

# Retrospective Analysis Of Efficacy And Tolerability Of Keppra XR In An Outpatient Setting

B Kirmani, G Jones, E Crisp

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## Abstract

Keppra XR - Extended release (levetiracetam extended-release tablets) recently became available for use as an add-on to other antiepileptic treatments for people with partial onset seizures who were 16 years of age and older as of September 2008. There is limited data about its efficacy and tolerability at the present time. We retrospectively analyzed data from 25 epilepsy patients who received Keppra XR ranging from 500 - 3000 mg per day as standard once a day dosing. The mean age was 33.8 years. 19 (76%) patients have partial and 6 (24%) have generalized epilepsy. In 17 (68%) patients, Keppra XR was used as monotherapy and in 8 (40 %) as adjunctive therapy. A favorable response to Keppra XR was seen in 21 (84%) patients in terms of efficacy. No major side-effects were reported. However, Keppra XR was tapered off in 4 subjects secondary to dizziness, somnolence and lack of efficacy. From our limited retrospective analysis, Keppra XR was also found to be effective as a monotherapy.

## INTRODUCTION

Keppra XR became available in September 2008 as an adjunctive antiepileptic treatment for people with partial onset seizures (16 years of age and older). Presently, there are limited data about its efficacy and tolerability. Bioavailability of Keppra XR tablets is similar to that of the Keppra Immediate Release tablets. The pharmacokinetics were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg extended-release levetiracetam [1,2]. Plasma half-life of extended-release levetiracetam is approximately 7 hours. Plasma half-life of levetiracetam across studies is approximately 6-8 hours. The half-life is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment. Extended-release levetiracetam peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with extended-release levetiracetam compared with immediate-release tablets. The effectiveness of KEPPRA XR as adjunctive therapy (added to other antiepileptic drugs) was established in one multicenter, randomized, double-blind, placebo-controlled clinical study across 7 countries in patients who had refractory partial onset seizures with or without secondary generalization. The estimated percent reduction over placebo in weekly partial onset seizure frequency over the treatment period was 14.4%

(statistically significant) [3]. The relationship between the effectiveness of the same daily dose of KEPPRA XR and immediate-release levetiracetam has not been studied and is unknown. In our study we report our clinic experience in terms of efficacy and tolerability of Keppra XR.

## METHODS

Subject data were acquired from the electronic medical records of all intractable epilepsy patients seen in the Neurology Clinic at Scott and White/ Texas A&M Health Science Center College of Medicine from September 2008 to December 2009. Demographic data and subjects' medical histories (seizure types and frequency experienced, underlying diagnoses, number of antiepileptic drugs before initiation of Keppra XR, MRI Brain and EEG results) were recorded. Subjects were monitored for efficacy and adverse events by regular follow-up with a neurologist. The study was approved by the hospital's Institutional Review Board.

## RESULTS

Retrospective Analysis of Demographics and Background Data

A total of 25 subjects were analyzed in this retrospective analysis, 17 (68%) were female.

The mean age was  $33.8 \pm 18$  years (16-74 years). Most

subjects, 19 of 25 (76%), experienced complex partial seizures with and without secondary generalization; 6 subjects (24%) experienced generalized tonic-clonic seizures. There were 17 white patients, 5 black patients and 3 patients were Hispanic. Most subjects (96%) were being treated with anticonvulsants before the initiation of Keppra XR. The most common anticonvulsant used was levetiracetam (Immediate release). Other anticonvulsants used included dilantin, depakote, clonazepam, neurontin, topamax, phenobarbital, lamictal, tegretol and carbatrol. Keppra XR was used as monotherapy in 17 (68%) and as an adjunctive therapy in 8 patients (32%) as standard once-a-day dosing. The most common dose of Keppra XR in our subjects was 1000 mg/day seen in 12 subjects. Five subjects were on 2000 mg/day, 4 on 1500 mg/day, 3 on 500 mg/day and 1 on 3000mg/day.

The most common underlying disease diagnosis was idiopathic epilepsy, seen in 21 patients (84%). However, 2 patients had brain tumor and one each has arteriovenous malformation and tuberous sclerosis. Eighteen patients were switched from levetiracetam (Immediate release) to Keppra XR: 11 because of compliance issues, 3 because of breakthrough seizures and 4 for intolerable side-effects on generic Levetiracetam. A 1:1 switch was made in 6 subjects. In 3 patients, the dose of Keppra XR was increased as compared to Keppra IR. In 2 patients, dose was increased by 10% and 20%, respectively, to achieve better control. For the third subject, the dose was increased by 30%, and the second anticonvulsant was tapered. This subject became well controlled on Keppra XR monotherapy. In 9 subjects, seizure control was achieved with a decrease of Keppra XR as compared to levetiracetam (Immediate release). The dose was decreased 50% in 4 subjects, 30 and 20% in 2 subjects each, and by 10% in one subject. This was attributed to good compliance because of once a day dosing. The patients noticed decreased somnolence on Keppra XR as compared to levetiracetam (Immediate release). Three patients were switched from dilantin because of lack of efficacy and gingival hyperplasia and one was switched from topamax because of lack of efficacy.

### **OUTCOME FOLLOWING TREATMENT**

The 6-month follow-up showed that 8 patients with seizure frequency of 1-3 months became well (controlled after initiation of Keppra XR with occasional breakthrough seizures in 2 subjects secondary to compliance). In 6 patients with seizure frequency of

8-10 seizures / month the seizure frequency decreased by 40%. Four cases of new onset seizures did not report any further seizure activity. Three patients with seizure frequency of 1-2 per year did not experience any breakthrough seizures. One patient reported improvement in myoclonic jerks. Three patients who experienced breakthrough seizures on switching to generic levetiracetam did not experience more seizures after initiation of Keppra XR. Seizure frequency remained the same in the long term follow-up. Similarly, 2 patients who developed intolerable side-effects on generic levetiracetam seemed to tolerate Keppra XR well without any problems.

Overall, 21 (84%) subjects had a positive response with Keppra XR, both in terms of tolerability and efficacy. The adverse events are reported in 4 subjects. Dizziness and mood problems were reported in 3 subjects and 1 subject experienced increased frequency of seizures. Side-effects were experienced soon after the initiation of the drug. The drug was tapered off within two weeks. Keppra XR was tapered in all 4 subjects. The duration of follow up ranged between 6 months to 3 years. Fourteen patients (56%) remained on Keppra XR monotherapy and 7 (28%) on adjunctive therapy on follow-up. No major side-effects were reported in long term follow-up.

### **DISCUSSION**

Our study showed that Keppra XR was found to be effective both as adjunctive and monotherapy. Overall, 21 subjects had a favorable response to Keppra XR in terms of efficacy and tolerability. We also saw that 8 patients achieved good seizure control on a lower doses of keppra XR as compared to Keppra IR. The most common dose used in our patient population was 1000 mg/day. This also has been shown in a phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of extended-release levetiracetam tablets (2x500 mg) once-daily as adjunctive therapy in 158 refractory epilepsy patients (12 to 70 years of age) with partial onset seizures. In the extended-release levetiracetam group 10.1% of patients had 100% reduction in partial onset seizures and 8.9% were free from any type of seizure over the treatment period, compared to 2.5% and 1.3% in the placebo group, respectively. The study also found that extended-release levetiracetam tablets were generally well tolerated. The most common reported adverse events that occurred more frequently in the extended-release levetiracetam group were somnolence, influenza, nausea, nasopharyngitis, irritability, and dizziness [3]. Similar central nervous system side-effects

including dizziness and somnolence were reported in our patient population. Side-effects experienced in our patient population were immediate. No side-effects were reported in a long term follow-up. Compliance was the major contributing factor because of once a day dosing which led to decreased frequency of seizures and fewer central nervous system side-effects. In a long term follow-up, 14 patients (56%) remained well – controlled on Keppra XR monotherapy which showed that it can be used as monotherapy. However, larger prospective trials are needed to establish the efficacy and tolerability of Keppra XR as monotherapy.

### **References**

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**Author Information**

**Batool F. Kirmani, M.D.**

Department of Neurology, Epilepsy Center, Scott & White Neuroscience Institute and Texas A&M Health Science Center  
College of Medicine

**Gary Jones, D.O.**

Department of Pediatrics, Scott & White Hospital and Texas A&M Health Science Center College of Medicine

**Edwin Darrell Crisp, M.D**

Department of Neurology, Epilepsy Center, Scott & White Neuroscience Institute and Texas A&M Health Science Center  
College of Medicine