S26. Funnel plot of the effect of 120 mg/d dose of duloxetine compared to routine care, on SF-36 Survey Bodily Pain.



Supplementary Figure S27. Funnel plot of the effect of 60 mg/d dose of duloxetine compared with doses of 300 to 900 mg/d of gabapentin, on VAS.

Table S1. Excluded studies and the reasons for their exclusion.

N°	Reference	Reason
1	Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, Freynhagen R, Tesfaye S, Lledó A, Choy E, Marchettini P, Micó JA, Spaeth M, Skljarevski V, Tölle T. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. Pain. 2014 Oct;155(10):2171-9. doi: 10.1016/j.pain.2014.08.020. Epub 2014 Aug 27. PMID: 25168665.	Mixes duloxetine with a variety of antidepressants in different doses.
2	Boyle J, Eriksson ME, Gribble L, Gouni R, Johnsen S, Coppini DV, Kerr D. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 2012 Dec;35(12):2451-8. doi: 10.2337/dc12-0656. Epub 2012 Sep 18. PMID: 22991449; PMCID: PMC3507552.	Mixes duloxetine with a variety of antidepressants in different doses.
3	Gaynor PJ, Liu P, Weller MA, Wohlreich MM. Comparison of safety outcomes among Caucasian, Hispanic, Black, and Asian patients in duloxetine studies of chronic painful conditions. Curr Med Res Opin. 2013 May;29(5):549-60. doi: 10.1185/03007995.2013.784191. Epub 2013 Apr 3. PMID: 23477538.	Evaluates adverse reactions to medications in different races.
4	Irving G, Tanenberg RJ, Raskin J, Risser RC, Malcolm S. Comparative safety and tolerability of duloxetine vs. pregabalin vs. duloxetine plus gabapentin in patients with diabetic peripheral neuropathic pain. Int J Clin Pract. 2014 Sep;68(9):1130-40. doi: 10.1111/ijcp.12452. Epub 2014 May 18. PMID: 24837444.	Evaluates adverse reactions to pregabalin, duloxetine, and both together.
5	Kaur H, Hota D, Bhansali A, Dutta P, Bansal D, Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. Diabetes Care. 2011 Apr;34(4):818-22. doi: 10.2337/dc10-1793. Epub 2011 Feb 25. PMID: 21355098; PMCID: PMC3064034.	Mixes duloxetine with a variety of antidepressants in different doses.
6	Marchettini P, Wilhelm S, Petto H, Tesfaye S, Tölle T, Bouhassira D, Freynhagen R, Cruccu G, Lledó A, Choy E, Kosek E, Micó JA, Späth M, Skljarevski V, Lenox-Smith A, Perrot S. Are there different predictors of analgesic response between antidepressants and anticonvulsants in painful diabetic neuropathy? Eur J Pain.	Mixes duloxetine with a variety of antidepressants in

	2016 Mar;20(3):472-82. doi: 10.1002/ejp.763. Epub 2015 Aug 27. PMID: 26311228.	different doses.
7	Raskin J, Wang F, Pritchett YL, Goldstein DJ. Duloxetine for patients with diabetic peripheral neuropathic pain: a 6-month open-label safety study. Pain Med. 2006 Sep-Oct;7(5):373-85. doi: 10.1111/j.1526-4637.2006.00207.x. PMID: 17014595.	Compares same dose of duloxetine in different modalities.
8	Rizea-Savu S, Duna SN, Ghita A, Iordachescu A, Chirila M. The Effect of Food on the Single-Dose Bioavailability and Tolerability of the Highest Marketed Strength of Duloxetine. Clin Pharmacol Drug Dev. 2020 Oct;9(7):797-804. doi: 10.1002/cpdd.759. Epub 2019 Dec 2. PMID: 31793229; PMCID: PMC7586977.	Evaluates bioavailability of duloxetine in association with food.
9	Skljarevski V, Desaiah D, Zhang Q, Chappell AS, Detke MJ, Gross JL, Ziegler D. Evaluating the maintenance of effect of duloxetine in patients with diabetic peripheral neuropathic pain. Diabetes Metab Res Rev. 2009 Oct;25(7):623-31. doi: 10.1002/dmrr.1000. PMID: 19637208.	Mixes different doses of duloxetine with each other.
10	Skljarevski V, Desaiah D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, Iyengar S, Atkinson JH, Backonja M. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine (Phila Pa 1976). 2010 Jun 1;35(13):E578-85. doi: 10.1097/BRS.0b013e3181d3cef6. PMID: 20461028.	Evaluates chronic low back pain.
11	Tanenberg RJ, Irving GA, Risser RC, Ahl J, Robinson MJ, Skljarevski V, Malcolm SK. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. Mayo Clin Proc. 2011 Jul;86(7):615-26. doi: 10.4065/mcp.2010.0681. PMID: 21719618; PMCID: PMC3127557.	Mixes duloxetine with a variety of antidepressants in different doses.
12	Tanenberg RJ, Clemow DB, Giaconia JM, Risser RC. Duloxetine Compared with Pregabalin for Diabetic Peripheral Neuropathic Pain Management in Patients with Suboptimal Pain Response to Gabapentin and Treated with or without Antidepressants: A Post Hoc Analysis. Pain Pract. 2014 Sep;14(7):640-8. doi: 10.1111/papr.12121. Epub 2013 Oct 24. PMID: 24152185.	Mixes duloxetine with a variety of antidepressants in different doses.
13	Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, Cruccu G, Skljarevski V, Freynhagen R. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013 Dec;154(12):2616-2625. doi: 10.1016/j.pain.2013.05.043. Epub 2013 May 31. PMID: 23732189.	Mixes duloxetine with a variety of antidepressants in different doses.
14	Wernicke JF, Prakash A, Kajdasz DK, Houston J. Safety and tolerability of duloxetine treatment of diabetic peripheral neuropathic pain between patients with and without cardiovascular conditions. J Diabetes Complications. 2009 Sep-Oct;23(5):349-59. doi: 10.1016/j.jdiacomp.2008.07.004. Epub 2008 Sep 2. PMID: 18768332.	Evaluates safety in patients with cardiovascular diseases.
15	Wu EQ, Birnbaum HG, Mareva MN, Le TK, Robinson RL, Rosen A, Gelwicks S. Cost-effectiveness of duloxetine versus routine treatment for U.S. patients with diabetic peripheral neuropathic pain. J Pain. 2006 Jun;7(6):399-407. doi: 10.1016/j.jpain.2006.01.443. PMID: 16750796.	Evaluates the monetary cost-benefit of duloxetine treatment.
16	Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain. 2012 Jun;153(6):1193-1198. doi: 10.1016/j.pain.2012.02.021. Epub 2012 Apr 3. PMID: 22480803.	Mixes different doses of duloxetine with each other.
17	Yasuda H, Hotta N, Kasuga M, Kashiwagi A, Kawamori R, Yamada T, Baba Y, Alev L, Nakajo K. Efficacy and safety of 40 mg or 60 mg duloxetine in Japanese adults with diabetic neuropathic pain: Results from a randomized, 52-week, open-label study. J Diabetes Investig. 2016 Jan;7(1):100-8. doi: 10.1111/jdi.12361. Epub 2015 May 18. PMID: 26816607; PMCID: PMC4718094.	Mixes the results of groups of 40 and 60 mg/d of duloxetine.
18	Yuen E, Gueorguieva I, Bueno-Burgos L, Iyengar S, Aarons L. Population pharmacokinetic/pharmacodynamic models for duloxetine in the treatment of diabetic peripheral neuropathic pain. Eur J Pain. 2013 Mar;17(3):382-93. doi: 10.1002/j.1532-2149.2012.00209.x. Epub 2012 Aug 14. PMID: 22893563.	Evaluates PK/PD pharmacokinetic model but not pain.

Table S2. PRISMA.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pages 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pages 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 7-8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7-8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7-8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Page 10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 11

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplemental table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Supplemental tables 1 and 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supplemental figures 3 to 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplemental figures 3 to 8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplemental table 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplemental figures 3 to 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 10 to 14
	23b	Discuss any limitations of the evidence included in the review.	Pages 11 and 12
	23c	Discuss any limitations of the review processes used.	Pages 12 and 13
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 12 to 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 15
Competing interests	26	Declare any competing interests of review authors.	Page 15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Methods, 2.3 Electronic search

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table S3. GRADE. Summary of Findings (SoF) and quality of evidence (GRADE) for Duloxetine in patients with neuropathic pain associated with Diabetes Mellitus.

Certainty assessment							№ of patients		Effect		Quality of evidence (GRADE)	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Duloxetine	Control group	Relative (95% CI)	SMD (95% CI)		
Effect on 24- hour Average pain severity scorte (60 mg)												
4	RCT	Not Serious	Serious	Not serious	Serious	None	483	480	-	-1.06 (-1.09 to -1.03)	⊕◯◯◯ Very low	CRITICAL
Effect on 24- hour Average pain severity scorte (120 mg)												
3	RCT	Not Serious	Very serious	Not serious	Serious	None	305	307	-	-1.09 (-1.12 to -1.06)	⊕◯◯◯ Very low	CRITICAL
Effect on 24- hour Average pain severity scorte (60 mg VS 120 mg)												
3	RCT	Not serious	Very serious	Not serious	Serious	None	311	305	-	0,05(-0,02 to 0,08)	⊕⊕◯◯ Low	CRITICAL
Effect on BPI severity (60 mg)												
4	RCT	Not Serious	Very serious	Not serious	Serious	None	506	500	-	-0.70 (-0.72 to -0.68)	⊕⊕◯◯ Low	IMPORTANT

Effect on BPI severity (120 mg)												
3	RCT	Not serius	Serius	Not serious	Serious	None	324	325	-	-1.08, (-1.11 to -1.04)	⊕⊕◯◯ Low	IMPORTANT
Effect on BPI severity (60 mg VS 120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	333	324	-	0.19, (0.16 to 0.22)	⊕◯◯◯ Very low	IMPORTANT
Effect on BPI interference (60 mg)												
4	RCT	Serious	Serious	Not serious	Serious	None	505	501	-	-0.65, (-0.67 to – 0.63)	⊕◯◯◯ Very low	IMPORTANT
Effect on BPI interference (120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	324	325	-	-0.86, (-0.88 to – 0.83)	⊕⊕◯◯ Low	IMPORTANT
Effect on BPI interference (60 mg VS 120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	331	324	-	0.16, (0.13 to 0.18)	⊕◯◯◯ Very low	IMPORTANT
Effect on CGI severity (60 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	330	326	-	-0.49, (-0.50 to -0.47)	⊕◯◯◯ Very low	IMPORTANT
Effect on CGI severity (120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	325	326	-	-0.65, (-0.66 to -0.64)	⊕⊕◯◯ Low	IMPORTANT
Effect on CGI severity (120 mg VS 60 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	330	325	-	0.14, (0.12 to 0.15)	⊕◯◯◯ Very low	IMPORTANT
Effect on PGI improvement (60 mg)												
4	RCT	Serious	Serious	Not serious	Serious	None	504	505	-	-0.35, (-0.34 to -0.36)	⊕⊕◯◯ Low	IMPORTANT
Effect on PGI improvement (120 mg)												

3	RCT	Serious	Serious	Not serious	Serious	None	327	328	-	-0.57,(-0.59 to -0.55)	⊕⊕◯◯ Low	IMPORTANT
Effect on PGI improvement (60 mg VS 120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	332	327	-	-0.03,(-0.03 to -0.05)	⊕⊕◯◯ Low	IMPORTANT
Effect on SF-MPQ total score (60 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	294	288	-	-2.77,(-2.87 to -2.66)	⊕⊕◯◯ Low	IMPORTANT
Effect on SF-MPQ total score (120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	294	288	-	-3.42,(-3.53 to -3.31)	⊕⊕◯◯ Low	IMPORTANT
Effect on SF-MPQ total score (60 mg VS 120 mg)												
3	RCT	Serious	Serious	Not serious	Serious	None	294	303	-	0.65,(0.55 to 0.76)	⊕⊕◯◯ Low	IMPORTANT
Effect on Euro Quality of life Questionnaire (60 mg)												
2	RCT	Serious	Serious	Not serious	Serious	None	212	206	-	0.06,(0.06 to 0.06)	⊕◯◯◯ Very low	IMPORTANT
Effect on Euro Quality of life Questionnaire (120 mg)												
2	RCT	Serious	Serious	Not serious	Serious	None	212	210	-	0.06,(0.06 to 0.06)	⊕◯◯◯ Very low	IMPORTANT
Effect on Euro Quality of life Questionnaire (60 mg VS 120 mg)												
2	RCT	Serious	Serious	Not serious	Serious	None	212	210	-	0.00,(0.00 to 0.00)	⊕◯◯◯ Very low	IMPORTANT
Effect on Euro Quality of life Questionnaire (120 mg vs routine care)												
2	RCT	Serious	Serious	Not serious	Serious	None	332	148	-	-0.04,(-0.04 to -0.03)	⊕◯◯◯ Very low	IMPORTANT
Effect on SF-36 Survey Bodily Pain (60 mg)												

2	RCT	Serious	Serious	Not serious	Serious	None	213	208	-	-5.56,(-5.96 to -5.21)	⊕⊕◯◯ Low	CRITICAL
Effect on SF-36 Survey Bodily Pain (120 mg)												
2	RCT	Serious	Serious	Not serious	Serious	None	212	208	-	-8.19,(-8.57 to -7.81)	⊕⊕◯◯ Low	CRITICAL
Effect on SF-36 Survey Bodily Pain (60 VS 120 mg)												
2	RCT	Serious	Serious	Not serious	Serious	None	213	212	-	2.69,(2.32 to 3.06)	⊕⊕◯◯ Low	CRITICAL
Effect on SF-36 Survey Bodily Pain (120 mg vs routine care)												
2	RCT	Serious	Serious	Not serious	Serious	None	334	150	-	-5.86,(-6.28 to -5.44)	⊕◯◯◯ Very low	CRITICAL
Effect on VAS (60 mg)												
2	RCT	Serious	Serious	Not serious	Serious	None	90	84	-	2.76,(-1.88 to 7.39)	⊕◯◯◯ Very low	CRITICAL

SMD: Standard Mean Difference; **RCT:** Randomized clinical trial; **Quality of evidence:** High: The research provides a very good indication of the likely effect. The probability that the effect is different is low; Moderate: The research provides a good indication of the likely effect. The probability that the effect is substantially different is moderate; Low: The research gives some indication of the probable effect. However, the probability that the effect is substantially different is high; Very low: The research does not provide a reliable estimate of the probable effect. The probability that the effect is substantially different is very high. **Downgrading:** GRADE approach has four reasons for possible rate down the quality of evidence. Begins with the study designs (trials or observational studies), secondly downgrading the evidence one level: (1) for study limitation if the majority of studies (>50%) was rated as high risk of bias; (2) for inconsistency, if heterogeneity was greater than the accepted low level (I^2 >40%); (3) for indirectness, directness was undoubled; (4) for imprecision, if meta-analysis had a small sample size (n <400) or confidence interval very wide