EDITORIAL

Conclusions of the Available Meta-Analyses Exploring the Efficacy of Levetiracetam

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Levetiracetam (LEV) is an antiepileptic medication with a favourable pharmacokinetic profile, and minimal drug-drug interactions. The study of Lo et al is a new meta-analysis exploring the efficacy and tolerability of levetiracetam as a first line and adjunctive treatment for seizures[1]. This is not the first meta-analysis or systematic review exploring safety or efficacy of levetiracetam. The first systematic reviews were published by French et al and Privitera et al[2,3]. French explored the safety of levetiracetam in 3347 patients exposed to LEV in clinical trials for epilepsy, cognition, and anxiety disorders. This study showed that the main adverse effects of LEV were somnolence, asthenia and dizziness and occurred in the first month of treatment. Overall the systematic review concluded that LEV is well tolerated and safe for patients. Privitera et al reviewed the results of the three initial pivotal multicenter, double blind, placebo-controlled studies of LEV as a treatment for partial onset seizures[3]. Three doses were analyzed; 1000 mg, 2,000 and 3,000 mg/day. The percentage of patients achieving a > or = 50% reduction from baseline in seizure frequency compared with the treatment period was between 20.8% and 37.1% in the dose of 1,000-mg/day, 35.2% for the dose of 2,000-mg/day, and between 39.6% to 39.4% for the dose of 3,000-mg/day. These responder rates were significantly higher than those for placebo. The results from these three pivotal studies demonstrate that levetiracetam, as adjunctive therapy, is a safe and effective treatment for refractory partial-onset seizures in adults.

Leppik et al analyzed information of three randomized, placebo controlled clinical trials where LEV was used as an add-on treatment for patients with partial epilepsy[4]. This meta-analysis focused on the number of days without seizures and showed that LEV increased the number of days without seizures by 5.19 days compared with placebo. In a subsequent analysis Leppik et al demonstrated that LEV reduces the frequency of simple and complex partial seizures[5]. Cramer et al explored the behavioural effects of LEV in patients who participated in short-term, placebo-controlled studies for epilepsy, cognitive disorders and anxiety disorders[6]. Affective symptoms were more frequent in patients with epilepsy than in patients receiving placebo and the most common were depression, nervousness, hostility anxiety and emotional lability. The authors of this meta-analysis concluded that the incidence of behavioural events in LEV-treated patients was lower than rates reported for some other antiepileptic drugs, which is difficult to state because the authors did not compare the rate of behavioural events between LEV and other antiepileptic drugs in the same study. Otoul et al performed a meta-analysis including randomized placebo controlled clinical trials of add-on therapy using levetiracetam, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and zonisamide in patients with refractory epilepsy[7]. The study showed that levetiracetam was more effective in terms of responder rate than gabapentin and lamotrigine and equally well tolerated. Levetiracetam had a significant lower withdrawal rate than topiramate and oxcarbazepine with comparable efficacy. Gidal et al performed a pool analysis to determine the influence of levetiracetam in the serum concentrations of other antiepileptic drugs[8]. The study showed that LEV does not affect the concentration of carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, phenobarbital and primidone. Richy et al published recently a meta-analysis with the objective to compare side effects among LEV extended release and LEV immediate release analyzing studies where LEC was used as adjunctive treatment for partial onset seizures[9]. The analysis indicated that LEV extended release may be associated with a lower incidence of nervous system, psychiatric, and nutritional and metabolic treatment-emergent adverse events. In this study headache was less frequent in patients using LEV immediate release and was the most significant observation.

The meta-analysis of Lo et al included ten randomized controlled trials; eight studies investigated adjunctive levetiracetam for refractory seizures, one study used LEV as monotheraphy and one as a prophylaxis for traumatic brain injury[1]. The study showed that adjunctive LEV was more effective than placebo in achieving at least 50% reduction of seizure frequency. The likelihood of serious adverse events requiring withdrawal from study was not significantly different between levetiracetam and controls. I consider that this meta-analysis complements the findings reported in previous studies and analyzed the information with a different approach, but the main conclusions of this study were anticipated. There is a plethora of studies in the literature, including previous meta-analyses, prospective and retrospective cohorts and randomized clinical trials showing similar results to this meta-analysis. Probably the only aspect that is different from previous meta-analyses is the inclusion of studies where patients with multiple seizure types were enrolled, showing a similar efficacy for simple partial, complex partial, partial seizure with secondary generalization, as well as generalized tonic-clonic seizures. In a similar way as the initial review of Privitera the metanalysis showed adequate efficacy of levetiracetam at different doses[3]. The study excluded prospective and retrospective cohorts that in my opinion could show interesting information and I think is a bias of this study. The inclusion of only randomized clinical trials, mainly funded by the pharmaceutical industry may show a better response of LEV. The meta-analysis did not have enough studies to make conclusions about the efficacy of LEV as a monotheraphy and also as a prophylaxis for traumatic brain injury.

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