Pain Improvement With Novel Combination Analgesic Regimens (PAIN-CARE): Randomized Controlled Trial Protocol

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Abstract

Background: Neuropathic pain (NP) (including painful diabetic neuropathy, postherpetic neuralgia, etc) affects approximately 7% to 8% of the population and is associated with a devastating symptom burden as well as a profound economic impact for patients, their families, and the health care system. Current therapies have limited efficacy and dose-limiting adverse effects (AEs). Rational combination therapy with carefully selected NP drugs has shown potential for measurable improvements in pain relief, quality of life, and health care use. Today, over half of NP patients concurrently receive 2 or more analgesics but combination use is based on little evidence. Research is urgently needed to identify safer, more effective combinations.

Objective: We hypothesize that analgesic combinations containing at least 1 nonsedating agent would be as safe but more effective than either monotherapy without increasing overall AEs because of additive pain relief. Pregabalin (PGB), a sedating anticonvulsant, is proven effective for NP; the antioxidant alpha-lipoic acid (ALA) is one of the only nonsedating systemic agents proven effective for NP. Thus, we will conduct a clinical trial to compare a PGB+ALA combination to each monotherapy for NP.

Methods: Using a double-blind, double-dummy, crossover design, 54 adults with NP will be randomly allocated to 1 of 6 sequences of treatment with PGB, ALA and PGB+ALA combination. During each of 3 different treatment periods, participants will take 2 sets of capsules containing (1) ALA or placebo and (2) PGB or placebo for 31 days, followed by an 11-day taper/washout period. The primary outcome will be mean daily pain intensity (0-10) at maximally tolerated dose (MTD) during each period. Secondary outcomes, assessed at MTD, will include global improvement, adverse events, mood, and quality of life.

Results: Participant recruitment is expected to begin September 1, 2017. The proposed trial was awarded external peer-reviewed funding by the Canadian Institutes of Health Research (Canada) on July 15, 2016.

Conclusions: This trial will provide rigorous evidence comparing the efficacy of a PGB+ALA combination to PGB alone and ALA alone in the treatment of NP.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN14577546; http://www.isrctn.com/ISRCTN14577546?q=&filters=conditionCategory:Signs%20and%20Symptoms,trialStatus:Ongoing,recruitmentCountry:Canada&sort=&offset=1&totalResults=2&page=1&pageSize=10&searchType=basic-search (Archived by WebCite at http://www.webcitation.org/6qvHFDc6m)

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KEYWORDS
neuropathic pain; alpha-lipoic acid; antioxidant; pregabalin; anticonvulsant

Introduction

Chronic pain has a prevalence of 20% to 25% [1] and is one of the most frequent reasons to seek health care and miss work [2]. Pain impairs physical, social, and occupational function and thus exerts a devastating impact on patients, their families, and society. Each year in North America, chronic pain costs over $650 billion in health care and lost productivity thus exceeding costs of heart disease, cancer, and diabetes [3].

Neuropathic pain (NP) is a common form of chronic pain caused by nervous system diseases [4,5], including radiculopathy, diabetic neuropathy, HIV-neuropathy, and cancer-related NP [6]. NP is more prevalent in the elderly and we need to prioritize treatment research as our population ages [7]. NP management involves treating underlying causes, reducing pain, and improving function. Systemic oral pharmacotherapy is a valuable component of multimodal NP management [8] given ease of administration and engagement of drug effect sites throughout the sensory nervous system. However, current treatments give only partial benefit due to incomplete efficacy and dose-limiting adverse effects (AEs) [8]. In addition to reversible AEs such as sedation, excessive pain-contingent dosing of drugs with incomplete efficacy can lead to catastrophic outcomes such as opioid-related [9] and anti-inflammatory drug (NSAID)-related toxicity and death [10].

Due to perceived benefits of combination therapy [11,12], more than 50% of NP patients concurrently receive 2 or more analgesics [13]. However, current combination prescribing is based on little evidence, some combinations may be harmful, and authorities have demanded more research to develop rational combination strategies [8]. This field has received little attention from industry, emphasizing the need for public funding. Rational combination therapy with mechanistically different agents has shown potential for measurable improvements in pain relief, quality of life, and health care utilization and, indirectly, fewer NSAID-related and opioid-related mortalities. Combination therapy has been studied in many therapeutic areas but only recently in NP. Although our previous trials [14-16] support the merits of combination therapy, other data indicate that some combinations confer no benefit in some conditions [17] and other combinations do more harm than good [18]. Our Cochrane review [11] identified only 21 NP trials of different combinations. This dearth of evidence emphasizes the urgent need for more research.

A combination of pregabalin (PGB, Lyrica) plus alpha-lipoic acid (ALA) is now the most important to study because (1) high-quality evidence supports the efficacy of these agents as monotherapies in NP; (2) ALA is inexpensive, widely accessible, and currently the only nonsedating systemic agent for NP [19]; (3) PGB also improves sleep, mood, and anxiety [20]; (4) PGB and ALA have complementary mechanisms providing the expectation of greater synergy; and (5) AE profiles are different and combining PGB+ALA will not increase overall AEs. Combining a sedating and nonsedating agent is a novel approach with vast potential for improved patient outcomes. This project directly addresses a desperate need to improve chronic pain treatment.

Both PGB and ALA are approved by Health Canada for clinical use and proven for the treatment of NP [8,19]. PGB blocks the $\alpha_2\-\delta$ subunit of N-type voltage gated calcium channels, resulting in decreased calcium influx and neurotransmitter release [21,22]. PGB is recommended as first-line treatment for NP [8], and a recent meta-analysis of 19 trials (7003 participants) yielded a number-needed-to-treat (NNT for 50% pain reduction) of 5.0 for NP [20]. AEs (at 600 mg per day) included sedation (15%-25%) and dizziness (27%-46%). Our experience with PGB includes a Pfizer-sponsored trial [23] and, more recently, an investigator-initiated trial of PGB plus duloxetine for fibromyalgia [24]. ALA has been extensively studied in NP, and its therapeutic effects in this setting appear to be, in part, due to its antioxidant actions [25]. In a rat model of streptozocin-induced diabetes, ALA delayed the onset of polyneuropathy [26]. Mechanistic studies suggest decreased nociceptive sensitivity by inhibition of T-type calcium (Cav3.2) channels [27], distinct from that of PGB, which inhibits N-type calcium channels [22], suggesting potential for synergy at these different sites of action. At least 16 trials of over 1320 patients have reported reductions in pain and other symptoms [19,28], and a recent meta-analysis reported an NNT of 6.3 [19]. Also, 1 trial reported improvement in NP symptoms after 4 years of treatment [29]. AEs of nausea, vomiting, headache, and vertigo have been reported in studies involving more than 1200 mg per day of ALA. There have also been rare reports of hypoglycemia (low blood sugar) in diabetic patients taking ALA and reporting symptoms of sweating, paleness, chills, headache, dizziness, and confusion. We identified only 1 study of a combination similar to PGB+ALA—ALA plus gabapentin (related to PGB) in the treatment of burning mouth syndrome [30]. Despite major methodological flaws, the study suggested greater benefit with this combination versus monotherapy, and AEs were reported overall as very mild [30].

Thus, our objective is to conduct an innovative double-blind, randomized controlled trial (RCT) to compare a combination of the anticonvulsant PGB with the nonsedating antioxidant ALA to each monotherapy in NP.

Methods

Ethics

This study underwent ethics review and received a compliance notice by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board on December 15, 2016. This trial will be conducted at one site, Providence Care Centre, Kingston, Ontario, Canada.

Aims and Hypothesis

The objective of this trial is to compare the safety and efficacy of a PGB+ALA combination to each monotherapy in treating participants with NP. Our primary hypothesis is that PGB+ALA has greater analgesic efficacy versus either monotherapy.
Trial Design

We have designed a single center double-blind, double-dummy, randomized, controlled, 3-period crossover trial (compliant with Health Canada; International Conference on Harmonization; Methods, Measurement, and Pain Assessment in Clinical Trials; and Consolidated Standards of Reporting Trials [CONSORT]) comparing a PGB+ALA combination to monotherapy in treating NP (Figures 1 and 2). Using a flexible dose titration, Latin Square crossover design, treatments will be titrated during each of 3 treatment periods to maximal tolerated dose (MTD) with primary and secondary trial analyses comparing the 3 treatments using end-of-period outcomes. Given ethical issues and since PGB and ALA are proven with multiple trials confirming superiority over placebo [19,20], this active control superiority design does not include a placebo alone treatment. Furthermore, our previous trials [14-16] have confirmed assay sensitivity with a similar design. Internal validity of our crossover design is supported by stability of NP over time [14-17,31] and the risk of carryover from one period to the next is very low because each period is followed by an 11-day dose taper and drug washout, and the final MTD week for each period (from which the primary outcome is obtained) is separated from the next period’s final week by 7 weeks (ie, ≥20 half-lives of the drugs studied). Nevertheless, exploratory analyses will be conducted to identify if any low-order carryover effect does exist.

During each of 3 trial periods, using a double-blind randomized crossover design, patients will receive 2 sets of capsules (Figure 3): (1) blue capsules (ALA 300 mg or placebo) and (2) gray capsules (PGB 75 mg or placebo). During the combination period, blue will contain ALA and gray will contain PGB. During the ALA alone period, blue will contain ALA and gray will contain placebo. During the PGB alone period, blue will contain placebo and gray will contain PGB.

Consenting patients on ALA or PGB (or gabapentin) pretrial will agree to be weaned gradually for a washout of at least 7 days. Patients taking and perceiving benefit from opioids (<90 mg morphine equivalents), antidepressants (tricyclic, selective serotonin reuptake inhibitor, or serotonin–norepinephrine reuptake inhibitor), NSAIDs, or acetaminophen may continue these at a steady dose for the entire study. Any cognitive behavioral therapy or exercise programs may continue only if they can be scheduled evenly across all treatment periods. Research staff will monitor and advise patients weekly about prohibited cointerventions throughout the study. A thorough understanding of the threats to validity of using forbidden cointerventions is heavily emphasized to participants. Patients will not be allowed to start new cognitive behavioral therapy or exercise programs after study initiation and must avoid any procedural therapies (eg, nerve blocks or acupuncture) during the entire study. Any pain exacerbations that in the opinion of the patient warrant initiation of a new therapy would necessitate trial discontinuation and immediate weaning from study medications, but these patients would still be included in the trial analyses.

Dose Titration

Study medication will follow a flexible dose titration to MTD to balance tolerability and relief, with regular weekly calls by research personnel. This means that doses of study medication will not be further increased if intolerable AEs are encountered at higher doses or if “a lot” or “complete” pain relief is achieved. If AEs are experienced subsequent to a dose increase of study medications, the protocol will allow for dose reduction to the previous dosage level in order to improve tolerability. The MTD fixed dose week will be from days 25 to 31. However, if MTD is reached before day 25, that MTD dose will continue up to and including the day 25 to 31 period. For ALA, the maximum possible daily dose will be 1800 mg, and for PGB the maximum possible daily dose will be 450 mg. The MTD fixed dose week will be followed by a 7-day dose taper and 4-day complete washout. Daily pain ratings will be completed throughout the trial. During dose taper and washout periods only, patients may take acetaminophen, ≤8 tablets per day (325 mg per tablet) as needed. This rescue medication is very unlikely to affect the primary outcome measure of pain intensity during the MTD phase of each treatment period.

Participant Allocation

As per the 3-period Latin Square crossover, patients are randomly allocated to 1 of 6 sequences of ALA, PGB, and combination (Figure 1). Before the trial, an independent pharmacist and biostatistician will prepare a concealed allocation schedule using a computer-generated block randomization process to randomly assign treatment sequences to a consecutive series of numbers within a block. Each patient will be assigned to the next consecutive number, and the corresponding sequence of medications will be dispensed. All study personnel will be blinded to the block sizes to preserve allocation concealment.
**Figure 1.** Trial design.

This will each be a 3-period, active treatment-controlled randomized double-blind trial, using a double-dummy, balanced Latin Square crossover design in which patients will be allocated to one of 6 treatment sequences of the three treatments: ALA, PGB and ALA-PGB combination

*see below for specific treatment sequences

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**TREATMENT SEQUENCES**

(each patient is randomized to ONE of these sequences)

[All patients complete all three treatment periods (i.e. A, B and C) as per the treatment sequence they were randomized to (i.e. 1, 2, 3, 4, 5 or 6)]

| Baseline | A | B | C |
|----------|---|---|---|
| 7 day washout of prohibited medications (e.g. gabapentin, pregabalin, alpha-lipoic acid) | Sequence | 8 weeks (24 day titration; 7 day fixed; 7 day taper; 4 day washout) | 8 weeks (24 day titration; 7 day fixed; 7 day taper; 4 day washout) | 8 weeks (24 day titration; 7 day fixed; 7 day taper; 4 day washout) |
| 1 | COMBINATION (A + P) | Alpha-lipoic acid (A + Pp) | PREGABALIN (Pa + P) |
| 2 | PREGABALIN (Pa + P) | COMBINATION (A + P) | Alpha-lipoic acid (A + Pp) |
| 3 | Alpha-lipoic acid (A + Pp) | PREGABALIN (Pa + P) | COMBINATION (A + P) |
| 4 | COMBINATION (A + P) | PREGABALIN (Pa + P) | Alpha-lipoic acid (A + Pp) |
| 5 | PREGABALIN (Pa + P) | Alpha-lipoic acid (A + Pp) | COMBINATION (A + P) |
| 6 | Alpha-lipoic acid (A + Pp) | COMBINATION (A + P) | PREGABALIN (Pa + P) |

**Legend:** Symbols in parentheses indicate the content of the corresponding blinded study drug capsules as per the double-dummy design. A=alpha-lipoic acid; Pa= “alpha-lipoic acid” placebo; P=pregabalin; Pp= “pregabalin” placebo
**Figure 2.** Trial design, continued.

LEGEND:

1. Screening

2. Wean off current alpha-lipoic acid, gabapentin and pregabalin for ≥1 week prior to commencing
   - patients taking, and perceiving benefit from opioids (<90/day morphine equivalents), antidepressants, nonsteroidal anti-inflammatory agents or acetaminophen may continue these at a steady dose during the study.
   - patients required to avoid any procedural pain therapies (e.g. neurosurgical interventions, nerve blocks or acupuncture) during the entire study as these treatments may be unevenly distributed across treatment periods and could skew the study's results.

3. BL – 7 day baseline period

4. Double-blind randomization to one of six possible treatment sequences (e.g. sequence 1: combination-alpha-lipoic acid-pregabalin) such that each patient progresses through each of three 6 week treatment periods (i.e. periods “A”, “B” and “C”).

5. Each treatment period starts with a 24 day study drug dose titration towards maximal tolerated dose (MTD). If MTD is reached before the end of this 24 day period, that dose will be continued up to and including days 25-31 of the treatment period and then concluded with a 7 day taper/4 day washout (T-WO).

A study nurse will contact patients by telephone at least twice a week to evaluate adverse effects, guide study drug titration and encourage compliance. Study patients will be encouraged to contact a study physician, as needed, who will be available 24 hours a day by pager in order to deal with study-related problems that may occur between scheduled study nurse telephone calls.

With each dosage increase of study medication in the titration schedule, if mild to moderate treatment-emergent adverse effects are encountered, patients will be asked if they can tolerate continuing at that dose for another 2-3 days. If so, this dosage will be continued with the expectation that tolerance to side effects will occur. If side effects are intolerable or do not improve, both study medications will be decreased to the next lowest possible dose and an increase will be attempted one more time at the next scheduled dose increase. If this again results in intolerable side effects, both study drugs will be decrease back to the previous dose, which will be defined as the maximally tolerated dose (MTD) for that individual.
For each trial period, patients receive blue “A” (ALA 300 or placebo), and grey “P” (PGB 75mg or placebo), capsules. Each step above indicates the number of each capsules taken before breakfast & in the evening. The schedule above indicates uppermost dose ceilings at each timepoint. Titration towards individual maximally tolerated dose (MTD) will be guided by safety determined by weekly AE monitoring. Thus, titration may be slower and MTD may be lower than shown above.

Protecting Against Bias
Medications will be encapsulated (ALA, blue; PGB, gray) in an identical fashion across all periods. As per a double-blind, double-dummy design, patients will take both sets of medications so all treatment conditions will be identical across all 3 treatment periods. Treatment codes will be generated by the investigational pharmacist and concealed until trial completion. In case of emergency, individual codes will be disclosed by an investigational pharmacist to a nonstudy clinician. A questionnaire completed by every participant at the end of each period will ask patients to guess the treatment they received to assess blinding.

Inclusion and Exclusion Criteria
With the input of longstanding specialist and primary care colleagues in the Kingston and Queen’s University catchment area, men and women meeting the diagnostic criteria for peripheral NP will be considered for the trial. Participants must have a score of 3 or higher on the Douleur Neuropathique 4 interview, a validated questionnaire that distinguishes between neuropathic and nonneuropathic pain [32]. As indicated, investigations will be done to confirm NP diagnosis including, but not limited to, nerve conduction studies and electromyography. After preliminary phone screening, candidates will be invited to the clinic for a detailed history, physical, neurological examination, and a review of recent (within the last 3 months) lab studies including complete blood count, glucose, electrolytes, urea, creatinine, aspartate transaminase and alanine transaminase (AST/ALT), glycosylated hemoglobin, and electrocardiogram. Laboratory analysis will be conducted for study candidates with no recent records. Eligible patients will have daily pain (≥3/10) for at least 3 months, AST/ALT ≤120% upper limit of normal, creatinine clearance ≥60 mL per minute, and glycosylated hemoglobin ≤9.5%. Patients will have necessary abilities, visual acuity, and language skills for questionnaire completion and phone communication with nurses. Patients with major organ system disease, cardiovascular autonomic neuropathy, moderate to severe sedation or ataxia due to other required drugs, hypersensitivity to study medications, seizure disorder, or other painful condition >50% as severe as their NP will be excluded. Those who live alone and cannot assure daily communication will be excluded. Those who have a history of angioedema will be excluded. Those who live alone and cannot assure daily
contact with a friend, family member, or caregiver will be excluded. Women of childbearing potential will be required to receive a highly effective form of contraception (total abstinence, hormonal birth control methods, intrauterine devices, confirmed successful vasectomy of partner, double barrier methods, etc) and a negative pregnancy test at baseline. If a study participant becomes pregnant, she must stop using study medications immediately and will be withdrawn from the study. Eligible patients will be enrolled into the study following informed consent.

**Trial Duration and Follow-Up Frequency**

Each of the 3 treatment periods will be 6 weeks, for a total trial duration of 18 weeks. The nurse will phone patients weekly to evaluate AEs, guide drug titration, and encourage compliance. Patients will be seen in the clinic at the end of each treatment period for assessment of vital signs and measurement of secondary outcomes (Figure 4). Patients will be followed up by phone 2 weeks and 3 months after trial completion (including patients who were withdrawn from the trial prematurely) to document any subsequent AEs.

**Outcome Measures and Safety Assessment**

The primary outcome is mean daily pain (0-10 numerical rating scale with 0 = no pain, 10 = worst pain imaginable) averaged over the MTD fixed dose week (days 25-31) of each period (Figure 4). Secondary outcomes include daily pain at other time points, the MTDs of PGB and ALA, frequency and severity of AEs and global relief, the short form McGill Pain Questionnaire [33], the Neuropathic Pain Symptom Inventory [34], the Brief Pain Inventory [35], the Beck Depression Inventory-II [36], Beck Anxiety Inventory [37], the Short Form survey (SF-36) [38], blinding questionnaires, and acetaminophen consumption. Timing of outcome assessments is described in Figure 4. Patient safety will be ensured by vigilant AE assessment and judicious drug titration. Any occurrences of major AEs will be tracked as secondary outcomes and also reported to the Queen’s Ethics Board, Health Canada. Assessment and reporting of AEs will adhere to CONSORT recommendations [39].

**Sample Size**

Based on previous estimates of within-patient variation, variance=2.3, from our previous study in NP [15], we calculate that a sample of 55 trial completers would provide an 80% chance of detecting (alpha=0.05) a mean treatment difference of 1 point (0-10 scale). For a sample size divisible by 6, the number of treatment sequences, we adjusted the sample size to 54 trial completers.

**Statistical Analyses**

Analyses for this trial are based on the null hypothesis of no difference between PGB, ALA, and PGB+ALA and the alternative hypothesis that at least 2 treatments are different. When a patient contributes data from only one period, sensitivity analyses including all patients will also be performed by assuming some reasonable but extreme values for the remaining periods. All patients receiving at least one dose of drug will be included in the safety analyses.
The primary outcome—mean daily pain from the last 7 days (at MTD) of each treatment period—will be calculated as an average of pain scores as recorded in the pain diary if more than 50% of the information (ie, at least 4 days) is not missing. Otherwise, mean daily pain will be treated as missing. This is based on the half rule often used to summarize repeated responses and which has proven unlikely to introduce bias to trial results [40]. Sensitivity analyses based on the average of all available pain scores will also be performed to confirm the results of the primary analysis. Although carryover effects are unlikely, we recognize this possibility. Therefore, a linear mixed model with sequence, period, treatment, and the first order carryover term as fixed effects and patient as a random effect [41] will be used to test for differences among the 3 treatments and to estimate the least square mean of the mean daily pain intensity for each treatment, adjusting for carryover as well as period effects (ie, stability of pain levels). The following 3 pair-wise comparisons will be performed based on the least square means and standard deviations from the linear mixed model: combination versus ALA alone, combination versus PGB alone, and ALA alone versus PGB alone. Sensitivity analyses will be performed using a pattern-mixture model [42] based on patterns of missing data so as to check the robustness of results in the case that data may not be missing at random. A Fisher's least significant difference [43] procedure will be used to adjust the P values for these 3 comparisons.

Secondary outcomes will be analyzed similarly except that (1) only one measurement is analyzed in the last week for the singular measures (ie, final week questionnaires) and (2) the scoring algorithms developed for the Brief Pain Inventory, Beck Depression Inventory-II, and SF-36 will be first used to derive the subscales or domains within these instruments, and the scores on these subscales or domains will be used as response variables in the linear mixed model analysis.

### Results

Participant recruitment is expected to begin September 1, 2017. The proposed trial was awarded external peer-reviewed funding by the Canadian Institutes of Health Research (Canada) on July 15, 2016.

### Discussion

NP remains a challenging condition to treat, with current analgesic drugs providing only partial relief, often at the risk of disabling AEs. To the best of our knowledge, this proposed trial is the first to compare the combination of an anticonvulsant with an antioxidant to treat NP. Because ALA and PGB have different AE profiles, we expect their combination to provide superior analgesic efficacy in NP without increasing AEs. Potential threats to completing this trial include challenges with participant enrollment, noncompliance, protocol violations, and early dropouts. However, we are confident that the proposed trial design and our experience with recent and previous RCTs will minimize these concerns. Also, noncompliance, protocol violations, and early dropouts will be minimized by the crossover design as well as thorough patient teaching and careful follow-up of trial patients.

As discussed above, there is an urgent need for improved NP treatments with better analgesic efficacy and better safety and tolerability. Thus, this trial shall provide rigorous evidence for a potentially improved treatment strategy for NP.
1. Reitsma ML, Tranner JE, Buchanan DM, Vandenkerkhof EG. The prevalence of chronic pain and pain-related interference in the Canadian population from 1994 to 2008. Chronic Dis Inj Can 2011 Sep;31(4):157-164 [FREE Full text] [Medline: 21978639]

2. St Sauver JL, Warner DO, Yawn BP, Jacobson DJ, McGree ME, Pankratz JJ, et al. Why patients visit their doctors: assessing the most prevalent conditions in a defined American population. Mayo Clin Proc 2013 Jan;88(1):56-67 [FREE Full text] [doi: 10.1016/j.mayocp.2012.08.020] [Medline: 23274019]

3. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Press; 2011.

4. VanDenKerkhof EG, Mann EG, Torrance N, Smith BH, Johnson A, Gilron I. An epidemiological study of neuropathic pain symptoms in Canadian adults. Pain Res Manag 2016;2016:9815750 [FREE Full text] [ doi: 10.1155/2016/9815750] [Medline: 27445636]

5. Gilron I, Baron R, Jensen TS. Neuropathic pain: principles of diagnosis and treatment. Mayo Clin Proc 2015 Apr;90(4):532-545. [ doi: 10.1016/j.mayocp.2015.01.018] [Medline: 25841257]

6. Gilron I, Watson C, Cahill C, Moulin D. Neuropathic pain: a practical guide for the clinician. CMAJ 2006 Aug 01;175(3):265-275 [FREE Full text] [Medline: 16880448]

7. Schmader KE, Baron R, Haanpää ML, Mayer J, O’Connor AB, Rice AS, et al. Treatment considerations for elderly and frail patients with neuropathic pain. Mayo Clin Proc 2010 Mar;85(3 Suppl):S26-S32 [FREE Full text] [ doi: 10.4065/mcp.2009.0646] [Medline: 20194145]

8. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015 Feb;14(2):162-173 [FREE Full text] [ doi: 10.1016/S1474-4422(14)70251-0] [Medline: 25575710]

9. Dhallia IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. CMAJ 2009 Dec 08;181(12):891-896 [FREE Full text] [ doi: 10.1503/cmaj.090784] [Medline: 19969578]

10. Lanas A, Perez-Aisa MA, Feu F, Ponce J, Saperas E, Santolaria S, Investigators of the Asociación Española de Gastroenterología (AEG). A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal antiinflammatory drug use. Am J Gastroenterol 2005 Aug;100(8):1685-1693. [ doi: 10.1111/j.1572-0241.2005.41833.x] [Medline: 16086703]

11. Chapman L, Wiffen P, Moore R, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev 2012 Jul 11(7):CD008943. [ doi: 10.1002/14651858.CD008943.pub2] [Medline: 22786518]

12. Gilron I, Jensen T, Dickerson A. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013 Nov;12(11):1084-1095. [ doi: 10.1016/S1474-4422(13)70193-5] [Medline: 24074723]

13. Berger A, Sadowsky A, Dukes E, Edelsberg J, Oster G. Clinical characteristics and patterns of healthcare utilization in patients with painful neuropathic disorders in UK general practice: a retrospective cohort study. BMC Neurol 2012 Mar 06;12:8 [FREE Full text] [ doi: 10.1186/1471-2377-12-8] [Medline: 22949606]

14. Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. Pain 2015 Aug;156(8):1440-1448. [ doi: 10.1097/j.pain.0000000000000149] [Medline: 25749306]

15. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005 Mar 31;352(13):1324-1334. [ doi: 10.1056/NEJMoa042580] [Medline: 15800228]

16. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet Neurol 2009 Oct;10;374(9697):1252-1261. [ doi: 10.1016/S1474-4422(09)70111-3] [Medline: 19796802]

17. Khoromi SM, Cui L, Naickers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 2007;130:66-75. [ doi: 10.1016/j.pain.2006.10.029]

18. Graff-Radford SB, Shaw LR, Naiboff BN. Amitriptyline and clonazepam in the treatment of postherpetic neuralgia. Clin J Pain 2000 Sep;16(3):188-192. [ Medline: 11014390]

19. Ziegler D, Nowak H, Kempler P, Varga P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. Diabet Med 2004 Feb;21(2):114-121. [ Medline: 14984445]

20. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev 2009 Jul 08(3):CD007076 [FREE Full text] [ doi: 10.1002/14651858.CD007076.pub2] [Medline: 19588419]

21. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, et al. Upregulation of dorsal root ganglion (alpha(2)delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci 2003 Mar 15;23(16):1868-1875 [FREE Full text] [ Medline: 11245671]

22. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 2007 Feb;73(2):137-150. [ doi: 10.1016/j.eplepsyres.2006.09.008] [Medline: 17126531]

23. Gilron I, Wajsbrod D, Thirion F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clin J Pain 2011;27(3):185-193. [ doi: 10.1097/AJP.0b013e3181fe13f6] [Medline: 21178603]
24. Gilron I, Chaparro L, Tu D, Holden R, Milev R, Towheed T, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. Pain 2016 Dec;157(7):1532-1540. [doi: 10.1097/j.pain.0000000000000558] [Medline: 26982602]

25. Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. Free Radic Biol Med 1995 Aug;19(2):227-250. [Medline: 7649494]

26. Nagamatsu M, Nickander KK, Schmelzer JD, Raya A, Wittrock DA, Tritschler H, et al. Lipoic acid improves nerve blood flow, reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy. Diabetes Care 1995 Aug;18(8):1160-1167. [Medline: 7587852]

27. Lee WY, Orestes P, Latham J, Naik AK, Nelson MT, Vitko I, et al. Molecular mechanisms of lipoic acid modulation of T-type calcium channels in pain pathway. J Neurosci 2009 Jul 29,29(30):9500-9509 [FREE Full text] [doi: 10.1523/JNEUROSCI.5803-08.2009] [Medline: 19641113]

28. Han T, Bai J, Liu W, Hu Y. A systematic review and meta-analysis of alpha-lipoic acid in the treatment of diabetic peripheral neuropathy. Eur J Endocrinol 2012 Oct;167(4):465-471 [FREE Full text] [doi: 10.1530/EJE-12-0555] [Medline: 22837391]

29. Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, et al. Efficacy and safety of antioxidant treatment with alpha-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes Care 2011 Sep;34(9):2054-2060 [FREE Full text] [doi: 10.2337/dc11-0503] [Medline: 21775555]

30. López-D'alejandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of Burning Mouth Syndrome: a randomized, double-blind, placebo controlled trial. Med Oral Patol Oral Cir Bucal 2011 Aug 01;16(5):e635-e640 [FREE Full text] [Medline: 20711135]

31. Partanen J, Niskanen L, Lehtinen J, Mervaaia E, Siltonen O, Ulusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995;333:93-99. [doi: 10.1056/NEJM199507133330203]

32. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005 Mar;114(1-2):29-36. [doi: 10.1016/j.pain.2004.12.010] [Medline: 15733628]

33. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987 Aug;30(2):191-197. [Medline: 3670870]

34. Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004 Apr;108(3):248-257. [doi: 10.1016/j.pain.2003.12.024] [Medline: 15030944]

35. Cleaveal CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994 Mar;23(2):129-138. [Medline: 8080219]

36. Beck A. BDI-II: Beck Depression Inventory Manual, 2nd Edition. San Antonio: Harcourt Brace and Company; 1996.

37. Steer RA, Kumar G, Ranieri WF, Beck AT. Use of the Beck Anxiety Inventory with adolescent psychiatric outpatients. Psychol Rep 1995 Apr;76(2):459-465. [doi: 10.2466/pr0.1995.76.2.459] [Medline: 7667457]

38. Ware JE. SF-36 Health Survey Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Centre; 1993.

39. Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz KF, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004 Nov 16;141(10):781-788. [Medline: 15545678]

40. Fairclough DL. Analyzing studies with missing data. In: Fayers PM, Hays RD, editors. Assessing Quality of Life in Clinical Trials, 2nd Edition. Oxford: Oxford University Press; 2005:182.

41. Jones B, Kenward MG. Design and Analysis of Cross-Over Trials, 3rd Edition. Boca Raton: CRC Press; 2015.

42. Molenberghs G, Kenward MG. Missing Data in Clinical Studies. Hoboken: John Wiley and Sons; 2007.

43. Hochberg Y, Tamhane A. Multiple Comparison Procedures. New York: Wiley; 1987.

**Abbreviations**

AE: adverse effect  
ALA: alpha-lipoic acid  
AST/ALT: aspartate transaminase and alanine transaminase  
CONSORT: Consolidated Standards for Reporting Trials  
MTD: maximal tolerated dose  
NNT: number-needed-to-treat  
NP: neuropathic pain  
NSAID: nonsteroidal anti-inflammatory drug  
PGB: pregabalin  
RCT: randomized controlled trial  
SF-36: Short Form survey
