Are there data that support concurrent use of gabapentin and a TCA for treatment of chronic non-cancer pain?

Chronic pain is typically defined as pain that persists beyond the expected tissue healing time, generally lasting longer than 3-6 months.[1] Several organizations have published guidelines regarding treatment of chronic non-cancer pain (CNCP); however, many of these have focused on opioid prescribing.[2-7] Several of these guidelines address use of adjuvant agents such as antidepressants or antiepileptic drugs (AEDs) for irritability, sleep disturbances, or neuropathic pain; however, specific recommendations regarding combined use of gabapentin and a tricyclic antidepressant (TCA) are lacking.[2,3,5,7] Regarding combination treatment, the Centers for Disease Control and Prevention (CDC) recommend a multimodal treatment approach and assert that patients not responding to a single type of treatment may benefit from combination treatment.[5] However, the CDC did not identify specific multimodal treatment options.

In terms of other guidelines which do not primarily focus on opioid prescribing, several organizations have published guidelines on various types of common chronic pain conditions including low back pain, neuropathic pain, and postherpetic neuralgia. See Table 1 for a summary of the recommendations.

Table 1: Recommendations for combined pharmacologic treatment in various types of chronic pain.

Organization (publication date)	Type of pain	Comments regarding combination therapy
AAN (2011)[8]	Painful diabetic neuropathy	-Recommends use of AEDs or antidepressants; does not address combined use
AAN (2004*)[9]	Postherpetic neuralgia	-Recommends use of AEDs or antidepressants; does not address combined use
APS/ACP (2009)[10]	Low back pain	-Lack of evidence for combination therapy; patients often prescribed multiple medications in clinical practice
ASA/ASRA (2010)[11]	Chronic pain (excludes pain due to cancer, DJD, HA, TJS, TN)	-Recommends a multimodal approach; AEDs and TCAs strongly recommended
CDLE (2015)[12]	Chronic pain	-Recommends a multimodal approach -Combination treatment with nortriptyline and gabapentin more effective for pain relief vs. monotherapy
CPS (2014)[13]	Neuropathic pain	-Combination therapy may improve efficacy and decrease side effects as a result of high-dose monotherapy
EFNS (2010)[14]	Neuropathic pain	-Recommends combination therapy with gabapentin and a TCA for patients with partial response to monotherapy -Additional larger trials needed
ICSI (2013)[15]	Chronic pain	No specific recommendations
NICE (2013)[16]	Neuropathic pain	-Combination therapy is common; consider if initial treatment lacks efficacy -May allow for lower doses & improved tolerability -Lack of evidence for efficacy, safety, cost-effectiveness; additional research needed
NeuPSIG (2007)[17]	Neuropathic pain	-Recommends combination therapy for patients with partial response to monotherapy -May provide more rapid pain relief by using an agent with a rapid onset combined with an agent with delayed onset -Need to consider potential for adverse events, drug interactions, cost, and adherence; additional research needed

*Reaffirmed in 2008; AAN=American Academy of Neurology; ACP=American College of Physicians; AEDs=antiepileptic drugs; APS=American Pain Society; ASA=American Society of Anesthesiologists; ASRA=American Society of Regional Anesthesia and Pain Medicine; CDLE=Colorado Department of Labor and Employment; CPS=Canadian Pain Society; DJD=degenerative joint disease; EFNS=European Federation of Neurological Societies; HA=headache; ICSI=Institute for Clinical Systems Improvement; NeuPSIG=Neuropathic Pain Special Interest Group; NICE=National Center for Health and Care Excellence; TCAs=tricyclic antidepressants; TJS=temporomandibular joint syndrome; TN=trigeminal neuralgia

In addition to reviewing treatment guidelines, a review of the medical literature was conducted in order to determine whether other data are available regarding combined use of gabapentin and a TCA for chronic pain. A systematic review and meta-analysis was identified which evaluated pharmacologic treatment of neuropathic pain.[18] The objective was to update existing recommendations made by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain. The study included 229 randomized, double-blind trials published between 1966 and April 2013; trials involving gabapentin, TCAs, serotonin-norepinephrine reuptake inhibitors, and several other pharmacologic agents were included. In terms of combination therapy, 7 trials were identified which used a variety of pharmacologic combinations. One trial found that the combination of gabapentin and nortriptyline was superior to monotherapy; combination therapy also allowed for lower doses without additional side effects. Other trials used combinations of morphine/gabapentin and pregabalin/duloxetine. Based on the results, the authors concluded that combination therapy is an "inconclusive recommendation" due to poor quality data and discrepant results (based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) rating system). The authors asserted that combination therapy may be considered when patients fail to respond to monotherapy or when wishing to avoid adverse events associated with high-dose monotherapy. Finally, although combination treatment is an "inconclusive recommendation," the authors indicated that this practice is common in clinical practice and is considered to be safe.

In conclusion, numerous guidelines recommend use of adjuvant agents such as antidepressants or AEDs for chronic pain.[2,3,5,7] In terms of combination treatment, multiple guidelines recommend a multimodal approach such as gabapentin and a TCA for various types of chronic pain.[11-14,16,17] Although combination therapy is common in clinical practice, several organizations have cautioned that additional research is needed in order to further establish efficacy and safety.[14,16,17] A recent meta-analysis concluded that combination treatment could not be conclusively recommended due to poor quality data and discrepant results from clinical trials.[18] As such, combination therapy may be considered when patients fail to respond to monotherapy or experience adverse events as a result of high-dose monotherapy.

References:

1. International Association for the Study of Pain. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Task Force on Taxonomy. 2nd ed. 2002; IASP Press. http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf. Accessed October 18, 2016
2. Veterans Affairs and Department of Defense clinical practice guideline for management of opioid therapy for chronic pain. 2010; http://www.va.gov/painmanagement/docs/cpg_opioidtherapy_fulltext.pdf. Accessed October 18, 2016.
3. Washington State interagency guideline on prescribing opioids for pain, 3rd edition. 2015; http://www.agencymeddirectors.wa.gov/files/opioidgdline.pdf. Accessed October 18, 2016.
4. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.
5. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. *MMWR Recomm Rep.* 2016;65(1):1-49.
6. Hegmann KT, Weiss MS, Bowden K, et al. American College of Occupational and Environmental Medicine (ACOEM) practice guidelines: opioids for treatment of acute, subacute, chronic, and postoperative pain. *J Occup Environ Med.* 2014;56(12):e143-159.
7. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician.* 2012;15(3 Suppl):S67-116.
8. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *PM R.* 2011;3(4):345-352, 352 e341-321.

9. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2004;63(6):959-965.
10. Chou R, Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med.* 2007;147(7):505-514.
11. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology.* 2010;112(4):810-833.
12. Colorado Department of Labor and Employment. Medical treatment guidelines: chronic pain disorder. Revised December 27, 2011. https://www.colorado.gov/pacific/sites/default/files/MTG_Ex9_CPD.pdf. Accessed October 19, 2016.
13. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag.* 2014;19(6):328-335.
14. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;17(9):1113-e1188.
15. Hooten T, Timming R, Belgrade M, Gaul J, Goertz M. Institute for Clinical Systems Improvement. Assessment and management of chronic pain. 2013; https://www.icsi.org/_asset/bw798b/ChronicPain.pdf. Accessed October 19, 2016.
16. National Center for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings clinical guideline. 2013; https://www.nice.org.uk/. Accessed October 19, 2016.
17. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* 2007;132(3):237-251.
18. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162-173.