Efficacy and Safety of Medications for Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a neuropathic pain disorder common in older adults that is associated with shingles (varicella zoster) and nerve damage secondary to a shingles infection. Few neuropathic pain disorders have been studied more extensively than PHN. Cases of PHN can last for months to years after a single outbreak and are characterized by mild to severe pain, often described as aching, stabbing or burning in nature. Importantly, PHN is a condition that is associated with a vaccine-preventable disease, therefore, pharmacists have the ability to eliminate or reduce the incidence of PHN in vulnerable populations through strong vaccine advocacy. Unfortunately, for those patients who experience shingles and resultant PHN, pharmacists can be prepared to offer advice and guidance with respect to treatment selection, counseling and therapeutic monitoring. This issue of CLIPS briefly summarizes a systematic review of medications used to treat PHN in the context of efficacy, safety and tolerability. If you need further information, please contact the Samford University Drug Information Service at (205)726-2659.


METHODS

- Systematic review of all available data from English-language, placebo-controlled randomized controlled trials studying the efficacy, safety or tolerability of medications (oral or transdermal) used to treat PHN.
- Investigators chose to examine PHN as a subgroup of neuropathic pain disorders as this population is subject to less heterogeneity compared to patients suffering from other neuropathic pain disorders.
- Controlled MEDLINE and EMBASE searches plus bibliographic searches were utilized to extract data for the analysis.
- Studies with duration of less than 4 weeks were excluded, as well as those studies utilizing adjunctive therapies (i.e., other pain medications or holistic approaches), medications that were not oral or transdermal, drugs no longer approved for use in neuropathic pain and clinical trials conducted in non-diseased study populations.
- Of those trials included, a Jadad score was assigned to ensure validity and 4 critical elements of reported results were examined and compared:
  - Reduction of pain intensity from baseline to end of active treatment using a validated rating scale.
  - Withdrawal rates due to lack of therapeutic effect.
  - Risk of adverse events for most common adverse events.
  - Risk of withdrawal from therapy due to adverse events.
- Data from the included studies was extracted by two separate reviewers and compiled in two separate spreadsheets, which were then compared for discrepancies in interpretation. Any conflicting conclusions between the two blinded reviewers were adjudicated by a third independent reviewer to achieve reconciliation.

RESULTS

- A total of 12 studies met inclusion criteria and studied 8 different agents for the treatment of PHN, with three agents (pregabalin, capsaicin, gabapentin) being studied in more than one trial.
- Single reports were available for amitriptyline, nortriptyline, morphine, tramadol and divalproex sodium.
- Mean study duration of all included studies was 7.8 weeks and all studies had a mean sample size of 63 subjects (range: 12-113); all studies except for two were published after 1998 and no study had a Jadad score < 3.
Mean difference reduction (percentage) in pain intensity from baseline to end of study vs. placebo:
- Gabapentin (2 studies): 21.93; 95% CI 14.62 to 29.23
- Pregabalin (3 studies): 22.39; 95% CI 13.84 to 31.23
- Amitriptyline: 42.42; 95% CI 33.14 to 51.70
- Nortriptyline: 17.43; 95% CI 16.54 to 18.33
- Morphine: 29.08; 95% CI 27.59 to 30.58
- Capsaicin (2 studies): 16.72; 95% CI: 10.75 to 23.87
- Tramadol: 13.81; 95% CI 13.81 to 15.05
- Divalproex sodium: 38.75; 95% CI 33.64 to 43.86

All results are statistically significant.

Relative risk (RR) of treatment withdrawal due to lack of efficacy vs. placebo:
- Gabapentin: 0.26; 95% CI 0.04 to 1.56
- Pregabalin: 0.33; 95% CI 0.10 to 1.06
- Amitriptyline: 1.17; 95% CI 0.03 to 54.63
- Nortriptyline: Not reported
- Morphine: Not reported
- Capsaicin: Not reported
- Tramadol: Not reported
- Divalproex sodium: 0.20; 95% CI 0.01 to 4.17

All results not statistically significant and confounded by small sample sizes of studies (e.g., wide confidence interval ranges). Small samples have the ability to affect determination of meaningfulness of risk of withdrawal.

Relative risk (RR) of treatment withdrawal due to adverse events vs. placebo:
- Gabapentin: 1.91; 95% CI 1.02 to 3.56
- Pregabalin: 3.24; 95% CI 1.93 to 5.42
- Amitriptyline: 2.36; 95% CI 0.08 to 63.99
- Nortriptyline: Not reported
- Morphine: Not reported
- Capsaicin: 8.39 95% CI 2.02 to 34.84
- Tramadol: Not reported
- Divalproex sodium: 1.64; 95% CI 0.06 to 46.05

Results for gabapentin, pregabalin and capsaicin are statistically significant.

Adverse events were erratically reported in the 12 studies included in this systematic review. Agents and associated adverse events that were statistically significant compared to placebo included:
- Gabapentin (dizziness): RR 3.76; 95% CI 2.27 to 6.22
- Gabapentin (somnolence): RR 4.09.; 95% CI 2.29 to 7.31
- Pregabalin (dizziness): RR 2.46; 95% CI 1.68 to 3.60
- Pregabalin (somnolence): RR 3.18; 95% CI 1.87 to 5.41
- Pregabalin (xerostomia): RR 2.73; 95% CI 1.12 to 6.63
- Pregabalin (ataxia): RR 11.70; 95% CI 1.55 to 88.54
- Nortriptyline (dizziness): RR 39.17; 95% CI 2.49 to 616.66
- Morphine (nausea): RR 5.47; 95% CI 2.03 to 14.76

Small study sample sizes have the possibility to confound the clinical meaningfulness of these results as well.

DISCUSSION/SUMMARY
- Only amitriptyline, divalproex and morphine were associated with a >25% reduction in pain from baseline. While all results for reduction of pain intensity are statistically significant, application of the results is difficult.
- The interpretation of results and subsequent application to practice is confounded by small patient samples, the small number of studies included in the analysis and the exclusion of studies that utilized combination therapies, as this treatment approach is gaining popularity.
- Treatment decisions for PHN should be guided by efficacy, patient preference, cost and safety (e.g., avoidance of tricyclic agents in the elderly).

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