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. Several organizations have published guidelines regarding treatment of chronic non-cancer pain (CNCP); however, many of these have focused on opioid prescribing. 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. 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. 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.

<table>
<thead>
<tr>
<th>Organization (publication date)</th>
<th>Type of pain</th>
<th>Comments regarding combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN (2011)¹⁸</td>
<td>Painful diabetic neuropathy</td>
<td>-Recommends use of AEDs or antidepressants; does not address combined use</td>
</tr>
<tr>
<td>AAN (2004*)⁹</td>
<td>Postherpetic neuralgia</td>
<td>-Recommends use of AEDs or antidepressants; does not address combined use</td>
</tr>
<tr>
<td>APS/ACP (2009)¹⁰</td>
<td>Low back pain</td>
<td>-Lack of evidence for combination therapy; patients often prescribed multiple medications in clinical practice</td>
</tr>
<tr>
<td>ASA/ASRA (2010)¹¹</td>
<td>Chronic pain (excludes pain due to cancer, DJD, HA, TJS, TN)</td>
<td>-Recommends a multimodal approach; AEDs and TCAs strongly recommended</td>
</tr>
</tbody>
</table>
| 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. 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. In terms of combination treatment, multiple guidelines recommend a multimodal approach such as gabapentin and a TCA for various types of chronic pain. 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. A recent meta-analysis concluded that combination treatment could not be conclusively recommended due to poor quality data and discrepant results from clinical trials. 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:


