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Quality of life, anxiety and depression in adult patients after add-on of levetiracetam and conversion to levetiracetam monotherapy

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Summary The aim of this study was to investigate the change of health related quality of life (HRQoL), anxiety and depression in adult patients in whom an adjunctive treatment with levetiracetam (LEV) was converted to a LEV monotherapy. A prospective, open, investigator initiated multicenter study enrolled 140 patients in whom LEV was added to the existing antiepileptic medication. A total of 65 patients who benefited from the 16-week add-on treatment with LEV (≥50% seizure reduction) were converted to LEV monotherapy (16-week follow-up). In LEV responders, HRQoL, anxiety and depression improved after add-on of LEV. The subsequent conversion to LEV monotherapy did not lead to a significant change in HRQoL, anxiety and depression. However, comparing baseline with LEV monotherapy, the improvements remained significant for most dimensions of HRQoL and for anxiety and depression. Patients' ratings of efficacy of LEV were related with their HRQoL after the conversion to monotherapy. Add-on therapy of LEV improved HRQoL, anxiety and depression in LEV responders. Conversion to a LEV

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monotherapy did not inevitably improve HRQoL in LEV responders, but the positive effect was maintained in the majority of the patients. The effects were highly related to seizure reduction.

Introduction

Antiepileptic monotherapy may have several advantages compared to polytherapy such as better tolerability, improved adherence, less interactions and lower cost (Guberman, 1998). When patients profit from the adjunctive treatment with a second antiepileptic drug (AED) in so far as good seizure control is achieved, it is therefore reasonable to attempt a conversion to a monotherapy. Several clinical trials have tested this method (Gilliam et al., 1998; Ben-Menachem and Falter, 2000).

Although health related quality of life (HRQoL) gains more and more importance as a patient-rated outcome measure, the impact of a conversion to a monotherapy on HRQoL has rarely been investigated. From the few studies dealing with this topic, no final conclusions can be drawn (Cramer et al., 2004; Deckers et al., 2001; Pirio Richardson et al., 2004). For levetiracetam (LEV), the influence of a conversion to a monotherapy on HRQoL has, to our knowledge, not been investigated up to now.

LEV is a newer AED with favorable pharmacological and pharmacokinetic characteristics. Its efficacy and tolerability have been shown in several studies, mainly as adjunctive treatment for partial epilepsies (Cereghino et al., 2000; Morrell et al., 2003) but also as add-on therapy for generalized epilepsies and as monotherapy for partial epilepsies (Brodie et al., 2007; De Smedt et al., 2007; Noachtar et al., 2008).

Adjunctive treatment with LEV has been shown to have a positive influence on HRQoL. In a randomized, placebo-controlled, double-blind study the improvements in HRQoL were larger in the LEV-groups than in the placebo-group with treatment responders ($\geq$50% seizure reduction) reporting the greatest increase (Cramer et al., 2000). The effects were stable in long-term follow-up (Cramer and Van Hammee, 2003). Other studies have confirmed the positive influence of adjunctive LEV on HRQoL (Steinhoff et al., 2007; Lopez-Gongora et al., 2008).

Anxiety and depression are common comorbid disorders in patients with epilepsy (Harden, 2002; Brandt et al., 2010b) and are negatively correlated with HRQoL (Cramer et al., 2005). For this reason it is useful to consider anxiety and depression in the context of HRQoL. The effects of LEV on anxiety and depression have only been investigated in small open-label studies (Mazza et al., 2008; Ciesielski et al., 2006) from which a positive influence of LEV on anxiety and depression can be concluded.

The aim of the present study is to investigate the change of HRQoL, anxiety and depression in patients in whom an adjunctive treatment with LEV was converted to a LEV monotherapy. The data was assessed in a prospective open multicenter study that was performed to determine the efficacy and tolerability of LEV as add-on treatment and as a monotherapy (Brandt et al., 2010a). Our main hypothesis was that HRQoL would improve under LEV add-on in comparison with antiepileptic treatment without LEV and that this effect would at least be maintained during the subsequent conversion to LEV monotherapy.

Methods

Study design and patients

A prospective, open, investigator initiated, multicenter study enrolled 140 adult patients with focal or generalized epilepsy from 12 centers in Germany. Main inclusion criteria were at least two seizures during a baseline period of four weeks and a current treatment with one or two antiepileptic drugs. Main exclusion criteria comprised a current treatment with phenobarbital, primidone or bromide (because of the long half-life of these drugs which would have had an impact on the ability to withdraw them during the study) and a previous treatment with an adequate dose of LEV ($\geq$2000 mg/d). LEV was added for 16 weeks (LEV add-on). The target dose of 2000 mg/d could be adjusted within a range between 1000 mg/d and 4000 mg/d if efficacy was insufficient or intolerable adverse effects occurred. In patients treated with two AEDs, one was withdrawn in parallel (within the first three weeks) while the dose of the other AED was held stable during LEV add-on. Patients with $\geq$50% reduction of seizure frequency during the last four weeks of add-on phase compared to a four-week baseline period preceding the add-on of LEV should be converted to LEV monotherapy (16 weeks, including four weeks conversion period) (Fig. 1). The primary target group were those patients who entered the monotherapy phase ($N = 65$).

The primary endpoints of the current analysis were the change in HRQoL from baseline to LEV add-on and from LEV add-on to LEV monotherapy. Anxiety and depression were analyzed as secondary endpoints.

The primary objective was to examine the effect of add-on of LEV on HRQoL and especially of a subsequent conversion to LEV monotherapy on HRQoL.

Assessment of quality of life, depression and anxiety

The German version of the QOLIE-31 (Cramer et al., 1998) was used to assess epilepsy-specific HRQoL. This self-administered questionnaire consists of 30 items forming seven subscales (Seizure Worry, Overall QoL, Emotional Well-Being, Energy/Fatigue, Cognitive Functioning, Medication Effects, Social Functioning) which are weighted and summed up to obtain a total score, and a single Health Status Item. The raw scores are converted into 0—100 scores with higher values representing higher HRQoL. The German version of the QOLIE-31 has comparably favorable psychometric properties (May et al., 2001) with internal consistency reliability coefficients ranging from $\alpha = 0.76$ (Medication Effects and Social Functioning scales) to $\alpha = 0.90$ (Cognitive Functioning scale).