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Critical Review

Systematic Review of the Comparative Effectiveness of Antiepileptic Drugs for Fibromyalgia

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Abstract: Fibromyalgia is a difficult-to-treat chronic pain syndrome that affects 2% of the US population. Pregabalin is an antiepileptic recently FDA approved for fibromyalgia treatment. Other antiepileptics have been suggested for treatment. This systematic review examines the relative benefits and harms of antiepileptic drugs in the treatment of fibromyalgia. A literature search was conducted and 8 studies matched criteria (7 studies of pregabalin, 1 of gabapentin). Both drugs reduced mean pain scores more than placebo at a modest rate (pregabalin, 38% to 50%; gabapentin, 51%). In a 6-month trial of pregabalin responders, 32% continued to have response at 6 months, with a mean time to loss of response of 34 days. Compared to placebo, the drugs had similarly high rates of adverse events and withdrawals. Without a head-to-head trial it is not possible to conclude if 1 antiepileptic is more effective or harmful than the other, although limited evidence suggests potential differences. Future studies must directly compare the drugs, include a more broadly defined population, examine long term benefits and harms, and include cointerventions. We conclude that pregabalin and gabapentin are modestly effective for the treatment of fibromyalgia but that their long-term safety and efficacy remain unknown.

***Perspective:** This systematic review evaluates the benefits and harms of using the antiepileptic drugs gabapentin and pregabalin for the treatment of fibromyalgia. Conclusions from this paper can help clinicians to more effectively treat the pain associated with fibromyalgia.*

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***Key words:** Review, antiepileptic, fibromyalgia, gabapentin, pregabalin, anticonvulsant.*

Fibromyalgia is a chronic syndrome characterized by widespread musculoskeletal pain.[11] It is defined by the American College of Rheumatology as a combination of pain for a minimum of 3 months and tenderness in 11 of 18 specific sites on the body.[29] Other symptoms can include fatigue, anxiety, depression, sleep disturbances, bowel dysfunction, and joint swelling.[30] This syndrome is also associated with increased work absenteeism, disability, and decreased quality of life.[17] Fibromyalgia affects 2% of the U.S. population, predominantly women,[6] although its prevalence is likely underestimated and was more recently estimated at 3.3% in Canada.[19] Prevalence is highest in those aged 60 to 79 years, so the overall prevalence in the US will continue to grow as our population ages.[30] Although the exact etiology is unknown, growing evidence suggests that fibromyalgia may be a syndrome of dysfunctional pain processing in the central nervous system. This abnormal pain processing may be associated with multiple pathways, including central pain sensitization and alterations in neurotransmitters.[4,25] Treatment of fibromyalgia is usually multifactorial and concentrated on symptomatic relief. Pharmacological interventions frequently include nonsteroidal anti-inflammatory drugs (NSAIDS), opioids, sedatives, muscle relaxants, and analgesics, but relief is often elusive.[8,13,27] While nonpharmacological interventions are frequently used, recent research has focused on finding more effective pharmacological treatments for the chronic pain associated with this disorder.[16]

Interest in antiepileptic drugs for treatment of fibromyalgia has increased in recent years. Antiepileptic drugs,

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also known as anticonvulsant drugs, are a diverse group of medications initially developed for the treatment of seizures. Some of the drugs in this group have also been used to effectively treat neuropathic pain.[14,18] Neuropathic pain shares some similarities to fibromyalgia in etiology and symptoms experienced. Pregabalin (Lyrica®), a classic antiepileptic drug, was approved by the US Federal Drug Administration for use to treat fibromyalgia in 2007. Pregabalin and gabapentin are structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Both anticonvulsants bind with high affinity to the alpha-2-delta subunit of voltage-gated calcium channels in the CNS. In vitro, pregabalin and gabapentin reduce the calcium-dependent release of several neurotransmitters, including glutamate, norepinephrine, calcitonin gene-related peptide, and substance P. Although the exact mechanism of action of these drugs is not known, it is thought that this action may be involved in their analgesic and anticonvulsant effects.[21] It is not yet clear how pregabalin compares to other antiepileptic drugs or other treatments in terms of overall effectiveness when considering both benefits and harms. Antiepileptics are a diverse group of drugs with wide variation in mechanisms of action, adverse event profiles, and potential efficacy in treating fibromyalgia. It will be important for clinicians to understand the available evidence regarding their use in this difficult-to-treat disease.

This systematic review analyzes the clinical evidence on comparative benefits and harms of antiepileptic drugs used to treat fibromyalgia. We posed the following critical questions: 1) Can antiepileptic drugs effectively treat fibromyalgia and is one drug more effective than the others? 2) What are the adverse effects of antiepileptic use and is one drug more harmful than the others? 3) Are there differences in effectiveness of antiepileptics across subpopulations of patients with the disease, eg, patients with comorbidities?

Methods

Inclusion Criteria

Studies eligible for this review had inclusion criteria of adults (≥18 years) who had been diagnosed with fibromyalgia according to American College of Rheumatology standards.[29] We included studies of any antiepileptic drug compared to placebo or another antiepileptic using a randomized controlled trial or observational design. Outcomes included were the impact on pain (the proportion of patients with response, change in pain score from baseline, functional status, or sleep quality) and adverse events (discontinuation from study due to adverse events, and the type and incidence of adverse events).

Literature Search

To identify relevant studies, we conducted literature searches in Ovid Medline (1996-2009, including in-process and nonindexed citations), the Database of Abstracts of Reviews of Effects, and the Cochrane Registry of Controlled Trials. We used the search terms fibromyalgia/or fibromyalg$ and the following antiepileptic drugs: carbamazepine, valproic acid, ethotoin, gabapentin, lamotrigine, levetiracetam, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, pregabalin, tiagabine hydrochloride, topiramate, divalproex sodium, and zonisamide. We used Medical Subject Headings as search terms when available or key words when appropriate. Searches were limited to human and English language. The timeframe of the searches was limited to 1996-2009. Additionally, manual searches of the reference lists of included studies, reviews, and documents on the FDA Center for Drug Evaluation Research web site were conducted.

Study Selection

Two reviewers independently screened each title and abstract for potential full-text review, applying the aforementioned inclusion criteria. Disagreements were resolved through discussion and consensus. After retrieving the full-text of these studies, each was again independently screened for eligibility by 2 reviewers with disagreements resolved through consensus to arrive at the final set of included studies.

Data Abstraction

Two reviewers abstracted the following data from each included study: study design, eligibility criteria, intervention (drug, dosage, and length of treatment), other permitted concurrent medications and interventions, methods of outcome assessment, study demographics, sample size, loss to follow-up, reported adverse events, withdrawals due to adverse events, and results. We recorded intention-to-treat (ITT) results when available. Abstracted data were checked by a second reviewer.

Quality Assessment

Internal validity of included studies was graded "good", "fair", or "poor" based on the US Preventive Services Task Force (USPSTF) criteria.[15] Elements of internal validity assessment for trials include methods of randomization and allocation concealment, the presence of balanced treatment arms at baseline, ITT analysis, consideration of confounders in analysis, and overall and differential loss to follow-up. For each identified study, 2 reviewers independently rated quality with any disagreements resolved through discussion and consensus. According to the USPSTF methods, good studies meet all criteria; poor studies fail to meet combinations of criteria thought to constitute a fatal flaw, and the remainder are fair quality.

Synthesis

We analyzed results qualitatively and quantitatively. Our primary outcome measure for analyses was response to treatment, defined as a reduction of pain greater than or equal to 30% from baseline to end point using an 11-point pain scale. Secondary measures included duration of response measured in days, overall discontinuation rates, and rates of specific adverse events. We examined discontinuations from study due to any cause and due to adverse events, and we assessed the rates of

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