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# Appendix A: Search strategies

Appendix A.1. Search strategy: Pharmacological interventions for children with chronic pain (April 2020)

Database searched	Date searched
CENTRAL (The Cochrane Library) Issue 4 of 12, 2020	9/4/20
	8/4/20
6th 2020	
EMBASE (OVID) 1980 to 2020 week 14	8/4/20

# CENTRAL (The Cochrane Library)

#1 MeSH descriptor: [Child] explode all trees

#2 MeSH descriptor: [Infant] this term only

#3 MeSH descriptor: [Adolescent] this term only

#4 ((child\* or infant\* or baby or babies or preschooler\* or pre-schooler\* or toddler\* or schoolchild\* or girl\* or boy\* or adolescen\* or teen\*)):ti,ab,kw (Word variations have been searched)

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Analgesics, Opioid] explode all trees

#7 ((morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone)):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Ketamine] this term only

#9 ((ketamine or ketalar or calipsol or ketanest)):ti,ab,kw (Word variations have been searched)

#10 ((ketaset or calypsol or kalipsol)):ti,ab,kw (Word variations have been searched)

#11 (ci-581):ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees

#13 (NSAID\*):ti,ab,kw (Word variations have been searched)

#14 ((ibuprofen or aspirin or naproxen or fenoprofen or ketoprofen or tiaprofenic acid or diclofenac or aceclofenac or etodolac or indometacin or mefenamic acid or meloxicam or nabumeton or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or parecoxib or celecoxib or etoricoxib)):ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Acetaminophen] this term only

#16 ((acetaminophen or paracetamol or Panadol or Tylenol)):ti,ab,kw (Word variations have been searched)

#17 MeSH descriptor: [Antidepressive Agents] explode all trees

#18 ((amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline)):ti,ab,kw (Word variations have been searched)

#19 MeSH descriptor: [Anticonvulsants] explode all trees

#20 (non-steroidal anti-inflammatory drug):ti,ab,kw (Word variations have been searched)

#21 (non-steroidal anti-inflammatory agent):ti,ab,kw (Word variations have been searched)

#22 MeSH descriptor: [Acetaminophen] this term only

#23 ((acetaminophen or paracetamol or Panadol or Tylenol)):ti,ab,kw (Word variations have been searched)

#24 MeSH descriptor: [Antidepressive Agents] explode all trees

#25 ((amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline)):ti,ab,kw (Word variations have been searched)

#26 MeSH descriptor: [Anticonvulsants] explode all trees

#27 ((carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide)):ti,ab,kw (Word variations have been searched)

#28 MeSH descriptor: [Duloxetine Hydrochloride] this term only

#29 (duloxetine):ti,ab,kw (Word variations have been searched)

#30 (serotonin norepinephrine reuptake inhibitor):ti,ab,kw (Word variations have been searched)

#31 (SNRI):ti,ab,kw (Word variations have been searched)

#32 MeSH descriptor: [Milnacipran] this term only

#33 (milnacipran):ti,ab,kw (Word variations have been searched)

#34 (Flupirtine):ti,ab,kw (Word variations have been searched)

#35 (gabapentinoid\*):ti,ab,kw (Word variations have been searched)

#36 (Indomethacin):ti,ab,kw (Word variations have been searched)

#37 MeSH descriptor: [Venlafaxine Hydrochloride] this term only

#38 (Venlafaxine):ti,ab,kw (Word variations have been searched)

#39 MeSH descriptor: [Desipramine] this term only

#40 (Desipramine):ti,ab,kw (Word variations have been searched)

#41 MeSH descriptor: [Tramadol] this term only

#42 (tramadol):ti,ab,kw (Word variations have been searched)

#43 MeSH descriptor: [Nefopam] explode all trees

#44 (Nefopam):ti,ab,kw (Word variations have been searched)

#45 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44

#46 MeSH descriptor: [Fibromyalgia] this term only

#47 ((headache\* or migraine\* or fibromyalgia\* or neuralgia\*)):ti,ab,kw (Word variations have been searched)

#48 (pain):ti,ab,kw (Word variations have been searched)

#49 MeSH descriptor: [Pain] this term only

#50 MeSH descriptor: [Abdominal Pain] explode all trees

#51 MeSH descriptor: [Arthralgia] explode all trees

#52 MeSH descriptor: [Back Pain] explode all trees

#53 MeSH descriptor: [Breakthrough Pain] explode all trees

#54 MeSH descriptor: [Cancer Pain] this term only

#55 MeSH descriptor: [Chest Pain] explode all trees

#56 MeSH descriptor: [Chronic Pain] this term only

- #57 MeSH descriptor: [Earache] this term only
- #58 MeSH descriptor: [Eye Pain] this term only
- #59 MeSH descriptor: [Facial Pain] explode all trees
- #60 MeSH descriptor: [Flank Pain] this term only
- #61 MeSH descriptor: [Glossalgia] this term only
- #62 MeSH descriptor: [Headache] explode all trees
- #63 MeSH descriptor: [Mastodynia] this term only
- #64 MeSH descriptor: [Metatarsalgia] this term only
- #65 MeSH descriptor: [Musculoskeletal Pain] explode all trees
- #66 MeSH descriptor: [Neck Pain] explode all trees
- #67 MeSH descriptor: [Neuralgia] explode all trees
- #68 MeSH descriptor: [Nociceptive Pain] explode all trees
- #69 MeSH descriptor: [Pelvic Pain] explode all trees
- #70 MeSH descriptor: [Renal Colic] this term only
- #71 MeSH descriptor: [Pain, Referred] this term only
- #72 MeSH descriptor: [Pain, Intractable] this term only
- #73 #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72
- #74 #5 and #45 and #73

# **MEDLINE (OVID)**

- 1. \*child/ or \*child, preschool/
- 2. \*Infant/
- 3. \*Adolescent/

4. (child\* or infant\* or baby or babies or preschooler\* or pre-schooler\* or toddler\* or schoolchild\* or girl\* or boy\* or adolescen\* or teen\*).tw.

- 5. 1 or 2 or 3 or 4
- 6. exp Analgesics, Opioid/

7. (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).ti,ab. 8. Ketamine/

- 9. (ketamine or ketalar or calipsol or ketanest).ti,ab.
- 10. (ketaset or calypsol or kalipsol).ti,ab.
- 11. ci-581.tw.
- 12. exp Anti-Inflammatory Agents, Non-Steroidal/
- 13. NSAID\*.tw.
- 14. "non-steroidal anti-inflammatory drug\*".tw.

15. (ibuprofen or aspirin or naproxen or fenoprofen or ketoprofen or tiaprofenic acid or diclofenac or aceclofenac or etodolac or indometacin or mefenamic acid or meloxicam or nabumeton or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or parecoxib or celecoxib or etoricoxib).tw.

- 16. "non-steroidal anti-inflammatory agent\*" tw.
- 17. Acetaminophen/
- 18. (acetaminophen or paracetamol or Panadol or Tylenol).tw.

19. exp Antidepressive Agents/

20. (amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline).tw.

21. exp Anticonvulsants/

22. (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).tw.

- 23. Duloxetine Hydrochloride/
- 24. duloxetine.tw.
- 25. serotonin norepinephrine reuptake inhibitor.mp.
- 26. SNRI.tw.
- 27. Milnacipran/
- 28. milnacipran.tw.
- 29. Flupirtine.tw.
- 30. gabapentinoid\*.tw.
- 31. Indomethacin.tw.
- 32. Venlafaxine Hydrochloride/
- 33. Venlafaxine.tw.
- 34. Desipramine/
- 35. Desipramine.tw.
- 36. Tramadol/
- 37. tramadol.tw.
- 38. Nefopam/
- 39. Nefopam.tw.
- 40. or/6-39
- 41. randomized controlled trial.pt.
- 42. controlled clinical trial.pt.
- 43. randomized.ab.
- 44. placebo.ab.
- 45. drug therapy.fs.
- 46. randomly.ab.
- 47. trial.ab.
- 48. exp Clinical Trials as topic/
- 49. Cross-Over Studies/
- 50. PLACEBOS/
- 51. Research Design/
- 52. latin square.tw.
- 53. Comparative Study/
- 54. Evaluation Studies/
- 55. or/41-54
- 56. exp animals/ not humans.sh.
- 57. 55 not 56

58. pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or breakthrough pain/ or cancer pain/ or exp chest pain/ or chronic pain/ or earache/ or eye pain/ or facial pain/ or flank pain/ or glossalgia/ or exp headache/ or mastodynia/ or metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or neuralgia/ or exp nociceptive pain/ or pain, intractable/ or pain, referred/ or exp pelvic pain/ or renal colic/

59. pain.tw.

60. (headache\* or migraine\* or fibromyalgia\* or neuralgia\*).tw.

61. Fibromyalgia/

62. 58 or 59 or 60 or 61

63. 5 and 40 and 57 and 62

# **EMBASE (OVID)**

- 1. \*child/ or \*child, preschool
- 2. \*Infant/
- 3. \*Adolescent/

4. (child\* or infant\* or baby or babies or preschooler\* or pre-schooler\* or toddler\* or schoolchild\* or girl\* or boy\* or adolescen\* or teen\*).tw.

- 5. 1 or 2 or 3 or 4
- 6. exp Analgesics, Opioid/

7. (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).ti,ab.

8. \*Ketamine/

9. (ketamine or ketalar or calipsol or ketanest).ti,ab.

10. (ketaset or calypsol or kalipsol).ti,ab.

11. ci-581.tw.

12. exp Anti-Inflammatory Agents, Non-Steroidal/

13. NSAID\*.tw.

14. "non-steroidal anti-inflammatory drug\*".tw.

15. (ibuprofen or aspirin or naproxen or fenoprofen or ketoprofen or tiaprofenic acid or diclofenac or aceclofenac or etodolac or indometacin or mefenamic acid or meloxicam or nabumeton or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or parecoxib or celecoxib or etoricoxib).tw.

16. "non-steroidal anti-inflammatory agent\*".tw.

17. \*Acetaminophen/

18. (acetaminophen or paracetamol or Panadol or Tylenol).tw.

19. exp Antidepressive Agents/

20. (amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline).tw.

21. exp Anticonvulsants/

22. (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).tw.

23. \*Duloxetine Hydrochloride/

- 24. duloxetine.tw.
- 25. serotonin norepinephrine reuptake inhibitor.mp.
- 26. SNRI.tw.
- 27. \*Milnacipran/
- 28. milnacipran.tw.
- 29. Flupirtine.tw.
- 30. gabapentinoid\*.tw.
- 31. Indomethacin.tw.

- 32. \*Venlafaxine Hydrochloride/
- 33. Venlafaxine.tw.
- 34. \*Desipramine/
- 35. Desipramine.tw.
- 36. \*Tramadol/
- 37. tramadol.tw.
- 38. \*Nefopam/
- 39. Nefopam.tw.
- 40. or/6-39
- 41. \*pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or

\*breakthrough pain/ or \*cancer pain/ or exp chest pain/ or \*chronic pain/ or \*earache/ or \*eye pain/ or \*facial pain/ or \*flank pain/ or \*glossalgia/ or exp headache/ or \*mastodynia/ or \*metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or \*neuralgia/ or exp nociceptive pain/ or \*pain, intractable/ or exp pain, postoperative/ or \*pain, referred/ or exp pelvic pain/ or \*renal colic/

- 42. pain.tw.
- 43. (headache\* or migraine\* or fibromyalgia\* or neuralgia\*).tw.
- 44. Fibromyalgia/
- 45. 41 or 42 or 43 or 44
- 46. 5 and 40 and 45
- 47. random\$.tw.
- 48. factorial\$.tw.
- 49. crossover\$.tw.
- 50. cross over\$.tw.
- 51. cross-over\$.tw.
- 52. placebo\$.tw.
- 53. (doubl\$ adj blind\$).tw.
- 54. (singl\$ adj blind\$).tw.
- 55. assign\$.tw.
- 56. allocat\$.tw.
- 57. volunteer\$.tw.
- 58. Crossover Procedure/
- 59. double-blind procedure.tw.
- 60. Randomized Controlled Trial/
- 61. Single Blind Procedure/
- 62. placebo/
- 63. methodology/
- 64. latin square.tw.
- 65. comparative study/
- 66. evaluation study/
- 67. or/47-66
- 68. (animal/ or nonhuman/) not human/
- 69. 67 not 68
- 70.46 and 69

# Appendix A.2. Search Overview Physical interventions for children with chronic pain (April 2020)

Database searched	Date searched	
CENTRAL (The Cochrane Library) Issue 4 of 12 2020	14/4/20	
MEDLINE & MEDLINE in Process (OVID) 1946 to April 13 2020	14/4/20	
EMBASE (OVID) 1980 to 2020 week 15 2020	14/4/20	

# CENTRAL (The Cochrane Library)

#1 MeSH descriptor: [Physical Education and Training] this term only

#2 MeSH descriptor: [Exercise Therapy] explode all trees

#3 ((exercise\* or physical activit\*)):ti,ab,kw (Word variations have been searched)

- #4 MeSH descriptor: [Exercise Therapy] explode all trees
- #5 MeSH descriptor: [Muscle Stretching Exercises] this term only #6 #4 not #5
- #6 #4 not #5
- #7 MeSH descriptor: [Physical Therapy Modalities] explode all trees
- #8 (physiotherap\*):ti,ab,kw (Word variations have been searched)
- #9 (physical therap\*):ti,ab,kw (Word variations have been searched)
- #10 (manipulative therapy):ti,ab,kw (Word variations have been searched)
- #11 (((therapeutic or therapy) Near/2 exercise)):ti,ab,kw (Word variations have been searched)
- #12 ("graded motor imagery"):ti,ab,kw (Word variations have been searched)
- #13 (mirror therapy):ti,ab,kw (Word variations have been searched)
- #14 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees
- #15 (hydrotherapy):ti,ab,kw (Word variations have been searched)
- #16 ((pain Near/3 (advice or education))):ti,ab,kw (Word variations have been searched)
- #17 ((flexibility Near/2 exercise\*)):ti,ab,kw (Word variations have been searched)
- #18 MeSH descriptor: [Yoga] this term only
- #19 (yoga):ti,ab,kw (Word variations have been searched)
- #20 MeSH descriptor: [Tai Ji] this term only
- #21 ((tai chi or tai ji)):ti,ab,kw (Word variations have been searched)
- #22 MeSH descriptor: [Qigong] this term only
- #23 (Qigong):ti,ab,kw (Word variations have been searched)
- #24 (ch'i kung):ti,ab,kw (Word variations have been searched)
- #25 MeSH descriptor: [Mind-Body Therapies] this term only
- #26 #1 or #2 or #3 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
- #27 MeSH descriptor: [Child] explode all trees
- #28 MeSH descriptor: [Infant] this term only
- #29 MeSH descriptor: [Adolescent] this term only
- #30 ((child\* or infant\* or baby or babies or preschooler\* or pre-schooler\* or toddler\* or schoolchild\* or girl\* or boy\* or adolescen\* or teen\*)):ti,ab,kw (Word variations have been searched)
- #31 #27 or #28 or #29 or #30
- #32 (pain):ti,ab,kw (Word variations have been searched)

#33 ((headache\* or migraine\* or fibromyalgia\* or neuralgia\*)):ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Fibromyalgia] this term only #34 #35 MeSH descriptor: [Pain] this term only #36 MeSH descriptor: [Abdominal Pain] explode all trees #37 MeSH descriptor: [Arthralgia] explode all trees #38 MeSH descriptor: [Back Pain] explode all trees #39 MeSH descriptor: [Breakthrough Pain] this term only #40 MeSH descriptor: [Cancer Pain] this term only #41 MeSH descriptor: [Chest Pain] explode all trees #42 MeSH descriptor: [Chronic Pain] this term only #43 MeSH descriptor: [Earache] this term only #44 MeSH descriptor: [Eye Pain] this term only #45 MeSH descriptor: [Facial Pain] this term only #46 MeSH descriptor: [Facial Pain] this term only #47 MeSH descriptor: [Glossalgia] this term only #48 MeSH descriptor: [Headache] explode all trees #49 MeSH descriptor: [Mastodynia] this term only #50 MeSH descriptor: [Metatarsalgia] this term only #51 MeSH descriptor: [Musculoskeletal Pain] explode all trees #52 MeSH descriptor: [Neck Pain] explode all trees #53 MeSH descriptor: [Sciatic Neuropathy] this term only #54 MeSH descriptor: [Pain, Intractable] this term only #55 MeSH descriptor: [Pain, Referred] this term only #56 MeSH descriptor: [Pelvic Pain] explode all trees #57 MeSH descriptor: [Renal Colic] this term only #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #58 #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 #59 #26 and #31 and #58

#### **MEDLINE (OVID)**

- 1. randomized controlled trial.pt.
- 2. controlled clinical trial.pt.
- 3. randomized.ab.
- 4. placebo.ab.
- 5. drug therapy.fs.
- 6. randomly.ab.
- 7. trial.ab.
- 8. exp Clinical Trials as topic/
- 9. Cross-Over Studies/
- 10. PLACEBOS/
- 11. Research Design/
- 12. latin square.tw.
- 13. Comparative Study/
- 14. Evaluation Studies/
- 15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
- 16. exp animals/ not humans.sh.
- 17. 15 not 16

- 18. "physical education and training"/
- 19. exp Exercise Therapy/
- 20. (exercise\* or physical activit\*).tw.
- 21. exp Exercise/ not Muscle Stretching Exercises/
- 22. exp Physical Therapy Modalities/
- 23. physiotherap\*.tw.
- 24. "physical therap\*".tw.
- 25. manipulative therapy.tw.
- 26. ((therapeutic or therapy) adj2 exercise).tw.
- 27. "graded motor imagery".tw.
- 28. mirror therapy.tw.
- 29. exp Musculoskeletal Manipulations/
- 30. hydrotherapy.tw.
- 31. (pain adj3 (advice or education)).tw.
- 32. (flexibility adj2 exercise\*).tw.
- 33. (mobility adj2 exercise\*).tw.
- 34. Yoga/
- 35. yoga.tw.
- 36. Tai Ji/
- 37. (tai chi or tai ji).tw.
- 38. Qigong/
- 39. Qigong.tw.
- 40. ch'i kung.tw.
- 41. Mind-Body Therapies/
- 42. \*child/ or \*child, preschool/
- 43. \*Infant/
- 44. \*Adolescent/

45. (child\* or infant\* or baby or babies or preschooler\* or pre-schooler\* or toddler\* or schoolchild\* or girl\* or boy\* or adolescen\* or teen\*).tw.

46. 42 or 43 or 44 or 45

47. pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or breakthrough pain/ or cancer pain/ or exp chest pain/ or chronic pain/ or earache/ or eye pain/ or facial pain/ or flank pain/ or glossalgia/ or exp headache/ or mastodynia/ or metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or neuralgia/ or exp nociceptive pain/ or pain, intractable/ or pain, referred/ or exp pelvic pain/ or renal colic/

48. pain.tw.

- 49. (headache\* or migraine\* or fibromyalgia\* or neuralgia\*).tw.
- 50. Fibromyalgia/
- 51. 47 or 48 or 49 or 50
- 52. or/18-41
- 53. 17 and 46 and 51 and 52

# **EMBASE (OVID)**

- 1. "physical education and training"/
- 2. exp Exercise Therapy/
- 3. (exercise\* or physical activit\*).tw.
- 4. exp Exercise/ not Muscle Stretching Exercises/
- 5. exp Physical Therapy Modalities/
- 6. physiotherap\*.tw.

- 7. "physical therap\*".tw.
- 8. manipulative therapy.tw.
- 9. ((therapeutic or therapy) adj2 exercise).tw.
- 10. "graded motor imagery".tw.
- 11. mirror therapy.tw.
- 12. exp Musculoskeletal Manipulations/
- 13. hydrotherapy.tw.
- 14. (pain adj3 (advice or education)).tw.
- 15. (flexibility adj2 exercise\*).tw.
- 16. (mobility adj2 exercise\*).tw.
- 17. Yoga/
- 18. yoga.tw.
- 19. Tai Ji/
- 20. (tai chi or tai ji).tw.
- 21. Qigong/
- 22. Qigong.tw.
- 23. ch'i kung.tw.
- 24. Mind-Body Therapies/
- 25. \*child/ or \*child, preschool/
- 26. \*Infant/
- 27. \*Adolescent/

28. (child\* or infant\* or baby or babies or preschooler\* or pre-schooler\* or toddler\* or schoolchild\* or girl\* or boy\* or adolescen\* or teen\*).tw.

29. 25 or 26 or 27 or 28

30. pain/ or exp abdominal pain/ or exp arthralgia/ or exp back pain/ or breakthrough pain/ or cancer pain/ or exp chest pain/ or chronic pain/ or earache/ or eye pain/ or facial pain/ or flank pain/ or glossalgia/ or exp headache/ or mastodynia/ or metatarsalgia/ or exp musculoskeletal pain/ or exp neck pain/ or neuralgia/ or exp nociceptive pain/ or pain, intractable/ or pain, referred/ or exp pelvic pain/ or renal colic/

- 31. pain.tw.
- 32. (headache\* or migraine\* or fibromyalgia\* or neuralgia\*).tw.
- 33. Fibromyalgia/
- 34. 30 or 31 or 32 or 33
- 35. random\$.tw.
- 36. factorial\$.tw.
- 37. crossover\$.tw.
- 38. cross over\$.tw.
- 39. cross-over\$.tw.
- 40. placebo\$.tw.
- 41. (doubl\$ adj blind\$).tw.
- 42. (singl\$ adj blind\$).tw.
- 43. assign\$.tw.
- 44. allocat\$.tw.
- 45. volunteer\$.tw.
- 46. Crossover Procedure/
- 47. double-blind procedure.tw.
- 48. Randomized Controlled Trial/
- 49. Single Blind Procedure/
- 50. placebo/

- 51. methodology/
- 52. latin square.tw.
- 53. comparative study/
- 54. evaluation study/
- 55. or/35-54
- 56. (animal/ or nonhuman/) not human/
- 57. 55 not 56
- 58. or/1-24
- 59. 29 and 34 and 57 and 58

# Appendix A.3. Search Overview Psychological interventions for children with chronic pain (April 2020)

Database searched	Date searched
CENTRAL (The Cochrane Library) Issue 3 of 12, 2020	16/3/20
MEDLINE & MEDLINE in Process (OVID) 1946 to March 2020	16/3/20
EMBASE (OVID) 1980 to March 2020	16/3/20
PsycINFO (EBSCO) to March 2020	16/3/20

For the psychological therapies search, we updated the following Cochrane systematic reviews:

- Fisher, E., Law, E., Dudeney, J., Palermo, T.M., & Eccleston, C. (2019). Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No: CD011118. DOI: 10.1002/14651858.CD011118.pub3.
- Fisher, E., & Law, E., Dudeney, J., Palermo, T.M., Steward, G., & Eccleston, C. (2018). Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database of Systematic Reviews, 9*, CD003968. DOI: 10.1002/14651858.
- Law, E. F., Fisher, E., Eccleston, C., & Palermo, T. M. (2019). Psychological therapies for parents of children and adolescents with chronic illness. *Cochrane Database of Systematic Reviews,* Issue 3. Art. No: CD009660. DOI: 10.1002/14651858.CD009660.pub4.

We also ran a search for children and cancer-related pain from inception.

# Appendix C. Additional results

#### **Pharmacological trials**

Risk of bias judgements can be found in Appendix D. Risk of bias figures for RCTs can be found in Figures 4 & 7. ROBINS-I judgements can be found in Appendix D.

**Random sequence generation (checking for possible selection bias):** We rated seven studies as low risk of random sequence generation. The remaining studies did not describe their method of randomisation and we judged these as unclear.

Allocation concealment (checking for possible selection bias): Four studies described their allocation concealment method, and we judged these studies as low risk of bias. The remaining studies did not describe allocation concealment and so we judged these studies as unclear risk of bias.

**Blinding of personnel and participants (checking for possible detection bias):** We rated 13 studies as low risk of bias for blinding of personnel and participants. These studies provided a convincing methodology of blinding personnel and participants to the assigned group. We judged 15 studies as unclear risk of bias; these studies did not provide a convincing methodology. One study was rated as high risk of bias, as the drugs differed in appearance.

**Blinding of outcome assessment (checking for possible detection bias).** We rated 11 studies as low risk of bias for blinding outcome assessment. We rated 17 studies as unclear, and one study as high risk of bias which did not mention blinding and delivered in number and appearance of drugs.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): We rated 11 studies as low risk of bias; these studies reported less than 10% attrition. We rated 13 studies as unclear risk of bias; these studies reported more than 10% attrition and used last observation carried forward or were unclear about their data imputation. The remaining five studies reported more the 10% attrition and used completer analyses, so were rated as high risk of bias.

**Selective reporting (checking for reporting bias):** We rated four studies as low risk of bias; these studies reported a trial registration and reported all outcomes. Five studies were judged to be high risk of bias, where the manuscript differed to the protocol. The remaining 20 studies did not report a protocol or trial registration, or it was not available.

For non-randomised comparative studies with a control group, we used the Cochrane Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I). For non-randomised comparative studies where we considered the bias due to confounding to be "serious" or "critical", the overall risk of bias for the study was also considered "serious" or "critical" and other domains were not assessed. We considered the most important confounders to be age, sex, baseline pain intensity and co-interventions. We rated five studies using the ROBINS criteria (Appendix D). We found all five studies were critical risk of bias and confounding variables were not controlled for in the analyses.

# **Physical therapies**

We did not judge physical therapy interventions for blinding of participants and personnel. Risk of bias judgements for the 24 RCTs can be found in Appendix C and D. Risk of bias figures can be found in Figures 5 & 8. One trial registry (non-

comparative study) was not rated for risk of bias as there was insufficient evidence to rate it from the trial registration.

**Random sequence generation (checking for possible selection bias):** We rated 18 studies as low risk of bias for random sequence generation. These studies provided a convincing method of randomisation. The remaining six studies did not provide a clear description, and we rated these studies as unclear risk of bias.

Allocation concealment (checking for possible selection bias): Similar to randomisation, we found 13 studies that provided a convincing method of allocation concealment, and we rated these studies as low risk of bias. Eleven studies did not provide adequate detail, and we rated these studies as unclear risk of bias.

**Blinding of outcome assessment (checking for possible detection bias):** We rated two studies as low risk of bias for blinding outcome assessment. We rated 22 studies as unclear.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): We rated eight studies as low risk of bias; these studies reported less than 10 % attrition or used baseline observation carried forwards. Eight studies were rated as unclear risk of bias; these studies reported more than 10% attrition or used last observation carried forward. The remaining eight studies used completer analyses and reported more than 10% attrition, as so we rated these studies as high risk of bias.

**Selective reporting (checking for reporting bias):** We rated seven studies as low risk of bias; these studies reported a prospective trial registration and reported outcomes in the manuscript. Eleven studies did not report a trial registration or protocol, or one was not available, and we rated these studies as unclear risk of bias. We rated six studies as high risk of bias. These studies incompletely reported data or the outcomes did not match the trial registration.

#### **Psychological trials**

We did not judge psychological trials for blinding of participants and personnel. Risk of bias judgements can be found in Appendix D. Risk of bias figures can be found in Figures 6 & 8.

**Random sequence generation (checking for possible selection bias):** We judged 28 studies as low risk of bias, which provided a convincing method of randomisation. We judged the remaining 35 studies as unclear risk of bias

Allocation concealment (checking for possible selection bias): We judged 23 studies as low risk of bias as they provided a convincing method of allocation concealment. Two studies were rated as high risk of bias, and we judged the remaining 38 studies as unclear risk of bias, as they did not describe how participants were allocated to the trial arms.

Blinding of outcome assessment (checking for possible detection bias): We rated 22 studies as low risk of bias for blinding of outcome assessors and 41 studies as unclear risk of bias. No studies were rated as high risk of bias. Most studies did not have a description of how outcomes were assessed.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): We rated 20 studies as low risk of bias for incomplete outcome data. These studies had a low attrition rate (<10%) or used baseline observation carried forwards. We rated 24 studies as unclear risk of bias, as they did not describe how they imputed missing data or used last observation carried forwards. We rated 19 studies as high risk of bias, most of which used completer analyses despite >10% dropout.

**Selective reporting (checking for reporting bias):** We rated seven studies as low risk of bias. These studies had a pre-registered protocol and reported all outcomes from the pre-registration in their manuscripts. We rated 38 studies as unclear risk of bias, these studies did not report a protocol or trial registration. We rated 18 studies as high risk of bias; these studies did not report all outcomes from their trial registration in the manuscript.

# Description of superiority analyses; cross-over and non-randomised studies

# **Critical outcomes**

*Pain intensity:* Two parallel RCTs did not report data, but narratively reported that sumatriptan reduced migraines compared to placebo<sup>1</sup> and a further study reported no difference between amitriptyline compared to placebo.<sup>2</sup>

One cross-over trial<sup>3</sup> reported that zolmitriptan and ibuprofen showed similar pain reduction for children with migraine, and that this was superior compared to placebo post-treatment and at follow-up. Another crossover trial,<sup>4</sup> reported that participants in the acetylsalicylic acid group reported significantly greater pain reduction compared to the control group. A third cross-over trial<sup>5</sup> reported reduced migraines in the zolmitriptan group compared to the placebo group. Four remaining cross-over trials did not provide data. One reported no difference between fluoxetine and placebo for children with chronic headache<sup>6</sup> and another showed no difference between montelukast vs placebo for menstrual symptoms.<sup>7</sup> Two trials reported sumatriptan naproxen<sup>8</sup> or progestin<sup>9</sup> improved symptoms in migraine and abdominal pain respectively, compared to placebo.

Finally, two non-randomised studies with no data reported no differences for reducing pain between amitriptyline and relaxation<sup>10</sup> or between mefenamic acid and fennel extract.<sup>11</sup>

In one study<sup>12</sup>, we found no beneficial effect of 30% pain reduction for psychological therapies post-treatment or at follow-up (RR 1.13, 95% CI 0.64 to 2.02; RR 1.07, 95% CI 0.77 to 1.49, respectively). We rated both outcomes as very low-certainty, downgraded twice for very serious limitations to study design and imprecision, and once for indirectness.

*HRQOL:* One pharmacological study with 33 participants reported the amitriptyline treatment group were more likely to improve quality of life from baseline to post-treatment and follow-up, compared to placebo.<sup>13</sup> We rated this outcome as very low-certainty at post-treatment and follow-up, downgraded once for serious limitation to study design and indirectness, and twice for very serious imprecision.

*Functional disability:* one pharmacological study comparing antidepressants (duloxetine) to placebo post-treatment for functional disability showed no beneficial effect. We rated this outcome as very low-certainty, downgraded for serious limitations to study design, indirectness, and very serious imprecision. No studies reported functional disability at follow-up. No studies reported functional disability at follow-up.

*Role functioning:* One pharmacological cross-over trial (29 participants<sup>4</sup>) reported fewer school absences compared to baseline in the treatment group compared to the control group (very low-certainty evidence, downgraded for serious limitations to study design, indirectness, and very serious imprecision). One physical therapy study reported the number of absences from school post-treatment<sup>14</sup> and another study with (43 participants) reported participation in school.<sup>15</sup> There were no differences reported between groups post-treatment for either study. We rated this outcome as very low-certainty, downgraded twice for limitations for study design and imprecision, and once for indirectness. At follow-up, one study reported no differences between groups<sup>15</sup> on role/social physical functioning. Again, we judged this as very low-certainty, downgraded twice for limitations for study design and imprecision.

*Sleep:* One pharmacological study (104 participants) comparing anticonvulsants (pregabalin) to placebo for sleep outcomes post-treatment did not find a beneficial effect (SMD -0.09, 95% CI -0.47 to 0.30). We rated this outcome as very low, downgraded once for indirectness and twice for very serious imprecision. No pharmacological studies reported data at follow-up, and there were no data we could analyse for physical therapy studies at either time-point.

*Adverse events:* One cross-over trial comparing zolmitriptan, ibuprofen and placebo reported no SAEs in the trial.<sup>3</sup>

There were four cross-over studies that reported AEs. The first reported significantly more AEs in the zolmitriptan compared to placebo, but ibuprofen did not differ to placebo.<sup>3</sup> A second study reported 9/31 participants in the fluoxetine and 3/29 participants in the placebo group reported AEs.<sup>6</sup> Four participants in the fluoxetine group stopped receiving the drug. Two other studies did not report any AEs in either group (dydrogesterone or montelukast vs placebo).<sup>7,9</sup>

Four physical therapy studies with 161 participants reported adverse events in their trials. Two studies<sup>16,17</sup> reported no AEs during testing or training sessions. A separate study<sup>18</sup> reported two children had accidental injuries, five reported joint pain, two reported somatic symptoms, and one reported another illness. The authors did not report which group these AEs occurred, but these AEs were not associated with participation in the study. However, children participating in physical exercise in the treatment group, reported muscle soreness associated with learning new exercises, which was typically resolved within a couple of days. One study also reported one AE in the treatment group (n = 18) and none in the control group (n = 14).<sup>19</sup> We rated AEs as very low-certainty, downgraded due to serious imprecision and indirectness. No treatment-related SAEs or other AEs were reported across physical therapy trials.

For psychological trials, AEs, SAEs and other AEs were poorly reported. We found 5 studies reported no adverse events (SAEs or treatment-related AEs) in any condition. One study reported more AEs in the control group (education + amitriptyline) compared to control, and most were attributed to amitriptyline. A final study reported mild headache in the treatment group when listening to CDs. We rated this certainty of evidence as low-certainty, downgraded once each for indirectness and imprecision.

Activity participation: One non-randomised pharmacological study<sup>20</sup> reported activity participation post-treatment and reported no differences between children receiving

citalopram and placebo post-treatment (very low-certainty). No studies reported activity participation at follow-up. One physical therapy study (63 participants)<sup>14</sup> reported fewer absences from physical activity in the exercise group compared to the control group (very low-certainty). No psychological studies assessed activity participation post-treatment, and one study (44 participants) reported a beneficial effect of psychological therapies at improving activity participation at follow-up. We rated the post-treatment outcome as very low, downgraded once for limitations to study design, indirectness, and twice for imprecision.

*Global satisfaction with treatment:* Across pharmacological trials, one study (490 participants) reported a higher percentage of subjects treated with sumatriptan and naproxen versus placebo reported being satisfied/very satisfied for 'how effective the medication is overall' and 'overall satisfaction with medication' at 2- and 24-hours post-dose (p = 0.014). Two further studies (205 participants<sup>20,21</sup>) comparing antidepressants (citalopram and amitriptyline) to placebo did not find any differences between groups in the intention-to-treat analyses (low-certainty). At follow-up, one study comparing citalopram to placebo with 115 participants<sup>20</sup> did not find any differences between groups (p = 0.491; very low-certainty). We rated post-treatment as low-certainty of evidence; we downgraded once for inconsistency and indirectness. At follow-up, we rated the certainty of evidence as very low; downgraded once for indirectness and twice for imprecision. No physical therapy studies reported global satisfaction with treatment at post-treatment or follow-up.

*Patient global impression of change:* We found one study with 104 participants reported participants in the pregabalin groups reported significant improvement compared to placebo (p = 0.013) with 53.1% of subjects much improved or very much improved at endpoint (very low-certainty, downgraded once for serious limitations to study design, indirectness, and twice for imprecision).<sup>22</sup> No studies reported the outcome at follow-up. One physical therapy trial (42 participants) reported that 18/21 participants in the treatment group reported a 'slight but noticeable change', and 10/21 reported a 'definite improvement that has made a real and worthwhile difference'. In the waitlist control group, only one participant agreed with either of the categories, which we rated as very low-certainty.<sup>16</sup> We downgraded this outcome twice for imprecision and once for indirectness. One psychological therapy trial (143 participants) assessed patient global impression of change post-treatment and at follow-up. The study reported participants in the psychological therapy reported a greater global impression of change at both time points<sup>23</sup> (very low-certainty, downgraded twice for imprecision and once for indirectness).

# Effects of pharmacological therapies; subgroup analysis of two pharmacological interventions

Forest plots for the below analyses are shown in Appendix G.1. For comprehensiveness, we have included pharmacological intervention vs. non-pharmacological control and pharmacological intervention vs another pharmacological intervention in the forest plots. The individual drugs, pain condition, and age of participants are included in Table 1.

## Pain intensity

We found two studies that compared two NSAIDs post-treatment (529 participants, rofecoxib vs naproxen and meloxicam vs. naproxen), and no beneficial effect was found (SMD -0.10, 95% CI -0.38 to 0.18, I<sup>2</sup> 58%, very low-certainty). At post-treatment, one study with 34 participants showed no difference between anticonvulsants (gabapentin) and antidepressants (amitriptyline; SMD -0.17, 95% CI -0.85 to 0.50, very low-certainty). One study (300 participants) comparing mefenamic acid plus vitamin E to mefenamic acid showed beneficial effects for the former group (SMD - 2.55, 95% CI -2.85 to -2.24, very low-certainty). At follow-up, one study comparing antidepressants vs. anticonvulsants (57 participants; SMD 2.96, 95% CI 2.19 to 3.72, very low-certainty) and one study comparing two NSAIDs (meloxicam vs. naproxen, 225 participants; SMD 0.03, 95% CI -0.25 to 0.30, very low-certainty). Neither study showed a superior beneficial effect.

No studies compared two pharmacological interventions and assessed 30% or 50% pain reduction, at either time-point.

# Health-related quality of life

We found one study with 303 participants that could be entered into a health-related quality of life, post-treatment analysis comparing two types of NSAIDs (rofecoxib vs naproxen). This analysis did not show a beneficial effect of either treatment for improving health-related quality of life, very low-certainty evidence. No studies reported follow-up data that could be entered into a meta-analysis.

A second study <sup>24</sup> compared naproxen and two doses of Celecoxib (3mg/kg; 6mg/kg) and reported improvements in all groups, but no significant differences.

A non-randomised study <sup>25</sup> showed greater health-related quality of life benefits for participants in the steroid group compared to participants in the NSAID and Methotrexate group.

# **Functional disability**

Three studies comparing two NSAIDs (770 participants, celecoxib, rofecoxib and meloxicam vs. naproxen) reported on functional disability, post-treatment, but no beneficial effect was found (SMD -0.08, 95% CI -0.07 to 0.23, I<sup>2</sup> 0%, very low-certainty). At follow-up, one study (225 participants, meloxicam vs. naproxen) comparing two NSAIDs did not find any beneficial effects, very low-certainty.

#### Role functioning

No studies reported role functioning as a separate outcome, that was not included in overall health-related quality of life assessments.

# **Emotional functioning**

We analysed studies assessing changes in depression and anxiety across trials. For depression, we found one study (225 participants) compared two NSAIDs which did not show a beneficial effect on reducing depression (meloxicam vs. naproxen, SMD 0.00, 95% CI -0.27 to 0.28, very low-certainty). At follow-up, the same study (225 participants) comprising two NSAIDs also failed to show any beneficial effect (SMD - 0.05, 95% CI -0.33 to 0.22, very low-certainty)

We found no studies comparing two pharmacological interventions for anxiety at either time point.

## Treatment-related serious adverse events

We could conduct one subgroup analyses investigating SAEs; NSAID vs. NSAID (two studies comparing rofecoxib or meloxicam vs. naproxen, 535 participants) and there were no differences between groups (RD 0.02, 95% CI -0.05 to 0.10, very low-certainty).

#### **Treatment-related adverse events**

We could conduct two subgroup analyses; anticonvulsants vs antidepressants (two studies comparing amitriptyline to gabapentin or topiramate, 91 participants) and NSAID vs. NSAID (five studies, 801 participants comparing celebcoxib, piroxicam, rofecoxib, and meloxicam to naproxen, and aspirin vs. ibuprofen). Neither analysis showed a higher number to adverse events (anticonvulsants vs. antidepressants RD -0.04, 95% CI -0.16 to 0.07, very low-certainty; NSAIDs vs NSAIDs -0.04, 95% CI - 0.12 to 0.03, I<sup>2</sup> 55%, very low-certainty).

Moran et al., (1979) <sup>26</sup> reported 1/23 participants in the naproxen group compared to 6//23 participants in the aspirin group reported an AE. Leak et al., (1988) <sup>27</sup> reported AEs in the tolmetin group (3/29), naproxen group (3/29) and diclofenac group (6/29). Price et al., (1985) <sup>28</sup> reported seven patient reported gastrointestinal symptoms during the study, but it was not clear which drug they were associated with (indoprofen, aloxiprin). One patient withdrew from the study but the authors did not report if this was linked to the drugs. Soriani et al., (2001) <sup>29</sup> reported no significant difference in AEs between groups taking acetaminophen and nimesulide.

#### Other adverse events

One study comparing two NSAIDs (225 participants, meloxicam vs. naproxen) did not find any difference between groups when assessing other types of AEs (RD 0.91, 95% CI 0.80 to 1.03, very low-certainty).

#### Sleep

A study comparing two anticonvulsants found no differences between gabapentin and amitriptyline <sup>30</sup>.

# Secondary outcomes

# Activity participation

No studies compared two pharmacological interventions to each other and assessed activity participation.

# Global judgement of satisfaction with treatment

One study with 28 participants compared naproxen, tolmetin and diclofenac on global judgement of satisfaction. The study reported 9 participants preferred naproxen, 8 preferred tolmetin and 6 preferred diclofenac. Five participants had not preferences <sup>27</sup>.

# Patient global impression of change

One study with 46 participants compared ibuprofen to aspirin and found 22/26 in the ibuprofen group and 18/20 in the aspirin group rated themselves as improved. There were no differences between groups.

# Fatigue

No studies reported data on fatigue at post-treatment or at follow-up.

## Physical therapies vs. other physical therapies

Of the 13 studies that compared two physical therapy arms, there were eight studies that we could enter into a meta-analysis investigating how physical therapies compare to each other. We included TOAT video based games vs TOAT daily living conditions;<sup>31</sup> Resistive underwater exercises and interferential current vs standard physical therapy;<sup>32</sup> land physiotherapy vs combined hydrotherapy and land physiotherapy;<sup>33</sup> targeted exercise group vs generalised physiotherapy;<sup>34</sup> Pilates vs. conventional exercise;<sup>17</sup> hypermobile range group vs neural control group (included similar exercises;<sup>35</sup> aerobics vs Qigong;<sup>36</sup> and unsupervised vs. supervised home exercise programme.<sup>37</sup> NCT03046472<sup>38</sup> was a non-randomised trial report with results, but with no attached peer-reviewed publication. This trial compared physical therapy for postural behaviour and daily home exercise vs physical therapy for postural behaviour and daily not include it in the meta-analyses.

Please note, the first mentioned intervention above was entered as the 'experimental' condition in the meta-analysis and the second intervention was entered as the 'control' intervention in the analyses. We did not conduct certainty of evidence assessments on these outcomes. Forest plots for the below analyses are shown in Appendix G.2.

## Pain intensity

Of the eight studies and 305 participants we could enter into a forest plot on pain intensity post-treatment, we found four studies showed a beneficial effect <sup>17,32,36,37</sup> and four did not.<sup>31,34,35,39</sup> At follow-up, three studies with 94 participants showed only one study with a beneficial effect.<sup>32</sup>

A further, non-randomised study<sup>38</sup> reported lower back pain in the group that received physical therapy for postural behaviour and daily home exercise plus a group exercise class once per week vs those who only received physical therapy for postural behaviour and daily home exercise, post-treatment.

# Health-related quality of life

Three studies including 154 participants reported on health-related quality of life and could be entered into a forest plot. One showed a significant effect post-treatment,<sup>17</sup> and the remaining two studies did not.<sup>33,36</sup> No studies reported at follow-up which could be entered into a meta-analysis.

# **Functional disability**

Five studies with 180 participants reported functional disability post-treatment, and two studies with 64 participants reported at follow-up, which we entered into a forest plot. We found two studies were beneficial at reducing functional disability post-treatment,<sup>17,36</sup> two studies were not beneficial <sup>34,35</sup> and one study favoured the "control".<sup>37</sup> At follow-up, neither study that reported follow-up data showed beneficial effects.<sup>34,37</sup>

# Role functioning (e.g., school attendance)

One study with 25 participants reported participation in school and activities between groups having physical therapy three times/week vs once/week. No differences between groups were found at post-treatment.

# **Emotional functioning**

Only one study reported depression outcomes post-treatment<sup>36</sup> and this did not show a beneficial effect of either treatment.

# Sleep

We found no studies that reported sleep outcomes at post-treatment or follow-up. Treatment-related adverse events, serious adverse events, and other adverse events Two studies with 96 participants delivering different forms of physical exercise reported not adverse events during testing or training sessions.<sup>17,40</sup> NCT03046472<sup>38</sup> also reported no adverse events from treatments.

# Secondary outcomes Activity participation

One study<sup>36</sup> with 30 participants reported a higher number of hours involved in activity in participants in the aerobics group compared to the Qigong group. The authors reported no differences between baseline and post-treatment, but differences between groups were not reported.

# Global judgement of satisfaction with treatment

No studies reported global satisfaction with treatment.

# Patient global impression of change

Two studies reported patient global impression of change at post-treatment.<sup>35,37</sup> Neither study found differences between groups in relation to global impression of change.

# Fatigue

No studies assessed fatigue separate from health-related quality of life.

# **Psychological therapies: Subgroup analyses**

Following our protocol, we conducted subgroup analyses on outcomes that included more than 10 studies. We had initially planned to conduct a subgroup analysis by age of participants; however, this was not possible. All studies included children and adolescents and did not present data separately. The average age was 12.8 years. We also made several post-hoc decisions in order to help aid the GDG decision-making. We initially planned only to investigate route of intervention in pharmacological studies. As there were a number of remotely delivered psychological trials, we also conducted a subgroup analysis by route of intervention. It also seemed pertinent to analyse studies by therapy type, to help the GDG in recommending any specific types of therapies in their recommendations. Finally, there were no studies that we could include in our planned sensitivity analysis of trials with less or more than 20 participants/arm. In summary, we conducted the following subgroup analyses:

- Control type (active; placebo)
- Chronic pain condition following the ICD-11 classification
- Dose/duration of treatment
- Route of delivery
- Therapy type
- Size

We conducted subgroup analyses on 10 outcomes that included more than 10 studies; pain intensity post-treatment and follow-up, 50% reduction in pain post-treatment, functional disability post-treatment and follow-up, health-related quality of life post-treatment, and emotional functioning (depression and anxiety) post-treatment and follow-up. The remaining outcomes did not include 10 or more studies and therefore were not included in any subgroup analysis. GRADE profiles are provided for each subgroup analysis. Reasons for downgrading are included in the GRADE profiles, but are not included here, in the interests to brevity.

# Subgroup analysis: by control type

We analysed studies by active or standard care control and waitlist control. There were 52 active control arms and 17 waitlist control across the included studies. The GRADE evidence profile is shown in Appendix H and forest plots in Appendix G.3.

Overall, we found beneficial effects for the same outcomes in both active and waitlist control, as we found in the main analyses. However, we found that active control analyses were more similar to the overall effect size, most likely because they included the majority of studies. Therefore, certainty ratings were similar to the certainty ratings of the overall effect. We found the waitlist control subgroup analyses were rated mostly as very low-certainty, mainly because they included few studies and had serious limitations to study designs.

We found beneficial effects of psychological therapies versus active control for the outcomes of pain intensity post-treatment (low-certainty), 50% reduction in pain post-treatment (low-certainty), and functional disability post-treatment (moderate-certainty) and at follow-up (high-certainty). No other beneficial effects were found for pain at follow-up (low-certainty), health-related quality of life post-treatment (moderate-certainty), or emotional distress at either time point (depression was rated high-

certainty at both time points; anxiety was rated moderate-certainty post-treatment and high-certainty at follow-up).

For waitlist control, we found the same pattern of results. Psychological therapies were beneficial compared to waitlist control for the outcomes of pain intensity post-treatment (low-certainty), 50% reduction in pain post-treatment (very low-certainty), and functional disability post-treatment and at follow-up (very low-certainty). No other beneficial effects were found for pain at follow-up (very low-certainty), health-related quality of life post-treatment (very low-certainty), or emotional distress (very low-certainty post-treatment, no studies available at follow-up).

## Subgroup analysis: by pain condition

We categorised trials by the pain condition, according to the ICD-11 classification. There were three subgroup analyses that included most studies and therefore we can draw conclusions from: chronic primary visceral pain, mixed pain conditions, and non-chronic headache. Non-chronic headache included studies of children with headache, but did not meet the IHS criteria for a chronic headache condition. Beneficial effects followed the same pattern as the main findings in subgroups with sufficient data. We could only include a limited number of studies for most subgroups, and therefore it is not possible to conclude if psychological therapies are more beneficial for any particular pain condition compared to another. The GRADE profile is shown in Appendix H and forest plots in Appendix G.4. We did not include analyses with two or less studies in the GRADE profile due to length, but all analyses were rated as very low, downgraded due to very serious imprecision.

Psychological therapies were beneficial for children with chronic primary visceral pain (10 studies, 844 participants, very low-certainty), mixed pain conditions (12 studies, 968 participants, moderate-certainty), but not for children with non-chronic headache (10 studies, 574 participants, low-certainty) at reducing pain intensity. Analyses investigating children with chronic secondary visceral pain and chronic widespread pain showed beneficial effects, but included a maximum of two studies (both very low-certainty). Analyses of children with secondary musculoskeletal pain and chronic secondary headache or orofacial pain also only included a maximum of two studies, but did not show a beneficial effect (very low-certainty). Lack of effect is most likely to be due to lack of data. No subgroup analyses showed a beneficial effect at follow-up for pain intensity.

Chronic primary headache or orofacial pain (low-certainty), mixed pain conditions (moderate-certainty), and children with non-chronic headache (low-certainty) provided data that could be included in the analysis assessing 50% pain reduction. All three subgroups showed a beneficial effect of psychological interventions compared to control.

Beneficial effects for disability were found in subgroup analyses of participants with chronic primary visceral pain (low-certainty) and mixed chronic pain conditions (moderate-certainty), post-treatment. No other subgroups showed beneficial effects post-treatment or at follow-up.

Beneficial effects were found in the primary chronic visceral pain subgroup for healthrelated quality of life (very low-certainty). Psychological therapies were not beneficial for other pain conditions.

There were no other beneficial effects of subgroup analyses for the other outcomes showing that psychological therapies do not work more effectively for one particular pain group compared to another.

#### Subgroup analysis: by treatment duration (dose)

For duration of treatment, we calculated the median hours of treatment delivered. Of the 63 full texts included, 46 reported treatment duration. The remaining 26 studies either reported sessions with no duration or did not report duration of treatment. The median duration of treatment from the studies reported was 4 hours. Therefore, treatments 4 hours and less were analysed separately to 5 hours and more. Studies where we could not calculate a duration are grouped in an 'unknown' category, which we did not conduct GRADE certainty of evidence ratings for or report here. The GRADE profile is shown in Appendix H and forest plots in Appendix G.5.

Overall, we did not find conclusive results that shorter or longer treatment duration was more favourable across multiple outcome domains. We found longer duration of treatment showed benefits for reducing pain intensity post-treatment (low-certainty) and achieving 50% reduction in pain post-treatment (very low-certainty). No other outcomes showed beneficial effects for longer treatment duration.

Shorter treatment duration showed benefits for reducing 50% pain reduction (very lowcertainty), functional disability post-treatment and at follow-up (moderate-certainty). The remaining outcomes on pain intensity post-treatment and follow-up, health-related quality of life post-treatment, and emotional functioning at either time-point did not show beneficial effects for shorter treatment duration.

Certainty of evidence ranged from very low to high, following a similar pattern to the certainty of ratings of the main analyses.

# Subgroup analysis: by delivery mode (route)

We analysed studies by whether they delivered treatment face-to-face or remote from the therapist. Remotely delivered therapies (14 studies) are most often delivered via the internet or smartphone, but have also been delivered via CD ROM or manuals. It is important to recognise that the evidence regarding remote therapies is smaller, and all subgroup analyses including remote therapies included fewer studies (although not always fewer participants) compared to remote therapist. Another theme that emerged is that subgroups of remotely delivered treatments were rated either the same or higher certainty of evidence, compared to face-to-face therapies. We believe that remote therapies could be utilised and improve symptoms in children. The GRADE profile is shown in Appendix H and forest plots in Appendix G.6.

We found that face-to-face therapies were beneficial at reducing pain intensity posttreatment (low-certainty), reducing pain by 50% or more post-treatment (very lowcertainty), and reducing disability post-treatment (low-certainty) and at follow-up (moderate certainty). There were no beneficial findings for reducing emotional distress post-treatment or at follow-up. Conversely, remote therapies were also beneficial at reducing pain intensity post-treatment (moderate-certainty) and 50% pain reduction (low-certainty) but no other beneficial effects were found.

## Subgroup and sensitivity analysis: by therapy classification

We originally planned to analyse studies by individual therapy types, using classifications of cognitive behavioural therapy, acceptance commitment therapy, hypnosis, and relaxation. These results are summarised Appendix G.7 and Appendix H. The WHO GDG requested a sensitivity analysis of the combined effects of CBT, relaxation, BT and ACT for outcomes, which we performed and can be found in Appendix G.8. The WHO GDG also requested a sensitivity analysis of the combined effects of CBT, relaxation, BT and ACT for outcomes, which we performed and can be found in Appendix G.8. The WHO GDG also requested a sensitivity analysis of the combined effects of CBT, relaxation, BT and ACT by route (face-to-face vs. remote) for outcomes, which we performed and can be found in Appendix G.9.

We found small beneficial effects for combined CBT on the following outcomes; pain intensity post-treatment (low-certainty), 50% pain reduction post-treatment and follow-up (low-certainty and very low-certainty, respectively), functional disability post-treatment (low-certainty) and at follow-up (moderate-certainty). We did not find beneficial effects of CBT for pain at follow-up (low-certainty) and emotional functioning (depression: moderate-certainty post-treatment, high-certainty follow-up; anxiety: moderate-certainty post-treatment, high-certainty follow-up). For important outcomes, we found few studies could be included in analyses. In one study, there was a beneficial effect for activity participation at follow-up (very low-certainty), global satisfaction with treatment post-treatment (6 studies, moderate-certainty) and at follow-up (1 study, very low-certainty). No data was reported for fatigue outcomes and no other beneficial effects were found.

The WHO GDG also requested analyses combined CBT separated by remote or faceto-face delivery. These findings were very similar to those presented for the subgroup analysis on delivery. Face-to-face delivery was beneficial at reducing pain intensity post-treatment (low-certainty), reducing 50% reduction pain intensity post-treatment and follow-up (very low-certainty), functional disability post-treatment and follow-up (low-certainty and moderate-certainty, respectively), and global satisfaction with treatment post-treatment (very low-certainty). No benefit of combined CBT therapies were found for reducing pain intensity at follow-up (low-certainty), 30% reduction in pain intensity post-treatment and follow-up (very low-certainty), health-related quality of life post-treatment and follow-up (very low-certainty), role functioning (very lowcertainty), emotional functioning (moderate to high-certainty), or sleep quality (very low-certainty). No data were available for other outcomes.

For remote therapies, we found beneficial effects for reducing pain intensity posttreatment (moderate-certainty), 50% reduction in pain post-treatment (very lowcertainty), global satisfaction with treatment post-treatment and at follow-up (low and very low-certainty), patient global impression of change post-treatment and at followup (very low-certainty). Please note only one study could be included in the analyses of global satisfaction with treatment and patient global impression of change. No beneficial effect was found for pain intensity (low-certainty) and 50% reduction in pain at follow-up (very low-certainty), health-related quality of life post-treatment and followup (moderate-certainty), and functional disability (moderate-certainty), role functioning (moderate-certainty post-treatment, very low-certainty follow-up), emotional functioning (moderate to high-certainty) sleep quality (low-certainty), at either timepoint. There were no data available for analysis for the remaining outcomes.

## Subgroup analysis: by size

There were no studies that included more than 200 participants per arm at posttreatment, meaning we could not conduct our a-priori size sensitivity analysis. The largest study at post-treatment included 265 participants in total <sup>41</sup>. Therefore, we made a post-hoc decision to run a subgroup analysis of studies with more or less than 20 participants per arm. Both treatment arms had to include more than 20 participants per arm to be included as a 'larger study' in the analysis. There were 23 studies with at least one arm including less than 20 participants. The GRADE profile is shown in Appendix H and forest plots in Appendix G.10.

Overall, larger studies were consistently produced smaller effects and were rated as higher certainty evidence compared to smaller studies. We found smaller studies consistently had poorer study quality, larger confidence intervals and smaller number of participants, reducing our overall confidence in the estimates of effect.

For larger studies, we found small beneficial effects for pain intensity post-treatment (low-certainty), 50% reduction in pain intensity (very low-certainty), and small beneficial effects for reducing functional disability post-treatment (moderate-certainty) and at follow-up (high-certainty). We did not find any other beneficial effects for reducing pain intensity at follow-up (low-certainty), health-related quality of life post-treatment (high-certainty), or emotional distress at either time point (all high-certainty). We found beneficial effects for smaller studies; we found moderate beneficial effects for pain intensity post-treatment (very low-certainty), 50% reduction in pain intensity (very low-certainty), moderate beneficial effects for reducing functional disability post-treatment and large effect at follow-up (both very low-certainty). No beneficial effects were found for health-related quality of life or emotional distress at either timepoint (all very low-certainty).

# **Psychological therapies: Sensitivity analyses**

We planned to conduct a sensitivity analysis only including low risk of bias studies. However, we rated only two studies as low risk of bias across all domains <sup>42,43</sup>. Therefore, we did not complete subgroup analyses on these two trials alone.

Sensitivity analysis excluding headache and migraine studies

We ran a sensitivity analysis excluding studies of children with migraine, tension-type headache, or migraine. We continued to include children with chronic headaches and migraines.

We found beneficial effects for the same outcomes as analyses run with the headache and migraine studies included. There were no notable differences between analyses including non-chronic headache studies and those that did not, and there were no notable differences in the certainty ratings for outcomes. The results are summarised in Appendix H and forest plots in Appendix G.11.

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## Appendix E Appendix E.1. WHO review: Pharmacological interventions for children with chronic pain

Comparison: Pharmacological therapies versus placebo, non-pharmacological or waitlist control
Population: Children and adolescents with chronic pain
Setting: Any setting
Studies: Randomised controlled trials
Please note, pharmacological interventions compared to other pharmacological interventions are not included in these analyses.

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of outcome assessment (detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post-treatment Higher scores indicate higher pain intensity	Pain intensity, post-treatment Study or Subgroup Mean SD Total Mean SD Total Weight V, Random, 95% CI N, Random, 95% C	Overall: $\oplus \oplus \oplus \bigcirc$ MODERATE Anticonvulsants vs. placebo: $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW Antidepressants vs. placebo: $\oplus \oplus \bigcirc \bigcirc$ LOW NSAID vs. other: $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW


















	Treatment-related serious adverse events	
	Experimental Control Risk Difference Risk Difference Risk of Bias Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI A B C D E F	
	3.11.1 Anticonvulsant vs. placebo Arnold 2016 1 54 0 53 3.0% 0.02 [−0.03, 0.07]	
	Total events 1 0 Heterogeneity: Not applicable Test for overall effect: Z = 0.73 (P = 0.47) 3.11.2 Antidepressants vs. placebo Upadhyaya 2019 2 91 0 93 5.8% 0.02 [-0.01, 0.06]	Overall: ⊕◯◯◯ VERY LOW
	Subtotal (95% CI) 91 93 5.8% 0.02 [-0.01, 0.06] Total events 2 0 Heterogeneity: Not applicable Test for overall effect: Z = 1.19 (P = 0.24)	Anticonvulsants
	3.11.4 NSAID + other vs. placebo Derosler 2012 0 345 0 145 72.2% 0.00 [-0.01, 0.01]	vs. placebo: ⊕◯◯◯
Treatment- related serious	Subtotal (95% CI)       622       215 $91.2\%$ $0.00$ [ $-0.01$ , $0.01$ ]         Total events       0       0         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.00, df = 1 (P = 1.00); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.00 (P = 1.00)	VERY LOW Antidepressants
adverse events	Total (95% CI)       767       361       100.0%       0.00 [-0.01, 0.01]         Total events       3       0         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.87, df = 3 (P = 0.41); i <sup>2</sup> = 0%       -1       -0.5       0       0.5       1         Test for overall effect: Z = 0.41 (P = 0.68)       Favours experimental Favours control       Favours experimental Favours control         Risk of bias legend       (clusting bias)       (clusting bias)	vs. placebo: ⊕○○○ VERY LOW
	<ul> <li>(A) Random sequence generation (selection bias)</li> <li>(B) Allocation concealment (selection bias)</li> <li>(C) Blinding of participants and personnel (performance bias)</li> <li>(D) Blinding of outcome assessment (detection bias)</li> <li>(E) Incomplete outcome data (attrition bias)</li> <li>(F) Selective reporting (reporting bias)</li> </ul>	NSAID + other vs. placebo: ⊕◯◯◯ VERY LOW
	<ul> <li>Arnold 2016: Pregabalin vs. placebo; Chronic widespread pain (Fibromyalgia), 14 years</li> <li>Upadhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> <li>Derosier 2012: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine)</li> </ul>	
	<ul> <li>Winner 2015: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine), 15 years, 15 years</li> </ul>	

	Treatment-related adverse events	
	Experimental Control Risk Difference Risk Difference Risk of Bias Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI A B C D E F	
	3.12.2 Anticonvulsant vs. placebo Arnold 2016 38 54 34 53 23.4% 0.06 [-0.12, 0.24] Subtotal (95% CI) 54 53 23.4% 0.06 [-0.12, 0.24] Total events 38 34	Overall:
	Heterogeneity: Not applicable Test for overall effect: Z = 0.69 (P = 0.49) 3.12.3 Antidepressants vs. placebo	⊕⊖⊖⊖ VERY LOW
	Upadhyaya 2019 75 91 56 93 31.8% 0.20 [0.07, 0.33] Subtotal (95% Cl) 91 93 31.8% 0.20 [0.07, 0.33] Total events 75 56 Heterogeneity: Not applicable Test for overall effect: Z = 3.13 (P = 0.002)	Anticonvulsants vs. placebo:
Treatment-	3.12.5 NSAID+other vs. placebo Derosier 2012 40 345 12 145 44.8% 0.03 [-0.02, 0.09]	
related adverse	Total events 40 12 Heterogeneity: Not applicable Test for overall effect: Z = 1.16 (P = 0.25)	Antidepressants
events	Total (95% Cl) 490 291 100.0% 0.09 [-0.02, 0.21] Total events 153 104 Heterogenetty: Tau <sup>2</sup> = 0.01; Cht <sup>2</sup> = 6.34, df = 2 (P = 0.04); t <sup>2</sup> = 68% Test for overall effect: Z = 1.55 (P = 0.12) Test for subgroup differences: Cht <sup>2</sup> = 5.67, df = 2 (P = 0.06), t <sup>2</sup> = 64.7% Risk of bias legend	vs. placebo: ⊕○○○ VERY LOW
	<ul> <li>(A) Random sequence generation (selection bias)</li> <li>(B) Allocation concealment (selection bias)</li> <li>(C) Blinding of participants and personnel (performance bias)</li> <li>(D) Blinding of outcome assessment (detection bias)</li> <li>(E) Incomplete outcome data (attrition bias)</li> <li>(F) Selective reporting (reporting bias)</li> </ul>	NSAID + other vs. placebo: ⊕○○○
	<ul> <li>Arnold 2016: Pregabalin vs. placebo; Chronic widespread pain (Fibromyalgia), 14 years</li> <li>Derosier 2012: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine), 15 years</li> </ul>	VERY LOW
	<ul> <li>Upadhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> </ul>	

# Appendix E.2. WHO review: Physical interventions for children with chronic pain

**Comparison:** Physical therapies versus treatment as usual, waitlist control, or non-physical therapy control **Population:** Children with any chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

## Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of outcome assessment (detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post-treatment <i>Higher scores</i> <i>indicate higher</i> <i>pain intensity</i>	Pain intensity, post-treatmentStudy or SubgroupExperimentalControlStd. Mean DifferenceRisk of BiasStudy or SubgroupMeanSDTotalWeightIV, Random, 95% CIRisk of BiasChaudhuri 2013A 36A 13S33.55Total WeightIV, Random, 95% CIRisk of BiasFallah 201842.4196.52.115.5%	⊕○○○ VERY LOW

Pain intensity, follow-up Higher scores indicate higher pain intensity	Pain intensity, follow-upStudy or SubgroupExperimental Mean SD TotalStd. Mean Difference IV, Random, 95% CIRisk of Bias A B C D EChaudhuri 2013 Kashikar-Zuck 20182.96A.14482.062.526439.4% 29.4%0.27 [-0.11, 0.65] IV, Random, 95% CIRisk of Bias A B C D EChaudhuri 2013 Kashikar-Zuck 20184.621.9176.262.061929.4% 29.4%0.81 [-1.49, -0.12]Total (95% CI)4.621.9102100.0%Total (95% CI)85102100.0% 29.4%-0.13 [-0.74, 0.48]Total (95% CI)85102100.0% 	⊕OOO VERY LOW
Health-related quality of life, post-treatment <i>Lower scores</i> <i>indicate better</i> <i>quality of life</i>	Health-related quality of life, post-treatmentStudy or SubgroupExperimentalControlStd. Mean DifferenceStd. Mean DifferenceRisk of BiasTotal VeightVR andom, 95% CIStd. Mean DifferenceRisk of BiasTotal VeightVR andom, 95% CIStd. Mean DifferenceRisk of BiasTotal VeightVR andom, 95% CIRisk of BiasTotal (95% CI)81-1.65Std. Mean DifferenceRisk of BiasTotal (95% CI)81-2.6Std. Mean DifferenceRisk of BiasTotal (95% CI)81Std. Mean DifferenceNNTotal (95% CI)81-2.2100.0%-0.64 [-1.91, 0.63]Heterogenetty: Tau <sup>2</sup> = 0.75; Ch <sup>2</sup> = 9.45, df = 1 (P = 0.002); P = 89%Favours experimental Favours controlRisk of bias legend(A) Random sequence generation (selection bias)(B) Allocation concealment (selection bias)(B) Allocation concealment (selection bias)(C) Blinding of outcome assessment (detection bias)(D) Incomplete outcome data (attrition bias)(E) Selective reporting (reporting bias)	⊕⊖⊖⊖ VERY LOW

Functional disability, post- treatment <i>Higher scores</i> <i>indicate lower</i> <i>disability</i>	Functional disability, post-treatmentStd. version of SubgroupKisk of BiasStd. Mean DifferenceStd. Mean DifferenceRisk of BiasEvans 201115.7210.0419.23ControlStd. Mean DifferenceRisk of BiasKashikar-Zuck 2018BI.714.6117.23.9511.0419.23CO.0330.47I.8.8 of BiasKutmer 200624.3412.2511.1419.23CO.0310.020.020.020.00%0.040.00%0.040.020.00%0.040.00%0.040.00%0.040.00%0.040.00%0.040.020.00%0.040.00%0.040.00%0.040.00%0.040.00%0.040.00%0.040.00%0.040.00%0.040.00%0.020.00%0.020.020.020.020.02
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Emotional functioning: Anxiety, post- treatment <i>Higher scores</i> <i>indicate higher</i> <i>anxious</i> <i>symptomology</i>	ExperimentalControlStd. Mean DifferenceRisk of BiasStudy or SubgroupMeanSDTotalMeanSDTotalWeightStd. Mean DifferenceStd. Mean DifferenceRisk of BiasEvans 201137.7223.251821.5714.551450.8%0.79[0.06, 1.52]Kuttner 200610.645.21414.756.421149.2%-0.69[-1.51, 0.13]Total (95% Cl)3225100.0%0.06[-1.39, 1.51]Heterogenetty:Tau <sup>2</sup> = 0.94; Ch <sup>2</sup> = 7.02, df = 1 (P = 0.008); P = 86%66%Favours experimentalFavours controlRisk of bias legend(A) Random sequence generation (selection bias)(B) Allocation concealment (selection bias)(C) Blinding of outcome assessment (detection bias)(C) Blinding of outcome data (attrition bias)(C) Blinding of course data (attrition bias)(E) Selective reporting (reporting bias)(E) Selective reporting (reporting bias)(C) Blinding of autome data (attrition bias)(C) Blinding of provide the set of th	⊕OOO VERY LOW
Treatment- related adverse events, post- treatment	Treatment-related adverse eventsStudy or SubgroupExperimental EventsControl WeightRisk Difference Risk DifferenceRisk Difference M-H, Random, 95% CIRisk of Bias A B C D EAndias 201802102229.7%0.00 [-0.09, 0.09]A B C D EKashikar-Zuck 201801701921.1%0.00 [-0.10, 0.10]	⊕OOO VERY LOW

# Appendix E.3. WHO review: Psychological interventions for children with chronic pain

Comparison: Psychological therapies versus any control (standard care, waitlist control, active (non-psychological therapy) control) Population: children with any chronic pain Setting: Any setting Studies: Randomised controlled trials

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of outcome assessment (detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

Outcome							For	rest p	lot			Quality of evidence (GRADE)
Pain intensity, post-treatment <i>Higher scores</i> <i>indicate higher</i> <i>pain intensity</i>	Study or Subgroup Barakat 2010 Bonnert 2017 Bussone 1968 Chen 2014 Connelly 2006 Connelly 2019 Grob 2013 Gulewitsch 2013 Hechler 2014 Hicks 2006 Humphreys 2000 Kashikar-Zuck 2005 Kashikar-Zuck 2005 Kashikar-Zuck 2012 Kroener-Herwig 2002 Lalouni 2019 Law 2015 Lester 2020 Levy 2010 Levy 2010 Levy 2010 Levy 2017 Nieto 2019 Osterhaus 1997 Palermo 2016 (f2f) Palermo 2016 (f2f) Sanders 1990 Rapoff 2014 Richter 1986 Robins 2005 Sanders 1994 Schatz 2015 Stinson 2010 Trautmann 2010 Van der Veek 2013 Van Tilburg 2009 Vileger 2007 Wahlund 2015 Wicksell 2009 Total (95% CI)	Mean 16.6 4.53 65.4 25 2.69 3.1 0.16 1.6 1.6 5.7 3.4 0.78 4.4 3.58 1.64 4.09 12.72 2.3 3.54 5.58 5.87 5.83 2.31 9 3 4.44 3.64 4.43 3.54 5.58 5.87 5.88 5.87 5.83 2.32 1.64 2.17 5.3 2.31 9 3 4.44 3.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.52 1.64 2.53 2.31 5.36 3.54 5.86 5.87 5.88 5.86 5.87 5.83 2.32 3.54 5.83 2.33 3.54 5.86 5.87 5.83 2.32 3.54 5.32 3.54 5.86 5.87 5.83 2.33 3.54 5.32 3.54 5.32 3.54 5.32 3.54 5.32 3.54 5.33 2.31 9 3.54 3.56 5.32 3.54 5.32 3.54 5.32 3.54 5.32 3.54 5.32 3.54 5.33 2.31 9 3.54 3.56 5.32 3.56 5.32 3.56 5.32 5.3	gical ther SD 16.57 2.54 55.1 18 1.24 2.45 0.32 2.45 2.4 2.4 2.4 1.4 1.9 1.16 2.55 2.42 2.3 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 2.42 2.32 1.16 2.55 1.98 0.32 2.93 2.95 1.98 0.33 1.16 7.88 8.33 1.34 2.15 1.55 1.55 1.66 7.88 8.33 3.44 1.66 2.3	Total           17           47           200           45           17           144           15           20           21           25           46           14           57           29           45           40           245           23           31           134           73           65           22           32           22           32           22           32           15           366           223           32           15           36           22           32           15           36           22           32           16           1584	C Mean 17.29 5.53 96.3 377 2.88 2.9 1.93 4.46 5.9 4.7 4.2905 5.92 5.92 5.92 5.92 5.92 5.92 5.92 5.9	ontrol 23.21 2.42 73.8 21 1.01 2.5 2.5 2.2 2.77 2.04 1.9 0.96 2.52 2.26 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.15 2.12 2.22 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.15 2.15 2.15 2.15 2.15 2.12 2.22 2.26 2.26 2.26 2.26 2.26 2.26 2.15 2.15 2.15 2.12 2.22 2.26 2.26 2.26 2.26 2.26 2.26 2.26 2.15 2.15 2.15 2.12 2.22 2.26 2.15 2.15 2.12 2.22 2.26 2.15 2.12 2.29 2.9	Total 20 54 10 20 145 14 145 222 15 135 546 44 37 135 546 44 37 135 546 144 30 135 704 17 12 25 223 24 13 55 21 21 22 23 24 13 55 22 23 24 13 55 22 23 24 13 55 22 23 24 13 55 22 23 24 13 55 22 23 24 13 55 22 23 24 13 55 24 14 15 13 55 26 13 13 55 26 13 13 57 14 14 15 26 13 13 57 13 13 57 14 14 15 22 22 15 13 57 14 16 16 17 17 17 17 17 17 17 17 17 17	Weight 2.2× 3.2× 1.6× 2.2× 3.9× 1.6× 2.0× 3.9× 2.4× 2.1× 1.6× 2.4× 2.4× 2.1× 1.6× 2.4× 2.4× 2.1× 3.3× 2.4× 2.5× 2.5× 2.7× 3.6× 3.3× 2.4× 2.2× 2.5× 2.7× 3.6× 2.2× 2.5× 2.7× 3.6× 3.3× 2.4× 2.4× 2.4× 3.5× 2.4× 2.4× 3.5× 2.4× 3.5× 2.4× 3.5× 2.4× 3.5× 3.5× 2.4× 3.5× 3.5× 3.5× 3.5× 3.5× 3.5× 3.5× 3.5	-0.17 [-0.81, 0.48] 0.08 [-0.15, 0.31] -1.48 [-2.32, -0.65] 1.17 [-1.86, -0.47] -0.08 [-0.47, 0.31] -0.55 [-1.14, 0.03] -1.90 [-2.58, -1.22] -0.75 [-1.53, 0.04] 0.10 [-0.37, 0.56] -0.48 [-0.91, -0.06] 0.13 [-0.32, 0.57] 0.27 [-0.32, 0.86] 0.21 [-0.10, 0.51] -0.21 [-0.48, 0.05] 0.12 [-0.98, 0.33] -0.57 [-1.12, -0.01] -0.06 [-0.56, 0.44] 0.13 [-0.23, 0.49] -0.68 [-1.36, 0.01] 0.10 [-0.66, 0.86] -0.40 [-0.22, 0.14] -0.43 [-1.03, 0.17] -0.09 [-0.67, 0.49]	Std. Mean Difference IV, Random, 95% CI	Risk of Bias         A B C D E         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ?         ? ? ? ? ? ? ? ?         ? ? ? ? ? ? ? ?         ? ? ? ? ? ? ? ?         ? ? ? ? ? ? ? ? ?         ? ? ? ? ? ? ? ? ? ? ? ? ?         ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?	
	Heterogeneity: Tau <sup>2</sup> = 0.1 Test for overall effect: Z =			- 57 (*	< 0.000	v1); F ■	4/7		F	-4 -2 0 2 Favours intervention Favours contro	<b>4</b>	



	30% pain reduction, post-treatment		
30% reduction, post-treatment	Study or Subgroup       Psychological therapies       Control Total       Risk Ratio       Risk Ratio       Risk Ratio       Risk Ratio       Risk of Bias         Van der Veek 2013       17       52       15       52       100.0%       1.13 [0.64, 2.02]       Image: Control Favours control Favours experimental         Total (95% CI)       52       52       100.0%       1.13 [0.64, 2.02]       Image: Control Favours experimental         Total (95% CI)       52       52       100.0%       1.13 [0.64, 2.02]       Image: Control Favours experimental         Total (95% CI)       52       52       52       100.0%       1.13 [0.64, 2.02]       Image: Control Favours experimental         Total (95% CI)       52       52       52       100.0%       1.13 [0.64, 2.02]       Image: Control Favours experimental         Total (95% CI)       52       52       52       100.0%       1.13 [0.64, 2.02]       Image: Control Favours experimental         Test for overall effect: Z = 0.42 (P = 0.67)       Image: Control Favours control Favours experimental       Image: Control Favours experimental         Risk of bias legend       (A) Random sequence generation (selection bias)       Image: Control Favours experimental         (C) Blinding of outcome assessment (detection bias)       Image: Control Favours experimental         (D) In	⊕○○○ VERY LOW	
30% reduction, follow-up	30% pain reduction, follow-up         Study or Subgroup       Psychological therapies       Control       Risk Ratio       Risk Ratio       Risk of Bias         Yan der Veek 2013       31       52       100.0%       1.07 [0.77, 1.49]         Yan der Veek 2016       31       29       52       100.0%       1.07 [0.77, 1.49]         Total events       31       29         Total events <td colspa="&lt;/td"><td>⊕OOO VERY LOW</td></td>	<td>⊕OOO VERY LOW</td>	⊕OOO VERY LOW

	Study or Subgroup	Psychological th Events		Contr		Weight	Risk Ratio M-H, Random, 95% CI	Risk Rati M-H, Random,		CDE	
	Barry 1997	2	12		17	1.9%	1.42 [0.23, 8.70]	M-H, Kandom,			
	Connelly 2006	7	14	4	20	4.7%	2.50 [0.90, 6.94]				
	Griffiths 1996	12	15	3	12		3.20 [1.16, 8.80]			2 6 2	
	Hicks 2006	15	21	3	16	4.5%	3.81 [1.33, 10.94]	—	- ??	222	
	Jong 2018	35	66	15	37	9.6%	1.00 [0.63, 1.60]	+		? 🗣 🛑	
	Kroener-Herwig 2002	16	29	6	19	8.0%	1.31 [0.70, 2.44]	+		???	
	Labbe 1984	13	14	1	14	1.6%		-		? 🕂 ?	
	Labbe 1995	19	20	6	10	9.2%	1.58 [0.95, 2.65]			777	
	Larsson 1967	6	12		24	2.8%	6.00 [1.42, 25.39]			222	
	Larsson 1987a	13	30		11	1.6%	4.77 [0.70, 32.29]			? • •	
	Larsson 1990	6	31	0	17	0.9%				777	
	Larsson 1996 Law 2015	12	13 44	17	13 39	1.7% 6.1%	9.00 [1.32, 61.24] 1.52 [0.66, 3.47]			<b>? - ?</b>	
	McGrath 1992	26	44	é	25	6.6%	2.30 [1.10, 4.85]			200	
	Osterhaus 1997	12	25	ŏ	14		14.42 [0.92, 226.60]			2	
	Palermo 2009	10	23	š	21	4.0%	3.04 [0.97, 9.58]	L.	— <b>ě</b> ě		
	Palermo 2016 (remote)	2	48	2	47	1.7%	0.98 [0.14, 6.67]		— ăă	ăăă	
	Powers 2013	42	64	26	71		1.79 [1.26, 2.55]	+	ěě	<b>47</b>	
0% reduction,	Rapoff 2014	7	18	6	17	5.7%	1.10 [0.46, 2.62]		??	• • ?	$\Theta \Theta O O$
ost-treatment	Sartory 1998	20	30	5	13	6.9%	1.73 [0.83, 3.61]	+	- ??	???	LOW
Jost-liealment	Scharff 2002	7	13	1	23	1.6%		-	———	? 🖶 🛑	LOW
	Trautmann 2010	16	35	2	16	3.1×	3.66 [0.95, 14.05]		- ?9	🕂 🛑 ?	
	Total (95% CI)		644		496	100.0%	2.11 [1.61, 2.77]	•			
	Total events	307		104							
	Heterogeneity: Tau <sup>2</sup> = $0.1$ Test for overall effect: Z =			= 0.02);	i <sup>2</sup> = 4)	1%	Ō	Favours control Fav	10 200 ours experimental		
	<u>Risk of bias legend</u> (A) Random sequence gen (B) Allocation concealment (C) Blinding of outcome as: (D) Incomplete outcome da (E) Selective reporting (rep	(selection bias) sessment (detection ata (attrition bias)									







Functional disability, follow-up Higher scores indicate lower disability	Functional disability, follow-up         Study or Subgroup       Mean SD Total Weight IV, Random, 95% CI         Concelly 2019       2 2.0 Total Weight IV, Random, 95% CI         Concelly 2019       2 2.0 Total Weight IV, Random, 95% CI         Concelly 2019       2 2.1 144 1.9 2.2 145 10.90 0.05 to 1.90, 208         Concelly 2019       2 2.2 145 10.9 % 0.05 to 1.90, 208         Kashkar-Zuck 2012       1.34 6.9 57 1.7 10.5 55 7.86 • 0.37 to 7.4, 0.01]         Levy 2015       5.19 5.02 28 5.27 4.61 22 4.9% • 0.02 to 5.7, 0.07]         Levy 2016       5.6 6.8 66 8.4% • 0.12 to 4.64, 0.21 0         Levy 2016 (27 7.84 5.5 31 8.75 4.64 30 0.56 7 6.05 315 10.76 10.95 82 10.00 * 0.37 to 4.05 to 2.08, 0.09]         Palermo 2016 (27 7.84 5.5 31 8.75 4.64 30 0.56 7 6.05 31.6.01, 0.10 + 0.45 10.28, 0.09]         Palermo 2016 (27 7.84 5.5 31 8.77 70 8.7% - 0.04 to 31, 0.20 + 0.45 to 31, 0.20 to complexed colspan=3, 0.45 to 4.35 to 4.35 to 4.35 to 4.35 to 4.35	Risk of Bias A B C D E 7 7 7 7 7 7 7 7 7 7 7 7 7	⊕⊕⊕⊖ MODERATE
Role functioning	Role functioning (school absence), post-treatment		⊕OOO VERY LOW

(school absence), post- treatment <i>Higher scores</i> <i>indicate more</i> <i>absence from</i> <i>school</i>	Psychological therapiesControlStd. Mean DifferenceStd. Mean DifferenceRisk of BiasStudy or SubgroupMeanSDTotalMeanSDTotalWeightIV, Random, 95% CIIV, Random, 95% CIA B C D EBonnert 20171.041.1471.311.15412.5%-0.24 [-0.64, 0.15]Provide Colspan="4">Provide Colspan="4">Provide Colspan="4">Std. Mean DifferenceRisk of BiasGulewitsch 20130.560.651.40.571.68.7%-0.13 [-0.63, 0.57]Provide Colspan="4">Provide Colspan="4">ControlBonnert 20171.041.1471.311.15412.5%-0.24 [-0.64, 0.15]Provide Colspan="4">Provide Colspan="4">Colspan="4">Colspan="4">Provide Colspan="4">Provide Col	
Role functioning (school absence), post- treatment <i>Higher scores</i> <i>indicate more</i> <i>absence from</i> <i>school</i>	(E) Selective reporting (reporting bias) Role functioning (school absence), follow-up Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI V, Random, 95	⊕OOO VERY LOW







Anxiety, follow- up Higher scores indicate higher anxious symptomology	Psychological therapies         Control         Std. Mean Difference         Nisk of Bias           Std. Yeandom, 95% CI         New Psychological therapies         Control         Std. Mean Difference         Nisk of Bias           Bussone 1988         27.8         2.3         20         29.1         1.4         10         1.7%         -0.62 [-1.39, 0.16]         70.7         6         70.7	
Sleep quality, post-treatment <i>Lower scores</i> <i>indicate worse</i> <i>sleep quality</i>	(b) Incomplete outcome assessment (detection bias) (c) Selective reporting (reporting bias) (c) Selective reporting (reporting bias) (c) Selective reporting (reporting bias) Study or Subgroup Rean SD Total Mean SD Total Weight (V, Random, 95% Cl V, Random, 95	⊕⊕⊖⊖ LOW
Sleep quality, follow-up	Sleep quality, follow-up	⊕⊖⊖⊖ VERY LOW

Lower scores	Study or Subgroup	Psycholog Mean	ical ther SD		C Mean	ontrol		Weight	Std. Mean Difference IV, Random, 95% C		Risk of Bias A B C D E	
indicate worse	Palermo 2016 (remote)	-3.76	0.6	134	-3.76	-		100.0%	0.00 [-0.24, 0.24]		99999	
sleep quality	Total (95% CI) Heterogeneity: Not applic Test for overall effect: Z =		L.00}	134			135	100.0%	0.00 [-0.24, 0.24	] -4 -2 0 2 4 Favours experimental Favours control	_	
	Risk of bias legend (A) Random sequence get (B) Allocation concealmen (C) Blinding of outcome as (D) Incomplete outcome d (E) Selective reporting (rep	t (selection b sessment (d ata (attrition	ias) etection I bias)									
Activity					Acti	vity	par	ticipa	tion, follow-u	ıp		
participation, follow-up (no	Study or Subgroup	Psychologi Mean	ical thera SD			ntrol SD T	otal V		d. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV. Random, 95% CI	Risk of Bias A B C D E	
post-treatment	Sanders 1994	0.3	0.8	22	1.9			-	0.99 [-1.62, -0.36]		<b>? ? ? ● ?</b>	
data)	Total (95% CI)	P		22			22 1	.00.0% -	0.99 [-1.62, -0.36]			000
Higher scores	Heterogeneity: Not app Test for overall effect: 2		= 0.002)						Fav	-4 -2 0 2 4 vours experimental Favours control		VERY LOW
indicate higher	Risk of bias legend											
interference with child activities	<ul> <li>(A) Random sequence</li> <li>(B) Allocation concealm</li> <li>(C) Blinding of outcome</li> <li>(D) Incomplete outcome</li> <li>(E) Selective reporting (</li> </ul>	ent (selection assessment data (attriti	n bias) (detectio ion bias)									
Global satisfaction												
with treatment, post-treatment			Glob	al sa	atisfa	actic	on w	ith tre	eatment, pos	t-treatment		⊕⊕⊕⊖ MODERATE

Lower scores indicate higher satisfaction with treatment	Psychola         Study or Subgroup       Mean         Bonnert 2017       -25.23         Kroener-Herwig 2002       -2.65         Larsson 1967a       -4.1         Palermo 2016 (remote)       -32.2         Sanders 1994       -59.42         Trautmann 2010       -2.3         Total (95% Cl)       Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =         Test for overall effect: Z = 4.86 (P <         Risk of bias legend         (A) Random sequence generation (see (B) Allocation concealment (selection (C) Blinding of outcome assessment (D) Incomplete outcome data (attrittic (E) Selective reporting (reporting bia)	16.32 47 0.55 29 0.6 14 4.7 134 9.94 22 0.6 17 263 4.63, df = 5 (P = 0.44 6.00001) election bias) bias) (detection bias) on bias)	22.62 16.31 -2.37 0.79 -3.9 0.5 -29.9 5 1 50.17 9.28 -2 0.9 2	tal Weight 54 19.3% 27 10.5% 16 5.6% 35 50.4% 22 7.5% 18 6.6%	Std. Mean Difference IV, Random, 95% C -0.16 [-0.55, 0.23 -0.41 [-0.94, 0.12 -0.35 [-1.08, 0.37 -0.47 [-0.71, -0.23 -0.94 [-1.57, -0.32 -0.38 [-1.05, 0.29 -0.43 [-0.60, -0.26	I IV, Random, 95% CI	Risk of Bias A B C D E ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? • ? ? ? • ? ? ? • ? ? ? • ? • • ? ? ? • ? • • ? ?	
Global satisfaction with treatment, follow-up <i>Lower scores</i> <i>indicate higher</i> <i>satisfaction</i> <i>with treatment</i>	Study or Subgroup       Psych         Mea       Palermo 2016 (remote)       -31.         Total (95% Cl)       Heterogeneity: Not applicable       Test for overall effect: Z = 3.33 (f         Risk of bias legend       (A) Random sequence generation       (B) Allocation concealment (selecti         (C) Blinding of outcome assessmet       (D) Incomplete outcome data (attr         (E) Selective reporting (reporting b	blogical therapies n SD Total 9 4.9 134 134 2 = 0.0009} (selection bias) on bias) tt (detection bias) ition bias)	Control Mean SD Tota -29.7 5.9 13	al Weight 5 100.0% –	treatment, fc <u>Mean Difference</u> <u>IV, Fixed, 95% CI</u> <b>2.20 [-3.50, -0.90]</b> 2.20 [-3.50, -0.90] Fa	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E	⊕OOO VERY LOW
Patient global impression of		Patient glo	bal impres	sion of	change, pos	st-treatment		⊕⊖⊖⊖ VERY LOW

change, post- treatment <i>Lower scores</i> <i>indicate higher</i> <i>impression of</i> <i>change</i>	Psychological therapies       Control       Std. Mean Difference       Std. Mean Difference       Risk of Bias         Study or Subgroup       Mean       SD       Total       Mean       SD       Total       Weight       IV, Random, 95% CI       IV, Random, 95% CI       A B C D E         Palermo 2020       -3.9       1.8       73       -2.9       1.8       70       100.0%       -0.55 [-0.89, -0.22]       -	
Patient global impression of change, follow- up Lower scores indicate higher impression of change	(C) Blinding of outcome assessment (detection bias) (D) Incomplete outcome data (attrition bias) (E) Selective reporting (reporting bias)	⊕OOO VERY LOW

Appendix F. Appendix F.1. WHO GRADE Profile: Pharmacological therapies vs. any control for children and adolescents with chronic pain Question: Should pharmacological treatments compared to any control be used for children and adolescents with chronic pain (post-treatment)? Setting: Any healthcare setting

			Certainty as	sessment			Nº of pat	ients	Effe	ct			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological treatment	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance	

Pain intensity, post-treatment

5	randomised controlled trials	serious <sup>a</sup>	not serious	not serious	not serious	none	277	346	-	SMD 0.19 lower (0.35 lower to 0.03 lower)	⊕⊕⊕⊖ MODERATE	CRITICAL	
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## 30% pain reduction, post-treatment

2	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	65/144 (45.1%)	49/142 (34.5%)	<b>RR 1.33</b> (1.00 to 1.77)	<b>114</b> <b>more per</b> <b>1,000</b> (from 0 fewer to 266 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL	
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50% pain reduction, post-treatment

2	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c</sup>	none	45/144 (31.3%)	26/142 (18.3%)	<b>RR 1.71</b> (1.13 to 2.58)	<b>130</b> more per <b>1,000</b> (from 24 more to 289 more)	⊕○○○ VERY LOW	CRITICAL
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Health-related quality of life, post-treatment

1	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious d	none	No studies reported data that could be analysed on health- related quality of life, post-treatment. One study (33 participants) reported the treatment group were more likely to improve quality of life from baseline, compared to placebo.	⊕○○○ VERY LOW	CRITICAL
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			Certainty as	sessment			Nº of pat	ients	Effe	ect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological treatment	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Functiona	al disability, po	ost-treatment										
1	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious d	none	91	93	-	SMD 0.1 higher (0.19 lower to 0.39 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Role fund	ctioning, post-t	reatment - no	t reported				·			••		
0			nat could be analy to the control gro		ctioning, post-tr	eatment. However, on	e cross-over trial rep	orted fewer scho	ool absences c	ompared to ba	aseline in the	CRITICAL
Emotiona	al functioning (	depression), p	post-treatment									
3	randomised controlled trials	not serious	not serious	serious <sup>b</sup>	serious °	none	196	193	-	SMD 0.06 lower (0.25 lower to 0.14 higher)	⊕⊕⊖⊖ LOW	CRITICAL
Emotiona	al functioning (	anxiety), post	-treatment									
2	randomised controlled trials	not serious	not serious	serious <sup>b</sup>	serious °	none	150	149	-	SMD 0.07 lower (0.3 lower to 0.16 higher)	⊕⊕⊖⊖ LOW	CRITICAL

Sleep, post-treatment

			Certainty as	sessment			Nº of pat	ients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological treatment	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
1	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious d	none	54	50	-	SMD 0.09 lower (0.47 lower to 0.3 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL

3/767 (0.4%) 0/361 (0.0%) RD 0.00 ⊕OOO VERY LOW CRITICAL randomised not serious not serious serious b very serious none 0 fewer 4 (-0.01 to 0.01) controlled е per 1,000 (from 10 fewer to trials 10 more)

### Treatment-related adverse events

3	randomised controlled	serious <sup>a</sup>	serious <sup>f</sup>	serious <sup>b</sup>	not serious	none	153/490 (31.2%)	104/238 (43.7%)	not estimable	110 fewer	⊕⊖⊖⊖ VERY LOW	CRITICAL
	trials									<b>per</b> <b>1,000</b> (from 280 fewer to 70 more)		

Other adverse events - not reported

	No studies re	ported other t	ypes of adverse e	events.					CRITICAL					
Activity p	Activity participation, post-treatment - not reported													
1	Non- randomised study	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious d	none	One non-randomised study (110 participants) reported no differences between groups on activity participation, post-treatment.	⊕⊖⊖⊖ VERY LOW	IMPORTANT					

Global judgement of satisfaction with treatment, post-treatment

Certainty assessment							№ of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological treatment	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
3	randomised controlled trials	not serious	serious 9	serious <sup>b</sup>	not serious	none	One study (490 participants) reported a higher percentage of subjects treated with sumatriptan and naproxen versus placebo reported being satisfied/very satisfied for "how effective the medication is overall" and "overall satisfaction with medication" at 2 and 24 hours post dose (unadjusted $P \le .014$ ). Two further studies (205 participants) did not note any differences between groups in the ITT analyses.				⊕⊕⊖⊖ LOW	IMPORTANT

One study (104 participants) reported PGIC response was  $\Theta \cap \cap \Theta$ IMPORTANT randomised serious <sup>a</sup> not serious serious b very serious none 1 significantly improved with pregabalin versus placebo (P = d controlled VERY LOW 0.013), with 53.1% of subjects much improved or very much trials improved at endpoint with pregabalin, compared with 29.5% with placebo.

Fatigue, post-treatment - not reported

No studies reported fatigue, post-treatment

CI: Confidence interval; SMD: Standardised mean difference; RR: Risk ratio

### Explanations

a. Downgraded one level for limitations in study design or execution: >50% of risk of bias judgements were rated unclear or high risk of bias.

b. Downgraded by one level for indirectness: few conditions presented in the meta-analysis.

c. Downgraded by one level for imprecision: small number of participants (<400 participants) or studies (<2 studies) contributing to the analyses.

d. Downgraded by two levels for imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses.

e. Downgraded by two levels for serious imprecision: very few events

f. Downgraded one level for inconsistency: unexplained statistical heterogeneity >50%.

g. Downgraded by one level for inconsistency: unable to combine results in meta-analysis and estimates from the different studies were contradictory leading to inconsistency.

IMPORTANT

WHO GRADE Profile: Pharmacological therapies vs. any control for children and adolescents with chronic pain (follow-up) Question: Should pharmacological treatments compared to any control be used for children and adolescents with chronic pain (follow-up, within 12 months)? Setting: Global

etting: G	lobal											
Certainty assessment							№ of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological treatment	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Pain inte	nsity, follow-up	)										
2	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious c	none	75	73	-	SMD 0.22 lower (0.54 lower to 0.1 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
30% pair	reduction, fol	low-up - not r	reported							•		
	No studies reported 30% pain reduction at follow-up.											CRITICAL
50% pair	reduction, fol	low-up - not r	reported									
-	-	-	-	-	-	-	No randomised con reduction at follow- participants reacher groups, and 25/29 i	up. One crossov d 50% pain redu	56/58		CRITICAL	
Health-re	lated quality o	f life, follow-u	ıp		<u> </u>		•					•
1	randomised controlled trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	very serious c	none	No studies reported data that could be analysed on health- related quality of life, post-treatment. One study (33 participants) reported the treatment group were more likely to improve quality of life from baseline, compared to placebo.				⊕○○○ VERY LOW	CRITICAL
Function	al disability, fol	low-up - not	reported				•					
-	No studies reported functional disability at follow-up.										-	CRITICAL
Role fund	ctioning, follow	-up - not repo	orted									·
-	No studies reported role functioning at follow-up.										-	CRITICAL

Emotional functioning (depression), follow-up
			Certainty as	sessment			Nº of pat	ients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological treatment	any control	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
1	randomised controlled trials	not serious	not serious	serious <sup>b</sup>	very serious c	none	59	56	-	SMD 0.26 lower (0.63 lower to 0.11 higher)	⊕○○○ VERY LOW	CRITICAL
Emotiona	al functioning (a	anxiety), follo	w-up									
1	randomised controlled trial	not serious	not serious	serious <sup>b</sup>	very serious c	none	59	56	-	SMD 0.03 higher (0.34 lower to 0.39 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Sleep, fo	llow-up - not re	eported										
-	No studies re	ported sleep	at follow-up.								-	CRITICAL
Activity p	articipation, fol	llow-up - not	reported									
-	No studies re	ported activit	ty participation at f	ollow-up.							-	IMPORTANT
Global ju	dgement of sa	tisfaction with	n treatment, follow	-up						•••••		
1	randomised controlled trial	not serious	not serious	serious <sup>b</sup>	very serious c	none	One study (115 par groups in the ITT a			s between	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Patient g	lobal impressio	on of change	, follow-up - not re	ported			•					,
-	No studies re	ported patier	nt global impressio	on of change at t	follow-up.						-	IMPORTANT
Fatigue,	follow-up - not	reported								•		
-	No studies re	ported fatigu	e at follow-up.								-	IMPORTANT

#### CI: Confidence interval; SMD: Standardised mean difference

#### Explanations

a. Downgraded one level for limitations in study design or execution: >50% of risk of bias judgements were rated unclear or high risk of bias.
b. Downgraded by one level for indirectness: few conditions presented in the meta-analysis.
c. Downgraded by two levels for imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses.</li>

Appendix F.2. WHO GRADE Profiles: Physical therapies vs. any control for children and adolescents with chronic pain Question: Should physical therapies compared to any control be used for children with chronic pain (post-treatment)? Setting: Global

	Certainty assessment						Nº of p	atients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical therapies	control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Pain inte	nsity, post-trea	atment										
6	randomised trials	serious <sup>a</sup>	very serious <sup>b</sup>	not serious	serious <sup>c</sup>	none	179	195	-	SMD <b>0.6</b> <b>lower</b> (1.15 lower to 0.04 lower)	⊕○○○ VERY LOW	CRITICAL
30% pair	n reduction, po	st-treatment -	not reported									
-	-	-	-	-	-	-	No studies repo	orted 30% pain re	eduction.		-	CRITICAL
50% pair	n reduction, po	st-treatment -	not reported									
-	-	-	-	-	-	-	No studies repo	orted 50% pain re	eduction.		-	CRITICAL
Health-re	elated quality o	f life, post-trea	tment							-		
2	randomised trials	serious <sup>a</sup>	very serious <sup>b</sup>	serious <sup>d</sup>	very serious e	none	81	52	-	SMD 0.64 lower (1.91 lower to 0.63 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Function	al disability, po	ost-treatment										
4	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious e	none	92	82	-	SMD 0.64 lower (0.95 lower to 0.34 lower)	⊕○○○ VERY LOW	CRITICAL

			Certainty as	sessment			Nº of p	atients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical therapies	control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Role fund	ctioning, post-t	reatment					-					
2	randomised trials	very serious <sup>a</sup>	not serious	serious <sup>d</sup>	very serious e	none		were found betw ) post-treatment.		ther study	⊕◯◯◯ VERY LOW	CRITICAL
Emotiona	al functioning (	depression), p	ost-treatment									
3	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious e	none	49	44	-	SMD 0.25 lower (0.66 lower to 0.16 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Emotiona	al functioning (	anxiety), post-	treatment				•					
2	randomised trials	serious <sup>a</sup>	very serious <sup>b</sup>	not serious	very serious e	none	32	25	-	SMD 0.06 higher (1.39 lower to 1.51 higher)	⊕○○○ VERY LOW	CRITICAL
Sleep, po	ost-treatment -	not reported										
-	-	-	-	-	-	-	No studies repo	orted sleep outco	mes, post-treatr	nent.	-	CRITICAL
Treatmer	nt-related seric	ous adverse ev	vents, post-treatm	ent - not reporte	d							
-	-	-	-	-	-	-	No studies repo events, post-tre	orted treatment-re atment.	elated serious ad	dverse	-	

Treatment-related adverse events

			Certainty as	sessment			Nº of p	atients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical therapies	control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
4	randomised trials	serious <sup>a</sup>	not serious	not serious	very serious e	none	1/81 (1.2%)	0/80 (0.0%)	<b>RD 0.01</b> (-0.04 to 0.05)	<b>10 fewer</b> <b>per 1,000</b> (from 50 fewer to 40 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Other ad	verse events,	post-treatment	- not reported		••				<u>.</u>	•		
-	-	-	-	-	-	-	No studies repo	orted other adver	rse events, post-	treatment.	-	CRITICAL
Activity p	articipation, po	ost-treatment										
1	randomised trials	very serious <sup>a</sup>	not serious	serious <sup>d</sup>	very serious e	none			ences were repor ared to control gro		⊕○○○ VERY LOW	IMPORTANT
Global ju	dgement of sa	tisfaction with	treatment - not re	ported	•							
-	-	-	-	-	-	-	No studies repo treatment, post-		ement of satisfac	tion with	-	IMPORTANT
Patient g	lobal impression	on of change					•					
1	randomised trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	very serious e	none	18/21 reported 'slight but noticeable change' and 10/21 reported 'definite improvement' in the treatment group. 1 reported 'slight but noticeable' or 'definite improvement' the control group.			group. 1/22	⊕○○○ VERY LOW	IMPORTANT

Fatigue, post-treatment - not reported

-	-	-	-	-	-	-	No studies reported fatigue outcomes, post-treatment.	-	IMPORTANT			
CI. Confid	Confidence interval. SMD: Standardicad maan difference											

**CI:** Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Downgraded by one level for limitations in study design or execution: >50% of risk of bias judgements were rated unclear or high risk of bias.
b. Downgraded by two levels for serious inconsistency: unexplained statistical heterogeneity >75%.
c. Downgraded by one level for imprecision: small number of participants (<400 participants) or studies (<2 studies) contributing to the analyses.</li>
d. Downgraded by two levels for serious imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses.</li>
e. Downgraded by two levels for serious imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses.</li>

WHO GRADE Profiles: Physical therapies vs. any control for children and adolescents with chronic pain at follow-up (within 12 months) Question: Should physical therapies compared to any control be used for children with chronic pain (follow-up, within 12 months)? Setting: Global

	Certainty assessment Nº of patients Effect									ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical therapies	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Pain inte	nsity, follow-up	)										
3	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	very serious c	none	85	102	-	SMD 0.13 lower (0.74 lower to 0.48 higher)	⊕○○○ VERY LOW	CRITICAL
30% pair	n reduction, foll	ow-up - not re	ported									
0	No studies re	ported 30% pa	ain reduction at fo	llow-up.								CRITICAL
50% pair	n reduction, foll	low-up - not re	ported									
0	No studies re	ported 50% pa	ain reduction at fo	llow-up.								CRITICAL
Health-re	elated quality o	f life, follow-up	- not reported									
0	No studies re	ported overall	quality of life at fo	bllow-up.								CRITICAL
Role fund	ctioning, follow	-up										
1	randomised trials	serious <sup>a</sup>	not serious	serious <sup>d</sup>	very serious c	none	One study report follow-up, data to be entered in reported betwe	⊕○○○ VERY LOW	CRITICAL			
Function	al disability, fol	low-up										
1	randomised trials	not serious	not serious	serious <sup>d</sup>	very serious c	none	17	19	-	SMD 0.38 lower (1.04 lower to 0.28 higher)	⊕○○○ VERY LOW	CRITICAL

			Certainty as	sessment			Nº of p	oatients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physical therapies	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Emotiona	al functioning (	depression), fo	ollow-up									
1	randomised trials	not serious	not serious	serious <sup>d</sup>	very serious c	none	17	19	-	SMD 0.22 lower (0.88 lower to 0.44 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Emotiona	al functioning (	anxiety), follow	v-up - not reported	ł						• • •		
	No studies re	ported emotio	nal functioning (a	nxiety) at follow	-up.							CRITICAL
Sleep, fo	llow-up - not re	eported										
	No studies re	ported sleep a	at follow-up.									CRITICAL
Activity p	articipation, fo	llow-up - not re	eported									
	No studies re	ported activity	participation at fo	bllow-up.								IMPORTANT
Global ju	dgement of sa	tisfaction with	treatment - not re	ported								
	No studies re	ported global	judgement of satis	sfaction with trea	atment at follow	-up.						IMPORTANT
Patient g	lobal impressio	on of change, t	follow-up - not rep	orted								
	No studies re	ported patient	global impression	n of change at fo	ollow-up.							IMPORTANT
Fatigue -	not reported											<del>!</del>
	No studies re	ported fatigue	at follow-up.									IMPORTANT

#### CI: Confidence interval; SMD: Standardised mean difference

#### Explanations

a. Downgraded one level for limitations in study design or execution: >50% of risk of bias judgements were rated unclear or high risk of bias.
b. Downgraded one level for inconsistency: unexplained statistical heterogeneity >50%.

c. Downgraded by two levels for serious imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses. d. Downgraded by one level for indirectness: few conditions presented in the meta-analysis.

# Appendix F.3. WHO GRADE Profile: Psychological therapies vs. any control for children and adolescents with chronic pain, post-treatment Question: Psychological therapies compared to any control in children and adolescents with chronic pain (post-treatment) Setting: Global

			Certainty ass	sessment			Nº of pa	atients	Effec	:t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	psychological therapies	any control	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Pain inter	nsity, post-trea	Itment										
38	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	1584	1441	-	SMD 0.29 lower (0.43 lower to 0.16 lower)	⊕⊕⊖⊖ LOW	CRITICAL
30% pain	reduction, pos	st-treatment										
1	randomised trials	very serious <sup>c</sup>	not serious	not serious	very serious	none	17/52 (32.7%)	15/52 (28.8%)	<b>RR 1.13</b> (0.64 to 2.02)	<b>37 more</b> <b>per 1,000</b> (from 104 fewer to 294 more)	⊕○○○ VERY LOW	CRITICAL

50% reduction in pain, post-treatment

22	randomised trials	serious <sup>a</sup>	not serious	serious <sup>e</sup>	not serious	none	307/644 (47.7%)	104/496 (21.0%)	<b>RR 2.11</b> (1.61 to 2.77)	233 more per 1,000 (from 128 more to 371 more)		CRITICAL	
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Health-related quality of life, post-treatment

13	randomised trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	703	594	-	SMD 0.14 SD lower (0.33 lower to 0.05 higher)	⊕⊕⊖⊖ LOW	CRITICAL
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Functional disability, post-treatment

	Certainty assessment						Nº of pa	atients	Effe	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	psychological therapies	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
24	randomised trials	serious ª	serious <sup>b</sup>	not serious	not serious	none	1209	1149	-	SMD 0.25 lower (0.39 lower to 0.11 lower)	⊕⊕⊖⊖ LOW	CRITICAL

#### Role functioning (school absence), post-treatment

trials trials to the second of	randomised serious <sup>a</sup> trials		none 483	373 -	(0.52 lower to 0.1	CRITICAL
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#### Emotional functioning (depression), post-treatment

#### Emotional functioning (anxiety), post-treatment

19	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	1084	947	-	SMD 0.08 lower (0.21 lower to 0.04 higher)	⊕⊕⊕⊖ MODERATE	CRITICAL
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Sleep quality, post-treatment

			Certainty ass	sessment			Nº of pa	tients	Effec	;t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	psychological therapies	any control	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
3	randomised trials	not serious	not serious	very serious <sub>e.g</sub>	not serious	none	212	214	-	SMD 0.08 SD lower (0.11 lower to 0.27 higher)	⊕⊕⊖⊖ LOW	CRITICAL

#### Adverse events

7	randomised trials	not serious	not serious	serious <sup>e</sup>	very serious h	none	5 studies (524 participants) reported no adverse events (SAEs, TAEs, and other AEs) in any trial arm. One study (135 participants) reported more AEs in the control arm (education + amitriptyline) compared to treatment arm, and most were attributed to amitriptyline. A final study (43 participants) reported mild headache in the treatment arm when listening to CDs.	⊕○○○ VERY LOW	CRITICAL
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Activity participation, post-treatment

0	randomised	No studies assessed activity participation post-treatment.	IMPORTANT
	trials		

Global satisfaction with treatment, post-treatment

6	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	263	272	-	SMD <b>0.43</b> <b>lower</b> (0.6 lower to 0.26 lower)	⊕⊕⊕⊖ MODERATE	IMPORTANT	
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Patient Global Impression of Change, post-treatment

1	randomised trials	not serious	not serious	serious <sup>e</sup>	very serious i	none	73	70	-	SMD <b>0.55</b> <b>lower</b> (0.89 lower to 0.22 lower)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
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Fatigue, post-treatment

			Certainty ass	sessment			№ of pa	atients	Effec	ct		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	psychological therapies	any control	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
0	randomised trials	No studies as	ssessed fatigue p	ost-treatment.								IMPORTANT

CI: Confidence interval; SMD: Standardised mean difference; RR: Risk ratio

#### Explanations

a. Downgraded one level for limitations in study design or execution: >50% of risk of bias judgements were rated unclear or high risk of bias.

b. Downgraded one level for inconsistency: unexplained statistical heterogeneity >50%.

c. Downgraded two levels for serious limitations in study design or execution: >75% of risk of bias judgements were rated unclear or high risk of bias.

d. Downgraded by two levels for serious imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses.

e. Downgraded by one level for indirectness: few conditions presented in the meta-analysis so estimate may not be applicable to other chronic pain conditions.

f. Downgraded by two levels for serious inconsistency: unexplained statistical heterogeneity >75%.

g. Downgraded by one level for indirectness: 2/3 studies came from same the same setting.

h. Downgraded by two levels for serious imprecision: small number of events.

i. Downgraded by one level for imprecision: small number of participants (<400 participants) or studies (<2 studies) contributing to the analyses.

## WHO GRADE Profile: Psychological therapies vs. any control for children and adolescents with chronic pain, follow-up (up to 12 months) Question: Psychological therapies compared to any control in children and adolescents with chronic pain (follow-up; up to 12 months) Setting: Global

			Certainty as	sessment			Nº of pa	atients	Effec	xt		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological therapies	any control	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
Pain inter	nsity											
21	randomised controlled trials	serious <sup>a</sup>	serious <sup>b</sup>	not serious	not serious	none	997	884	-	SMD 0.14 lower (0.3 lower to 0.02 higher)	⊕⊕⊖⊖ LOW	CRITICAL
30% pain	reduction											
1	randomised controlled trials	very serious <sup>c</sup>	not serious	serious <sup>d</sup>	very serious e	none	31/52 (59.6%)	29/52 (55.8%)	<b>RR 1.07</b> (0.77 to 1.49)	<b>39 more</b> <b>per 1,000</b> (from 128 fewer to 273 more)	⊕○○○ VERY LOW	CRITICAL
50% redu	uction in pain,		ł						<u> </u>			
9	randomised controlled trials	serious <sup>a</sup>	serious <sup>b</sup>	serious <sup>d</sup>	not serious	none	109/242 (45.0%)	46/203 (22.7%)	<b>RR 2.09</b> (1.29 to 3.38)	247 more per 1,000 (from 66 more to 539 more)	⊕○○○ VERY LOW	CRITICAL

Health-related quality of life

			Certainty as	sessment			Nº of pa	atients	Effec	t		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological therapies	any control	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
67	randomised controlled trials	serious <sup>a</sup>	not serious	not serious	not serious	none	449	346	-	SMD 0.09 SD higher (0.35 lower to 0.16 higher)	⊕⊕⊖⊖ LOW	CRITICAL

#### Functional disability

14	randomised not seric controlled trials	rious serious <sup>b</sup>	not serious	not serious	none	914	841	-	SMD 0.23 SD lower (0.38 lower to 0.08 lower)	⊕⊕⊕⊖ MODERATE	CRITICAL
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#### Role functioning (school absence)

4	randomised controlled trials	serious <sup>a</sup>	very serious <sup>f</sup>	not serious	not serious	none	270	206	-	SMD 0.14 SD higher (0.32 lower to 0.6 higher)	⊕○○○ VERY LOW	CRITICAL
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### Emotional functioning (depression)

12	randomised controlled trials	not serious	not serious	not serious	not serious	none	709	666	-	SMD 0.06 higher (0.05 lower to 0.16 higher)	⊕⊕⊕⊕ HIGH	CRITICAL	
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Emotional functioning (anxiety)

			Certainty as	sessment			№ of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological therapies	any control	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
13	randomised controlled trials	not serious	not serious	not serious	not serious	none	820	695	-	SMD 0.07 lower (0.17 lower to 0.03 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Sleep qu	ality											
1	randomised controlled trials	not serious	not serious	serious <sup>d</sup>	very serious g	none	134	135	-	SMD 0 SD (0.24 lower to 0.24 higher)	⊕⊕⊕⊖ VERY LOW	CRITICAL
Activity p	participation	•	<u>+</u>	•			•					
1	randomised controlled trials	very serious <sup>c</sup>	not serious	serious <sup>d</sup>	very serious g	none	22	22	-	SMD 0.99 lower (1.62 lower to 0.36 lower)	⊕○○○ VERY LOW	IMPORTANT
Global sa	atisfaction with	treatment								, ,		
1	randomised controlled trials	not serious	not serious	serious <sup>d</sup>	very serious g	none	134	135	-	MD 2.2 lower (3.5 lower to 0.9	⊕○○○ VERY LOW	IMPORTANT

lower)

Patient Global Impression of Change

Nº or studies       Study design       Risk or bias       Inconsistency       Indirectness       Imprecision       Other considerations       Psychological therapies       any control       Relative (95% Cl)       Absolute (95% Cl)         1       randomised       not serious       serious d       very serious       none       73       70       -       SMD       ⊕○○○       IMF		
		Importance
controlled trials     9     0.43     VERY LOW       0.76     10wer     (0.76)       10wer to     0.1       10wer)     10wer)	1	IMPORTANT

0	No studies assessed fatigue at follow-up.	IMPORTANT

CI: Confidence interval; SMD: Standardised mean difference; RR: Risk ratio; MD: Mean difference

#### Explanations

a. Downgraded one level for limitations in study design or execution: >50% of risk of bias judgements were rated unclear or high risk of bias.

b. Downgraded one level for inconsistency: unexplained statistical heterogeneity >50%.

c. Downgraded two levels for serious limitations in study design or execution: >75% of risk of bias judgements were rated unclear or high risk of bias.

d. Downgraded by one level for indirectness: few conditions presented in the meta-analysis so estimate may not be applicable to other chronic pain conditions.

e. Downgraded by one level for imprecision: small number of participants (<400 participants) or studies (<2 studies) contributing to the analyses.

f. Downgraded two levels for serious inconsistency: unexplained statistical heterogeneity >75%.

g. Downgraded by two levels for serious imprecision: very small number of participants (<200 participants) or studies (<2 studies) contributing to the analyses.

## Appendix G Appendix G.1. WHO review: Pharmacological interventions for children with chronic pain

**Comparison:** Pharmacological therapies versus placebo, waitlist control, or other pharmacological control **Population:** Children and adolescents with chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of outcome assessment (detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post-treatment <i>Higher scores</i> <i>indicate</i> <i>higher pain</i> <i>intensity</i>	Pain intensity, post-freatment           Study or Subproup Maan SD Total Mean SD Total Weight Nr, Random, 95% CI         X Man Difference Nr, Rick of Bias           21.11 Anticonvulsants vs. placebo         30 Total Weight Nr, Random, 95% CI         X Man Difference Nr, Rick of Bias         X Man Difference Nr, Rick of Bias         X Man Difference Nr, Rick of Bias           21.12 Anticonvulsants vs. placebo         -1.56         2.27         17         -1.16         2.26         17         10.2%         -0.17 [-0.85, 0.50]           21.12 Anticonvulsants vs. placebo         Armode 2016         -1.64         2.28         54         -0.77         -0.89 [-0.77, -0.00]           Armode 2016         -1.64         2.28         54         -0.77         2.18         53         11.2%         -0.39 [-0.77, -0.00]           Armode 2016         -1.64         2.28         54         -0.27         2.18         53         11.2%         -0.39 [-0.77, -0.00]           State Name Difference Name         54         -0.29         76         11.4%         -0.29 [-0.44, 0.83]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.27 [-0.47, 0.26]         0.28 [-0	Anticonvulsants vs. antidepressants: $\oplus$ VERY LOW Anticonvulsants vs. placebo: $\oplus$ VERY LOW Antidepressants vs. placebo: $\oplus \oplus$ LOW NSAID vs NSAID vs NSAID vs VERY LOW NSAID vs. other: $\oplus$ VERY LOW
	<ul> <li>Bahar 2008: Amitriptyline vs. placebo; Chronic secondary visceral pain (IBS), 14 years.</li> </ul>	

<ul> <li>Brown 2016: Gabapentin vs. amitriptyline; CRPS/neuropathic pain, 13 years.</li> <li>Ilyas 201: Mefenamic acid plus vitamin E vs. mefenamic acid; dysmenorrhea, 15 years.</li> <li>Roohafza 2014: Citalopram vs. placebo; Chronic primary visceral pain (Functional abdominal pain), 9 years</li> <li>Reiff 2006: Rofecoxib vs. naproxen; juvenile idiopathic arthritis, 10 years.</li> <li>Ruperto 2005: Meloxicam vs. naproxen, functional abdominal pain, 8 years.</li> <li>Upadhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> <li>Pouresmall 2002: Ibuprofen vs. acupressure or sham acupressure; Chronic primary visceral pain (Dysmenorrhea), 14-18 years</li> </ul>	

	Pain intensity, follow-up	
	Experimental         Control         Std. Mean Difference         Std. Mean Difference         Risk of Bias           Study or Subgroup         Mean         SD         Total         Meight         IV, Random, 95% CI         IV, Random, 95% CI         A         B         C         D         F           1.2.1         Antidepressant vs. anticonvulsant         A         B         C         D         F	
	Sezer 2013 3.9 0.1 29 3.6 0.1 28 23.3% 2.96 [2.19, 3.72] Subtotal (95% CI) 29 28 23.3% 2.96 [2.19, 3.72] Heterogeneity: Not applicable	
	Test for overall effect: Z = 7.57 (P < 0.00001)	Antidepressants vs. anticonvulsants: ⊕◯◯◯ VERY LOW
	1.2.3 NSAID vs. NSAID         Ruperto 2005       15.9       21.3       78       15.3       20.05       147       26.5%       0.03 [-0.25, 0.30]       ●       ? ? ● ● ? ?         Subtotal (95% CI)       78       147       26.5%       0.03 [-0.25, 0.30]       ●         Heterogeneity: Not applicable       Test for overall effect: Z = 0.21 (P = 0.83)       ●	Antidepressants vs. placebo:
Pain intensity, follow-up Higher scores indicate higher pain intensity	Total (95% CI)182248100.0%Heterogeneity: Tau² = 0.96; Chi² = 57.61, df = 3 (P < 0.00001); I² = 95%	⊕⊕⊖⊖ LOW NSAID vs. NSAID: ⊕⊖⊖⊖ VERY LOW
	<ul> <li>Sezer 2014: Amitriptyline vs. topiramate; mixed pain conditions, 15 years.</li> <li>Bahar 2008: Amitriptyline vs. placebo; Chronic secondary visceral pain (IBS), 14 years</li> <li>Roohafza 2014: Citalopram vs. placebo; Chronic primary visceral pain (Functional abdominal pain), 9 years</li> <li>Ruperto 2005: Meloxicam vs. naproxen</li> </ul>	

	30% reduction, post-treatment	
	Experimental         Control         Risk Ratio         Risk Ratio         Risk of Bias           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% CI         M-H, Random, 95% CI         A         B         C         D         F	
	1.3.1 Anticonvulsant vs. placebo         Arnold 2016       18       54       16       51       26.9%       1.06 [0.61, 1.85]         Subtotal (95% Cl)       54       51       26.9%       1.06 [0.61, 1.85]       ●       ? ? ? • ●         Total events       18       16         Heterogeneity: Not applicable       Test for overall effect: Z = 0.21 (P = 0.83)       ●       ●       ?       ?       ●	
	1.3.2 Antidepressant vs. placebo         Upadhyaya 2019       47       90       33       91       73.1%       1.44 [1.03, 2.02]         Subtotal (95% CI)       90       91       73.1%       1.44 [1.03, 2.02]       ●         Total events       47       33         Heterogeneity: Not applicable         Test for overall effect: Z = 2.12 (P = 0.03)	Anticonvulsants vs. placebo: ⊕◯◯◯ VERY LOW
30% reduction, post-treatment	<ul> <li>Total (95% CI) 144 142 100.% 1.33 [1.00, 1.77] Total events 65 49 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.85, df = 1 (P = 0.36); P = 0% Test for overall effect Z = 1.93 (P = 0.05) Test for subgroup differences: Chi<sup>2</sup> = 0.35, df = 1 (P = 0.36), P = 0% Risk of bias legend (A) Random sequence generation (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)</li> <li>Arnold 2016: Pregabalin vs. placebo; Chronic widespread pain (Fibromyalgia), 14 years (D) Padhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> </ul>	Antidepressants vs. placebo: ⊕○○○ VERY LOW

					50	% pain reduct	ion		
	Study or Subgroup			ntrol is Total	Weight	Risk Ratio M-H, Random, 95% C	Risk Ratio M-H, Random, 95% Cl	Risk of Bias A B C D E F	
	1.4.1 Anticonvulsant Arnold 2016 Subtotal (95% CI)	9	54 5 <b>4</b>	4 51 <b>51</b>	13.7% <b>13.7%</b>			• ? ? ? • ●	
	Total events Heterogeneity: Not a Test for overall effect		18)	4					
	1.4.2 Antidepressan	t vs. placebo							
	Upadhyaya 2019 Subtotal (95% CI)		30 2 30	2 91 91	86.3% 86.3%			•?•??•	Anticonvulsan
	Total events Heterogeneity: Not a Test for overall effect			2					vs. placebo: ⊕◯◯◯
	Total (95% CI)	1	14	142	100.0%	1.71 [1.13, 2.58]	◆		VERY LOW
50% pain reduction, post-treatment	Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect Test for subgroup dif <u>Risk of bias legend</u> (A) Random sequen (B) Allocation concea (C) Blinding of partici (D) Blinding of outcon (E) Incomplete outco (F) Selective reporting	Z = 2.56 (P = 0 ferences: Chi <sup>2</sup> = ce generation (s Iment (selectio pants and pers ne assessmen me data (attritio	17, df = 1 01) 0.17, df = relection I n bias) onnel (per t (detection n bias)	= 1 (P = 0 bias) formanc	1.68), I² =		0.01 0.1 1 10 Favours control Favours exp		Antidepressar vs. placebo: ⊕○○○ VERY LOW
		•		•			spread pain (Fibromy widespread pain (Fib	yalgia), 14 years promyalgia), 15 years	











	Emotional functioning: Anxiety, post-treatment	
	Experimental         Control         Std. Mean Difference         Std. Mean Difference         Risk of Bias           Study or Subgroup         Mean         SD         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI         A         B         C         D         F	
Emotional functioning: Anxiety, post- treatment <i>Higher scores</i> <i>indicate</i> <i>higher</i> <i>depressive</i> <i>symptomology</i>	1.10.1 Antidepressant vs. placeboRohafza 2014-0.913.3959-14.145638.5% $0.02 [-0.34, 0.39]$ Upadhyaya 2019-3.286.5191-2.456.59361.5% $-0.13 [-0.42, 0.16]$ Subtotal (95% CI)150149100.0% $-0.07 [-0.30, 0.16]$ $2 \bullet 2 \bullet$	Antidepressants vs. placebo: ⊕○○○ VERY LOW
	<ul> <li>Roohafza 2014: Citalopram vs. placebo; Chronic primary visceral pain (Functional abdominal pain), 9 years</li> <li>Upadhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> </ul>	



	Treatment-related serious adverse events	
	Experimental Control Risk Difference Risk Difference Risk of Bias Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI A B C D E F	
	2.12.1 Anticonvulsant vs. placebo Arnold 2016 1 54 0 53 7.3% 0.02 [−0.03, 0.07] Subtotal (95% CI) 54 53 7.3% 0.02 [−0.03, 0.07]	
	Total events 1 0 Heterogeneity: Not applicable Test for overall effect: Z = 0.73 (P = 0.47)	Anticonvulsants vs. placebo:
	2.12.2 Antidepressants vs. placebo Upadhyaya 2019 2 91 0 93 12.0% 0.02 [-0.01, 0.06]	
	Total events 2 0 Heterogeneity: Not applicable Test for overall effect: Z = 1.19 (P = 0.24)	Antidepressants
Treatment-	2.12.3 NSAID vs. NSAID Reiff 2006 3 209 1 101 19.1% 0.00 [-0.02, 0.03] Ruperto 2005 10 78 11 147 2.8% 0.05 [-0.03, 0.14] Subtotal (95% CI) 287 248 21.9% 0.02 [-0.05, 0.10] Total events 13 12	vs. placebo: ⊕◯◯◯ VERY LOW
related serious	Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 3.07, df = 1 (P = 0.08); l <sup>2</sup> = 67% Test for overall effect: Z = 0.58 (P = 0.56) 2.12.4 NSAID + other vs. placebo	NSAID vs
adverse events	Derosler 2012       0       345       0       145       35.0%       0.00 [-0.01, 0.01]       •       •       •       ?       0       0       0       ?       ?       0       ?       ?       ?       ?       ?       ?       ?       ?       ?       ?       ?       ?       ?       ?       ?       ? <td>NSAID: ⊕◯◯◯ VERY LOW</td>	NSAID: ⊕◯◯◯ VERY LOW
	Total (95% CI)       1054       609       100.0%       0.01 [-0.01, 0.02]         Total events       16       12         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 9.27, df = 5 (P = 0.10); i <sup>2</sup> = 46%       -1       -0.5       0       0.5       1         Test for overall effect: Z = 0.64 (P = 0.40)       Favours experimental Favours control       Favours experimental Favours control         Risk of bias legend       Risk of bias legend       12       1000       1000       1000	NSAID+ other vs. NSAID: ⊕◯◯◯
	<ul> <li>(A) Random sequence generation (selection bias)</li> <li>(B) Allocation concealment (selection bias)</li> <li>(C) Blinding of participants and personnel (performance bias)</li> <li>(D) Blinding of outcome assessment (detection bias)</li> <li>(E) Incomplete outcome data (attrition bias)</li> <li>(F) Selective reporting (reporting bias)</li> </ul>	VERY LOW
	Arnold 2016: Pregabalin vs. placebo; Chronic widespread pain (Fibromyalgia), 14 years	
	<ul> <li>Upadhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> <li>Reiff 2006: Rofecoxib vs. naproxen; juvenile idiopathic arthritis, 10 years.</li> </ul>	

<ul> <li>Ruperto 2005: Meloxicam vs. naproxen, functional abdominal pain, 8 years.</li> <li>Derosier 2012: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine).</li> <li>Winner 2015: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine), 15 years, 15 years.</li> </ul>	

	Experimental Control Risk Differe Study or Subgroup Events Total Events Total Weight M-H, Random,		Risk of Bias A B C D E F	
	2.13.1 Anticonvulsants vs. antidepressants Brown 2016 1 17 2 17 6.5% -0.06 [-0.2 Sezer 2013 2 28 3 29 8.6% -0.03 [-0.1] Subtotal (95% Cl) 45 46 15.3% -0.04 [-0.1] Total events 3 5 Heterogenety: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 0.63); i <sup>2</sup> = 0% Test for overall effect: Z = 0.71 (P = 0.48)	8, 0.11]	<b>9 9 9 9 7 ●</b> 7 7 <b>9 9 9 7</b>	Anticonvulsan vs. placebo: ⊕◯◯◯
	2.13.2 Anticonvulsant vs. placebo Arnold 2016 38 54 34 53 7.1% 0.06 [-0.1; Subtotal (95% Cl) 54 53 7.1% 0.06 [-0.1; Total events 38 34 Heterogeneity: Not applicable Test for overall effect: Z = 0.69 (P = 0.49)		• 2 2 2 • •	VERY LOW Antidepressar
reatment- related	2.13.3 Antidepressants vs. placebo Upadhyaya 2019 75 91 58 93 10.3% 0.20 [0.0 Subtotal (95% CI) 91 93 10.3% 0.20 [0.0 Total events 75 58 Heterogenetty: Not applicable		020220	vs. placebo ⊕◯◯◯ VERY LOW
adverse events	Test for overall effect: Z = 3.13 (P = 0.002)         2.13.4 NSAID vs. NSAID         Foekdvari 2009       60       83       106       159       10.7%       0.06 [-0.0]         Garcia-Morteo 1987       3       14       2       12       3.2%       0.05 [-0.2]         Giannini 1990       0       45       1       47       16.2%       -0.02 [-0.0]         Reff 2006       43       209       28       101       12.1%       -0.07 [-0.1]         Ruperto 2005       10       78       18       53       8.8%       -0.21 [-0.36]         Subtotal (95% CI)       429       372       51.0%       -0.04 [-0.1]	5, 0.35]	••• ? ? ? ? ?         ? ? ? ? ? ?         ? ? ? ? ? •• ?         ? ? ? ? •• ?         ? ? ? ? •• ?         ? ? •• ? ?	NSAID vs NSAID: ⊕○○○ VERY LOW
	Total events 116 155 Heterogenetty: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 8.94, df = 4 (P = 0.06); i <sup>2</sup> = 55% Test for overall effect: Z = 1.11 (P = 0.26) 2.13.5 NSAID+other vs. placebo Derosler 2012 40 345 12 145 16.3% 0.03 [-0.0]			NSAID+ oth vs. placebo ⊕◯◯◯
	Subtotal (95% CI) 345 145 16.3% 0.03 [-0.0 Total events 40 12 Heterogenetty: Not applicable Test for overall effect: Z = 1.16 (P = 0.25)	2, 0.09]		VERY LOW
	Total (95% CI) 964 709 100.0% 0.00 [-0.0 Total events 272 264 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.57, df = 9 (P = 0.005); i <sup>2</sup> = 62% Test for overall effect: Z = 0.02 (P = 0.98)	6, 0.06]	1	

<ul> <li>Sezer 2013: Amitriptyline vs topiramate, mixed chronic pain conditions, 15 years.</li> <li>Arnold 2016: Pregabalin vs. placebo; Chronic widespread pain (Fibromyalgia), 14 years</li> <li>Upadhyaya 2019: Duloxetine vs. placebo; Chronic widespread pain (Fibromyalgia), 15 years</li> <li>Foeldvari 2009: Celecoxib vs. naproxen; juvenile idiopathic arthritis, 10 years.</li> <li>Garcia-Morteo 1978: Piroxicam vs. naproxen; juvenile idiopathic arthritis, 7 years.</li> <li>Giannini 1990: Aspirin vs. ibuprofen; juvenile idiopathic arthritis, 10 years.</li> <li>Reiff 2006: Rofecoxib vs. naproxen; juvenile idiopathic arthritis, 10 years.</li> <li>Ruperto 2005: Meloxicam vs. naproxen, functional abdominal pain, 8 years.</li> <li>Derosier 2012: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine)</li> <li>Winner 2015: Sumatriptan and Naproxen (varying doses) vs. placebo; Non-chronic headache (Migraine), 15 years.</li> </ul>	



## Appendix G.2. WHO review: Physical interventions for children with chronic pain

**Comparison:** Physical therapies versus other physical therapies **Population:** Children with any chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

#### Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of outcome assessment (detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

Outcome	Forest plot
Pain intensity, post-treatment Higher scores indicate higher pain intensity	Porest piot         Porest piot         Porest piot         Pain intensity, post-treatment         Study or Subgroup       Experimental       Control       Std. Mean Difference       It Mean SD       Total Mean SD       Total N, Random, 95% CI       Risk of Bias         Ahlgwist 2008       1.2       1.3       23       0.27 [-0.28]       Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Colspan="2">Image: Colspan="2">Image: Colspan="2" Colspan="2">Image: Colspan="2" Colspa="2" Colspa="2" Colspa="2" Colspan="2" Colspan="2" Colspa="2" Col




	Emotional functioning: Depression, post-treatment
Emotional functioning: Depression, post-treatment <i>Higher scores indicate higher</i> <i>depressive symptomology</i>	Study or Subgroup       Experimental Mean       Control SD       Std. Mean       Difference IV, Random, 95% CI       Std. Mean       Difference IV, Random, 95% CI       Risk of Bias         Stephens 2008       7.7       8.2       14       8       6.3       16       -0.04 [-0.76, 0.68]

## Appendix G.3. WHO review: Psychological interventions for children with chronic pain Subgroup analysis: by control type

**Comparison:** Psychological therapies versus active/standard care control or waitlist control **Population:** children with any chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of outcome assessment (detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post- treatment <i>Higher</i> <i>scores</i> <i>indicate</i> <i>higher pain</i> <i>intensity</i>	Psychological therapies Study or Subgroup         Mean         SD         Total         Weight         V, Random, 95% CI         N, Random, 95% CI         N, Random, 95% CI         N, Random, 95% CI         A B C D E           21.1 Active or standard care control         Barakat 2010         16.6         16.57         17         17.29         23.21         20         2.28         -0.03         1-0.68, 0.61]         0         0.27         0	Active or standard care control: ⊕⊕○○ LOW Waitlist control: ⊕⊕○○
	2.1.2 Waitlist control Bonnert 2017 4.53 2.54 47 5.53 2.42 54 3.2% $-0.40$ [ $-0.80$ , $-0.01$ ] Grob 2013 0.16 0.32 15 1.93 1.64 14 1.6% $-1.48$ [ $-2.32$ , $-0.65$ ] Gulewitsch 2013 1.6 2.45 20 4.46 2.33 18 2.0% $-1.17$ [ $-1.66$ , $-0.47$ ] Hechier 2014 5.7 2.4 51 5.9 2.5 52 3.2% $-0.08$ [ $-0.47$ , $0.31$ ] Kroener-Herwig 2002 0.86 1.16 29 0.76 0.96 46 2.9% 0.10 [ $-0.37$ , 0.56] Nieto 2019 12.72 10.32 25 11.55 8.84 36 2.7% 0.12 [ $-0.39$ , 0.63] Osterhaus 1997 2.3 1 25 2.6 0.7 14 2.2% $-0.32$ [ $-0.98$ , 0.33] Schatz 2015 16.4 14.3 23 17.7 14.9 23 2.4% $-0.09$ [ $-0.67$ , 0.49] Subtotal (95% CI) 235 257 20.2% $-0.34$ [ $-0.66$ , $-0.01$ ] Heterogenethy: Tau <sup>2</sup> = 0.14; Ch <sup>2</sup> = 20.87, df = 7 (P = 0.004); $P = 66\%$ Test for overall effect: Z = 2.04 (P = 0.04) Total (95% CI) 1584 1441 100.0% $-0.29$ [ $-0.43$ , $-0.16$ ] Heterogenethy: Tau <sup>2</sup> = 0.11; Ch <sup>2</sup> = 113.72, df = 37 (P < 0.00001); $P = 67\%$ Test for subgroup differences: Ch <sup>2</sup> = 0.09, df = 1 (P = 0.76), $P = 0\%$	LOW

												113
						F	Pain	inten	sity, follow-up			
	Study or Subgroup	Psycholo Mean	ogical thera SD		( Mean	Control	Total	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV. Random, 95% Cl	Risk of Bias ABCDE	
-	2.2.1 Active or standard			TUtai	Weall	30	TUtai	weight	IV, Kaliuolii, 55% Ci	IV, Kalidolli, 95% Cl	ADCDE	
	Barakat 2010	16.71	23.03	17	7.84	12.31	20	3.6%	0.48 [-0.18, 1.14]	<b></b>	???	
	Bussone 1988	20	18.1	20		110.3	10	2.8%	-1.04 [-1.85, -0.23]		2 2 2 🖶 🖨	
	Connelly 2019	3.1	2.5	144	2.7	2.4	145	7.6%	0.16 [-0.07, 0.39]	-	••••	
	Hicks 2006	2.9	2.1	25	4.9	1.3	22	3.9%	-1.11 [-1.73, -0.49]		?????	
	Kashikar-Zuck 2012	4.9	2.2	57	5.3	2.1	55	6.1%	-0.18 [-0.56, 0.19]		$\bullet \bullet \bullet \bullet \circ ?$	
	Law 2015	4.19	2.45	28	3.7	2.54	22	4.4%	0.19 [-0.37, 0.75]	+	••••	
	Lester 2020	2.67	1.9	21			18	3.8%	-0.17 [-0.80, 0.46]		• ? • • •	Active or
	Levy 2010	0.93	1.42	78	0.7	1.53	76	6.7%	0.16 [-0.16, 0.47]	+-		
	Levy 2017	3.48	2.33	151			78	7.2%	-0.13 [-0.40, 0.14]		• ? • ? •	standard
	Palermo 2016 (f2f)	5.42	2.05	31	5.3			4.8%	0.06 [-0.45, 0.56]			care control:
	Palermo 2016 (remote)	5.85	1.97	134				7.5%	0.15 [-0.09, 0.39]			
Pain intensity,	Palermo 2020	5.3	1.9	73	6.2		70	6.5%	-0.48 [-0.82, -0.15]	-		$\oplus \oplus \bigcirc \bigcirc$
follow-up	Rapoff 2014	4.46	1.88	11			11	2.6%	0.38 [-0.46, 1.23]			LOW
	Richter 1986	2.02	1.48	30			12	3.6%	0.00 [-0.67, 0.67]		????	LOW
Higher scores	Sanders 1994 Trautmann 2010	0.64	1.38		2.11	3.56	22	4.0%	-0.53 [-1.14, 0.07]		??? <b>?</b> ? <b>!</b>	
indicate	Trautmann 2010 Van der Veek 2013	4.9	1.4 17.0393	12		1.9 15.19	16 52	3.1% 6.0%	-0.34 [-1.10, 0.41] 0.08 [-0.30, 0.47]			Waitlist
	Wahlund 2015	19.03	17.0393	52 31	2.8		33	6.0% 5.0%	0.08 [-0.30, 0.47] 0.00 [-0.49, 0.49]			
higher pain	Wicksell 2009	2.0 3.1	2.7	ינ 16	4.5		- 33 16	3.3%	-0.53 [-1.24, 0.17]			control:
intensity	Subtotal (95% CI)	5.1	2.1	953	4.5	2.4	843	92.6%	-0.11 [-0.26, 0.05]	•	••••	$\oplus \bigcirc \bigcirc \bigcirc \bigcirc$
-	Heterogeneity: Tau² = 0.0 Test for overall effect: Z =			(P = 0.0)	01); I² =	57%						VERY LOW
	2.2.2 Wait-list control											
	Grob 2013	0.08	0.31	15		1.49	14	2.7%	-1.35 [-2.17, -0.53]		????++	
	Kroener-Herwig 2002	0.48	0.65	29	0.46	0.61	27	4.6%	0.03 [-0.49, 0.56]	-	??????	
	Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.8 Test for overall effect: Z =	3; Chi² = 7.7 0.90 (P = 0.	76, df = 1 (P 37)	<b>44</b> = 0.005)	); I² = 87	%	41	7.4%	-0.62 [-1.97, 0.73]			
	Total (95% CI)			997			884	100.0%	-0.14 [-0.30, 0.02]	•		
	Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =	•	•	(P = 0.0	001); I²:	= 61% )%				-4 -2 0 2 4 vours experimental Favours control	_	

	Study of Sub-	Psychological the	-	Cont		Mainta da	Risk Ratio	Risk Ratio	Risk of Bias	
	Study or Subgroup 2.3.1 Active or standard	Events	lotal	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDE	
					~~	4 700				
	Connelly 2006	7	14	4	20	4.7%	2.50 [0.90, 6.94]		22262	
	Griffiths 1996 Hicks 2006	12 15	15 21	3 3	12 16		3.20 [1.16, 8.80]		22222	
	Jong 2018	35	86	د 15		4.0% 9.8%	3.81 [1.33, 10.94] 1.00 [0.63, 1.60]	·		
	Labbe 1984	13	00 14	15	- 14	9.0%	13.00 [1.96, 86.42]	Ī	22202	
	Larsson 1987a	13	30	1	14	1.8%	4.77 [0.70, 32.29]		22200	
	Law 2015	13	44	7	39	6.1%	1.52 [0.66, 3.47]	_ <b>_</b>		
	McGrath 1992	26	44	6			2.30 [1.10, 4.85]		22200	
	Palermo 2009	10	23	3		4.0%	3.04 [0.97, 9.58]		<b>***</b> **	
	Palermo 2005 Palermo 2016 (remote)	2	48	2			0.98 [0.14, 6.67]			Active o
	Powers 2013	42	40 64	26			1.79 [1.26, 2.55]	-		
	Rapoff 2014	7	18	20		5.7%	1.10 [0.46, 2.62]	_ <b>_</b>	22.002	standar
	Sartory 1998	20	30	5	13		1.73 [0.83, 3.61]	<b></b>	22222	care conti
	Trautmann 2010	16	35	2		3.1%	3.66 [0.95, 14.05]		2 • • • ?	
	Subtotal (95% CI)		489	-	359		1.95 [1.46, 2.61]	♦		$\oplus \oplus \bigcirc \bigcirc$
	Total events	230		84			- / -	-		LOW
)%	Heterogeneity: Tau <sup>2</sup> = 0.0	9; Chi <sup>2</sup> = 19.89, df =	13 (P = 0.	10); I <sup>2</sup> = 0	35%					
	Test for overall effect: Z =	4.54 (P < 0.00001)								
duction,										Waitlist
st-treatment	2.3.2 Waitlist control									control:
Stucaution	Barry 1997	2	12	2	17	1.9%	1.42 [0.23, 8.70]	<del></del>	<b>? O ? O ?</b>	
	Kroener-Herwig 2002	16	29	8	19	8.0%	1.31 [0.70, 2.44]	+	<u>? ? ? ? ?</u>	$\oplus OOC$
	Labbe 1995	19	20	6	10	9.2%	1.58 [0.95, 2.65]	<b>⊢</b>	<u>? ? ? ? ?</u>	VERY LC
	Larsson 1987	6	12	2	24	2.8%	6.00 [1.42, 25.39]	—	? 🗬 ? ? ?	VLINILO
	Larsson 1990	6	31	0	17	0.9%	7.31 [0.44, 122.42]		??????	
	Larsson 1996	9	13	1	13	1.7%	9.00 [1.32, 61.24]	———	???? 🛨 ?	
	Osterhaus 1997	12	25	0		0.9%	14.42 [0.92, 226.60]		- ??? 🖶 🖶	
	Scharff 2002	7	13	1	23		12.38 [1.71, 89.86]		😠 ? ? 🗨 🖨	
	Subtotal (95% CI)		155		137	27.2%	3.17 [1.50, 6.67]			
	Total events	77		20						
	Heterogeneity: Tau² = 0.5		7 (P = 0.0	1); I <sup>z</sup> = 61	1%					
	Test for overall effect: Z =	3.03 (P = 0.002)								
	Total (95% CI)		644		496	100.0%	2.11 [1.61, 2.77]	•		
	Total events	307		104				•		
	Heterogeneity: Tau <sup>2</sup> = 0.1		21 (P = 0		41%		+		<del>t</del>	
	Test for overall effect: Z =						0.	.002 0.1 1 10 Favours control Favours experir	500	

Health-related quality of life, post-treatment <i>Lower scores</i> <i>indicate better</i> <i>quality of life</i>	<section-header></section-header>	Active or standard care control: ⊕⊕⊕⊖ MODERATE Waitlist control: ⊕○○○ VERY LOW
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			F	unctior	al dis	sabilit	y, post-treatme	ent	
Functional disability, post-treatment <i>Higher scores</i> <i>indicate lower</i> <i>disability</i>	Study or Subgroup2.5.1 Active or standard ofChen 2014Connelly 2006Connelly 2019Hickman 2015Kashikar-Zuck 2005Kashikar-Zuck 2012Law 2015Levy 2010Levy 2010Levy 2016Lewy 2017Nieto 2019Palermo 2016 (f2f)Palermo 2016 (remote)Palermo 2016 (remote)Palermo 2016 (remote)Palermo 2016 (remote)Palermo 2016 (remote)Palermo 2016 (remote)Palermo 2020Powers 2013Rapoff 2014Robins 2005Van der Veek 2013Van Tilburg 2009Wicksell 2009Subtotal (95% CI)Heterogeneity: Tau <sup>2</sup> = 0.02Test for overall effect: Z = 3Cotal (95% CI)Heterogeneity: Tau <sup>2</sup> = 0.14Test for overall effect: Z = 3Test for overall effect: Z = 3Test for overall effect: Z = 3Test for subgroup difference	16         8           12.2         9.92           2.2         2.4           38.25         32.21           15.07         9.06           16.7         8.7           0.56         0.54           5.6         5.7           5.51         8.14           5.96         6.25           3.6         2.86           9.52         6.41           5.68         4.36           34.9         25.4           15.5         17.4           7.82         10.55           18.1         4.9           7.17         8.76           17.1         5.1           12.3         13.9           2.5         17.4           7.17         8.76           12.3         13.9           2.5         1.7.1           12.3         13.9           2.61 (P = 0.0009)         5.33           5.33         6.64           18.52         9.44           27.9         9.7           3.64 (P = 0.0003)         3.6           2.64 (P = 0.0003)         3.6           3.64 <tr td=""></tr>	Total           45           17           144           16           144           57           20           84           80           159           23           31           134           73           64           18           40           52           16           1127           20 (P = 0.0)           47           82           (P = 0.09);           1209           23 (P < 0.0)	20 1 10.74 11.6 1.7 2 30.88 30.0 16.64 8 19.8 9 4.86 4 0.55 0.4 7.3 8 7.65 10.4 8.22 8.6 6.62 4.7 8.1 4.2 5.65 4.6 37.8 25 29.6 42 12.29 12.9 19.6 5 7.79 8.7 25.4 10 14.6 11 4); I <sup>2</sup> = 38% 24.52 14.0 27.67 7.0 34.2 8 I <sup>2</sup> = 58% 001); I <sup>2</sup> = 609	D         Total           0         45           1         20           2         145           2         16           3         13           4         55           4         37           8         84           3         78           4         52           6         21           8         30           9         135           6         70           2         71           4         17           9         268           8         52           6         144           3         165           6         14           7         18           8         52           6         144           7         18           52         84           7         18           7         18           8         52           84         52           84         52           84         52           54         52           54         52	Weight 4.6% 3.0% 6.5% 2.7% 2.4% 5.1% 3.6% 5.7% 6.1% 3.9% 6.4% 3.9% 6.4% 2.8% 4.0% 5.5% 5.4% 2.8% 4.0% 5.0% 2.3% 2.7% 2.8% 4.0% 5.0% 2.7% 2.0% 2.8% 4.0% 5.0% 2.7% 100.0%	-0.44 [-0.86, -0.02] 0.13 [-0.52, 0.78] 0.22 [-0.01, 0.45] 0.23 [-0.46, 0.93] -0.17 [-0.93, 0.58] -0.34 [-0.71, 0.03] -0.01 [-0.55, 0.54] 0.02 [-0.28, 0.32] -0.24 [-0.50, 0.03] -0.29 [-0.80, 0.22] -0.76 [-1.38, -0.15] 0.25 [-0.25, 0.76] 0.01 [-0.23, 0.25] -0.11 [-0.44, 0.20] -0.43 [-0.77, -0.08] -0.37 [-1.04, 0.30] -0.28 [-0.78, 0.22] -0.07 [-0.45, 0.31] -0.98 [-1.76, -0.20] -0.15 [-0.27, -0.04] -1.72 [-2.59, -0.85] -1.07 [-1.75, -0.38] -0.68 [-1.08, -0.27] -1.05 [-1.62, -0.49] -0.25 [-0.39, -0.11]	Std. Mean Difference IV, Random, 95% CI	Active or standard care control: $\oplus \oplus \oplus \bigcirc$ MODERATE Waitlist control: $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW

Functional disability, follow-up <i>Higher scores</i> <i>indicate lower</i> <i>disability</i>	Study or Subgroup 2.6.1 Active or standard Connelly 2019 Kashikar-Zuck 2012 Law 2015 Lew 2010 Lew 2016 Lew 2017 Palermo 2016 (f2f) Palermo 2016 (remote) Palermo 2020 Powers 2013 Rapoff 2014 Van der Veek 2013 Wicksell 2009 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z = 2.6.2 Waitlist control Grob 2013 Subtotal (95% Cl) Heterogeneity: Not applic Test for overall effect: Z =	2 13.4 5.19 0.36 5.1 4.5 7.84 5.46 34.1 7.6 0.91 5.8 8.8 1; Chi <sup>⊋</sup> = 14.5 3.18 (P = 0.0 4.22 able	SD 2.2 8.9 5.02 0.39 6.4 6.6 5.5 4.32 21.8 16.9 1.45 8.2 12.9 33, df = 12 ( 01) 5.26	Total 144 57 28 78 67 151 31 134 73 57 11 52 16 899 P = 0.27	Co Mean 1.9 17 5.27 0.48 5.9 7.6 8.75 6.16 35.1 19 3.5 4.87 14.7	2.2 10.5 4.61 0.56 6.8 10.85 4.64 5.05 27.7 30 4.86 6.6 12.1	Total 145 55 22 76 66 82 30	Weight 10.9% 7.8% 4.9% 8.9% 8.4% 10.0% 5.6%	ability, follow-u Std. Mean Difference IV, Random, 95% CI 0.05 [-0.19, 0.28] -0.37 [-0.74, 0.01] -0.02 [-0.57, 0.54] -0.25 [-0.57, 0.07] -0.12 [-0.46, 0.22] -0.37 [-0.64, -0.10] -0.18 [-0.68, 0.33] -0.15 [-0.39, 0.09] -0.04 [-0.37, 0.29] -0.46 [-0.81, -0.10] -0.69 [-1.56, 0.17] 0.12 [-0.26, 0.51] -0.46 [-1.16, 0.24] -0.18 [-0.28, -0.07] -1.91 [-2.82, -1.01] -1.91 [-2.82, -1.01]	JD Std. Mean Difference IV, Random, 95% CI	Risk of Bias         A       B       C       D       E         •       •       •       •       •       •         •       •       •       •       •       •       •         •       •       •       •       •       •       •       •         • <th>Active or standard care control: ⊕⊕⊕⊕ HIGH</th>	Active or standard care control: ⊕⊕⊕⊕ HIGH
	2.6.2 Waitlist control Grob 2013 Subtotal (95% CI) Heterogeneity: Not applic	4.22 able 4.17 (P < 0.0 4; Chi <sup>2</sup> = 28.7 2.96 (P = 0.0 nces: Chi <sup>2</sup> = 1 eneration (se nt (selection   ssessment ( data (attrition	5.26 001) '9, df = 13 ( 03) 4.11, df = lection bia: bias) detection b	<b>914</b> (P = 0.00 I (P = 0.0	7); I² = 6	55%	14 841		-1.91 [-2.82, -1.01] -0.23 [-0.38, -0.08]	-4 -2 0 2 4 avours experimental Favours control	2220	HIGH

	Study or Subgroup	Psycholog Mean		pies	Control		C	Depression, pos Std. Mean Difference IV, Random, 95% Cl	St-treatment Std. Mean Difference IV, Random, 95% Cl	Risk of Bias A B C D E	
Emotional functioning: Depression, post-treatment <i>Higher scores</i> <i>indicate</i> <i>higher</i> <i>depressive</i> <i>symptomology</i>	2.8.1 Active or standard of Connelly 2019 Jong 2018 Kashikar-Zuck 2012 Law 2015 Lester 2020 Levy 2010 Levy 2016 Palermo 2016 (f2f) Palermo 2016 (remote) Trautmann 2010 Van der Veek 2013 Wicksell 2009 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01 Test for overall effect: Z = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.01 Test for overall effect: Z = Test for subgroup differer <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmer (C) Blinding of outcome a (D) Incomplete outcome of (E) Selective reporting (rep	care control           45.5           6           8.7           44.75           15.93           7.89           4.4           11.53           9.55           7.26           1.85           18.1           0; Chi <sup>2</sup> = 8.05           1.01 (P = 0.3')           nccs: Not app           eneration (sel           nt (selection t           ssessment (i           lata (attrition 1	11 4.3 6.1 9.52 6.49 6.99 5.8 5.37 5.13 6.15 1.93 9.8 (, df = 11 (F 1) licable lection bia bias) detection t	144 45 57 28 21 78 67 31 134 36 52 16 <b>709</b> 9 = 0.71) <b>709</b> 9 = 0.71)	45 11.4 5 3.4 9.3 5.9 43.74 6.45 14.53 4.5 7.19 5.27 4.6 5.9 8.71 5.6 9.49 5.58 6.6 3.7 1.79 2.14 25.5 16.9	145 41 55 23 18 76 66 30 135 9 52 16 <b>666</b>	21.4% 6.3% 8.3% 3.7% 2.8% 11.4% 9.8% 4.4% 19.9% 2.1%	0.04 [-0.19, 0.28] 0.25 [-0.17, 0.68] -0.10 [-0.47, 0.27] 0.12 [-0.43, 0.67] 0.24 [-0.39, 0.87] 0.11 [-0.20, 0.43] -0.03 [-0.37, 0.31] 0.51 [-0.00, 1.02] 0.01 [-0.23, 0.25] 0.11 [-0.62, 0.84] 0.03 [-0.36, 0.41] -0.52 [-1.23, 0.18] 0.06 [-0.05, 0.16]	-4 -2 0 2 4 avours experimental Favours control		Active or standard care control: ⊕⊕⊕⊕ HIGH



			ł	Emot	iona	l fun	ctio	ning:	Anxiety, post-tre	eatment		
Emotional functioning: Anxiety, post- treatment <i>Higher scores</i>	Study or Subgroup 2.9.1 Active or standard of Bussone 1988 Connelly 2019 Hickman 2015 Kashikar-Zuck 2012 Lalouni 2019 Law 2015 Lester 2020 Lewy 2010 Lewy 2010 Lewy 2016 Lewy 2016 Lewy 2016 (remote) Stapersma 2018 Trautmann 2010 Van der Veek 2013 Wicksell 2009 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03 Test for overall effect: Z = 1	28.1 46.8 52.56 2.11 8.59 46.33 7.08 13.5 8.2 1.09 11.42 10.56 7.1 30.9 6.83 13.4 3; Chi <sup>z</sup> = 26.6	SD 3.49 11.3 7.36 0.72 7.71 8.99 6.24 4.86 2.8 0.94 5.33 5.91 4.14 7.95 6 3.9	Total 20 144 16 50 45 30 24 83 80 159 31 134 35 35 35 2 16 <b>957</b>	Mean           29.2           45.5           47.38           2.39           15.31           48.32           6.1           13.04           8.6           1.28           31.07           31.77           7.76           12.8	5.1 11 6.1 0.9 7.63 10.81 4.96 4.04 2.9 1.07 6.03 6.1 4.6 8.3 6.33 5.5	10	Weight 2.3% 9.2% 2.6% 5.8% 5.2% 4.0% 3.4% 7.5% 7.4% 8.3% 4.3% 9.0% 4.6% 3.7% 6.0% 2.6%	Std. Mean Difference IV, Random, 95% CI -0.26 [-1.02, 0.50] 0.12 [-0.11, 0.35] 0.75 [0.04, 1.46] -0.34 [-0.74, 0.05] -0.87 [-1.30, -0.43] -0.20 [-0.73, 0.33] 0.17 [-0.42, 0.76] 0.10 [-0.21, 0.41] -0.14 [-0.45, 0.17] -0.19 [-0.46, 0.08] -0.27 [-0.78, 0.23] -0.05 [-0.29, 0.19] -0.05 [-0.52, 0.43] -0.10 [-0.65, 0.24] 0.12 [-0.57, 0.82] -0.10 [-0.24, 0.03]	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias         A       B       C       D       E         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         2       2       2       2       2         3       4       4       4       4         2       4       4       4       4         2       4       4       4       4         2       4       4       4       4         2       4       4       4       4         3       4       4       4       4         4       4       4       4       4         4       4       4       4       4       4	Active or standard care control: ⊕⊕⊕○ MODERATE Waitlist
indicate higher depressive symptomology	2.9.2 Waitlist control Bonnert 2017 Griffiths 1996 Hechler 2014 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0 Test for overall effect: Z = 0 Test for subgroup differen <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmer (C) Blinding of outcome as (D) Incomplete outcome d (E) Selective reporting (rep	0.14 (P = 0.8 3; Chi <sup>2</sup> = 31.9 1.28 (P = 0.2 cces: Chi <sup>2</sup> = 0 eneration (see at (selection) ssessment ( lata (attrition)	99) 34, df = 18 0) 0.40, df = 1 election bia bias) (detection bias)	30 50 127 = 0.14); (P = 0.0 (P = 0.0 (P = 0.0	50  ² = 499 2);  ² = 4	9.5 11.4 6 .4%			0.16 [-0.23, 0.55] -0.55 [-1.24, 0.13] 0.21 [-0.19, 0.61] 0.03 [-0.35, 0.41] -0.08 [-0.21, 0.04] -4 Favo	4 -2 0 2 4 Purs experimental Favours control		control: ⊕○○○ VERY LOW



## Appendix G.4. WHO review: Psychological interventions for children with chronic pain Subgroup analysis: by control type

**Comparison:** Psychological therapies versus active/standard care control or waitlist control **Population:** children with any chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of outcome assessment (detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post- treatment <i>Higher</i> <i>scores</i> <i>indicate</i> <i>higher pain</i> <i>intensity</i>	Psychological therapies         Control Mean         Std. Mean         Difference N, Random, 95% CI         Risk of Bias           2.1.1 Active or standard care control         16.6         16.57         17         17.29         23.21         20         2.2%         -0.03 [-0.66, 0.61]         0.7%         0	Active or standard care control: ⊕⊕○○ LOW Waitlist control:
	2.1.2 Waitlist control Bonnert 2017 4.53 2.54 47 5.53 2.42 54 3.2% -0.40 [-0.80, -0.01] Grob 2013 0.16 0.32 15 1.93 1.64 14 1.6% -1.48 [-2.32, -0.65] Gulewitsch 2013 1.6 2.45 20 4.46 2.33 18 2.0% -1.17 [-1.86, -0.47] Hechier 2014 5.7 2.4 51 5.9 2.5 52 3.2% -0.08 [-0.47, 0.31] Kroener-Herwig 2002 0.86 1.16 29 0.76 0.96 46 2.9% 0.10 [-0.37, 0.56] Nieto 2019 12.72 10.32 25 11.55 8.84 36 2.7% 0.12 [-0.39, 0.63] Osterhaus 1997 2.3 1 2.25 2.6 0.7 14 2.2% -0.08 [-0.67, 0.49] Schatz 2015 16.4 14.3 23 17.7 14.9 23 2.4% -0.09 [-0.67, 0.49] Subtotal (95% Cl) 235 257 20.2% -0.34 [-0.66, -0.01] Heterogenetty: Tau <sup>2</sup> = 0.14; Chi <sup>2</sup> = 20.87, df = 7 (P = 0.004); i <sup>2</sup> = 66% Test for overall effect: Z = 4.22 (P < 0.0001) Test for subgroup differences: Chi <sup>2</sup> = 0.09, df = 1 (P = 0.76), i <sup>2</sup> = 0%	⊕⊕⊖⊖ LOW

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												124
						F	Pain	inten	sity, follow-up			
Pain intensity, follow-up Higher scores indicate higher pain intensity	Study or Subgroup         2.2.1 Active or standard         Barakat 2010         Bussone 1988         Connelly 2019         Hicks 2006         Kashikar-Zuck 2012         Law 2015         Lester 2020         Levy 2017         Palermo 2016 (721)         Palermo 2016 (remote)         Palermo 2020         Rapoff 2014         Richter 1986         Sanders 1994         Trautmann 2010         Van der Veek 2013         Wahlund 2015         Wicksell 2009         Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.0         Test for overall effect: Z =         2.2.2 Wait-List control         Grob 2013         Kroener-Herwig 2002         Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.8         Test for overall effect: Z =         Total (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.0         Test for overall effect: Z =         Test for subgroup differer	Mean           care control           16.71           20           3.1           2.9           4.9           4.19           2.67           0.93           3.48           5.42           5.85           5.3           4.46           2.02           0.64           4.9           19.03           2.8           3.1           6; Chi <sup>2</sup> = 41           1.32 (P = 0.           0.08           0.48           3; Chi <sup>2</sup> = 7.7           0.90 (P = 0.           8; Chi <sup>2</sup> = 51           1.67 (P = 0.	23.03 18.1 2.5 2.1 2.2 2.45 1.9 1.42 2.33 2.05 1.97 1.97 1.97 1.88 1.48 1.48 1.48 1.48 1.48 1.48 1.48 1.48 1.9 2.7 .84, df = 18 19) 0.31 0.65 76, df = 1 (P 37) .59, df = 20 09)	Total           17           20           144           25           57           28           151           31           134           73           11           30           22           31           16           953           (P = 0.005)           997           (P = 0.005)	Mean           7.84         88.8           2.7         4.9           5.3         3.7           0.7         3.07           0.7         3.79           5.35         6.2           3.68         2.02           2.11         5.5           17.72         2.8           4.5         01); I² =           1.55         0.46           0; I² = 87         001); I² =	2000 12.31 110.3 2.4 1.3 2.54 2.64 1.53 2.48 2.12 2.02 1.8 2.04 1.39 3.56 1.9 15.19 1.6 2.4 577% 1.49 0.61 *%	Total 20 10 145 22 55 22 18 76 78 30 135 70 135 70 112 22 16 52 33 16 843 14 27 41		Std. Mean Difference IV, Random, 95% CI 0.48 [-0.18, 1.14] -1.04 [-1.85, -0.23] 0.16 [-0.07, 0.39] -1.11 [-1.73, -0.49] -0.18 [-0.56, 0.19] 0.19 [-0.37, 0.75] -0.17 [-0.80, 0.46] 0.16 [-0.16, 0.47] -0.13 [-0.40, 0.14] 0.06 [-0.45, 0.56] 0.15 [-0.09, 0.39] -0.48 [-0.82, -0.15] 0.38 [-0.46, 1.23] 0.00 [-0.67, 0.67] -0.53 [-1.14, 0.07] -0.53 [-1.14, 0.07] -0.53 [-1.24, 0.17] 0.00 [-0.49, 0.49] -0.53 [-1.24, 0.17] -0.11 [-0.26, 0.05] -1.35 [-2.17, -0.53] 0.03 [-0.49, 0.56] -0.62 [-1.97, 0.73] -0.14 [-0.30, 0.02]	Std. Mean Difference IV, Random, 95% CI	Risk of Bias         A       B       C       D       E         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?         ?       ?       ?       ?       ?	Active or standard care control: ⊕⊕○○ LOW Waitlist control: ⊕○○○ VERY LOW

		Psychological th	erapies	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias	
	Study or Subgroup	Events				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDE	
	2.3.1 Active or standard	care control								
	Connelly 2006	7	14	4	20	4.7%	2.50 [0.90, 6.94]		🛨 🛨 🖶 🛑 ?	
	Griffiths 1996	12	15	3	12	4.7%	3.20 [1.16, 8.80]		???	
	Hicks 2006	15	21	3	16	4.5%	3.81 [1.33, 10.94]		<u>?????</u>	
	Jong 2018	35	86	15	37	9.8%	1.00 [0.63, 1.60]	+	•••?••	
	Labbe 1984	13	14	1	14	1.8%	13.00 [1.96, 86.42]		<b>3 3 3 4 3</b>	
	Larsson 1987a	13	30	1	11	1.8%	4.77 [0.70, 32.29]			
	Law 2015	12	44	7	39	6.1%	1.52 [0.66, 3.47]	_ <b>-</b> _		
	McGrath 1992	26	47	6	25	6.8%	2.30 [1.10, 4.85]		<b>3 3 3 0 0</b>	
	Palermo 2009 Balarma 2046 (ramata)	10	23	3	21	4.0%	3.04 [0.97, 9.58]			Active or
	Palermo 2016 (remote)	2	48	2		1.7%	0.98 [0.14, 6.67]			
	Powers 2013	42 7	64	26	71	11.2%	1.79 [1.26, 2.55]		22002	standard
	Rapoff 2014	20	18 30	6 5	17 13	5.7% 6.9%	1.10 [0.46, 2.62]		22222	care contro
	Sartory 1998 Trautmann 2010	20 16	30 35	2	13	0.9%	1.73 [0.83, 3.61] 3.66 [0.95, 14.05]	-	2	
	Subtotal (95% CI)	10	489	2	359	72.8%	1.95 [1.46, 2.61]	•		$\oplus \oplus \bigcirc \bigcirc$
	Total events	230	400	84	000	12.0%	100 [1140, 210 1]	•		LOW
00/	Heterogeneity: Tau <sup>2</sup> = 0.0		13(P = 0)		35%					LOW
0%	Test for overall effect: Z =		10 (1 = 0.	107,1 = 0						
eduction,										Waitlist
ost-treatment	2.3.2 Waitlist control									control:
USI-liealineni	Barry 1997	2	12	2	17	1.9%	1.42 [0.23, 8.70]		? 🖨 ? 🖨 ?	
	Kroener-Herwig 2002	16	29	8	19	8.0%	1.31 [0.70, 2.44]		?????	$\oplus OOO$
	Labbe 1995	19	20	6	10	9.2%	1.58 [0.95, 2.65]		<mark>?????</mark> ?	VERY LOV
	Larsson 1987	6	12	2	24	2.8%	6.00 [1.42, 25.39]		? 🖨 ? ? ?	VERTLOV
	Larsson 1990	6	31	0	17	0.9%	7.31 [0.44, 122.42]		<u>?????</u>	
	Larsson 1996	9	13	1	13	1.7%	9.00 [1.32, 61.24]		????	
	Osterhaus 1997	12	25	0	14	0.9%	14.42 [0.92, 226.60]		???	
	Scharff 2002	7	13	1	23	1.6%	12.38 [1.71, 89.86]		🕒 ? ? 🔁 🖨	
	Subtotal (95% CI)		155		137	27.2%	3.17 [1.50, 6.67]	-		
	Total events	77		20						
	Heterogeneity: Tau <sup>2</sup> = 0.5		7 (P = 0.0	1); I* = 61	96					
	Test for overall effect: Z =	3.03 (P = 0.002)								
	Total (95% CI)		644		496	100.0%	2.11 [1.61, 2.77]	•		
	Total events	307		104				•		
	Heterogeneity: Tau <sup>2</sup> = 0.1		21 (P = 0.		11%		+ 0.0	······································	+	
	Test for overall effect: Z =			21.			0.0	002 0.1 1 10 5 Favours control Favours experim		

Health-related quality of life, post-treatment <i>Lower scores</i> <i>indicate better</i> <i>quality of life</i>	Heterogenetic Tar 0 - 03; Ch2 - 2.8, 1 - 0.03; Ch2 - 2.8, 1 - 0.00; Ch2 - 2.8, 0 -	Active or standard care control: $\oplus \oplus \oplus \bigcirc$ MODERATE Waitlist control: $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW
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			Function	al disabili	ty, post-treatme	ent		
Functional disability, post-treatment <i>Higher scores</i> <i>indicate lower</i> <i>disability</i>	Study or Subgroup2.5.1 Active or standard cChen 2014Connelly 2006Connelly 2019Hickman 2015Kashikar-Zuck 2005Kashikar-Zuck 2012Law 2015Lewy 2016Lewy 2016Lewy 2017Nieto 2019Palermo 2016 (f2f)Palermo 2016 (remote)Palermo 2013Rapoff 2014Robins 2005Van der Veek 2013Van Tilburg 2009Wicksell 2009Subtotal (95% CI)Heterogeneity: Tau² = 0.02Test for overall effect: Z = 3Cotal (95% CI)Heterogeneity: Tau² = 0.07Test for overall effect: Z = 3Total (95% CI)Heterogeneity: Tau² = 0.07Test for overall effect: Z = 3Total (95% CI)Heterogeneity: Tau² = 0.07Test for subgroup difference	16       8         12.2       9.92         2.2       2.4         38.25       32.21         15.07       9.08         16.7       8.7         4.83       4.78         0.56       0.54         5.6       5.7         5.51       8.14         5.96       6.25         3.6       2.86         9.52       6.47         5.68       4.38         34.9       25.4         15.5       17.4         7.82       10.59         18.1       4.9         7.17       8.76         17.1       5.1         12.3       13.9         ; Chi² = 32.20, df = 1         .61 (P = 0.009)       5.33         5.33       6.64         18.52       9.44         27.9       9.7         ; Chi² = 4.77, df = 2       .64 (P = 0.0003)         ; Chi² = 58.06, df = 5       .43 (P = 0.0006)	Total         Mean         SI           45         20         11           17         10.74         11.6           144         1.7         2.           16         30.88         30.01           14         16.64         8:           57         19.8         9.           20         4.86         4.           84         0.55         0.44           80         7.3         8:           159         7.65         10.4           23         6.62         4.7           23         6.62         4.7           31         8.1         4.22           134         5.65         4.60           73         37.8         25.           64         29.6         42.           18         12.29         12.9           40         19.6         5.           52         7.79         8.7           15         24.52         14.0           20         (P = 0.04); P = 38%           15         24.52         14.0           20         27.67         7.0           47         34.2         8.	Total         Weight           0         45         4.6%           20         3.0%           2         145         6.5%           2         145         6.5%           2         16         2.7%           4         55         5.1%           4         55         5.1%           4         55         5.1%           4         37         3.6%           3         78         5.7%           4         84         6.1%           3         78         5.7%           4         84         6.1%           3         3         3.9%           3         135         6.4%           6         70         5.5%           2         71         5.4%           4         17         2.8%           5         2         6.0%           5         16         2.7%           1065         90.5%           5         14         2.0%           5         2         4.8%           5         2         4.8%           5         2         4.8% <tr tbody="">&lt;</tr>	<ul> <li>-0.44 [-0.86, -0.02]</li> <li>0.13 [-0.52, 0.78]</li> <li>0.22 [-0.01, 0.45]</li> <li>0.23 [-0.46, 0.93]</li> <li>-0.17 [-0.93, 0.58]</li> <li>-0.04 [-0.71, 0.03]</li> <li>-0.01 [-0.55, 0.54]</li> <li>-0.24 [-0.55, 0.07]</li> <li>-0.24 [-0.55, 0.07]</li> <li>-0.24 [-0.55, 0.07]</li> <li>-0.25 [-0.25, 0.76]</li> <li>0.01 [-0.25, 0.76]</li> <li>0.01 [-0.23, 0.25]</li> <li>-0.11 [-0.44, 0.22]</li> <li>-0.43 [-0.77, -0.08]</li> <li>-0.37 [-1.04, 0.30]</li> <li>-0.38 [-0.78, 0.22]</li> <li>-0.18 [-0.87, 0.52]</li> <li>-0.15 [-0.27, -0.04]</li> <li>-1.07 [-1.75, -0.38]</li> <li>-0.68 [-1.08, -0.27]</li> <li>-1.05 [-1.62, -0.49]</li> <li>-0.25 [-0.39, -0.11]</li> </ul>	Std. Mean Difference IV, Random, 95% CI	Risk of Bias         2       2         *       *         ?       ?         *       *         ?       ?         *       *         ?       ?         *       *         ?       ?         *       *         ?       ?         *       *         *<	Active or standard care control: ⊕⊕⊕○ MODERATE Waitlist control: ⊕○○○ VERY LOW

	Study or Subgroup 2.6.1 Active or standard of Connelly 2019 Kashikar-Zuck 2012	Mean	gical thera, SD 2.2 8.9	pies Total I 144 57	Contr Mean S	ol 5 <mark>0 Total</mark> .2 145	Weight 10.9%	ability, follow-u Std. Mean Difference IV, Random, 95% CI 0.05 [-0.19, 0.28] -0.37 [-0.74, 0.01]	p Std. Mean Difference IV, Random, 95% Cl	Risk of Bias A B C D E	
Functional disability, follow-up <i>Higher scores</i> <i>indicate lower</i>	Law 2015 Lew 2010 Lew 2016 Lew 2017 Palermo 2016 (f2f) Palermo 2016 (remote) Palermo 2020 Powers 2013 Rapoff 2014 Van der Veek 2013 Wicksell 2009 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0 <sup>o</sup> Test for overall effect: Z = 1	5.19 0.36 5.1 4.5 7.84 5.46 34.1 7.6 0.91 5.8 8.8 1; Chi≇ = 14.5	5.02 0.39 6.4 6.6 5.5 4.32 21.8 16.9 1.45 8.2 12.9 53, df = 12 (	28 78 67 151 134 73 57 11 52 16 <b>899</b>	7.6         10.4           8.75         4.1           6.16         5.1           35.1         27           19         3           3.5         4.4           4.87         6           14.7         12	31         22           36         76           .8         66           35         82           34         30           35         135           .7         70           30         67           36         11           .6         52	4.9% 8.9% 8.4% 10.0% 5.6% 10.7% 8.7% 8.1% 2.5% 7.5% 3.5%	-0.02 [-0.57, 0.54] -0.25 [-0.57, 0.07] -0.12 [-0.46, 0.22] -0.37 [-0.64, -0.10] -0.18 [-0.68, 0.33] -0.15 [-0.39, 0.09] -0.04 [-0.37, 0.29] -0.46 [-0.81, -0.10] -0.69 [-1.56, 0.17] 0.12 [-0.26, 0.51] -0.46 [-1.16, 0.24] <b>-0.18 [-0.28, -0.07]</b>			Active or standard care control: ⊕⊕⊕⊕ HIGH
disability	2.6.2 Waitlist control Grob 2013 Subtotal (95% CI) Heterogeneity: Not applic: Test for overall effect: Z = - Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z = - Test for subgroup differen <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmer (C) Blinding of outcome a: (D) Incomplete outcome of (E) Selective reporting (rep	4.17 (P < 0.0 4; Chi <sup>2</sup> = 28.7 2.96 (P = 0.0 inces: Chi <sup>2</sup> = 1 eneration (see tt (selection ssessment ( lata (attrition	79, df = 13 ( 03) I 4.11, df = 1 Iection bia: bias) (detection b bias)	<b>914</b> (P = 0.007 1 (P = 0.0	7); I² = 55%			-1.91 [-2.82, -1.01] -1.91 [-2.82, -1.01] -0.23 [-0.38, -0.08] - Fav	-4 -2 0 2 4 vours experimental Favours control	222	

		Dauchalani					ing: [	Depression, pos	st-treatment Std. Mean Difference	Risk of Bias	
Emotional functioning: Depression, post-treatment <i>Higher scores</i> <i>indicate</i> <i>higher</i> <i>depressive</i> <i>symptomology</i>	Study or Subgroup 2.8.1 Active or standard of Connelly 2019 Jong 2018 Kashikar-Zuck 2012 Law 2015 Lester 2020 Lewy 2010 Lewy 2016 Palermo 2016 (f2f) Palermo	45.5 6 8.7 44.75 15.93 7.89 4.4 11.53 9.55 7.25 1.85 18.1 Chi <sup>2</sup> = 8.05, .01 (P = 0.31 ces: Not appl neration (seli- t (selection b sessment (c ata (attrition b	SD 11 4.3 6.1 9.52 6.49 5.8 5.37 5.13 6.15 1.93 9.8 df = 11 (F) ) df = 11 (F) ) df = 11 (F) ) licable ection bia: ias)	Total 144 45 57 28 21 78 67 31 134 36 52 16 709 P = 0.71); 709 P = 0.71); s)	45 11. 5 3. 9.3 5. 43.74 6.43 14.53 4.3 7.19 5.2 4.6 5.9 8.71 5.0 9.49 5.56 6.6 3.1 1.79 2.14 25.5 16.9 ;  F = 0%	Total           145           41           55           23           18           76           66           30           135           9           52           166           666           666           666	Weight 21.4% 6.3% 8.3% 3.7% 2.8% 11.4% 9.8% 4.4% 19.9% 2.1% 2.3% 100.0%	0.04 [-0.19, 0.28] 0.25 [-0.17, 0.68] -0.10 [-0.47, 0.27] 0.12 [-0.43, 0.67] 0.24 [-0.39, 0.87] 0.11 [-0.20, 0.43] -0.03 [-0.37, 0.31] 0.51 [-0.00, 1.02] 0.01 [-0.23, 0.25] 0.11 [-0.62, 0.84] 0.03 [-0.36, 0.41] -0.52 [-1.23, 0.18] 0.06 [-0.05, 0.16]	Suc, Mean Difference IV, Random, 95% CI		Active or standard care control: ⊕⊕⊕⊕ HIGH

				Emo	otional	funct	ioning	: Depression, f	ollow up		
Emotional functioning: Depression, follow up Higher scores indicate higher depressive symptomology	Study or Subgroup         2.8.1 Active or standard c         Connelly 2019         Jong 2018         Kashikar-Zuck 2012         Law 2015         Lester 2020         Levy 2010         Levy 2016         Palermo 2016 (f2f)         Palermo 2016 (remote)         Trautmann 2010         Van der Veek 2013         Wicksell 2009         Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.00         Test for overall effect: Z = 1         Total (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.00         Test for subgroup difference         Risk of bias legend         (A) Random sequence gei         (B) Allocation concealmeni         (C) Blinding of outcome as         (D) Incomplete outcome da         (E) Selective reporting (rep	45.5 6 8.7 44.75 15.93 7.89 4.4 11.53 9.55 7.25 1.85 18.1 ; Chi <sup>2</sup> = 8.05 .01 (P = 0.31 ces: Not app neration (sel t (selection t sessment (cata (attrition 1)))	SD 11 4.3 6.1 9.52 6.49 6.99 5.8 5.37 5.13 6.15 1.93 9.8 , df = 11 (F )) df = 11 (F )) licable ection bia bias) detection bia	Total 144 45 57 28 21 78 67 31 134 36 52 16 709 P = 0.71) 709 P = 0.71) S)		Total           4         145           4         41           3         55           5         23           5         18           7         76           3         66           3         135           7         9           4         52           3         16           666         666	Weight 21.4% 6.3% 8.3% 3.7% 2.8% 11.4% 9.8% 4.4% 19.9% 2.1% 7.7%	0.04 [-0.19, 0.28] 0.25 [-0.17, 0.68] -0.10 [-0.47, 0.27] 0.12 [-0.43, 0.67] 0.24 [-0.39, 0.87] 0.11 [-0.20, 0.43] -0.03 [-0.37, 0.31] 0.51 [-0.00, 1.02] 0.01 [-0.23, 0.25] 0.11 [-0.62, 0.84] 0.03 [-0.36, 0.41] -0.52 [-1.23, 0.18] 0.06 [-0.05, 0.16]	Std. Mean Difference IV, Random, 95% CI	Risk of Bias         A B C D E         • • • • • • •         • • • • • • •         • • • • • • •         • • • • • • •         • • • • • •         • • • • • •         • • • • • •         • • • • • •         • • • • • • •         • • • • • •         • • • • • •         • • • • •         • • • • •         • • • • •         • • • • •         • • • • •         • • • • •         • • • • •         • • • • •	Active or standard care control: ⊕⊕⊕⊕ HIGH

			I	Emot	ional	fund	ctior	ning: /	Anxiety, post-tre	eatment		
Emotional functioning: Anxiety, post- treatment <i>Higher scores</i>	Study or Subgroup 2.9.1 Active or standard of Bussone 1988 Connelly 2019 Hickman 2015 Kashikar-Zuck 2012 Lalouni 2019 Law 2015 Lester 2020 Levy 2010 Levy 2016 Levy 2016 Levy 2016 Levy 2017 Palermo 2016 (f2f) Palermo 2016 (f2f) Palermo 2016 (remote) Stapersma 2018 Trautmann 2010 Van der Veek 2013 Wicksell 2009 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03 Test for overall effect: Z = 4	28.1 46.8 52.56 2.11 8.59 46.33 7.08 13.5 8.2 1.09 11.42 10.56 7.1 30.9 6.83 13.4 3; Chi <sup>z</sup> = 26.6	SD 3.49 11.3 7.36 0.72 7.71 8.99 6.24 4.86 2.8 0.94 5.33 5.91 4.14 7.95 6 3.9 6, df = 15	Total 20 144 16 50 45 30 24 83 80 159 31 134 35 38 52 16 957	Mean           29.2           45.5           47.38           2.39           15.31           48.32           6.1           13.04           8.6           1.28           13           10.85           7.3           31.7           7.76           12.8	5.1 11 6.1 0.9 7.63 4.04 2.9 1.07 6.03 6.1 4.6 8.3 6.33 5.5	10 145 50 44 25 21 80 78 81 30 135 33 18 52 16 <b>835</b>	Weight 2.3% 9.2% 2.6% 5.2% 4.0% 3.4% 7.5% 7.4% 8.3% 4.3% 4.3% 4.6% 3.7% 6.0% 2.6% 85.7%	Std. Mean Difference IV, Random, 95% Cl 0.12 [-0.11, 0.35] 0.75 [0.04, 1.46] -0.34 [-0.74, 0.05] -0.87 [1.30, -0.43] -0.20 [-0.73, 0.33] 0.17 [-0.42, 0.76] 0.10 [-0.21, 0.41] -0.14 [-0.45, 0.17] -0.19 [-0.46, 0.08] -0.27 [-0.78, 0.23] -0.05 [-0.29, 0.19] -0.05 [-0.52, 0.43] -0.10 [-0.66, 0.46] -0.15 [-0.53, 0.24] 0.12 [-0.57, 0.82] -0.10 [-0.24, 0.03]	Std. Mean Difference IV, Random, 95% CI	Risk of Bias         A       B       C       D       E         ?       ?       ?       •       •       ?         ?       ?       ?       •       •       ?         ?       ?       ?       ?       •       •       ?         ?       ?       ?       ?       •       ?       ?         ?       ?       ?       •       ?       •       ?       ?         ?       ?       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       •       ?       ?       •       ?       ?       ?       •       ?       ?       ?       •       ?	Active or standard care control: ⊕⊕⊕⊖ MODERATE Waitlist
indicate higher depressive symptomology	2.9.2 Waitlist control Bonnert 2017 Griffiths 1996 Hechler 2014 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for subgroup differen <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmer (C) Blinding of outcome as (D) Incomplete outcome d (E) Selective reporting (rep	0.14 (P = 0.89 3; Chi <sup>2</sup> = 31.9 1.28 (P = 0.21 ces: Chi <sup>2</sup> = 0 eneration (sel tseessment ( lata (attrition	9) 14, df = 18 0) 1.40, df = 1 lection bia bias) detection	30 50 127 = 0.14); 1 1084 (P = 0.02 (P = 0.5) 35)	² = 49% !);  ² = 44	9.5 11.4	54 12 46 112 947	5.8% 2.7% 5.7% 14.3%	0.16 [-0.23, 0.55] -0.55 [-1.24, 0.13] 0.21 [-0.19, 0.61] 0.03 [-0.35, 0.41] -0.08 [-0.21, 0.04] -4 Favou	-2 0 2 4 urs experimental Favours control		control: ⊕○○○ VERY LOW

				Er	notio	nal 1	func	ctionin	ng: Anxiety, follo	ow-up		
Emotional functioning: Anxiety, follow-up Higher scores indicate higher depressive symptomology	Study or Subgroup2.10.1 Active or standardBussone 1988Connelly 2019Kashikar-Zuck 2012Law 2015Lester 2020Lewy 2010Lewy 2016Lewy 2017Palermo 2016 (f2f)Palermo 2016 (remote)Trautmann 2010Van der Veek 2013Wicksell 2009Subtotal (95% Cl)Heterogeneity: Tau <sup>2</sup> = 0.00Test for overall effect: Z = 1Total (95% Cl)Heterogeneity: Tau <sup>2</sup> = 0.00Test for subgroup differenRisk of bias legend(A) Random sequence ge(B) Allocation concealmen(C) Blinding of outcome as(D) Incomplete outcome d(E) Selective reporting (rep	27.8 45.3 1.89 45.82 4.71 13.21 7.9 0.87 12.61 10.35 24.95 5.47 12.2 0; Chi <sup>2</sup> = 11.2 1.31 ( $P = 0.19$ ces: Not appl meration (sel t (selection b ssessment (c ata (attrition t	SD 2.3 12 0.82 10.96 5.09 3.98 3.3 0.88 6.05 6.12 7 5.22 4.6 1, df = 12 1) 1, df = 12 1, df = 12	Total 20 144 50 28 21 75 67 151 31 134 31 52 16 820 (P = 0.51 820 (P = 0.51 820 (P = 0.51)	Mean 29.1 46 2.22 45.36 4.07 12.59 8.2 1.1 10.23 28.1 5.82 11.7 1); I <sup>2</sup> = 0 <sup>4</sup>	1.4 11.4 9.9 2.99 4.14 3.2 0.98 5.55 5.45 9.9 6.09 5.8 %	10 145 50 22 18 63 66 78 30 135 10 52 16 <b>695</b>	Weight 1.7% 19.7% 6.7% 3.4% 2.6% 9.3% 13.9% 13.9% 2.0% 7.1% 2.2% 100.0%	Std. Mean Difference IV, Random, 95% Cl -0.62 [-1.39, 0.16] -0.06 [-0.29, 0.17] -0.38 [-0.77, 0.02] 0.04 [-0.52, 0.60] 0.15 [-0.48, 0.78] 0.09 [-0.43, 0.25] -0.25 [-0.52, 0.02] 0.24 [-0.27, 0.74] 0.02 [-0.22, 0.26] -0.40 [-1.12, 0.32] -0.06 [-0.45, 0.32] 0.09 [-0.60, 0.79] -0.07 [-0.17, 0.03] -0.07 [-0.17, 0.03]	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E	Active or standard care control: ⊕⊕⊕○ MODERATE

## Appendix G.5. WHO review: Psychological interventions for children with chronic pain Subgroup analysis: by treatment duration

**Comparison:** Psychological therapies versus active (non-psychological), standard care or waitlist control; by treatment duration **Population:** children and adolescents with chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of outcome assessment (detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post-treatment Higher scores indicate higher pain intensity	Decreation:         Decreation:         Decreation:         Decreation:         The provide former to real form	
	Total (95% CI)     1584     1441     100.0%     -0.29 [-0.43, -0.16]     ♦       Heterogeneity: Tau's = 0.11; Chi <sup>a</sup> = 113.72, df = 37 (P < 0.0001); P = 67%	

	Study or Subgroup			Co Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias ABCDE	
	4.2.1 Treatment duration										
	Bussone 1988	20 18		88.8		10	2.8%	-1.04 [-1.85, -0.23]		???	
	Law 2015 Lew 2010	4.19 2.4 0.93 1.4			2.54 1.53	22 76	4.4% 6.7%	0.19 [-0.37, 0.75] 0.16 [-0.16, 0.47]	-		
	Levy 2017	3.48 2.3			2.48	78	7.2%	-0.13 [-0.40, 0.14]	-	• ? • ? •	
	Palermo 2016 (remote)	5.85 1.9			2.02	135	7.5%	0.15 [-0.09, 0.39]	-		
	Palermo 2020 Subtotal (95% CI)	5.3 1		6.2	1.8	70 391	6.5% <b>35.1%</b>	-0.48 [-0.82, -0.15] - <b>0.11 [-0.39, 0.16]</b>		? • • • •	
	Heterogeneity: Tau² = 0.03 Test for overall effect: Z =		= 5 (P = 0.00)	3); I <b>²</b> = 72	%						
	4.2.2 Treatment duration	. ,									Less than 4
	Barakat 2010	16.71 23.0	03 17	7.84	12.31	20	3.6%	0.48 [-0.18, 1.14]	+	???	hours
	Connelly 2019	3.1 2	.5 144	2.7	2.4	145	7.6%	0.16 [-0.07, 0.39]	-	😠 🖶 🔁 🤋 🛑	$\oplus \oplus \oplus \bigcirc$
	Grob 2013	0.08 0.3		1.55	1.49	14	2.7%	-1.35 [-2.17, -0.53]		???++	•
in intensity,	Kroener-Herwig 2002	0.48 0.6			0.61	27	4.6%	0.03 [-0.49, 0.56]	+	<b>33333</b>	MODERAT
low-up	Lester 2020	2.67 1			2.64	18	3.8%	-0.17 [-0.80, 0.46]			
	Palermo 2016 (f2f)	5.42 2.0			2.12	30	4.8%	0.06 [-0.45, 0.56]	+		
gher scores	Sanders 1994	0.64 1.3		2.11	3.56	22	4.0%	-0.53 [-1.14, 0.07]		2 2 2 0 2	More than 4
diante bigbor	Van der Veek 2013	19.03 17.039		17.72		52	6.0%	0.08 [-0.30, 0.47]	Ť		
dicate higher	Wahlund 2015		.9 31	2.8	1.6	33	5.0%	0.00 [-0.49, 0.49]			hours
in intensity	Wicksell 2009 Subtotal (95% CI)	3.1 2	.7 16 378	4.5	2.4	16 <b>377</b>	3.3% <b>45.6%</b>	-0.53 [-1.24, 0.17] - <b>0.10 [-0.34, 0.14]</b>			$\oplus \oplus \bigcirc \bigcirc$
	Heterogeneity: Tau² = 0.03 Test for overall effect: Z =		= 9 (P = 0.02)	; I² = 559	6						LOW
	4.2.3 Treatment duration	, unknown									
	Hicks 2006		.1 25	4.9	1.3	22	3.9%	-1.11 [-1.73, -0.49]		<mark>?????</mark> ?	
	Kashikar-Zuck 2012		.2 57	5.3	2.1	55	6.1%	-0.18 [-0.56, 0.19]			
	Rapoff 2014	4.46 1.8		3.68	2.04	11	2.6%	0.38 [-0.46, 1.23]	+	?? 🖶 🖶 ?	
	Richter 1986	2.02 1.4			1.39	12	3.6%	0.00 [-0.67, 0.67]		2 2 2 2	
	Trautmann 2010 Subtotal (95% CI)	4.9 1	.4 12 135	5.5	1.9	16 <b>116</b>	3.1% <b>19.3%</b>	-0.34 [-1.10, 0.41] - <b>0.28 [-0.72, 0.17]</b>	•	<b>?</b> • • • <b>•</b> ?	
	Heterogeneity: Tau <sup>2</sup> = 0.1 Test for overall effect: Z =		= 4 (P = 0.04)	; I² = 619	b						
	Total (95% CI)		997			884	100.0%	-0.14 [-0.30, 0.02]	•		
	Heterogeneity: Tau² = 0.03 Test for overall effect: Z =		= 20 (P = 0.0) If = 2 (P = 0.7					Favou	-4 -2 0 2 4 urs experimental Favours control		

	Study or Subgroup	Psychological the Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E	
	4.3.1 Treatment duration									
	Barry 1997	2	12	2	17	1.9%	1.42 [0.23, 8.70]		? 🔿 ? 🔿 ?	
	Larsson 1987	6	12	2	24	2.6%	6.00 [1.42, 25.39]		2 🖸 2 2 2	
	Larsson 1996	9	13	1	13	1.7%	9.00 [1.32, 61.24]		- ???+?	
	Law 2015	12	44	7	39	6.1%	1.52 [0.66, 3.47]		•••••	
	Palermo 2009	10	23	3	21	4.0%	3.04 [0.97, 9.58]			
	Palermo 2016 (remote)	2	48	2	47	1.7%	0.98 [0.14, 6.67]		44444	
	Sartory 1998 Scharff 2002	20 7	30 13	5 1	13 23	6.9% 1.6%	1.73 [0.83, 3.61] 12.38 [1.71, 89.86]	Τ		
	Subtotal (95% CI)	'	195	1	197	26.8%	2.50 [1.47, 4.25]			
	Total events	68	155	23	157	20.0/0	2.50 [1.47, 4.25]	$\bullet$		
	Heterogeneity: $Tau^2 = 0.1$		- 7 (9 - 1		- 27%					
	Test for overall effect: Z =									Less than 4
	422 Treatment duration	Ahours								hours
	4.3.2 Treatment duration, Jong 2018	>4 nours 35	86	15	37	9.6%	1.00 [0.63, 1.60]			000
	Kroener-Herwig 2002	16	29	15	19	6.0%	1.31 [0.70, 2.44]		22222	
	Labbe 1964	13	14	1	14	1.6%	13.00 [1.96, 86.42]	Ē	- 22242	VERY LOV
	Labbe 1995	19	20	ė	10	9.2%	1.58 [0.95, 2.65]		22222	VEICIEOV
	Larsson 1987a	13	30	1	11	1.6%	4.77 [0.70, 32.29]		22200	
% reduction,	Osterhaus 1997	12	25	ō	14	0.9%	14.42 [0.92, 226.60]			
st-treatment	Subtotal (95% CI)	16	204	v	105	31.6%	1.92 [1.02, 3.60]	•		
st-treatment	Total events	108		31				-		More than
	Heterogeneity: Tau <sup>2</sup> = 0.32		if = 5 (P =		<sup>2</sup> - 667	<b>K</b>				
	Test for overall effect: Z =									hours
	4.3.3 Treatment duration	unknown								000
	Connelly 2006	7	14	4	20	4.7%	2.50 [0.90, 6.94]	<b></b>	<b>A A A A 7</b>	
	Griffiths 1996	12	15	3	12	4.7%	3.20 [1.16, 8.80]		22202	VERY LOV
	Hicks 2006	15	21	3	16	4.5%	3.81 [1.33, 10.94]		22222	
	Larsson 1990	6	31	ō	17	0.9%	7.31 [0.44, 122.42]	<b>_</b>		
	McGrath 1992	26	47	6	25	6.8%	2.30 [1.10, 4.85]	<b></b>	22200	
	Powers 2013	42	64	26	71	11.2%	1.79 [1.26, 2.55]	- <b>-</b> -	<b>.</b>	
	Rapoff 2014	7	16	6	17	5.7%	1.10 [0.46, 2.62]	<b>+</b>	?? 🗣 🗣 ?	
	Trautmann 2010	16	35	2	16	3.1%	3.66 [0.95, 14.05]	+	? 🖶 🖶 🔁 ?	
	Subtotal (95% CI)		245		194	41.6%	2.05 [1.58, 2.66]	◆		
	Total events	131		50						
	Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z =			0.46); ۴	- 0%					
	Total (95% CI)		644		496	100.0%	2.11 [1.61, 2.77]	•		
	Total events	307		104				l ·		
	Heterogeneity: $Tau^2 = 0.14$		if = 21 (P		$f^2 = 41$	1%	L .			
	Test for overall effect: Z =			/1			0.0		LOO'	
	Test for subgroup different			0.77)	2 _ AN			Favours control Favours experir	nental	

		Psycholog	vical thora	nioe	Con	trol			Std. Mean Difference	Std Mo	an Difference	Risk of Bias	
	Study or Subgroup	Mean	SD	Total			Total	Weight	IV, Random, 95% Cl		idom, 95% Cl	ABCDE	
	4.4.1 Treatment duration	, ≤4 hours											
	Hickman 2015	38.25	32.21	16	30.88 31	0.02	16	2.7%	0.23 [-0.46, 0.93]		+	<u>?????</u>	
	Law 2015	4.83	4.78	20	4.86	4.4	37	3.6%	-0.01 [-0.55, 0.54]		-		
	Levy 2010	0.56	0.54	84		0.48	84	5.8%	0.02 [-0.28, 0.32]		+	•••?•	
	Levy 2016	5.6	5.7	80		8.3	78	5.7%	-0.24 [-0.55, 0.07]				
	Levy 2017	5.51	8.14	159		0.44	84	6.1%	-0.24 [-0.50, 0.03]		-	• ? • ? •	
	Nieto 2019	5.96	6.25	25		8.61	36	3.9%	-0.29 [-0.80, 0.22]	-	-+	•?•?•	
	Palermo 2009	3.6	2.86	23		4.76	21	3.2%	-0.76 [-1.38, -0.15]		—	••••	
	Palermo 2016 (remote)	5.68	4.38	134			135	6.4%	0.01 [-0.23, 0.25]		+		
	Palermo 2020	34.9	25.4	73		25.6	70	5.5%	-0.11 [-0.44, 0.22]		-	? 🔁 🖶 🖶 🛑	Less than
	Van Tilburg 2009 Subtotal (95% Cl)	17.1	5.1	15 629	25.4	10.6	14 575	2.3% <b>45.2%</b>	-0.98 [-1.76, -0.20] <b>-0.16 [-0.31, -0.01]</b>		•	33333	hours
	Heterogeneity: Tau² = 0.02 Test for overall effect: Z = 3	•		P = 0.14);	I² = 33%								
unctional	4.4.2 Treatment duration	, >4 hours											MODERAT
isability, post-	Connelly 2019	2.2	2.4	144	1.7	2.2	145	6.5%	0.22 [-0.01, 0.45]		-	🔁 🖶 🖶 ? 🛑	
	Grob 2013	5.33	6.64		24.52 1.		14	2.0%	-1.72 [-2.59, -0.85]			???++	
eatment	Gulewitsch 2013	18.52	9.44			7.07	18	2.8%	-1.07 [-1.75, -0.38]		-	• ? ? • ?	
	Hechler 2014	27.9	9.7	47	34.2	8.8	52	4.8%	-0.68 [-1.08, -0.27]	_	- I	••??•	N.4 (1
ligher scores	Palermo 2016 (f2f)	9.52	6.47	31		4.28	30	3.9%	0.25 [-0.25, 0.76]		<b></b>		More than
dicate lower	Robins 2005	18.1	4.9	40	19.6	5.9	26	4.0%	-0.28 [-0.78, 0.22]	-	<u>_</u>	? • ? ? ?	hours
	Van der Veek 2013	7.17	8.76	52		8.78	52	5.0%	-0.07 [-0.45, 0.31]		-	• ? ? ? •	
isability	Wicksell 2009	12.3	13.9	16		11.3	16	2.7%	-0.18 [-0.87, 0.52]	-			$\oplus OOC$
	Subtotal (95% CI)	12.5	10.0	365	14.0	11.5	353	31.5%	-0.36 [-0.75, 0.02]		•		
	Heterogeneity: Tau <sup>2</sup> = 0.24 Test for overall effect: Z = 1	•			01); I² = 8	2%					•		VERY LO
	4.4.3 Treatment duration	, unknown											
	Chen 2014	16	8	45	20	10	45	4.6%	-0.44 [-0.86, -0.02]	-		2220	
	Connelly 2006	12.2	9.92		10.74 1		20	3.0%	0.13 [-0.52, 0.78]		<b>—</b>		
	Kashikar-Zuck 2005	15.07	9.08			8.3	13	2.4%	-0.17 [-0.93, 0.58]	_	<del>_</del>	•••??	
	Kashikar-Zuck 2012	16.7	8.7	57		9.4	55	5.1%	-0.34 [-0.71, 0.03]			<b>.</b>	
	Powers 2013	15.5	17.4	64		42.2	71	5.4%	-0.43 [-0.77, -0.08]	-		••••	
	Rapoff 2014 Subtotal (95% CI)	7.82	10.59	18 <b>215</b>	12.29 1:	2.94	17 221	2.8% 23.3%	-0.37 [-1.04, 0.30] -0.34 [-0.53, -0.15]	_	•	??••?	
	Heterogeneity: Tau² = 0.00 Test for overall effect: Z = 3	•		= 0.75); l <sup>a</sup>	= 0%								
	Total (95% CI)			1209		1	1149	100.0%	-0.25 [-0.39, -0.11]		•		
	Heterogeneity: Tau <sup>2</sup> = 0.07	7; Chi <sup>2</sup> = 58.0	16. df = 23	(P < 0.00)	01); <b>I<sup>2</sup> =</b> 6	0%				t t	<u> </u>	<del></del>	
	Test for overall effect: Z = 3	•	•		<i></i>				-	-4 -2	0 2 tal Favours control	. 4	

					Funct	iona	l disal	bility, follow-up			
	Study or Subgroup	Psychologica Mean	-		Control			Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias ABCDE	
	4.5.1 Treatment duration Law 2015 Lew 2010 Lew 2016 Lew 2017 Palermo 2016 (remote) Palermo 2020 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00	5.19 6 0.36 ( 5.1 4.5 5.46 4 34.1 2 D; Chi <sup>2</sup> = 3.28, df	4.32 <sup>-</sup> 21.8	78 0. 67 ( 51 ) 34 6. 73 3( <b>31</b>	27 4.61 48 0.56 6.9 6.8 7.6 10.85 16 5.05 6.1 27.7	66 82 135 70	8.9% 8.4% 10.0% 10.7%	-0.02 [-0.57, 0.54] -0.25 [-0.57, 0.07] -0.12 [-0.46, 0.22] -0.37 [-0.64, -0.10] -0.15 [-0.39, 0.09] -0.04 [-0.37, 0.29] <b>-0.19 [-0.31, -0.06]</b>	       +  		
Functional disability, follow- up <i>Higher scores</i>	Test for overall effect: Z = 4.5.2 Treatment duration Connelly 2019 Grob 2013 Palermo 2016 (f2f) Van der Veek 2013 Wicksell 2009 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.20 Test for overall effect: Z =	, >4 hours 2 4.22 € 7.84 5.8 8.8 1 0; Chi² = 19.40, c	5.26 5.5 8.2 2.9	15 24. 31 8. 52 4. 16 14 258	76 14 75 4.64 37 6.6 .7 12.1	14 30 52	5.6% 7.5% 3.5%	0.05 [-0.19, 0.28] -1.91 [-2.82, -1.01] -0.18 [-0.68, 0.33] 0.12 [-0.26, 0.51] -0.46 [-1.16, 0.24] - <b>0.33 [-0.79, 0.13]</b>	+ 		Less than 4 hours ⊕⊕⊕⊖ MODERATE More than 4 hours
indicate lower disability	4.5.3 Treatment duration Kashikar-Zuck 2012 Powers 2013 Rapoff 2014 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z =	13.4 7.6 1 0.91 1 D; Chi≊ = 0.48, df	= 2 (P = 0.	57 11 ( 1 <b>25</b>	17 10.5 19 30 35 4.86	67	7.8% 8.1% 2.5% <b>18.4%</b>	-0.37 [-0.74, 0.01] -0.46 [-0.81, -0.10] -0.69 [-1.56, 0.17] <b>-0.44 [-0.68, -0.19]</b>			⊕○○○ VERY LOW
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z = Test for subgroup differen <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmer (C) Blinding of outcome a (D) Incomplete outcome of (E) Selective reporting (rep	2.96 (P = 0.003) aces: Chi <sup>2</sup> = 3.26 eneration (select at (selection bias ssessment (dete lata (attrition bias	lf = 13 (P = , df = 2 (P = ion bias) ;) ection bias	: 0.20), P		841	100.0%	-0.23 [-0.38, -0.08]  Fav	-4 -2 0 2 4 ours experimental Favours control	-	



		Psycholog				Control	ng.		ession, post-trea	Std. Mean Difference	Risk of Bias	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDE	
	4.7.1 Treatment duration	, ≤4 hours										
	Hickman 2015	51.69	6.65	16	49.69	6.46	17	1.9%	0.30 [-0.39, 0.98]		<b>? ? ? ? ?</b>	
	Law 2015	46.3	10.03	27	47.48	9.5	23	2.8%	-0.12 [-0.68, 0.44]	—	••••?	
	Lester 2020	14.38	6.22	24		4.53	21	2.6%	-0.02 [-0.60, 0.57]			
	Levy 2010	9.96	6.16	84	8.35		84	9.5%	0.27 [-0.03, 0.57]	-		
	Levy 2016	7.6	7.1	80	8.8	7.6	78	9.0% 2.5%	-0.16 [-0.47, 0.15]	_ <u>T</u>		Loop then 4
	Palermo 2009 Palermo 2016 (f2f)	58.96 12.03	13.1 5.13	23 31	61.59 11.2		21 30	2.5% 3.5%	-0.16 [-0.75, 0.43] 0.16 [-0.35, 0.66]	-		Less than 4
	Palermo 2016 (remote)	9.71	5.1	134		5.37	135		0.07 [-0.16, 0.31]	-		hours
	Subtotal (95% CI)	0.11	5.1	419	0.02	0.01	409	46.9%	0.05 [-0.08, 0.19]	•		$\oplus \oplus \oplus \oplus$
Emotional	Heterogeneity: Tau² = 0.0 Test for overall effect: Z =			'= 0.61);	² = 0%							HIGH
unctioning:	4.7.2 Treatment duration	, >4 hours										
Depression,	Connelly 2019	46.4	11.2	144	45.2	12.1	145	16.4%	0.10 [-0.13, 0.33]	+	•••?•	
•	Hechler 2014	50.3	12	47	50.7	8.5	46	5.3%	-0.04 [-0.44, 0.37]	-+-	😑 😑 ? ? 🛑	More than 4
oost-treatment	Van der Veek 2013	2.17	1.96	52	2.33	1.97	52	5.9%	-0.08 [-0.47, 0.30]	-+-	🛨 ? ? ? 🔴	
ligher scores	Wicksell 2009	18.4	10	16	25	10.5	16	1.7%	-0.63 [-1.34, 0.08]		•••??	hours
	Subtotal (95% CI)	1.058-0.05		259	17 - 240	,	259	29.4%	-0.03 [-0.25, 0.18]	•		$\oplus \oplus \oplus \bigcirc$
ndicate higher	Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =	•		·= 0.27);	17 = 249	0						-
lepressive		0.20 () 0.1	• /									MODERATE
symptomology	4.7.3 Treatment duration	, unknown										
, ympternelegy	Griffiths 1996	2.45	0.64	31	2.6	0.9	12	2.0%	-0.20 [-0.87, 0.46]		??? 🗬 ?	
	Kashikar-Zuck 2005	49.57	17.6	14		12.89	13	1.5%	0.07 [-0.69, 0.82]		•••??	
	Kashikar-Zuck 2012	9.9	6.2	57	11.8	5.8	55	6.3%	-0.31 [-0.69, 0.06]			
	Lalouni 2019	1.99	2.88	45	2.89	2.85	44	5.0%	-0.31 [-0.73, 0.11]			
	Nieto 2019 Stanaroma 2019	18.2	6.22 6.51	20		4.53 6.89	21 33	2.3% 3.9%	-0.31 [-0.92, 0.31]			
	Stapersma 2018 Trautmann 2010	7.2 9.55	9.1	35 37	7.7	0.89 5.2	33 18	3.9% 2.7%	-0.07 [-0.55, 0.40] 0.23 [-0.34, 0.79]	1	2	
	Subtotal (95% CI)	3.00	5.1	239	(.(	J.Z	196	23.7%	-0.18 [-0.37, 0.01]	•		
	Heterogeneity: Tau <sup>z</sup> = 0.0 Test for overall effect: Z =	•		= 0.72);	I² = 0%							
	Total (95% CI)			917			864	100.0%	-0.02 [-0.11, 0.08]	•		
	Heterogeneity: Tau <sup>2</sup> = 0.0	0; Chi² = 16.7	2, df = 18		4); I² = 0	%					<del>.</del>	
	Test for overall effect: Z =	0.36 (P = 0.7)	2)						-4 Favou	-2 Ó 2 Irs experimental Favours control	4	
	Test for subgroup differer	ices: Chi <sup>z</sup> = 3	1.72, df = 2	2 (P = 0.1	6), I <sup>z</sup> = 4	46.2%						

			E	motic	onal	func	tior	ning:	Depression, follo	ow up		
	Study of Cubaroup	Psycholog Mean	ical therap SD			ntrol	Total	Weight	Std. Mean Difference	Std. Mean Difference	Risk of Bias	
	Study or Subgroup 4.8.1 Treatment duration		50	Total	wean	20	otai	weight	IV, Random, 95% Cl	IV, Random, 95% CI	ABCDE	
	Law 2015	44.75	9.52	28	43.74	6 4 5	23	3.7%	0.12 [-0.43, 0.67]	_ <b>_</b>		
	Lew 2010	7.89	6.99		7.19			11.4%	0.11 [-0.20, 0.43]	<u>+</u> -		
	Levy 2016	4.4	5.8	67		5.9	66	9.8%	-0.03 [-0.37, 0.31]		••••	
	Palermo 2016 (f2f)	11.53	5.37	31	8.71	5.6	30	4.4%	0.51 [-0.00, 1.02]	<b>⊢</b> ⊷−		
	Palermo 2016 (remote)	9.55	5.13	134	9.49	5.58	135	19.9%	0.01 [-0.23, 0.25]	<u>+</u>	$\bullet \bullet \bullet \bullet \bullet$	
	Subtotal (95% CI)		-16 4 (D	338			330	49.2%	0.08 [-0.07, 0.23]	Ť		
	Heterogeneity: Tau² = 0.00 Test for overall effect: Z = 1	•		= 0.48); P	ʻ= U%							Less than 4 hours
Emotional	4.8.2 Treatment duration	,>4 hours										
functioning:	Connelly 2019	45.5	11	144	45	11.4	145	21.4%	0.04 [-0.19, 0.28]	+	•••	$\oplus \oplus \oplus \oplus$
•	Jong 2018	6	4.3	45	5	3.4	41	6.3%	0.25 [-0.17, 0.68]	+	••?••	HIGH
Depression,	Lester 2020	15.93	6.49	21	14.53	4.5	18	2.8%	0.24 [-0.39, 0.87]	- <del>-</del>	••••	
follow up	Van der Veek 2013	1.85	1.93		1.79		52	7.7%	0.03 [-0.36, 0.41]	+-	•???•	
Higher scores	Wicksell 2009 Subtotal (95% CI)	18.1	9.8	16 278	25.5	16.9	16 272	2.3% 40.5%	-0.52 [-1.23, 0.18] 0.06 [-0.11, 0.22]		•••??	More than 4
	Heterogeneity: Tau <sup>2</sup> = 0.01	0. Chiz - 2.77	df - 1 /D -		- 004		212	40.3%	0.00[-0.11, 0.22]	Ť		hours
indicate higher depressive	Test for overall effect: Z = 1	•		- 0.44), 1	- 0 %							$\oplus \oplus \oplus \bigcirc$
	4.8.3 Treatment duration	, unknown										MODERATE
symptomology	Kashikar-Zuck 2012	8.7	6.1	57	9.3	5.9	55	8.3%	-0.10 [-0.47, 0.27]		$\bullet \bullet \bullet \bullet ?$	
	Trautmann 2010	7.25	6.15	36 93	6.6	3.7	9 64	2.1% 10.4%	0.11 [-0.62, 0.84] -0.06 [-0.39, 0.27]		? 🖶 🖶 🖨 ?	
	<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0				²= 0%		04	10.4%	-0.00 [-0.39, 0.27]	Ť		
	<b>Total (95% CI)</b> Heterogeneity: Tau² = 0.00	0; Chi² = 8.05	, df = 11 (P	<b>709</b> ? = 0.71);	I² = 0%		666	100.0%	0.06 [-0.05, 0.16]	<u> </u>	ţ	
	Test for overall effect: Z = Test for subgroup differen Risk of bias legend			(P = 0.77	), I² = 0	%			Favo	urs experimental Favours control	4	
	(A) Random sequence ge (B) Allocation concealmer	nt (selection b	oias)									
	<ul> <li>(C) Blinding of outcome a</li> <li>(D) Incomplete outcome d</li> <li>(E) Selective reporting (reporting)</li> </ul>	lata (attrition I		)ias)								

	Emotional functioning: Anxiety, post-treatment	
	Psychological therapies         Control         Std. Mean Difference         Std. Mean Difference         Risk of Bias           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, Random, 95% CI         IV, Random, 95% CI         A B C D E           4.9.1 Treatment duration, ≤4 hours         Bussone 1988         28.1         3.49         20         29.2         5.1         10         2.3%         -0.26 [-1.02, 0.50]         Provide	
	Subtotal (95% CI) 522 426 41.0% -0.05 [-0.21, 0.10] Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 7.80, df = 6 (P = 0.25); I <sup>2</sup> = 23% Test for overall effect: Z = 0.66 (P = 0.51)	Less than 4 hours ⊕⊕⊕⊖
Emotional functioning: Anxiety, post-	4.9.2 Treatment duration, >4 hours         Connelly 2019       46.8       11.3       144       45.5       11       145       9.2%       0.12 [-0.11, 0.35]       ●       ●       ?       ●         Hechler 2014       52.5       12.1       50       50       11.4       46       5.7%       0.21 [-0.19, 0.61]       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ●       ●       ?       ?       ●       ●       ?       ?       ●       ●       ?       ?       ●       ●       ?       ?       ●       ?       ?       ?       ●       ?       ?       ?       ●       ?       ?       ?       ●       ?       ?       ?       ?       ?	MODERATE More than 4 hours
treatment Higher scores	Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.75, df = 5 (P = 0.59); i <sup>2</sup> = 0% Test for overall effect: Z = 0.66 (P = 0.51) <b>4.9.3 Treatment duration, unknown</b>	⊕⊕⊕⊖ MODERATE
indicate higher depressive symptomology	Bonnert 2017       25.23       16.32       47       22.62       16.31       54       5.8%       0.16 [-0.23, 0.55]       +	
	Total (95% CI)1084947100.0%-0.08 [-0.21, 0.04]Heterogeneity: Tau" = 0.03; Chi" = 31.94, df = 18 (P = 0.02); I" = 44% Test for overall effect: $Z = 1.28$ (P = 0.20) Test for subgroup differences: Chi" = 3.46, df = 2 (P = 0.18), I" = 42.3% Risk of bias leqend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of outcome assessment (detection bias) (D) Incomplete outcome data (attrition bias) (E) Selective reporting (reporting bias)1084 947 	

			Em	otior	al fu	nctio	oning:	Anxiety, follow	-up		
	Chudu an Cubanaun	Psychologica			Control	Tetel		Std. Mean Difference	Std. Mean Difference	Risk of Bias	
	Study or Subgroup 4.10.1 Treatment duration	Mean A <4 hours	SD Tot	al Mea	n SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	ABCDE	
	Bussone 1988	-	2.3 2	0 29.	1 1.4	10	1.7%	-0.62 [-1.39, 0.16]		???	
	Law 2015			8 45.3		22		0.04 [-0.52, 0.60]	_ <del>_</del>	••••	
	Levy 2010			5 12.5		63		0.15 [-0.18, 0.49]	+-	•••?•	
	Levy 2016			7 8.		66	9.0%	-0.09 [-0.43, 0.25]	-+		Less than 4
	Levy 2017		.88 15		1 0.98	78		-0.25 [-0.52, 0.02]	-1	• ? • ? •	hours
	Palermo 2016 (remote) Subtotal (95% CI)	10.35 6	.12 13 47		3 5.45	135 374		0.02 [-0.22, 0.26] - <b>0.06 [-0.22, 0.09]</b>	T I I I I I I I I I I I I I I I I I I I		
	Heterogeneity: Tau <sup>2</sup> = 0.01	: Chi² = 5.95. df			i%	514	55.676	-0.00 [-0.22, 0.00]	1		$\oplus \oplus \oplus \oplus$
	Test for overall effect: Z = I		0,0 0.0								HIGH
Emotional											
functioning:	4.10.2 Treatment duration										Mana than 4
J	Connelly 2019		12 14		6 11.4	145		-0.06 [-0.29, 0.17]	<u> </u>		More than 4
Anxiety, follow-	Lester 2020 Palermo 2016 (f2f)			1 4.0 1 11.2	7 2.99	18 30	2.6% 4.1%	0.15 [-0.48, 0.78] 0.24 [-0.27, 0.74]			hours
up	Van der Veek 2013				2 6.09	52		-0.06 [-0.45, 0.32]	_	• ? ? ? •	$\oplus \oplus \oplus \oplus$
Higher scores	Wicksell 2009			6 11.		16	2.2%	0.09 [-0.60, 0.79]	_ <del>_</del>	•••??	
•	Subtotal (95% CI)		26			261	35.7%	-0.00 [-0.17, 0.17]	<b>•</b>		HIGH
indicate higher	Heterogeneity: Tau <sup>2</sup> = 0.00		= 4 (P = 0.8	3); I <b>z</b> = 01	Xo						
depressive	Test for overall effect: Z = I	0.01 (P = 0.99)									
symptomology	4.10.3 Treatment duration	n. unknown									
symptomology	Kashikar-Zuck 2012	-	.82 6	0 2.2	2 0.91	50	6.7%	-0.38 [-0.77, 0.02]			
	Trautmann 2010	24.95	7 3	1 28.	1 9.9	10	2.0%	-0.40 [-1.12, 0.32]		? 🖶 🖶 🛑 ?	
	Subtotal (95% CI)			1		60	8.7%	-0.38 [-0.73, -0.04]	•		
	Heterogeneity: Tau² = 0.00 Test for overall effect: Z = :		= 1 (P = 0.9)	6); I² = 01	б						
	Total (95% CI)		82	0		695	100.0%	-0.07 [-0.17, 0.03]			
	Heterogeneity: Tau <sup>2</sup> = 0.00	); Chi² = 11.21, d			0%						
	Test for overall effect: Z =	1.31 (P = 0.19)						-4 Eavo	4 -2 Ó 2 4 urs experimental Favours control	ł	
	Test for subgroup differen	ces: Chi² = 3.76,	df = 2 (P = 1	).15), I²÷	: 46.7%			1 400			
	Risk of bias legend										
	<ul> <li>(A) Random sequence ge</li> <li>(B) Allocation concealmer</li> </ul>										
	(C) Blinding of outcome as		·								
	(D) Incomplete outcome d										
	(E) Selective reporting (rep	oorting bias)									

# Appendix G.6. WHO review: Psychological interventions for children with chronic pain Subgroup analysis: by route

**Comparison:** Psychological therapies versus active (non-psychological), standard care or waitlist control; by route of intervention **Population:** Children and adolescents with chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of outcome assessment (detection bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)
| Outcome  | Forest plot   | Quality of<br>evidence<br>(GRADE)   |
|--|---|---|
| Pain intensity,<br>post-treatment<br><i>Higher scores</i><br><i>indicate</i><br><i>higher pain</i><br><i>intensity</i> | Definition for the second sec | Face to Face<br>with therapist:<br>⊕⊕○○<br>LOW<br>Remote from<br>therapist:<br>⊕⊕⊕○<br>MODERATE |

					ł	ain	mte	ISITY	, follow-up			
	Study or Subgroup	Mean	gical thera SD	-	C Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias A B C D E	
	6.2.1 Face-to-face with th	erapist										
	Barakat 2010	16.71	23.03		7.84		20	3.5%	0.48 [-0.18, 1.14]	+	????	
	Bussone 1988	20	18.1	20	88.8	110.3	10	2.6%	-1.04 [-1.85, -0.23]		???? 🛨 🖶	
	Grob 2013	0.08	0.31	15		1.49	14	2.6%	-1.35 [-2.17, -0.53]		???++	
	Kashikar-Zuck 2012	4.9	2.2	57	5.3	2.1	55	5.9%	-0.18 [-0.56, 0.19]	-+	$\bullet \bullet \bullet \bullet \bullet ?$	
	Kroener-Herwig 2002	0.48	0.65	29	0.46	0.61	27	4.4%	0.03 [-0.49, 0.56]	+	33333	
	Levy 2010	0.93	1.42	78	0.7	1.53	76	6.5%	0.16 [-0.16, 0.47]	+-		
	Levy 2017	3.41	2.35	81	3.79	2.48	37	5.7%	-0.16 [-0.55, 0.23]	-	• ? • ? •	
	Palermo 2016 (f2f)	5.42	2.05	31	5.3	2.12	30	4.6%	0.06 [-0.45, 0.56]	+		
	Richter 1986	2.02	1.48	30		1.39	12	3.4%	0.00 [-0.67, 0.67]		33330	
	Sanders 1994	0.64	1.38		2.11	3.56	22	3.8%	-0.53 [-1.14, 0.07]		3 3 3 🔴 3	
	Van der Veek 2013		17.0393		17.72		52	5.7%	0.08 [-0.30, 0.47]	Ť	•???	
	Wahlund 2015	2.8	1.9	31	2.8	1.6	33	4.7%	0.00 [-0.49, 0.49]	+	••???	Face to Fac
	Wicksell 2009	3.1	2.7	16	4.5	2.4	16	3.2%	-0.53 [-1.24, 0.17]		•••??	with therapis
ain intensity,	Subtotal (95% CI)			479			404	56.6%	-0.15 [-0.35, 0.06]	•		
follow-up	Heterogeneity: Tau² = 0.07 Test for overall effect: Z = 1	•	•	(P = 0.0	1); 1*= 5	2%						
igher scores	6.2.2 Remote from therap	bist										LOW
-	Connelly 2019	3.1	2.5	144	2.7	2.4	145	7.4%	0.16 [-0.07, 0.39]	-	•••	
indicate	Hicks 2006	2.9	2.1	25	4.9	1.3	22	3.7%	-1.11 [-1.73, -0.49]	_ <b>—</b>	22222	
higher pain	Law 2015	4.19	2.45	28	3.7		22	4.2%	0.19 [-0.37, 0.75]			
	Lester 2020	2.67	1.9	21	3.07	2.64	18	3.6%	-0.17 [-0.80, 0.46]	<b>_</b> _		Remote fror
intensity	Lew 2017	3.54	2.3	70	3.79	2.48	36	5.6%	-0.11 [-0.51, 0.30]	-	• ? • ? •	
•	Palermo 2016 (remote)	5.85	1.97	134	5.55	2.02	135	7.3%	0.15 [-0.09, 0.39]			therapist:
	Palermo 2020	5.3	1.9	73	6.2	1.8	70	6.3%	-0.48 [-0.82, -0.15]		? • • • •	$\oplus \oplus \bigcirc \bigcirc$
	Rapoff 2014	4.46	1.88	11	3.68	2.04	11	2.5%	0.38 [-0.46, 1.23]	<u> </u>	?? 🗨 🗬 ?	
	Trautmann 2010 Subtotal (95% CI)	4.9	1.4	12 <b>518</b>	5.5	1.9	16 <b>475</b>	2.9% <b>43.4%</b>	-0.34 [-1.10, 0.41] - <b>0.13 [-0.39, 0.13]</b>	•	? • • • ?	LOW
	Heterogeneity: Tau² = 0.09 Test for overall effect: Z = 0			P = 0.001	10); I² =	69%						
	Total (95% CI)			997			879	100.0%	-0.14 [-0.30, 0.02]	•		
	Heterogeneity: Tau² = 0.07 Test for overall effect: Z = 1 Test for subgroup differen	1.71 (P = 0.0	)9)						Favou	-4 -2 0 2 4 urs experimental Favours control	_	
	Risk of bias legend (A) Random sequence ge (B) Allocation concealment			as)								
	<ul> <li>(B) Allocation concealmer</li> <li>(C) Blinding of outcome as</li> <li>(D) Incomplete outcome d</li> </ul>	ssessment	(detection	bias)								
	(E) Selective reporting (rep											

			ţ	5U% re	edu	ICTION	, post-treatmen	IT		
	Study or Subgroup	Psychological th Events		Contro		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Risk of Bias A B C D E	
	6.3.1 Face-to-face with		Total	Events I	otai	weight	M-H, Kandom, 95% CI	M-H, Kandom, 95% CI	ABCDE	
	Barry 1997	2	12	2	17	1.6%	1.42 [0.23, 8.70]		? . ? . ?	
	Jong 2018	35	86	15	37	6.9%	1.00 [0.63, 1.60]			
	Kroener-Herwig 2002	16	29		19	7.4%	1.31 [0.70, 2.44]	_ <b>_</b>	22222	
	Labbe 1964	13	14	ĭ	14	1.7%	13.00 [1.96, 86.42]		- 22242	
	Labbe 1995	19	20	6	10	8.4%	1.58 [0.95, 2.65]		22222	
	Larsson 1987	6	12	2	24	2.7%	6.00 [1.42, 25.39]		7 6 7 7 7	
	Larsson 1987a	13	30	1	11	1.7%	4.77 [0.70, 32.29]		- ???	
	Larsson 1990	6	31	0	17	0.6%	7.31 [0.44, 122.42]			
	Larsson 1996	9	13	1	13	1.7%	9.00 [1.32, 61.24]		— ??? <del>?</del>	
	McGrath 1992	10	23	6	12	6.4%	0.87 [0.42, 1.81]		???	
	Osterhaus 1997	12	25	0	14	0.9%	14.42 [0.92, 226.60]	+		
	Powers 2013	42	64	26	71	10.0%	1.79 [1.26, 2.55]		••••?	Face to Fac
	Sartory 1998	20	30	5	13	6.4%	1.73 [0.83, 3.61]	+	<u>? ? ? ? ?</u>	
	Scharff 2002	7	13	1	23	1.6%	12.38 [1.71, 89.86]			with therapi
	Subtotal (95% CI)		402		295	60.3%	2.02 [1.36, 2.98]	•		
	Total events	210		74	_					<b>⊕</b> 00C
50%	Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z -			= 0.003);	۴ = 5	59%				VERY LOV
	6.3.2 Remote from ther	anist								
reduction,	Connelly 2006	7	14	4	20	4.4%	2.50 [0.90, 6.94]			Remote fro
st-treatment	Griffiths 1996	12	15	3	12	4.4%	3.20 [1.16, 8.80]		22262	
Stucaution	Hicks 2006	15	21	3	16	4.2%	3.61 [1.33, 10.94]		22222	therapist:
	Law 2015	12	44	7	39	5.6X	1.52 [0.66, 3.47]	<b></b> _		
	McGrath 1992	16	24	6	12	7.2%	1.33 [0.71, 2.51]	_ <b>_</b>	22200	$\oplus \oplus \bigcirc \bigcirc$
	Palermo 2009	10	23	3	21	3.6%	3.04 [0.97, 9.58]		<b>AAAAA7</b>	
	Palermo 2016 (remote)	2	48	2	47	1.7%	0.98 [0.14, 6.67]		<b>4444</b>	LOW
	Rapoff 2014	7	18	6	17	5.4%	1.10 [0.46, 2.62]		?? 🗭 🖨 ?	
	Trautmann 2010	16	35	ž	16	3.0%	3.66 [0.95, 14.05]		7 9 9 9 7	
	Subtotal (95% CI)		242		200	39.7%	1.91 [1.38, 2.66]	•		
	Total events	97		36						
	Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z •			0.41);	4%					
	Total (95% CI)		644		495	100.0%	1.94 [1.49, 2.54]	•		
	Total events	307		110						
	Heterogeneity: $Tau^2 = 0$ .	15; Chl <sup>2</sup> = 40.12, (	if = 22 (P	= 0.01); P	² = 45	58	L.	.01 0.1 1 10	100	
	Test for overall effect: Z	- 4.86 (P < 0.0000	)1)				υ.	Favours control Favours expe		
	Test for subgroup differe	nces: $Chl^2 = 0.04$ ,	df = 1 (P •	= 0.84), I <sup>2</sup>	= 0%			arous control ravous expe		
	Risk of bias legend									
	(A) Random sequence ge	neration (selection	bias)							
	(B) Allocation concealment									
	(C) Blinding of outcome a		n bias)							
	(D) Incomplete outcome of									
	(E) Selective reporting (re	porting bias)								



Functional disability,		Face to Face with therapist: ⊕⊕⊖⊖ LOW
post-treatment Higher scores indicate lower disability	Functional disability, post-treatment	Remote from therapist: ⊕⊕⊕⊖ MODERATE

	0	Osycholog	gical therap	nies	C	ontrol		9	Std. Mean Difference	Std. Mean Difference	Risk of Bias	
Stu	dy or Subgroup	Mean	SD	Total			Total		IV, Random, 95% Cl	IV, Random, 95% CI	ABCDE	
	.1 Face-to-face with thera		00	70101	mount	00	. viul	roight	reg canaong oon of			
	en 2014	16	8	45	20	10	45	4.5%	-0.44 [-0.86, -0.02]	_ <b>-</b>	???	
	b 2013	5.33	6.64		24.52		14	4.5%	-1.72 [-2.59, -0.85]		<b>?</b> ? ? <b>•</b> •	
	lewitsch 2013	18.52	9.44			7.07	18	2.6%	-1.07 [-1.75, -0.38]		<b>•</b> ? ? • ?	
	chler 2014	27.9	9.7		34.2	8.8	52	4.6%	-0.68 [-1.08, -0.27]		• • • • • •	
	kman 2015	38.25	32.21		30.88		16	2.6%	0.23 [-0.46, 0.93]		22222	
	shikar-Zuck 2005	15.07	9.08		16.64	8.3	13	2.3%	-0.17 [-0.93, 0.58]			
	shikar-Zuck 2003	16.7	8.7		19.8	9.4	55	4.9%	-0.34 [-0.71, 0.03]			
	v 2010	0.56	0.54	84	0.55	0.48	84	5.6%	0.02 [-0.28, 0.32]	<u> </u>	• • • ? •	
	y 2016	5.6	5.7	80	7.3	8.3	78	5.5%	-0.24 [-0.55, 0.07]			
	y 2010 y 2017	5.01	7.73		7.65		41	4.9%	-0.30 [-0.68, 0.07]			
	ermo 2016 (f2f)	9.52	6.47	31		4.28	30	4.3% 3.8%	0.25 [-0.25, 0.76]	<b>_</b>		
	wers 2013	15.5	17.4	64	29.6	42.2	71	5.2%	-0.43 [-0.77, -0.08]			
	bins 2005	18.1	4.9		19.6	5.9	26	3.8%	-0.28 [-0.78, 0.22]		2	
	n der Veek 2013	7.17	4.5	52	7.79	8.78	52	4.8%	-0.28 [-0.78, 0.22]		• ? ? ? •	
	ksell 2009	12.3	13.9		14.6		16	4.0% 2.6%	-0.18 [-0.87, 0.52]			
	ototal (95% CI)	12.5	13.8	666	14.0	11.5	611	59.4%	-0.31 [-0.49, -0.13]	•		
	terogeneity: Tau <sup>2</sup> = 0.06; C	`hi≅ – 32.1	0 df = 14.0		4): IZ = 1	56%	••••	001470	-0101 [-0140, -0110]	•		
	st for overall effect: Z = 3.39			- 0.00	4), 1 =	50 /0						
165	stilli üverali ellett. Z = 5.5	9 (F = 0.0	007)									
6.5.	.2 Remote from therapist	t										
Cor	nnelly 2006	12.2	9.92	17	10.74	11.61	20	2.8%	0.13 [-0.52, 0.78]	_ <del>_</del>	••••	
Cor	nnelly 2019	2.2	2.4	144	1.7	2.2	145	6.3%	0.22 [-0.01, 0.45]	-	••••?•	
Lav	v 2015	4.83	4.78	20	4.86	4.4	37	3.5%	-0.01 [-0.55, 0.54]	- <u>+</u> -	•••••?	
Lev	y 2017	6.01	8.54	74	7.65	10.44	40	4.8%	-0.18 [-0.56, 0.21]	+	•?•?•	
Nie	to 2019	5.96	6.25	25	8.22	8.61	36	3.7%	-0.29 [-0.80, 0.22]	+	• ? • ? •	
Pali	ermo 2009	3.6	2.86	23	6.62	4.76	21	3.0%	-0.76 [-1.38, -0.15]		•••••?	
Pali	ermo 2016 (remote)	5.68	4.38	134	5.65	4.69	135	6.2%	0.01 [-0.23, 0.25]	+		
Pali	ermo 2020	34.9	25.4	73	37.8	25.6	70	5.3%	-0.11 [-0.44, 0.22]		? 🔁 🔁 🖶 🛑	
Rap	poff 2014	7.82	10.59	18	12.29	12.94	17	2.7%	-0.37 [-1.04, 0.30]	-+	?? ? 🗣 🖨 ?	
	n Tilburg 2009	17.1	5.1		25.4	10.6	14	2.2%	-0.98 [-1.76, -0.20]	— <u> </u>	?????	
Sub	ototal (95% CI)			543			535	40.6%	-0.14 [-0.33, 0.06]	•		
Het	terogeneity: Tau² = 0.04; C	≿hi² = 18.6	61, df = 9 (P	= 0.03);	l² = 52	%						
Tes	st for overall effect: Z = 1.40	0 (P = 0.1)	6)									
Tat	al (95% CI)			1209			11/6	100.0%	-0.25 [-0.38, -0.11]			
			10 df= 24 4		043-12	50%	1140	100.0%	-0.20 [-0.08, -0.11]	<b>▼</b>	_	
	terogeneity: Tau² = 0.06; C			r = 0.00	01);1*=	: 59%			-4	-2 0 2 4		
	st for overall effect: Z = 3.51		,	(n – o o o	0.17-0	7.00			Favou	urs experimental Favours control		
	st for subgroup differences	s: Chine 1	.59, at = 1 (	(P = 0.2)	n, i <del>n</del> = 3	1.0%						
	k of bias legend	- Barrison de la	In all and the									
	Random sequence gener			5)								
	Allocation concealment (s											
	Blinding of outcome asse			ias)								
	Incomplete outcome data		bias)									
(E) :	Selective reporting (report	ting bias)										

		Psycholog	jical thera	pies	C	Control			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
	Study or Subgroup	Mean	SD		Mean		Total	Weight		IV, Random, 95% CI	ABCDE	
	6.6.1 Face-to-face with the	erapist										
	Grob 2013	4.22	5.26	15	24.76	14	14	2.2%	-1.91 [-2.82, -1.01]		??? 🛨 🛨	
	Kashikar-Zuck 2012	13.4	8.9	57	17	10.5	55	7.3%	-0.37 [-0.74, 0.01]		••••	
	Levy 2010	0.36	0.39	78	0.48	0.56	76	8.5%	-0.25 [-0.57, 0.07]		🛨 🛨 🛨 ? 🛑	
	Levy 2016	5.1	6.4	67	5.9	6.8	66	8.0%	-0.12 [-0.46, 0.22]	-+	••••	
	Levy 2017	4.71	6.13	81	7.6	10.85	37	7.0%	-0.36 [-0.76, 0.03]		•?•?●	
	Palermo 2016 (f2f)	7.84	5.5	31	8.75		30	5.2%	-0.18 [-0.68, 0.33]			
	Powers 2013	7.6	16.9	57	19	30	67	7.6%	-0.46 [-0.81, -0.10]			
	Van der Veek 2013	5.8	8.2	52	4.87	6.6	52	7.1%	0.12 [-0.26, 0.51]	+	• ? ? ? ●	
	Wicksell 2009	8.8	12.9	16	14.7	12.1	16	3.2%	-0.46 [-1.16, 0.24]		•••??	Face to Fac
	Subtotal (95% CI)			454			413	55.9%	-0.33 [-0.55, -0.10]	•		with therapis
	Heterogeneity: Tau <sup>2</sup> = 0.06	•		P = 0.01)	; I² = 59	%						
	Test for overall effect: Z = 2	.87 (P = 0.0	04)									$\oplus \oplus \oplus \bigcirc$
unctional	6.6.2 Remote from therap	iet										-
disability,					4.0			40.50	0.051040.000			MODERAT
	Connelly 2019	2	2.2	144	1.9	2.2		10.5%	0.05 [-0.19, 0.28]	<u> </u>		
follow-up	Law 2015 Lew 2017	5.19 4.3	5.02 7.15	28 70	5.27	4.61 10.85	22 76	4.5% 8.2%	-0.02 [-0.57, 0.54]	_+_		
gher scores	Palermo 2016 (remote)	4.3 5.46	4.32	134	7.6 6.16	5.05		8.2%	-0.35 [-0.68, -0.03] -0.15 [-0.39, 0.09]			
	Palermo 2020	34.1	4.32 21.8	73	35.1	27.7	70	8.2%	-0.04 [-0.37, 0.29]	1	2000	
dicate lower	Rapoff 2014	0.91	1.45	11		4.86	11	2.3%	-0.69 [-1.56, 0.17]		22002	Desire for
Disability	Subtotal (95% CI)	0.31	1.45	460	3.5	4.00	459	44.1%	-0.12 [-0.26, 0.03]	•		Remote fro
Disability	Heterogeneity: Tau <sup>2</sup> = 0.01 Test for overall effect: Z = 1			= 0.30);	I <sup>2</sup> = 17%	6						therapist: ⊕⊕⊕⊕
	Total (95% CI)			914			872	100.0%	-0.23 [-0.38, -0.09]	•		HIGH
	Heterogeneity: Tau <sup>2</sup> = 0.04	; Chi <sup>2</sup> = 28.8	0, df = 14	(P = 0.01	l); l² = 5	1%						
	Test for overall effect: Z = 3	.18 (P = 0.0	01)						- Eavou	4 -2 Ó 2 4 Irs experimental Favours control		
	Test for subgroup difference	es: Chi <sup>2</sup> = 2	.38, df = 1	(P = 0.1	2), I <sup>2</sup> = 5	58.0%			Favou	is experimental Pavous control		
	Risk of bias legend											
	(A) Random sequence get	neration (se	lection bia	is)								
	(B) Allocation concealment	(selection	bias)									
	(C) Blinding of outcome as			bias)								
	(D) Incomplete outcome da		bias)									
	(E) Selective reporting (rep	orting bias)										
												1

			Emot	ional	l fun	ctio	ning	j: Dej	pression, pos	st-treatmer	nt		
		Psycholog				ontrol			Std. Mean Difference		Difference	Risk of Bias	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rand	om, 95% Cl	ABCDE	
	6.7.1 Face-to-face with the Hechler 2014	50.3	12	47	50.7	8.5	46	5.3%	-0.04 [-0.44, 0.37]	-		•••?	
	Hickman 2015	50.3 51.69	6.65		49.69	6.46	40	0.3% 1.9%	0.30 [-0.39, 0.98]	-	<u> </u>	22222	
	Kashikar-Zuck 2005	49.57	17.6			12.89	13	1.5%	0.07 [-0.69, 0.82]	_	_	•••??	
	Kashikar-Zuck 2012	9.9	6.2	57	11.8	5.8	55	6.3%	-0.31 [-0.69, 0.06]	_	4	•••?	
	Levy 2010	9.96	6.16	84		5.73	84	9.5%	0.27 [-0.03, 0.57]		<b>+-</b>	•••	
	Levy 2016	7.6	7.1	80	8.8	7.6	78	9.0%	-0.16 [-0.47, 0.15]	-	+		
	Palermo 2016 (f2f) Van der Veek 2013	12.03 2.17	5.13 1.96	31		5.37	30	3.5% 5.9%	0.16 [-0.35, 0.66]	-			
	Van der Veek 2013 Wicksell 2009	2.17 18.4	1.96	52 16	2.33 25	1.97 10.5	52 16		-0.08 [-0.47, 0.30] -0.63 [-1.34, 0.08]		Ţ		Face to Face
	Subtotal (95% CI)	10.4	10	397	25	10.5	391	44.5%	-0.04 [-0.21, 0.13]		•		with therapist:
	Heterogeneity: Tau <sup>2</sup> = 0.02;	Chi <sup>2</sup> = 10.8	39, df = 8 (i	P = 0.21)	; <b>I</b> ² = 27	%					1		
Emotional	Test for overall effect: Z = 0.												$\oplus \oplus \oplus \bigcirc$
functioning:	6.7.2 Remote from therapi	st											MODERATE
Depression,	Connelly 2019	46.4	11.2	144	45.2	12.1	145	16.4%	0.10 [-0.13, 0.33]		+	🔁 🔁 🔁 🕐 🛑	
-	Griffiths 1996	2.45	0.64	31	2.6	0.9	12		-0.20 [-0.87, 0.46]		+	???	
post-treatment	Lalouni 2019	1.99	2.88		2.89	2.85	44		-0.31 [-0.73, 0.11]	_	+	•••??	
Higher scores	Law 2015	46.3	10.03		47.48	9.5	23		-0.12 [-0.68, 0.44]		+		
	Lester 2020 Nieto 2019	14.38 18.2	6.22 6.22	24		4.53 4.53	21 21	2.6% 2.3%	-0.02 [-0.60, 0.57]	_			
indicate	Palermo 2009	58.96	13.1			4.55	21	2.5%	-0.31 [-0.92, 0.31] -0.16 [-0.75, 0.43]	_	+		Remote from
higher	Palermo 2005 Palermo 2016 (remote)	9.71	5.1	134		5.37	135		0.07 [-0.16, 0.31]		+		therapist:
-	Stapersma 2018	7.2	6.51	35	7.7	6.89	33	3.9%	-0.07 [-0.55, 0.40]	-	+-	••?••	
depressive	Trautmann 2010	9.55	9.1	37	7.7	5.2	18	2.7%	0.23 [-0.34, 0.79]	-	+	? 🖲 🖶 🛑 ?	$\oplus \oplus \oplus \oplus$
symptomology	Subtotal (95% CI)			520			473	55.5%	-0.01 [-0.13, 0.12]		•		HIGH
	Heterogeneity: Tau² = 0.00; Test for overall effect: Z = 0.			= 0.77);	<sup>2</sup> = 0%								
	Total (95% CI)			917			864	100.0%	-0.02 [-0.11, 0.08]		•		
	Heterogeneity: Tau² = 0.00;			(P = 0.54)	4); l² = 0	%				-4 -2		+	
	Test for overall effect: $Z = 0$ .								F	avours experimental	Favours control	4	
	Test for subgroup difference	es: Chi <sup>z</sup> = (	0.09, df = 1	(P = 0.7	6), I <sup>2</sup> = 0	)%							
	Risk of bias legend		to all and big										
	<ul> <li>(A) Random sequence gen</li> <li>(B) Allocation concealment</li> </ul>			15)									
	(C) Blinding of outcome ass			bias)									
	(D) Incomplete outcome dat												
	(E) Selective reporting (repo		-										

Emotional	Emotional functioning: Depression, follow up         Psychological therapies       Control       Std. Mean Difference       N. Mean Difference       Risk of Bias         Study or Subgroup       Mean       SD       Total       Weight       V, Random, 95% CI       Risk of Bias         6.8.1 Face-to-face with therapist         Jong 2018       6       4.3       45       5       3.4       41       6.3%       0.25 [-0.17, 0.68]       Image: Colspan="2">Image: Colspan="2">Risk of Bias         Kashikar-Zuck 2012       8.7       6.1       57       9.3       5.9       55       8.3%       -0.10 [-0.47, 0.27]       Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Std. Mean Difference       IV, Random, 95% CI       A B C D E         6.8.1 face-to-face with therapist       Jong 2018       6       4.1       Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Colspan="2">Std. Mean Difference       IV, Random, 95% CI       A B C D E       Colspan="2"       Colspan= 2        Colspan	Face to Face with therapist:
functioning: Depression, follow up Higher scores indicate higher depressive symptomology	Test for overall effect $Z = 0.69$ (P = 0.49) <b>6.8.2 Remote from therapist</b> Connelly 2019 45.5 11 144 45 11.4 145 21.4% 0.04 [-0.19, 0.28] Law 2015 44.75 9.52 28 43.74 6.45 23 3.7% 0.12 [-0.43, 0.67] Laster 2020 15.93 6.49 21 14.53 4.5 18 2.8% 0.24 [-0.39, 0.87] Laster 2020 15.93 6.49 21 14.53 4.5 18 2.8% 0.24 [-0.39, 0.25] Trautmann 2010 7.25 6.15 36 6.6 3.7 9 2.1% 0.11 [-0.62, 0.84] Subtotal (95% CI) 363 363 330 49.9% 0.05 [-0.10, 0.20] Heterogeneity: Tau <sup>2</sup> = 0.00; ChP <sup>2</sup> = 0.55, df = 1 (P = 0.97); I <sup>2</sup> = 0% Test for overall effect $Z = 0.66$ (P = 0.51) Total (95% CI) 709 666 100.0% 0.06 [-0.05, 0.16] Heterogeneity: Tau <sup>2</sup> = 0.00; ChP <sup>2</sup> = 0.55, df = 1 (P = 0.94), P = 0% Test for subgroup differences: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.94), P = 0% Risk of bias legand (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of outcome data (attrition bias) (D) Incomplete outcome data (attrition bias) (E) Selective reporting (reporting bias)	⊕⊕⊕ HIGH Remote from therapist: ⊕⊕⊕⊕ HIGH

			E	motio	nal f	unc	tioni	ing: A	nxiety, post-trea	atment		
		Psycholo	gical thera	apies	С	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	ABCDE	
	6.9.1 Face-to-face with th	-										
	Bussone 1988	28.1	3.49	20	29.2	5.1	10		-0.26 [-1.02, 0.50]		22200	
	Hechler 2014	52.5	12.1	50	50	11.4	46		0.21 [-0.19, 0.61]			
	Hickman 2015	52.56	7.36		47.38	6.1	17	2.4%	0.75 [0.04, 1.46]	-	22222	
	Kashikar-Zuck 2012	2.11	0.72	50	2.39	0.9	50		-0.34 [-0.74, 0.05]			
	Levy 2010	13.5 8.2	4.86 2.8	83 80	13.04 8.6	4.04 2.9	80 78	7.2% 7.1%	0.10 [-0.21, 0.41]			
	Levy 2016	8.2 1.18	2.8 0.95	80 85	1.28	2.9	78 41	5.9%	-0.14 [-0.45, 0.17] -0.10 [-0.47, 0.27]			
	Levy 2017 Palermo 2016 (f2f)	11.42	5.33	31	1.20	6.03	30		-0.27 [-0.78, 0.23]			
	Van der Veek 2013	6.83	0.00 6	52	7.76	6.33	52		-0.15 [-0.53, 0.24]			
	Wicksell 2009	13.4	3.9	16	12.8	5.5	16		0.12 [-0.57, 0.82]			Face to Face
	Subtotal (95% CI)	10.4	0.0	483	12.0	0.0	420		-0.05 [-0.20, 0.11]	•	••••	
	Heterogeneity: Tau <sup>2</sup> = 0.01	l∶Chi <b>≧</b> = 11 √	47 df=9(	P = 0.24	· I <sup>2</sup> = 22	%				1		with therapist:
	Test for overall effect: Z = (			0.24)	11	~						•
Emotional			,									$\oplus \oplus \oplus \bigcirc$
functioning:	6.9.2 Remote from therap	oist										MODERATE
•	Bonnert 2017	25.23	16.32	47	22.62	16.31	54	5.6%	0.16 [-0.23, 0.55]			
Anxiety, post-	Connelly 2019	46.8	11.3	144	45.5	11	145	9.0%	0.12 [-0.11, 0.35]	+-	••••?•	
treatment	Griffiths 1996	9.6	5.9	30	13.6	9.5	12	2.6%	-0.55 [-1.24, 0.13]		????	
	Lalouni 2019	8.59	7.71	45	15.31	7.63	44	5.0%	-0.87 [-1.30, -0.43]		🙂 🔁 ? ? 🛑	
Higher scores	Law 2015	46.33	8.99	30	48.32	10.81	25	3.8%	-0.20 [-0.73, 0.33]		•••?	Remote from
indicate	Lester 2020	7.08	6.24	24	6.1	4.96	21	3.3%	0.17 [-0.42, 0.76]		••••	therapist:
	Levy 2017	0.99	0.93	74	1.28	1.07	40	5.7%	-0.29 [-0.68, 0.09]		• ? • ? •	
higher	Palermo 2016 (remote)	10.56	5.91	134	10.85	6.1	135	8.8%	-0.05 [-0.29, 0.19]	+		$\oplus \oplus \oplus \bigcirc$
depressive	Stapersma 2018	7.1	4.14	35	7.3	4.6	33	4.4%	-0.05 [-0.52, 0.43]	_ <del></del>	••?•	MODERATE
	Trautmann 2010	30.9	7.95	38	31.7	8.3	18	3.5%	-0.10 [-0.66, 0.46]		? 🖶 🖶 🛑 ?	WODERATE
symptomology	Subtotal (95% CI)			601			527	51.7%	-0.14 [-0.34, 0.06]	•		
	Heterogeneity: Tau² = 0.05 Test for overall effect: Z = 1		•	P = 0.01)	; I² = 57	%						
	Total (95% CI)			1084			947	100.0%	-0.09 [-0.21, 0.04]			
	Heterogeneity: Tau <sup>2</sup> = 0.03		•	(P = 0.03	i); l² = 4	1%			-4	-2 0 2	4	
	Test for overall effect: Z = 1		•			~			Favou	Irs experimental Favours control		
	Test for subgroup differen	ces: Chif = I	0.54, df = 1	(P = 0.4)	6), I* = C	%						
	Risk of bias legend											
	(A) Random sequence ge			as)								
	(B) Allocation concealmen			hine)								
	(C) Blinding of outcome as		-	ulas)								
	<ul> <li>(D) Incomplete outcome d</li> <li>(E) Selective reporting (rep</li> </ul>											
	(L) Selective reporting (rep	Johang bias)										

			Em	otional f	unctio	ning: Anxiety, f	ollow-up		
Emotional functioning: Anxiety, follow-up Higher scores indicate higher depressive	Study or Subgroup 6.10.1 Face-to-face with 1 Bussone 1988 Kashikar-Zuck 2012 Lew 2010 Lew 2016 Lew 2017 Palermo 2016 (721) Van der Veek 2013 Wicksell 2009 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0 6.10.2 Remote from thera Connelly 2019 Law 2015 Lester 2020 Lew 2017 Palermo 2016 (remote) Trautmann 2010	therapist         27.8         2           1.89         0.1         13.21         3.1           7.9         3         1         0.1           12.61         6.1         5.47         5.1           12.2         4         0.1         12.2         4           0; Chi <sup>a</sup> = 7.59, df = 0.81 (P = 0.42)         10.1         10.1         10.1           10         1.2.2         4         10.1         10.1         10.1           0; Chi <sup>a</sup> = 7.59, df = 0.81 (P = 0.42)         10.1	therapies           SD         Total           2.3         20           82         50           98         75           3.3         67           95         81           05         31           22         52           4.6         16           392         7           7         (P = 0.37);           12         144           96         28           09         21           81         70	Control           29.1         1.4           2.22         0.91           12.59         4.14           8.2         3.2           1.1         0.98           11.21         5.55           5.82         6.09           11.77         5.8	Total         We           10         1           50         6           63         9           66         8           37         6           30         4           52         6           16         2           324         46           145         18           22         3           18         2           76         9           135         17	Std. Mean Difference           tight         IV, Random, 95%           .7%         -0.62 [-1.39, 0.1           .5%         -0.38 [-0.77, 0.0           .1%         0.15 [-0.18, 0.4           .8%         -0.09 [-0.43, 0.2           .8%         -0.10 [-0.49, 0.2           .0%         0.24 [-0.27, 0.7           .9%         -0.06 [-0.45, 0.3           .1%         0.09 [-0.60, 0.7           .60%         -0.06 [-0.22, 0.0           .9%         -0.06 [-0.22, 0.0           .9%         -0.06 [-0.29, 0.1           .3%         0.04 [-0.52, 0.6           .6%         0.15 [-0.48, 0.7           .5%         -0.39 [-0.71, -0.0	Std. Mean Difference       Cl     IV, Random, 95% Cl       6]	Risk of Bias A B C D E	Face to Face with therapist: ⊕⊕⊕○ MODERATE Remote from therapist: ⊕⊕⊕⊕ HIGH
symptomology	Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 4 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 4 Test for subgroup differen <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmer (C) Blinding of outcome as (D) Incomplete outcome d (E) Selective reporting (rep	1.19 (P = 0.23) ); Chi <sup>2</sup> = 13.13, df 1.47 (P = 0.14) ces: Chi <sup>2</sup> = 0.05, d ineration (selection ti (selection bias) sessment (detection bias)	820 = 13 (P = 0.4 df = 1 (P = 0.8 on bias) ction bias)	4); I² = 1%	406 54 730 100	4.0% -0.09 [-0.24, 0.0 0.0% -0.08 [-0.18, 0.0		-	

## Appendix G. 7. WHO review: Psychological interventions for children with chronic pain Subgroup analysis: by therapy type

**Comparison:** Psychological therapies versus active (non-psychological), standard care or waitlist control, by therapy type **Population:** children and adolescents with chronic pain **Setting:** Any setting **Studies:** Randomised controlled trials

## Subgroup analysis: by therapy classification

We analysed studies by the type of therapy they delivered, using classifications of cognitive behavioural therapy, acceptance commitment therapy, hypnosis, and relaxation. Due to the small number of studies using certain types of therapy types, we could not conduct meta-analyses for all therapy types. CBT was the most commonly delivered therapy type. We could not draw any conclusions for ACT, hypnosis, or problem-solving therapy as only one study could be included in any given analysis. More evidence was available for relaxation training and behaviour therapy, although very low-certainty, mainly due to imprecision and the small number of participants that could be included in the subgroup analyses. We have excluded all analyses from the GRADE profiles (Table 12) where only one study or less could be included in the analysis, but these can still be found in the forest plots (Appendix F.5). All certainty of evidence for single study analyses was very low, downgraded twice for imprecision and once for indirectness.

We found small beneficial effects for CBT on the following outcomes; pain intensity post-treatment (low-certainty), 50% pain reduction post-treatment (low-certainty), functional disability post-treatment (low-certainty) and at follow-up (moderate-certainty). We did not find beneficial effects of CBT for pain at follow-up (low-certainty) and emotional functioning (depression: moderate-certainty post-treatment, high-certainty follow-up; anxiety: low-certainty post-treatment, moderate-certainty follow-up). We could analyse relaxation training for pain intensity post-treatment and at follow-up, and 50% reduction post-treatment; behaviour therapy for pain intensity post-treatment and 50% reduction in pain post-treatment. We did not find any benefits of these therapies on the outcomes. For the remaining therapy types and outcomes, we could only include a single studies in the analyses and therefore cannot draw any conclusions; we rated all evidence as very low-certainty, primarily due to imprecision and indirectness.

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of outcome assessment (detection bias)

(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

Outcome	Forest plot	Quality of evidence (GRADE)
Pain intensity, post-treatment <i>Higher scores</i> <i>indicate</i> <i>higher pain</i> <i>intensity</i>		CBT: $\oplus \oplus \bigcirc \bigcirc$ LOW Relaxation training: $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW Behavioural Therapy: $\oplus \bigcirc \bigcirc \bigcirc$ VERY LOW

					I	Pain	inte	ensity	/, follow-up				
	Study or Subgroup	Psycholo Mean	gical thera SD		( Mean	Control SD	Total	Weight	Std. Mean Difference IV, Random, 95% Cl		Difference om, 95% Cl	Risk of Bias ABCDE	
	7.2.1 CBT												
	Barakat 2010	16.71	23.03	17		12.31	20	3.6%	0.48 [-0.18, 1.14]		<b>+-</b>	33303	
	Connelly 2019	3.1	2.5	144	2.7	2.4	145	7.6%	0.16 [-0.07, 0.39]		-		
	Grob 2013	0.08	0.31	15	1.55		14	2.7%	-1.35 [-2.17, -0.53]			??? <b>**</b> ?????	
	Hicks 2006	2.9 4.9	2.1 2.2	25 57	4.9 5.3		22 55	3.9% 6.1%	-1.11 [-1.73, -0.49]	_			CBT:
	Kashikar-Zuck 2012 Kroener-Herwiq 2002	4.9	2.2	29	0.46		27	4.6%	-0.18 [-0.56, 0.19] 0.03 [-0.49, 0.56]	-		22222	
	Law 2015	4.19	2.45	29	3.7	2.54	22	4.0%	0.03 [-0.37, 0.75]		<b>_</b>		$\oplus \oplus \bigcirc \bigcirc$
	Lester 2020	2.67	2.40	20	3.07		18	4.4%	-0.17 [-0.80, 0.46]	_	_		
	Levy 2010	0.93	1.42	78	0.7	1.53	76	6.7%	0.16 [-0.16, 0.47]		<b>_</b>		LOW
	Lew 2017	3.48	2.33	151			78	7.2%	-0.13 [-0.40, 0.14]	-	-		_
	Palermo 2016 (f2f)	5.42	2.05	31	5.3		30	4.8%	0.06 [-0.45, 0.56]	-			
	Palermo 2016 (remote)	5.85	1.97	134	5.55		135	7.5%	0.15 [-0.09, 0.39]		-		Relaxatio
	Palermo 2020	5.3	1.9	73	6.2		70	6.5%	-0.48 [-0.82, -0.15]	-		2	
	Rapoff 2014	4.46	1.88	11			11	2.6%	0.38 [-0.46, 1.23]	-	<b></b>	22.002	training
	Richter 1986	2.02	1.48	30	2.02		12	3.6%	0.00 [-0.67, 0.67]	-	<b>↓</b>	2222	0
ain intensity,	Sanders 1994	0.64	1.38	22	2.11	3.56	22	4.0%	-0.53 [-1.14, 0.07]		-	2 2 2 9 2	$\oplus \bigcirc \bigcirc \bigcirc \bigcirc$
	Van der Veek 2013	19.03				15.19	52	6.0%	0.08 [-0.30, 0.47]		┣-	• ? ? ? ●	
follow-up	Subtotal (95% CI)			918			809	85.9%	-0.09 [-0.27, 0.08]		•		VERY LC
ligher scores indicate higher pain intensity	Test for overall effect: Z = 1 7.2.2 Relaxation training Trautmann 2010 Wahlund 2015 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Test for overall effect: Z = 0	4.9 2.8 ; Chi <sup>2</sup> = 0.5	1.4 1.9 5, df = 1 (P	12 31 <b>43</b> = 0.46);	5.5 2.8 I <sup>2</sup> = 0%	1.6	16 33 <b>49</b>	3.1% 5.0% <b>8.0%</b>	-0.34 [-1.10, 0.41] 0.00 [-0.49, 0.49] -0.10 [-0.51, 0.31]		-	? ● ● ? ? ? ● ● ? ? ? ?	Behaviou Therapy ⊕○○○ VERY LC
	7.2.3 Behavioural therapy												ACT:
	Bussone 1988 Subtotal (95% CI)	20	18.1	20 20	88.8	110.3	10 10	2.8% 2.8%	-1.04 [-1.85, -0.23] - <b>1.04 [-1.85, -0.23]</b>			???•●	-
	Heterogeneity: Not applica Test for overall effect: Z = 2		1)	20			10	2.0%	-1.04 [-1.03, -0.23]	•			
	7.2.4 ACT												
	Wicksell 2009 Subtotal (05% CI)	3.1	2.7	16 16	4.5	2.4	16	3.3%	-0.53 [-1.24, 0.17]	-	İ	•••??	
	Subtotal (95% CI)			16			16	3.3%	-0.53 [-1.24, 0.17]	-	1		
	Heterogeneity: Not applica Test for overall effect: Z = 1		4)										
	Total (95% CI)			997			884	100.0%	-0.14 [-0.30, 0.02]				
	Heterogeneity: Tau² = 0.08 Test for overall effect: Z = 1 Test for subgroup differenc	.67 (P = 0.0	9)						Favou	-4 -2 rs experimental	0 2 4 Favours control	 I	

			50% pa	ain re	educti	on, post-treatn	nent		
	Psv	chological the		ntrol	Saaoti	Risk Ratio	Risk Ratio	Risk of Bias	
	Study or Subgroup	Events			d Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDE	
	7.3.1 CBT								
	Barry 1997	2	12	2 17	7 2.1%	1.42 [0.23, 8.70]		? \varTheta ? 🕒 ?	
	Connelly 2006	7	14	4 21	• • • • • •	2.50 [0.90, 6.94]		••••	
	Griffiths 1996	12	15	3 12		3.20 [1.16, 8.80]		22202	
	Hicks 2006	15	21	3 10		3.61 [1.33, 10.94]		22222	
	Kroener-Herwig 2002 Law 2015	16 12	29 44	8 19 7 39		1.31 [0.70, 2.44]		22222	
	McGrath 1992	26	44	6 2		1.52 [0.66, 3.47] 2.30 [1.10, 4.85]			CBT:
	Palermo 2009	10		3 2		3.04 [0.97, 9.58]			
	Palermo 2016 (remote)	2		2 47		0.98 [0.14, 6.67]			$\oplus \oplus \bigcirc \bigcirc$
	Powers 2013	42		6 7		1.79 [1.26, 2.55]		<b>4444</b>	
	Rapoff 2014	7	18	6 12	7 5.2%	1.10 [0.46, 2.62]	_ <b>_</b>	2 2 🗣 🔁 2	LOW
	Trautmann 2010	10	16	2 1		2.50 [0.71, 8.80]	+	? 🗣 🗣 😨 ?	
	Subtotal (95% CI)		351	312	2 55.4%	1.86 [1.48, 2.32]	•		
	Total events	161		2					Relaxation
	Heterogeneity: $Tau^2 = 0.00$ ; C			); # = 0;	<b>X</b>				
	Test for overall effect: $Z = 5.4$	2 (P < 0.0000)	.)						training:
	7.3.2 Relaxation therapy								0
	Larsson 1987	6	12	2 24	4 2.9%	6.00 [1.42, 25.39]		2 8 2 2 2	$\oplus OOO$
	Larsson 1987a	13		1 1:		4.77 [0.70, 32.29]		22200	VERY LOW
50%	Larsson 1990	6	31	0 13		7.31 [0.44, 122.42]		$\rightarrow \overline{2}\overline{2}\overline{2}\overline{2}\overline{2}$	VERTLOW
	Larsson 1996	9	13	1 13		9.00 [1.32, 61.24]		- ???.??	
reduction,	Osterhaus 1997	12	25	0 14		14.42 [0.92, 226.60]			
	Sartory 1998	12	15	5 (		0.96 [0.62, 1.49]	-	<u>? ? ? ? ?</u>	Behavioural
post-treatment	Trautmann 2010	6		2 1		1.26 [0.32, 4.97]		? 🖶 🖶 🤁 ?	
1	Subtotal (95% CI)		145	93	3 19.5%	3.78 [0.99, 14.46]			Therapy:
	Total events Heterogeneity: Tau <sup>2</sup> = 2.41; C	64 		.1	- 026				000
	Test for overall effect: Z = 1.9		= 0 (P < 0.00	VV1); F	= 03%				
	rest for overall effect. L = 1.5	+ (r = 0.03)							VERY LOW
	7.3.3 Behaviour therapy								
	Labbe 1984	13	14	1 14	4 2.0%	13.00 [1.96, 86.42]		— <b>????</b>	
	Labbe 1995	19	20	6 10	0 7.1%	1.58 [0.95, 2.65]	+	22222	
	Sartory 1998	6	15	5 (		0.64 [0.35, 1.16]		<u>? ? ? ? ?</u>	Hypnosis:
	Scharff 2002	7	13 62	1 23		12.38 [1.71, 89.86]		— 🗣 ? ? 🗣	
	Subtotal (95% CI)		*=	53	3 17.6%	2.71 [0.69, 10.60]			000
	Total events Heterogeneity: Tau <sup>2</sup> = 1.51; C	47 54 - 26 17 di		.3 0011- P	- 80%				VERY LOW
	Test for overall effect: $Z = 1.4$		- 5 (1 < 0.00	VV1), I	- 05/4				VLIXI LOW
	7.3.4 Hypnosis	_							
	Jong 2018	35	86 86	.5 32		1.00 [0.63, 1.60]	<b></b>	99?9	
	Subtotal (95% CI) Total events	35		3: .5	7 7.4%	1.00 [0.63, 1.60]			
	Heterogeneity: Not applicable	35		.5					
	Test for overall effect: $Z = 0.0$	2 (P = 0.99)							
		-,							
	Total (95% CI)		644		5 100.0%	1.91 [1.42, 2.58]	◆		
1	Total events	307	1						
	Heterogeneity: Tau <sup>2</sup> = 0.26; C			001); ř	- 60%	0.0	01 0.1 1 10	100	
	Test for overall effect: Z = 4.2 Test for subgroup differences:			n 14 – F	8 OK		Favours control Favours experi		
	rest for subgroup amerences:	ciii = 7.30, đ		n - = 5	0.5%				



			ſ	unctio	nal d	isabili	ity, post-treatm	ient		
	Study or Subgroup	Psychologica Mean		Con tal Mean		l Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias A B C D E	
	7.5.1 CBT									
	Chen 2014	16		45 20	10 4		-0.44 [-0.86, -0.02]		22200	
	Connelly 2006			17 10.74 1			0.13 [-0.52, 0.78]			
	Connelly 2019			44 1.7	2.2 14		0.22 [-0.01, 0.45]	-		
	Grob 2013			15 24.52 1			-1.72 [-2.59, -0.85]			
	Hechler 2014			47 34.2	8.8 5:		-0.68 [-1.08, -0.27]			CBT:
	Hickman 2015			16 30.88 3			0.23 [-0.46, 0.93]		33333	
	Kashikar-Zuck 2005			14 16.64	8.3 13		-0.17 [-0.93, 0.58]			$\oplus \oplus \bigcirc \bigcirc$
	Kashikar-Zuck 2012			57 19.8	9.4 5		-0.34 [-0.71, 0.03]			
	Law 2015			20 4.86	4.4 3		-0.01 [-0.55, 0.54]			LOW
	Levy 2010				).48 84 8.3 71		0.02 [-0.28, 0.32]			
	Levy 2016						-0.24 [-0.55, 0.07]			
	Levy 2017 Nijoto 2010			59 7.65 1) 25 8.22 ;			-0.24 [-0.50, 0.03]			ACT:
	Nieto 2019 Palermo 2009				3.61 31 1.76 21		-0.29 [-0.80, 0.22]			
					1.76 Z 1.69 13		-0.76 [-1.38, -0.15]			$\oplus OOO$
	Palermo 2016 (remote) Palermo 2020				25.6 71		0.01 [-0.23, 0.25]			
Functional	Powers 2013				2.0 71 2.2 71		-0.11 [-0.44, 0.22] -0.43 [-0.77, -0.08]			VERY LOW
diaghility/	Rapoff 2014			18 12.29 1:			-0.43 [-0.77, -0.08] -0.37 [-1.04, 0.30]			
disability,	Robins 2005				5.9 21		-0.28 [-0.78, 0.22]		20222	
post-treatment	Van der Veek 2013				5.9 20 3.78 5:		-0.07 [-0.45, 0.31]		<b>•</b> ? ? ? •	Hypnosis:
	Van Tilburg 2009				0.6 14		-0.98 [-1.76, -0.20]		22222	
Higher scores	Subtotal (95% CI)	17.1	J.1 114		108		-0.24 [-0.38, -0.10]	•		$\oplus O O O$
indicate lower	Heterogeneity: Tau <sup>2</sup> = 0.0	5 <sup>°</sup> Chi² = 48.77 .c						•		
Indicate lower	Test for overall effect: Z =			5.0000,1 = 0	5.00					VERY LOW
disability										
uisability	7.5.2 ACT									
	Wicksell 2009	12.3 1	3.9	16 14.6	1.3 10	6 2.7%	-0.18 [-0.87, 0.52]	<del></del>	•••??	Problem-
	Subtotal (95% CI)			16	1		-0.18 [-0.87, 0.52]	-		
	Heterogeneity: Not applic:	able						_		solving
	Test for overall effect: Z =									•
										therapy:
	7.5.3 Hypnosis									
	Gulewitsch 2013	18.52 9	.44	20 27.67	.07 10	3 2.8%	-1.07 [-1.75, -0.38]		•??	$\oplus O O O$
	Subtotal (95% CI)		:	20	18	3 2.8%	-1.07 [-1.75, -0.38]	◆		VERY LOW
	Heterogeneity: Not applic:	able								
	Test for overall effect: Z =	3.05 (P = 0.002)								
	7.5.4 Problem solving the	erapy								
	Palermo 2016 (f2f)	9.52 6		31 8.1			0.25 [-0.25, 0.76]	<u>t</u>	• • • • •	
	Subtotal (95% CI)			31	3	) 3.9%	0.25 [-0.25, 0.76]	<b>•</b>		
	Heterogeneity: Not applic: Test for overall effect: Z =									
	Total (05% CI)		40	00	444	9 100.0%	0.25 [ 0.30 0.44]			
	Total (95% CI)	. o	12( (- 00 (D - )			9 100.0%	-0.25 [-0.39, -0.11]	<b>_</b>		
	Heterogeneity: Tau <sup>2</sup> = 0.0			J.UUU1); I* = 6	1%		-4	-2 0 2	4	
	Test for overall effect: Z =			0.001 /7	nov.		Favou	rs experimental Favours contro	I	
	Test for subgroup differer	ices: Cni*= 9.31	ar = 3 (P =	0.03), i* = 67.	570					

					Fur	nctio	nal	disab	ility, follow-up			
Functional disability,	Psychological therapies         Control         Std. Mean Difference IV, Random, 95% CI         Std. Mean Difference IV, Random, 95% CI         Risk of Bias           7.6.1 CBT											CBT: $\oplus \oplus \oplus \bigcirc$ MODERATE ACT: $\oplus \bigcirc \bigcirc \bigcirc \bigcirc$
follow-up Higher scores indicate lower disability	7.6.2 ACT Wicksell 2009 Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1	8.8 able	12.9	16 <b>16</b>	14.7	12.1	16 <b>16</b>	3.5% 3.5%	-0.46 [-1.16, 0.24] -0.46 [-1.16, 0.24]	•	•••?	VERY LOW Problem- solving therapy:
	<b>7.6.3 Problem solving the</b> Palermo 2016 (f2f) <b>Subtotal (95% CI)</b> Heterogeneity: Not applica Test for overall effect: Z = (	7.84 able	5.5	31 <b>31</b>	8.75	4.64	30 <b>30</b>	5.6% <b>5.6%</b>	-0.18 [-0.68, 0.33] -0.18 [-0.68, 0.33]	•	••••	€ ⊕ VERY LOW
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04 Test for overall effect: Z = 2 Test for subgroup differen <u>Risk of bias legend</u> (A) Random sequence ge (B) Allocation concealmen (C) Blinding of outcome as (D) Incomplete outcome d (E) Selective reporting (rep	2.96 (P = 0.003 ces: Chi <sup>2</sup> = 0.4 neration (sele it (selection bi: ssessment (de ata (attrition bi	3) 15, df = 2 (P ction bias) as) etection bia	° = 0.80			841	100.0%	-0.23 [-0.38, -0.08]  Favou	4 -2 0 2 4 Irs experimental Favours control	-	

		E	motior	nal fur	nctio	ning	: Dep	ression, post-t	reatment		
	Study or Subgroup	Psychological Mean		( al Mean	Control SD	Total	S Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias ABCDE	
	7.7.1 CBT										
	Connelly 2019	46.4 1	1.2 14	44 45.2	12.1	145	16.4%	0.10 [-0.13, 0.33]	+	•••	
	Griffiths 1996	2.45 0	.64 🗧	31 2.6	0.9	12	2.0%	-0.20 [-0.87, 0.46]	-+	????	
	Hechler 2014			47 50.7	8.5	46	5.3%	-0.04 [-0.44, 0.37]		•••??•	
	Hickman 2015			6 49.69	6.46	17	1.9%	0.30 [-0.39, 0.98]	+	33333	
	Kashikar-Zuck 2005			4 48.46		13	1.5%	0.07 [-0.69, 0.82]			CBT:
	Kashikar-Zuck 2012			57 11.8	5.8	55	6.3%	-0.31 [-0.69, 0.06]			-
	Lalouni 2019			15 2.89	2.85	44	5.0%	-0.31 [-0.73, 0.11]			$\oplus \oplus \oplus \bigcirc$
	Law 2015			27 47.48	9.5	23	2.8%	-0.12 [-0.68, 0.44]			MODERATE
	Lester 2020			24 14.47 34 8.35	4.53 5.73	21	2.6% 9.5%	-0.02 [-0.60, 0.57]			MODERATE
	Levy 2010			34 8.35 30 8.8	5.73	84 78	9.5%	0.27 [-0.03, 0.57]			
	Levy 2016 Nieto 2019			30 8.8 20 19.9	=	21	9.0%	-0.16 [-0.47, 0.15] -0.31 [-0.92, 0.31]			Delevetien
	Palermo 2009			20 19.9		21	2.5%	-0.16 [-0.75, 0.43]			Relaxation
Emotional	Palermo 2005 Palermo 2016 (remote)			34 9.32		135	15.3%	0.07 [-0.16, 0.31]			therapy:
	Stapersma 2018			34 3.32 35 7.7	6.89	33	3.9%	-0.07 [-0.55, 0.40]			
functioning:	Trautmann 2010			17 7.7	5.2	9	1.3%	0.40 [-0.42, 1.21]		2	$\oplus O O O$
Depression,	Van der Veek 2013				1.97	52	5.9%	-0.08 [-0.47, 0.30]	-	• ? ? ? •	VERY LOW
	Subtotal (95% CI)	2		50	1.01	809	93.4%	-0.01 [-0.11, 0.08]	•		VERTLOW
post-treatment	Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 13.70. d	f = 16 (P = 0	).62); <b>I<sup>2</sup> =</b> (	)%				1		
Higher scores	Test for overall effect: Z = 0.			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,							ACT:
indicate	7.7.2 Relaxation therapy										000
higher	Trautmann 2010 Subtotal (95% CI)	8.1		20 7.7 20	5.2	9 9	1.4% <mark>1.4%</mark>	0.05 [-0.74, 0.84] 0.05 [-0.74, 0.84]	•	? 🖲 🖶 🖨 ?	VERY LOW
depressive symptomology	Heterogeneity: Not applicat Test for overall effect: Z = 0.										Problem-
,	7.7.3 ACT										
	Wicksell 2009 Subtotal (95% CI)	18.4		16 25 1 <b>6</b>	10.5	16 <b>16</b>	1.7% <b>1.7%</b>	-0.63 [-1.34, 0.08] - <b>0.63 [-1.34, 0.08]</b>	•	•••??	solving
	Heterogeneity: Not applicat								•		therapy:
	Test for overall effect: Z = 1.	73 (P = 0.08)									$\oplus \bigcirc \bigcirc \bigcirc$
	7.7.4 Problem solving there	ару									VERY LOW
	Palermo 2016 (f2f) Subtotal (95% CI)	12.03 5		31 11.2 3 <b>1</b>	5.37	30 <b>30</b>	3.5% <b>3.5%</b>	0.16 [-0.35, 0.66] 0.16 [-0.35, 0.66]	<b>↓</b>	••••	
	Heterogeneity: Not applicat Test for overall effect: Z = 0.							- ' *	Ĩ		
	Total (95% CI)			17		864	100.0%	-0.02 [-0.11, 0.08]			
	Heterogeneity: Tau² = 0.00; Test for overall effect: Z = 0. Test for subgroup difference	37 (P = 0.71)						Favo	4 -2 0 2 4 urs experimental Favours control		

			Emo	otion	al fu	ncti	oniı	ng: D	epression, follo	w up		
		Psychologi	ical thera	apies	C	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
	Study or Subgroup 7.8.1 CBT	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	ABCDE	
	Connelly 2019 Kashikar-Zuck 2012 Law 2015 Lester 2020	45.5 8.7 44.75 15.93	11 6.1 9.52 6.49		9.3 43.74 14.53	4.5	55 23 18	21.8% 8.4% 3.8% 2.9%	0.04 [-0.19, 0.28] -0.10 [-0.47, 0.27] 0.12 [-0.43, 0.67] 0.24 [-0.39, 0.87]			CBT:
	Levy 2010 Levy 2016 Palermo 2016 (remote) Van der Veek 2013 Subtotal (95% CI)	7.89 4.4 9.55 1.85	6.99 5.8 5.13 1.93	67 134 52 <b>581</b>	7.19 4.6 9.49 1.79	5.9 5.58	66	11.6% 10.0% 20.3% 7.9% <b>86.8%</b>	0.11 [-0.20, 0.43] -0.03 [-0.37, 0.31] 0.01 [-0.23, 0.25] 0.03 [-0.36, 0.41] <b>0.03 [-0.08, 0.15]</b>			⊕⊕⊕⊕ HIGH
Emotional	Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 0.			= 0.98);	I² = 0%				- / -			ACT:
functioning: Depression,	7.8.2 ACT Wicksell 2009 Subtotal (95% CI)	18.1	9.8	16 <b>16</b>	25.5	16.9	16 <b>16</b>	2.3% 2.3%	-0.52 [-1.23, 0.18] -0.52 [-1.23, 0.18]		•••??	⊕OOO VERY LOW
follow up <i>Higher scores</i>	Heterogeneity: Not applicat Test for overall effect: Z = 1.		))									Hypnosis:
indicate higher	7.8.3 Hypnosis Jong 2018 Subtotal (95% CI)	6	4.3	45 45	5	3.4	41 <mark>41</mark>	6.4% <mark>6.4%</mark>	0.25 [-0.17, 0.68] <mark>0.25 [-0.17, 0.68]</mark>		••?••	⊕ VERY LOW
depressive symptomology	Heterogeneity: Not applicat Test for overall effect: Z = 1.	17 (P = 0.24	)									Problem-
	7.8.4 Problem solving then Palermo 2016 (f2f) Subtotal (95% CI) Heterogeneity: Not applicat Test for overall effect: Z = 1.	11.53 le	5.37 ))	31 <b>31</b>	8.71	5.6	30 <mark>30</mark>	4.5% <b>4.5%</b>	0.51 [-0.00, 1.02] 0.51 [-0.00, 1.02]	-	••••	solving therapy: ⊕○○○
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 0. Test for subaroup differenc	-	VERY LOW									
	Risk of bias legend (A) Random sequence gen (B) Allocation concealment (C) Blinding of outcome as (D) Incomplete outcome da (E) Selective reporting (repo	eration (sel (selection b sessment (c ta (attrition b	ection bia ias) letection	as)								

			Emc	otiona	func	tioni	na: A	.nxiety, post-tr	reatment		
	Study or Subgroup	Psycholog Mean			Contro	1	•	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias A B C D E	CBT:
	7.9.1 CBT						-				
	Bonnert 2017	25.23	16.32	47 2	2.62 16.3	1 54	5.8%	0.16 [-0.23, 0.55]	- <b> -</b>	$\bullet \bullet \bullet \bullet \bullet$	$\oplus \oplus \bigcirc \bigcirc$
	Connelly 2019	46.8	11.3	144	45.5 1	1 145	9.0%	0.12 [-0.11, 0.35]	+	😠 🕀 🔁 ? 🛑	LOW
	Griffiths 1996	9.6	5.9	30	3.6 9.	5 12	2.8%	-0.55 [-1.24, 0.13]		????	LOW
	Hechler 2014	52.5	12.1	50	50 11.			0.21 [-0.19, 0.61]	+	•••??	
	Hickman 2015	52.56	7.36	16 4				0.75 [0.04, 1.46]		??????	<b>B I</b> ()
	Kashikar-Zuck 2012	2.11	0.72		2.39 0.			-0.34 [-0.74, 0.05]			Relaxation
	Lalouni 2019	8.59	7.71	45 1				-0.87 [-1.30, -0.43]	_ <b>_</b>	•••??•	thoropy
	Law 2015	46.33	8.99	30 4				-0.20 [-0.73, 0.33]		••••?	therapy:
	Lester 2020	7.08	6.24	24	6.1 4.9			0.17 [-0.42, 0.76]			000
	Levy 2010	13.5	4.86		3.04 4.0			0.10 [-0.21, 0.41]	-+	••••?•	
	Levy 2016	8.2	2.8	80	8.6 2.			-0.14 [-0.45, 0.17]			VERY LOW
	Levy 2017	1.09	0.94		.28 1.0			-0.19 [-0.46, 0.08]	+	• ? • ? ●	
	Palermo 2016 (remote)	10.56	5.91	134 1				-0.05 [-0.29, 0.19]			
	Stapersma 2018	7.1	4.14	35	7.3 4.			-0.05 [-0.52, 0.43]		•••?••	
	Trautmann 2010	27.1	7.1		31.7 8.			-0.59 [-1.41, 0.22]		3	Behavioural
	Van der Veek 2013	6.83	6		7.76 6.3			-0.15 [-0.53, 0.24]		• ? ? ? 🖶	thoropy
Emotional	Subtotal (95% CI)			997		882	88.5%	-0.09 [-0.23, 0.06]	•		therapy:
functioning	Heterogeneity: Tau <sup>2</sup> = 0.04			(P = 0.006)	; l² = 54%						$\oplus \bigcirc \bigcirc \bigcirc \bigcirc$
functioning:	Test for overall effect: Z = 1	.20 (P = 0.2)	3)								
Anxiety, post-	7.9.2 Relaxation therapy										VERY LOW
							0.000	0.044.040.440		? • • • • ?	
treatment	Trautmann 2010 Subtotal (95% CI)	34.7	8.8	20 20	31.7 8.	39 9		0.34 [-0.46, 1.13] 0.34 [-0.46, 1.13]			
		hla		20		9	2.270	0.34 [-0.40, 1.13]			AOT
Higher scores indicate	Heterogeneity: Not applica Test for overall effect: Z = 0		))								ACT:
	7.9.3 Behavioural therapy										$\oplus \bigcirc \bigcirc \bigcirc \bigcirc$
higher	Bussone 1988 Subtotal (95% CI)	28.1	3.49	20 <b>20</b>	29.2 5.	1 10 <b>10</b>		-0.26 [-1.02, 0.50] - <b>0.26 [-1.02, 0.50]</b>		??? ? 🖲 🖨	VERY LOW
depressive	Heterogeneity: Not applica	ble									
symptomology	Test for overall effect: Z = 0		))								
	7.9.4 ACT										Problem-
	Wicksell 2009	13.4	3.9	16	2.8 5.	5 16	2.7%	0.12 [-0.57, 0.82]	<u> </u>	•••??	
	Subtotal (95% CI)			16		16	2.7%	0.12 [-0.57, 0.82]			solving
	Heterogeneity: Not applica Test for overall effect: Z = 0		3)								therapy:
	7.9.5 Problem solving the	гару									000
	Palermo 2016 (f2f)	11.42	5.33	31	13 6.0			-0.27 [-0.78, 0.23]		••••	
	Subtotal (95% CI)			31		30	4.3%	-0.27 [-0.78, 0.23]	-		VERY LOW
	Heterogeneity: Not applica Test for overall effect: Z = 1		3)								
	Total (95% CI)			1084		947	100.0%	-0.08 [-0.21, 0.05]	•		
	Heterogeneity: Tau² = 0.03 Test for overall effect: Z = 1 Test for subgroup differen	.27 (P = 0.2)	)					Favo	2 -1 0 1 urs experimental Favours control	1	

			Ei	motio	onal	fun	ctic	oning	: Anxiety, follo	w-up		CBT:
		Psycholog	gical thera	pies	С	ontrol			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDE	$\oplus \oplus \oplus \bigcirc$
	7.10.1 CBT											MODERATE
	Connelly 2019	45.3	12	144		11.4	145	19.7%	-0.06 [-0.29, 0.17]			
	Kashikar-Zuck 2012	1.89	0.82	50	2.22 45.36		50	6.7%	-0.38 [-0.77, 0.02]			
	Law 2015 Lester 2020	45.82 4.71	10.96 5.09		45.36		22 18	3.4% 2.6%	0.04 [-0.52, 0.60] 0.15 [-0.48, 0.78]			Relaxation
	Lew 2010	4.71	3.98		12.59		63	2.0% 9.3%	0.15 [-0.48, 0.78]			
	Lew 2016	7.9	3.3	67		3.2	66	9.0%	-0.09 [-0.43, 0.25]			therapy:
	Levy 2017	0.87	0.88	151	1.1		78	13.9%	-0.25 [-0.52, 0.02]		• • • • • •	
	Palermo 2016 (remote)	10.35	6.12		10.23		135	18.3%	0.02 [-0.22, 0.26]	_ <b>_</b>		$\oplus O O O$
	Trautmann 2010	23.6	4.3	12	28.1	9.9	5	0.9%	-0.68 [-1.75, 0.40]		? 🗨 🖶 🗬 ?	VERY LOW
Emotional	Van der Veek 2013 Subtotal (95% CI)	5.47	5.22	52 <b>734</b>	5.82	6.09	52 634	7.1% 90.8%	-0.06 [-0.45, 0.32] -0.07 [-0.18, 0.03]	•	•???	
functioning: Anxiety,	Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 1.			= 0.52);1	I² = 0%							Behavioural therapy:
follow-up	7.10.2 Relaxation therapy											therapy.
Higher scores	Trautmann 2010 Subtotal (95% CI)	26.3	9.7	31 <b>31</b>	28.1	9.9	5 5	1.2% <mark>1.2%</mark>	-0.18 [-1.13, 0.76] - <b>0.18 [-1.13, 0.76]</b>		? 🖲 🖶 🖨 ?	000
indicate	Heterogeneity: Not applicat Test for overall effect: Z = 0.		1)									VERY LOW
higher	7.10.3 Behavioural therapy											ACT:
depressive	Bussone 1988	27.8	2.3	20	29.1	1.4	10	1.7%	-0.62 [-1.39, 0.16]		???? 🗣 🖶	ACT.
	Subtotal (95% CI)			20			10	1.7%	-0.62 [-1.39, 0.16]			$\oplus O O O$
symptomology	Heterogeneity: Not applicab Test for overall effect: Z = 1.		2)									VERY LOW
	7.10.4 ACT											
	Wicksell 2009 Subtotal (95% CI)	12.2	4.6	16 <b>16</b>	11.7	5.8	16 <b>16</b>	2.2% <b>2.2%</b>	0.09 [-0.60, 0.79] 0.09 [-0.60, 0.79]		•••??	
	Heterogeneity: Not applicat Test for overall effect: Z = 0.		9)									Problem- solving
	7.10.5 Problem solving the	rapy										
	Palermo 2016 (f2f) Subtotal (95% Cl)	12.61	6.05	31 <b>31</b>	11.21	5.55	30 <mark>30</mark>	4.1% <b>4.1%</b>	0.24 [-0.27, 0.74] 0.24 [-0.27, 0.74]			therapy:
	Heterogeneity: Not applicat Test for overall effect: Z = 0.		5)									000 VERY LOW
	Total (95% CI)			832			695	100.0%	-0.07 [-0.17, 0.03]	•		
	Heterogeneity: Tau² = 0.00; Test for overall effect: Z = 1. Test for subgroup differenci	31 (P = 0.1	9)						Favo	-2 -1 0 1 2 urs experimental Favours control		