TITLE: **Tramadol for the Management of Pain in Adult Patients: Clinical Effectiveness and Guidelines**

DATE: 24 October 2014

RESEARCH QUESTIONS

1. What is the clinical effectiveness of tramadol for the management of pain in adult patients?

2. What are the evidence-based guidelines regarding the use of tramadol for pain in adult patients?

KEY FINDINGS

Four systematic reviews, 17 randomized controlled trials, seven non-randomized studies, and five evidence-based guidelines were identified regarding the use of tramadol for the management of pain in adult patients.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 10), University of York Centre for Reviews and Dissemination (CRD), Pubmed, Medline (OVID) and Embase (OVID) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and October 16, 2014. 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	Adult patients requiring management of acute or chronic pain
Intervention	Oral tramadol or tramadol combination products
Comparator	Other analgesics (e.g.: narcotics, NSAIDs)
Outcomes	Effectiveness, safety, benefits and harms, guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and evidence-based guidelines

RESULTS

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

Four systematic reviews, 17 randomized controlled trials, seven non-randomized studies, and five evidence-based guidelines were identified regarding the use of tramadol for the management of pain in adult patients. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine. 2014 Apr 1;39(7):556-63.
PubMed: PM24480962

2. Mercier F, Claret L, Prins K, Bruno R. A Model-based meta-analysis to compare efficacy and tolerability of tramadol and tapentadol for the treatment of chronic non-malignant pain. Pain Ther [Internet]. 2014 Jun [cited 2014 Oct 23];3(1):31-44. Available from:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4108025
PubMed: PM25135386

3. Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. Pain Physician. 2013 Nov;16(6):E685-E704.
PubMed: PM24284847

4. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD008943.

Randomized Controlled Trials

Tramadol Alone

5. Das SK, Banerjee M, Mondal S, Ghosh B, Ghosh B, Sen S. A comparative study of efficacy and safety of lornoxicam versus tramadol as analgesics after surgery on head and neck. Indian J Otolaryngol Head Neck Surg [Internet]. 2013 Jul [cited 2014 Oct 23];65(Suppl 1):126-30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3718935 PubMed: PM24427628

6. Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blinded, placebo-controlled study. J Pain Res. [Internet] 2013 [cited 2014 Oct 23];6:471-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699253 PubMed: PM23837006

7. Saxena AK, Nasare N, Jain S, Dhakate G, Ahmed RS, Bhattacharya SN, et al. A randomized, prospective study of efficacy and safety of oral tramadol in the management of post-herpetic neuralgia in patients from north India. Pain Pract. 2013 Apr;13(4):264-75. PubMed: PM22882673

8. Zavareh SM, Kashefi P, Saghaei M, Emami H. Pre emptive analgesia for reducing pain after cholecystectomy: Oral tramadol vs. acetaminophen codeine. Adv Biomed Res [Internet] 2013 [cited 2014 Oct 23] 2:12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3732874 PubMed: PM23930257

9. Banerjee M, Bhattacharyya K, Sarkar RN, Ghosh B. Comparative study of efficacy and tolerability of flupirtine versus tramadol in non-steroidal anti-inflammatory drug intolerant mechanical low back pain. Indian Journal of Rheumatology. 2012;7(3):135-40.

10. Karabayirli S, Ayrim AA, Muslu B. Comparison of the analgesic effects of oral tramadol and naproxen sodium on pain relief during IUD insertion. J Minim Invasive Gynecol. 2012 Sep;19(5):581-4. PubMed: PM22766124

11. Naser SM, Sarkar N, Biswas A, Kamal F, Prakash R, Rahaman QM, et al. Efficacy and safety of flupirtine maleate and tramadol hydrochloride in postoperative pain management--a prospective randomised double blinded study. J Indian Med Assoc. 2012 Mar;110(3):158-60. PubMed: PM23029946

Tramadol Combination Therapy

12. Chandanwale AS, Sundar S, Latchoumibady K, Biswas S, Gabhane M, Naik M, et al. Efficacy and safety profile of combination of tramadol-diclofenac versus tramadol-paracetamol in patients with acute musculoskeletal conditions, postoperative pain, and acute flare of osteoarthritis and rheumatoid arthritis: a phase III, 5-day open-label study. J

Pain Res. [Internet] 2014 [cited 2014 Oct 23];7:455-63. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4140236
PubMed: PM25152629

13. Choy CY, Isquandar A. Effectiveness of tramadol/paracetamol compared with etoricoxib as postoperative analgesia in daycare surgery. Southern African Journal of Anaesthesia and Analgesia. 2014;20(3):155-9.

14. Park YB, Ha CW, Cho SD, Lee MC, Lee JH, Seo SS, et al. A randomized study to compare the efficacy and safety of extended-release and immediate-release tramadol HCl/acetaminophen in patients with acute pain following total knee replacement. Curr Med Res Opin. 2014 Oct 9;1-31.
PubMed: PM25299350

15. Schiphorst Preuper HR, Geertzen JH, van Wijhe M, Boonstra AM, Molmans BH, Dijkstra PU, et al. Do analgesics improve functioning in patients with chronic low back pain? An explorative triple-blinded RCT. Eur Spine J [Internet]. 2014 [cited 2014 Oct 23];Apr;23(4):800-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3960442
PubMed: PM24526247

16. Zhong TD, Liu Q, Zhao JN, Wang HW, Konstantatos A. A randomized trial to compare pain control using oral analgesia with epidural analgesia after cesarean section following combined spinal-epidural anesthesia. Genet Mol Res. 2014;13(3):7086-93.
PubMed: PM24682986

17. Chang JK, Yu CT, Lee MY, Yeo K, Chang IC, Tsou HK, et al. Tramadol/acetaminophen combination as add-on therapy in the treatment of patients with ankylosing spondylitis. Clin Rheumatol. 2013 Mar;32(3):341-7.
PubMed: PM23192419

18. Hyup LJ, Lee CS, Ultracet ER Study Group. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. Clin Ther. 2013 Nov;35(11):1830-40.
PubMed: PM24183364

19. Lasko B, Levitt RJ, Rainsford KD, Bouchard S, Rozova A, Robertson S. Extended-release tramadol/paracetamol in moderate-to-severe pain: a randomized, placebo-controlled study in patients with acute low back pain. Curr Med Res Opin. 2012 May;28(5):847-57.
PubMed: PM22458917

20. Lin FS, Lin WY, Lai CH, Chen CY, Lin CP, Lin TF, et al. Analgesic efficacy of tramadol/acetaminophen and propoxyphene/acetaminophen for relief of postoperative wound pain. Acta Anaesthesiol Taiwan. 2012 Jun;50(2):49-53.
PubMed: PM22769857

21. Park KS, Choi JJ, Kim WU, Min JK, Park SH, Cho CS. The efficacy of tramadol/acetaminophen combination tablets (Ultracet) as add-on and maintenance therapy in knee osteoarthritis pain inadequately controlled by nonsteroidal anti-

inflammatory drug (NSAID). Clin Rheumatol. 2012 Feb;31(2):317-23.
PubMed: PM21811797

Non-Randomized Studies

Tramadol Alone

22. Peng X, Robinson RL, Mease P, Kroenke K, Williams DA, Chen Y, et al. Long-Term Evaluation of Opioid Treatment in Fibromyalgia. Clin J Pain. 2014 Jan 28.
PubMed: PM24480913

23. van der Worp F, Stapel JT, Lako S, Hendriks J, Vissers KC, Steegers MA. The comparison of two analgesic regimes after ambulatory surgery: an observational study. Pain Pract. 2014 Mar;14(3):260-70.
PubMed: PM23615039

24. Yan LT, Kong LY, Ming CC. Who are prone to develop adverse effects with oral tramadol? A retrospective cohort study. Hong Kong Journal of Emergency Medicine. 2014;21(1):3-9.

25. Hsu SK, Yeh CC, Lin CJ, Hsieh YJ. An open label trial of the effects and safety profile of extended-release tramadol in the management of chronic pain. Acta Anaesthesiol Taiwan. 2012 Sep;50(3):101-5.
PubMed: PM23026168

Tramadol Combination Therapy

26. Madhusudhan SK. Novel analgesic combination of tramadol, paracetamol, caffeine and taurine in the management of moderate to moderately severeacute low back pain. Journal of Orthopaedics. 2013;10(3):144-8.

27. Colini BG, Cobianchi MR. Study of codeine-paracetamol combination treatment compared with tramadol-paracetamol in the control of moderate-to-severe low back pain. Minerva Med. 2012;103(3):177-82.

28. Guan D, Li Y, Wang C, Chen H, Zhang P, Zhang W. Analgesic effect and security of tramadol/acetaminophen during perioperative total knee arthroplasty. Chinese Journal of Tissue Engineering Research. 2012;16(26):4781-5.

Guidelines and Recommendations

29. Orr SL, Aube M, Becker WJ, Davenport WJ, Dilli E, Dodick D, et al. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. Cephalalgia. 2014 May 29.
PubMed: PM24875925

30. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); [1997] - . Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); Health care protocol: Thorson D, Biewen P, Bonte B, Epstein H, Haake B, Hansen C, et al. Acute pain assessment and opioid prescribing protocol. 2014

Jan. [Cited 23 Oct 2014]. Summary available from: http://www.guideline.gov/content.aspx?id=47765&search=pain+and+tramadol
See: 15. Prescription of Opioids

31. Neuropathic pain – pharmacological management: The pharmacological management of neuropathic pain in adults in non-specialist settings [Internet]. London: National Institute for Health and Clinical Excellence; 2013 [Cited 23 Oct 2014]. 41 p. (NICE guidelines CG173) Available from: https://www.nice.org.uk/guidance/cg173/chapter/1-recommendations
See: 1.1.10 and 1.1.12

32. Scottish Intercollegiate Guidelines Network (SIGN) [Internet]. Edinburgh: SIGN publication no. 136; 2013. Management of chronic pain; 2013 [cited 23 Oct 2014]. Available from: http://www.sign.ac.uk/pdf/SIGN136.pdf

33. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); [1997] - . American Medical Directors Association (AMDA). Pain management in the long term care setting. Columbia (MD): American Medical Directors Association (AMDA); 2012 [cited 2014 Oct 23]. Available from: http://www.guideline.gov/content.aspx?id=45524
See: Tramadol

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

APPENDIX – FURTHER INFORMATION:

Review Articles

34. Best Practice Advocacy Centre New Zealand [Internet]. Dunedin: Best Practice Advocacy Centre New Zealand; 2014. Helping patients cope with chronic non-malignant pain: it's not about opioids. Best Practice Journal; [Cited 2014 Oct 23]. Available from: http://www.bpac.org.nz/BPJ/2014/September/chronicpain.aspx

35. Kizilbash A, Ngo-Minh CT. Review of extended-release formulations of Tramadol for the management of chronic non-cancer pain: focus on marketed formulations. J Pain Res [Internet]. 2014 [cited 2014 Oct 23];7:149-61. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3968086 PubMed: PM24711710

36. Paisley P, Kinsella J. Pharmacological management of pain in chronic pancreatitis. Scott Med J. 2014 Feb;59(1):71-9. PubMed: PM24413930

37. Farquhar-Smith P, Gubbay A. Tramadol and acetaminophen combination for chronic non-cancer pain. Expert Opin Pharmacother. 2013 Nov;14(16):2297-304. PubMed: PM24067074

Additional References

38. Drug Enforcement Administration Office of Diversion Control [Internet]. Springfield: Drug Enforcement Administration Office of Diversion Control; 2014. Tramadol Designated as Schedule IV Drug; August 2014 [cited 2014 Oct 23]. Available from: http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0702.htm

39. Narcotics, Benzodiazepines, Stimulants, and Gabapentin: Policies, Initiatives, and Practices Across Canada evaluation [Internet]. Ottawa: Canadian Agency for Drugs and Technology in Health; 2014. (Environmental Scanning; Issue 45) [cited 2014 Oct 23]. Available from: http://www.cadth.ca/media/pdf/ES0285_Narcotics_BZD_Stimulants_Gabapentin_e.pdf