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Antidepressants for Chronic Pain in Pediatric Populations: Clinical Effectiveness

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Research Questions

1. What is the clinical effectiveness of tricyclic antidepressants for the treatment of chronic pain in pediatric patients?
2. What is the clinical effectiveness of serotonin-norepinephrine reuptake inhibitors for the treatment of chronic pain in pediatric patients?

Key Findings

Four systematic reviews, four randomized controlled trials, and one non-randomized study were identified regarding the clinical effectiveness of tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors for the treatment of chronic pain in pediatric patients.

Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were antidepressant medications and pediatric chronic pain. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and April 30, 2020. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pediatric patients with chronic pain, including pain from chronic daily headaches, migraines, back pain, abdominal pain, idiopathic local pain, chronic widespread pain and fibromyalgia, and complex regional pain syndrome
Interventions	Q1: Tricyclic antidepressants (e.g., amitriptyline, nortriptyline) Q2: Serotonin–norepinephrine reuptake inhibitors (e.g., duloxetine)
Comparators	Other pharmacological medications (e.g., ibuprofen, naproxen, ketorolac, acetaminophen, gabapentin, pregabalin) Placebo Non-pharmacological interventions (e.g., physiotherapy, exercise, counseling, neurostimulation)
Outcomes	Clinical effectiveness (e.g., change in pain symptoms, change in quality of life, functional outcomes, disability)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports and systematic reviews are presented first. These are followed by randomized controlled trials and non-randomized studies.

Four systematic reviews,[1-4] four randomized controlled trials,[5-8] and one non-randomized study[9] were identified regarding the clinical effectiveness of tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors for the treatment of chronic pain in pediatric patients. No health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Four systematic reviews,[1-4] four randomized controlled trials[5-8] and one non-randomized study[9] were identified regarding the clinical effectiveness of tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors for the treatment of chronic pain in pediatric patients. The identified studies varied in terms of their populations, interventions, comparators and outcomes.[1-9] As such, no clear trends in the clinical effectiveness of tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors for the treatment of chronic pain in pediatric patients were identified.

Detailed study characteristics are included in Table 2.

Table 2: Study and Patient Characteristics of Included Studies

First Author, Year	Study Characteristics/ Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
Systematic Reviews				
Egunsola, 2019[1]	• One relevant RCT included • N= NR • Pediatric patients with chronic regional pain syndrome/ neuropathic pain	• Amitriptyline vs. gabapentin	The SR assessed: • Analgesic effect • Adverse events	• No statistically significant difference in the study's primary outcome
Cooper, 2017[2]	• Three relevant RCTs included • N = 34 (amitriptyline vs. gabapentin) N = 123 (amitriptyline vs. placebo • Pediatric patients with chronic, non-cancer pain	• Amitriptyline vs. gabapentin (one RCT) • Amitriptyline vs. placebo (two RCTs)	The SR assessed: • Analgesic effect • Adverse events	• Authors concluded that there was no evidence to support or counter the use of antidepressants to treat chronic non-cancer pain in pediatric patients
Martin, 2017[3]	• Unclear number of relevant studies • N = unclear • Pediatric patients with recurrent abdominal pain	• TCAs vs. unclear comparators	The SR assessed: • Pain intensity • Pain duration • Pain frequency • Improvement in pain • School performance	• Authors concluded that there was no clear evidence to support the use of drugs including TCAs to treat recurrent abdominal pain in pediatric patients

First Author, Year	Study Characteristics/ Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
			• Social or psychological functioning • Quality of life	
Korterink, 2015[4]	• One relevant study included • N = unclear • Pediatric patients with abdominal pain-related functional gastrointestinal disorders	• Amitriptyline vs. placebo	• Overall quality of life score	• Significant improvement in overall quality of life score with amitriptyline compared to placebo
Randomized Controlled Trials				
Upadhyaya, 2019[5]	• N = 184 • Adolescent patients with juvenile fibromyalgia	• Duloxetine vs. placebo	• Mean change in 24-hour average pain severity of the BPI (baseline to week 13) • BPI severity and interferences scores • Treatment response (>30%, >50% reductions on BPI average pain severity) • Pediatric Pain Questionnaire • Clinical Global Impression of Severity • Overall and Mental Illness scales • Functional Disability Inventory • Children's Depression Inventory • Multidimensional Anxiety Scale for Children	• No statistically significant difference between duloxetine and placebo in mean change in 24-hour average pain severity of the BPI • Significant increase in treatment response (>30%, >50% reductions on BPI average pain severity) with duloxetine compared to placebo
Fallah, 2018[6]	• N = 80 • Pediatric patients with a diagnosis of migraines in whom preventative therapy was indicated	• Amitriptyline vs. melatonin	• Response to therapy • Severity of migraines • Duration of migraines • Pediatric Migraine Disability Assessment score	• Significant increase in treatment response with amitriptyline compared to melatonin
Powers, 2017[7]	• N = 361 • Pediatric patients with a diagnosis of migraines	• Amitriptyline vs. topiramate vs. placebo	• Relative reduction of 50% or more in the number of headache days (28-day baseline period compared to the last 28 days of the 24-week trial period) • Headache-related disability • Headache days	• Trial was concluded early due to futility (after a planned interim analysis) • No statistically significant between-group differences in the relative reduction of 50% or more in the number of headache days

First Author, Year	Study Characteristics/ Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
				• No statistically significant between-group differences in headache frequency or headache-related disability
Brown, 2016[8]	• N = 34 • Pediatric patients with complex regional pain syndrome type 1 or a neuropathic pain condition	• Amitriptyline vs. gabapentin	• Pain intensity • Sleep quality	• No statistically significant differences between groups in reduction of pain or sleep score
Non-Randomized Studies				
Zar-Kessler, 2017[9]	• Retrospective chart review • N = 176 • Pediatric patients with functional abdominal pain	• TCAs vs. SSRIs	• Treatment efficacy	• Significantly greater response to treatment with SSRIs compared to TCAs

BPI = Brief Pain Inventory; NR = not reported; RCT = randomized controlled trial; SR = systematic review; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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PubMed: PM30451725

2. Cooper TE, Heathcote LC, Clinch J, et al. Antidepressants for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017 08 05;8:CD012535.
PubMed: PM28779487

3. Martin AE, Newlove-Delgado TV, Abbott RA, et al. Pharmacological interventions for recurrent abdominal pain in childhood. *Cochrane Database Syst Rev*. 2017 Mar 06;3:CD010973.
PubMed: PM28262913

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PubMed: PM25449223

Randomized Controlled Trials

5. Upadhyaya HP, Arnold LM, Alaka K, Qiao M, Williams D, Mehta R. Efficacy and safety of duloxetine versus placebo in adolescents with juvenile fibromyalgia: results from a randomized controlled trial. *Pediatr Rheumatol Online J*. 2019 May 28;17(1):27. PubMed: PM31138224

6. Fallah R, Fazelishoroki F, Sekhavat L. A Randomized Clinical Trial Comparing the Efficacy of Melatonin and Amitriptyline in Migraine Prophylaxis of Children. *Iran J Child Neurol*. 2018;12(1):47-54. PubMed: PM29379562

7. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. *N Engl J Med*. 2017 01 12;376(2):115-124. PubMed: PM27788026

8. Brown S, Johnston B, Amaria K, et al. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. *Scand J Pain*. 2016 Oct;13:156-163. PubMed: PM28850523

Non-Randomized Studies

9. Zar-Kessler CAM, Belkind-Gerson J, Bender S, Kuo BM. Treatment of Functional Abdominal Pain With Antidepressants: Benefits, Adverse Effects, and the Gastroenterologist's Role. *J Pediatr Gastroenterol Nutr*. 2017 07;65(1):16-21. PubMed: PM28644344

Appendix — Further Information

Systematic Reviews and Meta-analyses

Unclear Intervention

10. Locher C, Kossowsky J, Koechlin H, et al. Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis. *JAMA Pediatr*. 2020 Feb 10;10:10.
PubMed: PM32040139

Randomized Controlled Trials

Unclear Population

11. Villani V, Prosperini L, Palombini F, Orzi F, Sette G. Single-blind, randomized, pilot study combining shiatsu and amitriptyline in refractory primary headaches. *Neurol Sci*. 2017 Jun;38(6):999-1007.
PubMed: PM28283760

12. Salviz M, Yuce T, Acar H, Karatas A, Acikalin RM. Propranolol and venlafaxine for vestibular migraine prophylaxis: A randomized controlled trial. *Laryngoscope*. 2016 Jan;126(1):169-174.
PubMed: PM26228645

Mixed Intervention

13. Kroner JW, Hershey AD, Kashikar-Zuck SM, et al. Cognitive Behavioral Therapy plus Amitriptyline for Children and Adolescents with Chronic Migraine Reduces Headache Days to <=4 Per Month. *Headache*. 2016 Apr;56(4):711-716.
PubMed: PM26992129

Non-Randomized Studies

No Comparator

14. Arnold LM, Bateman L, Palmer RH, Lin Y. Preliminary experience using milnacipran in patients with juvenile fibromyalgia: lessons from a clinical trial program. *Pediatr Rheumatol Online J*. 2015 Jun 26;13:27.
PubMed: PM26112278

Mixed Intervention

15. Przekop P, Przekop A, Haviland MG. Multimodal compared to pharmacologic treatments for chronic tension-type headache in adolescents. *J Bodyw Mov Ther*. 2016 Oct;20(4):715-721.
PubMed: PM27814849

Review Articles

16. Gmuca S, Sherry DD. Fibromyalgia: Treating Pain in the Juvenile Patient. *Paediatr Drugs*. 2017 Aug;19(4):325-338.
PubMed: PM28536810

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