Extended-release Antiepilepsy Drugs—Review of the Effects of Once-daily Dosing on Tolerability, Effectiveness, Adherence, Quality of Life, and Patient Preference

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Abstract

Long-term adherence to antiepilepsy drug (AED) regimens is frequently suboptimal. Poor adherence to therapy is associated with a number of negative consequences, including an increase in patient seizures and mortality. Nonadherence is related to a variety of factors, such as treatment-related adverse events, convenience of treatment, efficacy, and quality of life. There is therefore a need for treatment strategies in epilepsy that improve long-term adherence. One such strategy is the use of extended-release (ER) AED formulations. Advantages of ER AEDs over other AED formulations include the potential for once-daily dosing, a more stable mean drug concentration over time, improved tolerability profiles, maximal use of the therapeutic window, and the possibility to achieve better seizure control. Improvements in overall treatment effectiveness may therefore increase patient adherence. This review presents evidence related to patient adherence and preference patterns for ER AEDs and highlights the beneficial properties of ER AEDs.

Keywords

Epilepsy, antiepilepsy drugs, medication nonadherence, quality of life

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Epilepsy is a chronic neurologic disorder characterized by recurrent episodes that may vastly affect health, daily functioning, and quality of life (QoL). Although many antiepilepsy drugs (AEDs) are available (see *Table 1*),[1–14] a substantial proportion of patients with epilepsy experience seizures that are inadequately controlled because of the ineffectiveness of or nonadherence to their current regimen.

Nonadherence is a significant problem in patients with epilepsy.[15–17] A retrospective analysis of claims data from a large US adult managed care population noted an overall nonadherence rate of 39 % in patients with epilepsy following AED initiation (based on a medication possession ratio of <0.8).[16] According to a patient survey by Cramer et al., 71 % of patients reported missing at least one dose of medication, with a mean of two missed doses per month.[17]

Poor adherence is associated with negative patient outcomes.[15–18] In a patient survey by Cramer et al., 45 % of respondents who had missed a dose of AED at least once monthly reported that they experienced a seizure thereafter.[17] Based on healthcare insurance claims, individuals with epilepsy who are nonadherent to treatment are significantly more likely to experience seizures,[15] have increased morbidity,[18] require emergency department care and hospitalization,[16] and incur higher inpatient costs compared with adherent patients.[16] Analysis of a large insurance claims database revealed nonadherent adult patients with epilepsy were 21 % more likely to experience a seizure than were adherent patients (hazard ratio [HR] = 1.205, 95 % confidence interval [CI] 1.092–1.330; p=0.0002).[15] In an open cohort analysis of Medicaid claims from adults with epilepsy, mortality was approximately three times greater among patients nonadherent to their prescribed AED regimen compared with adherent patients (HR=3.32, 95 % CI 3.11–3.54).[18] Nonadherence to AEDs was also linked to a 50 % higher incidence of emergency room visits (incident rate ratio [IRR] = 1.50, 95 % CI 1.49–1.52) and an 86 % higher frequency of hospitalizations (IRR=1.86, 95 % CI 1.84–1.88).[18]

Table 1: Summary of Extended-release Antiepilepsy Drugs Approved by the US Food and Drug Administration or European Countries

Generic Name	Trade Name	Epilepsy Indications†	Dosage Strengths (Maximum Recommended Dose)	Dosage Form and Frequency	Technology[13]	Pharmacokinetics (Half-life)	Most Common Adverse Events†
Carbamazepine*	Carbatrol®[1]	Partial seizures with complex symptomatology; generalized tonic–clonic seizures; mixed seizure patterns	100, 200, 300 mg (1,000 mg/day patients 12–15 years; 1,200 mg/day patients >15 years; 1,600 mg/day adults)	Capsule, BID	Fixed ratio of three bead types: 25 % IR, 35 % enteric coated, 40 % Microtrol®[14]	Variable	Dizziness, drowsiness, unsteadiness, nausea, vomiting
Carbamazepine*	Tegretol® XR[2]	Partial seizures with complex symptomatology; generalized tonic–clonic seizures; mixed seizure patterns	100, 200, 400 mg (1,000 mg/day patients 6–15 years; 1,200 mg/day patients >15 years; 1,600 mg/day adults, in rare circumstances)	Tablet, BID	Osmotic release delivery system	Variable	Dizziness, drowsiness, unsteadiness, nausea, vomiting
Divalproex*	Depakote ER[3]	Monotherapy or adjunctive treatment of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizures including absence seizures	250 and 500 mg (60 mg/kg/day)	Tablet, QD	Hydrophobic matrix	9–16 hours	Headache, asthenia, nausea, vomiting, abdominal pain, drowsiness, dizziness, tremor
Lamotrigine*	Lamictal® XR™[4]	Adjunctive therapy for primary generalized tonic–clonic seizures and partial onset seizures, conversion to monotherapy in patients ≥13 years with partial seizures being treated with single AED	25, 50, 100, 200, 250, 300 mg (250–300 mg/day to 400–600 mg/day day dependent on additional medications taken)	Tablet, QD	DiffCORE™ modified-release eroding matrix, clear enteric coat with a drilled aperture through both faces of the tablet	25–70 hours depending if taken with AED	Dizziness, drowsiness, headache, rash nausea, nystagmus
Levetiracetam*	Keppra XR®[5]	Adjunctive therapy for partial onset seizures	500, 750 mg (3,000 mg/day)	Tablet, QD	Film-coated tablets	6–8 hours	Drowsiness, irritability
Oxcarbazepine	Oxtellar XR®[6]	Adjunctive therapy in treatment of partial seizures in patients ≥6 years	150, 300, 600 mg (900–1,800 mg/day [dependent on weight] patients 6–17 years; 1,200–2,400 mg/day adults)	Tablet, QD	Solutrol®[14]	7–12 hours	Dizziness, drowsiness, headache, balance disorder, tremor, vomiting, diplopia, asthenia
Phenytoin*	Dilantin® Kapseals®[7]	Generalized tonic–clonic and complex partial seizures and seizures occurring during neurosurgery	30 mg	Capsule, QD, TID, or QID	Various	7–42 hours	CNS most common including nystagmus, ataxia, slurred speech, decreased coordination, mental confusion
Phenytoin*	Phenytek®[8]	Generalized tonic–clonic and complex partial seizures and seizures occurring during neurosurgery	200, 300 mg	Capsule, QD, TID, or QID	Various	7–42 hours	CNS most common including nystagmus, ataxia, slurred speech, decreased coordination, mental confusion
Topiramate	Trokendi XR™[9]	Monotherapy in partial onset seizures or primary generalized tonic–clonic seizures in patients ≥10 years or adjunctively in patients ≥6 years; adjunctive therapy in Lennox-Gastaut Syndrome in patients ≥6 years	25, 50, 100, 200 mg	Capsule, QD	Microtrol®[14]	Approximately 31 hours	Paresthesia, drowsiness, anorexia, weight decrease, dizziness, difficulty with memory
Topiramate	Qudexy™ XR[10]	Monotherapy in partial onset seizures or primary tonic–clonic seizures in patients ≥10 years or adjunctively in patients ≥2 years; adjunctive therapy in Lennox-Gastaut Syndrome in patients ≥2 years	25, 50, 100, 150, 200 mg	Capsule, QD	Unknown	Approximately 56 hours	Paresthesia, anorexia, weight decrease, dizziness, drowsiness, difficulty with memory

Table 1: Summary of Extended-release Antiepilepsy Drugs Approved by the US Food and Drug Administration or European Countries (continued)

Generic Name	Trade Name	Epilepsy Indications†	Dosage Strengths (Maximum Recommended Dose)	Dosage Form and Frequency	Technology[13]	Pharmacokinetics (Half-life)	Most Common Adverse Events†
Valproate/ sodium valproate*	Epilim® Chrono,[11] Depakine® Chrono[12]	Epilepsy seizures	200, 300, 500 mg	Tablet, BID	Enteric coated	8–20 hours	Nausea, tremor

**Generics available. †See each product package insert for full indications and complete adverse event information.*

AED = antiepilepsy drug; BID = twice daily; CNS = central nervous system; ER, XR = extended-release; IR = immediate release; QD = once daily; QID = four times a day; TID = three times a day.

Despite the harmful consequences of missing doses, full adherence to epilepsy pharmacotherapy remains an elusive treatment goal and an unmet medical need. Patient- and drug-related factors that may contribute to nonadherence include younger age, adverse events (AEs), inconvenience, and social stigma.[19–23] In a study by Buck et al., 6 % of patients ≥60 years of age (n=180) missed a dose at least once a month, while 16 % of teenagers (n=25) did.[19] In the same study, AEs were noted as a factor in nonadherence in 16 % of patients (n=326).[19] Among persistent AEs that have been reported by patients taking AEDs that could potentially contribute to nonadherence were dizziness, somnolence, nausea, weight gain, irritability, diplopia, and cognitive impairment.[24] These AEs can be associated with peak AED blood levels for some AEDs.[25] Another aspect related to nonadherence is the complexity or inconvenience of the drug regimen. In general, more frequent doses are associated with lower adherence[19,21] as it increases the need to have sufficient medication on-hand at work, school, or when performing daily activities. Furthermore, when taking AEDs in public settings, some patients may be embarrassed and experience a feeling of stigmatization.[22,23] Patients subsequently may avoid taking AEDs in public, make excuses for using AEDs, or stop taking medication to avoid this perceived social stigma.[22]

One approach that has aided in improving adherence has been the reformulation of several immediate-release (IR) and delayed-release (DR) AEDs that are dosed as twice daily or more frequently to extended-release (ER) preparations that are dosed as once daily.[13,26] ER formulations (also denoted as XR) have the advantages of minimizing peak to trough variations seen with IR formulations, thereby reducing AEs associated with peak concentrations while allowing for more consistent plasma levels and reducing the number of daily doses. Furthermore, ER or XR formulations maximize the use of the therapeutic window by allowing necessary modest increases in the total daily dose for better efficacy while keeping maximum concentration (C_{max}) below the upper limit of the therapeutic range, thus avoiding peak-related AEs. These improvements in the pharmacokinetic properties of an individual particular AED by reformulation to an ER (or XR) preparation can vary and are dependent on the characteristics of the original molecule, such as bioavailability, solubility, and permeability properties, and the particular ER technology used. In the preparation of ER formulations, crystalline matrix, modified-release eroding matrix, film-coated tablet, osmotic release delivery system, and enteric coating technologies have been used. ER AEDs are dosed less frequently than IR formulations, either once or twice daily (see *Table 1*).[1–14]

This review will compare patient adherence patterns for ER AEDs with those observed with their IR counterparts (or equivalents), as well as assess patient preferences for these formulations. Furthermore, factors associated with patient adherence, such as AEs, tolerability, effectiveness, efficacy, and QoL will be discussed for the ER and other formulations of AEDs.

Adherence Patterns and Patient Preference for Extended-release Antiepilepsy Drugs Compared with Immediate-release Antiepilepsy Drugs

Various studies have shown increased adherence when patients were switched from an IR AED to an ER AED formulation (see *Table 2*).[21,27–34] In one prospective, observational study involving 2,031 patients, adherence improved from 40 % to 71 % ($p<0.001$) upon switching from an IR to an ER AED formulation of valproate.[21] Improved adherence was also seen in patients (n=358) switching from carbamazepine IR to carbamazepine ER (Carbatrol®, Shire, Wayne, PA) with 59 % of patients on the ER formulation stating that they 'strongly agreed' they rarely skipped or missed a dose of their medication compared with 39 % on the IR formulation.[27] Furthermore, in a recent pharmacokinetic switch study of adult patients with epilepsy (n=61) who were surveyed after switching from IR twice-daily topiramate (Topamax®, Janssen Pharmaceuticals, Inc., Titusville, NJ) to a once-daily XR formulation (SPN-538; Supernus Pharmaceuticals, Inc., Rockville, MD), 92 % expressed preference for the once-daily dosing and believed it facilitated treatment adherence after switching to the XR formulation.[29]

Similar concordance of patient preference with improved adherence with ER formulations of two other AEDs was also reported. In a study of 41 adult patients with epilepsy who switched from divalproex DR to divalproex ER, 71 % of patients preferred the ER formulation.[33] In a small pharmacokinetic study of lamotrigine ER involving 44 patients, 69 % of patients preferred the once-daily regimen while 17 % reported no preference.[34]

Properties of Extended-release Antiepilepsy Drugs Associated With Adherence

Reduced Adverse Events and Increased Tolerability

A tolerability advantage of long-acting AED formulations has been observed in various published reports for a number of different AEDs (see *Table 3*).[21,30,32–47] Several investigators have proposed that improved tolerability is likely due to lower C_{max} values and reduced peak-to-trough differences in plasma drug concentration over the post-dose period, resulting in less fluctuation of drug plasma levels.[13,36,40]

In a double-blind, crossover study of IR versus ER carbamazepine conducted in 48 patients, significantly fewer patients experienced AEs with carbamazepine ER treatment compared with carbamazepine IR (6

Table 2: Summary of Studies Examining Extended-release Medication Adherence, Quality of Life, and Patient Preference

Author/Year/Citation	Study Design	Treatment Arms	Patients (n)	Outcomes
Adherence				
Boggs et al. 2007[28]	Randomized, IR versus ER compliance comparison trial	Divalproex ER Valproate IR	20	Better compliance observed with Divalproex ER
Doughty et al. 2003[21]	Prospective, 3-month, open-label IR-ER switch	Valproate ER Valproate IR	2,031	Never missed dose: Valproate ER: 71 % Valproate IR: 40 % (p<0.001)
Moore et al. 2005[27]	Prospective, open-label, 3-month, IR-ER switch	Carbamazepine ER Carbamazepine IR	358	Compliance ('strongly agree that they rarely/never missed dose'): Carbamazepine ER: 59 % Carbamazepine IR: 39 %
Stocks et al. 2011[29]	Open-label, 4-week, IR-ER switch	Topiramate ER Topiramate IR	61	Improved adherence reported by 92 % of patients switched to Topiramate XR
QoL				
Ficker et al. 2005[30]	Prospective, 3-month, open-label, IR versus ER switch	Carbamazepine ER Carbamazepine IR	453	QOLIE 31 score: Carbamazepine IR: 62.8 Carbamazepine ER: 68.3 (p<0.001)
Steinhoff et al. 2009[31]	Questionnaire following IR to ER switch	Oxcarbazepine ER Oxcarbazepine IR	27	Significant improvement in QOLIE-10 score in 23 of 27 patients (p<0.001)
Yu et al. 2011[32]	Prospective, multicenter, 6-month, open-label	Valproate ER	958	Improved seizure worry, social functioning, overall QoL (all p<0.01) based on QOLIE-31
Patient Preference				
Doughty et al. 2003[21]	Prospective, open-label, 3-month IR-ER switch	Valproate ER Valproate IR	2,031	Satisfaction: Valproate ER: 91 % Valproate IR: 40 %
Pierre-Louis et al. 2009[33]	Prospective, open-label, 6-month IR-ER switch	Divalproex ER Divalproex DR	41	Patient preference: Divalproex ER: 71 % Divalproex DR: 14 %. No preference: 14 %
Stocks et al. 2011[29]	Open-label, 4-week IR-ER switch	Topiramate ER: (SPN-53) Topiramate IR	61	Prefer Topiramate XR: 93 %
Tompson et al. 2008[34]	Prospective, open-label, 2-period crossover IR-ER switch	Lamotrigine XR Lamotrigine IR	44	Patient preference: Lamotrigine ER: 69 % No preference: 17 %

DR = delayed-release; ER, XR = extended-release; IR = immediate-release; QoL = quality of life; QOLIE = Quality of Life in Epilepsy.

versus 26; p<0.001).[40] Additionally, a global evaluation of tolerability was significantly better with carbamazepine ER, with 31 patients giving a 'very good' ranking compared with 6 for the IR formulation (p<0.001).

In one of the largest open-label IR to ER switch studies reported, Ficker et al. compared AEs following a switch from carbamazepine IR to carbamazepine ER among 453 patients older than 12 years with partial epilepsy.[30] In adults, investigators reported significant reductions from baseline in AE profile total scores, as well as in central nervous system (CNS) side-effect scores measured by the AE profile (p<0.0001 for both). In adolescents, they also reported significant reductions at study conclusion in both the Hague Side Effect total score and sedation and confusion subscales compared with baseline (p<0.01 for each).

Similarly, in a 2-year retrospective chart review of patients (n=61) switched from carbamazepine IR to carbamazepine ER, Miller et al. reported a significant decrease in CNS AEs.[36] When receiving carbamazepine IR, 49 % of patients experienced sedation, diplopia, ataxia, confusion, or dizziness, while only 20 % of patients while receiving carbamazepine ER experienced such AEs (p=0.001). Of the patients who experienced CNS AEs with carbamazepine IR, 80 % reported complete resolution after switching to carbamazepine ER.

Treatment-emergent AEs (TEAEs) were compared for levetiracetam ER and levetiracetam IR in an analysis of pooled individual patient data derived from three similarly designed, randomized, double-blind, placebo-controlled clinical trials (n=555).[38] A significantly lower risk for TEAEs was observed for levetiracetam ER versus levetiracetam IR for CNS disorders (risk difference [RD] = –18 %; p=0.03), but not for psychiatric disorders (RD = –11 %; p=0.08), or metabolism and nutrition disorders (RD = –3 %; p=0.08).

ER formulations were also shown to decrease AEs associated with valproate in an open-label trial in which 41 patients taking multiple daily doses of valproate DR were switched to a once- or twice-daily regimen of valproate.[37] During 3 months of follow-up after switching to valproate ER, complaints of tremor, weight gain, and nausea/vomiting were decreased while other AEs, such as hair loss, remained unchanged. In an earlier study involving 2,031 patients, Doughty et al. reported a significant reduction in the mean side-effect score 3 months after patients switched from valproate IR to valproate ER (32.8 versus 28.5; p<0.001).[21] Smith et al. conducted a meta-analysis of pooled individual patient data from nine short-term, open-label studies of divalproex ER versus divalproex DR, which included 213 patients with epilepsy and 108 patients with psychiatric disorders.[35] Among patients with either epilepsy or a psychiatric disorder, fewer patients reported TEAEs with divalproex ER. Compared with divalproex IR, divalproex ER had a lower incidence of tremor, weight gain, and gastrointestinal complaints (p<0.001 for each comparison).

In a phase III study evaluating the safety and efficacy of oxcarbazepine XR in 366 patients with epilepsy, 30 % discontinued treatment at the highest dose

Table 3: Summary of Studies Examining Extended-release Antiepilepsy Drug Adverse Events, Tolerability, and Efficacy

Author, Year	Study Design	Treatment Arms	Patients (n)	Adverse Events/Tolerability	Efficacy
Canger et al. 1990[40]	Randomized, double-blind, 2-period crossover	Carbamazepine CR Carbamazepine IR	48	Absolute frequency of intermittent side effects: Carbamazepine CR: 6 Carbamazepine IR: 26 (p<0.001)	Monthly seizure frequency: Carbamazepine CR: 6.3±9.8 Carbamazepine IR: 9.3±15.6 (p=0.013)
Ficker et al. 2005[30]	Prospective, 3-month, open-label, IR versus ER switch	Carbamazepine ER Carbamazepine IR	453	AE profile improvement in nervous system AE (p<0.0001); AE profile total score decrease from 37.2 to 31.7 (p<0.0001); Hague side-effect score in adolescents improvement from 26.7 to 22.6 (p<0.01)	NR
Miller et al. 2004[36]	2-year retrospective chart review, IR-ER switch	Carbamazepine ER ≥1 year Carbamazepine IR ≥1 year	61	CNS effects (% of patients): Carbamazepine ER: 20 % Carbamazepine IR: 49 % (p=0.001)	Seizures/month: Carbamazepine ER: 3.0. Carbamazepine IR: 3.4 (p=0.29). Patients with 50 % decrease from baseline: 46 %. Seizure-free: 27 %
Pierre-Louis et al. 2009[33]	Prospective, open-label, 6-month IR-ER switch	Divalproex ER Divalproex IR	41	TEAE frequency similar (weight, nystagmus, gastrointestinal discomforts, fatigue, alopecia); in patients with baseline tremor, switch to ER improved tremor based on questionnaire but not Archimedes spiral drawing test	Median seizures/month: Divalproex ER: 0.7. Divalproex IR: 0.85 (p=0.14) Seizure-free: Divalproex ER: 42 % Divalproex IR: 32 % (p=0.06)
Reed et al. 2006[47]	Randomized, open-label, 3-period crossover, 14-day trial	Divalproex ER Divalproex IR	24	No conclusions were made due to low number of patients	Seizure frequency similar across all three regimens
Smith et al. 2004[35]	Meta-analysis, open-label, DR-ER switch	Divalproex ER Divalproex DR	322, n=213 patients with epilepsy; n=109 patients with psychiatric disorders	Divalproex ER/Divalproex DR Tremors: 30 %/39 % Weight gain: 15 %/28 % Gastrointestinal factors: 3 %/11 % (all p<0.001)	Seizure frequency: Divalproex ER: 19 % Divalproex DR: 32 % (p=0.02)
Thibault et al. 2002[39]	Randomized, open-label, 2-period crossover, 12-week trial	Divalproex ER Divalproex DR	43	TEAEs similar between formulations	Seizure control rate: Divalproex ER: 93 % Divalproex IR: 95 % (p=0.5637)
Biton et al. 2010[44]	Randomized, double-blind, placebo-controlled, parallel-group, 19-week trial	Lamotrigine XR Placebo	143	TEAEs ≥5 % Lamotrigine XR: headache, vomiting, nausea, pyrexia	Decreased primary generalized tonic-clonic seizure frequency/week: 75 % (p<0.0001 versus placebo). Seizure-free patients (maintenance): 46 % (p<0.0001 versus placebo)
Biton et al. 2013[41]	Pooled analysis of three randomized, double-blind clinical trials	Lamotrigine XR Lamotrigine IR	662	AEs with Lamotrigine XR similar to that reported for Lamotrigine IR with the most common TEAEs being dizziness (10 %) and headache (6 %)	NR
French et al. 2012[45]	Randomized, double-blind study with pseudo-placebo historical control, 22–23-week trial	Lamotrigine XR Historical pseudo-placebo	226	Headache and dizziness most common AE associated with Lamotrigine XR	Lamotrigine XR was deemed efficacious based on nonoverlap of 95 % confidence limit with historical control for escape criteria for seizure worsening
Naritoku et al. 2007[43]	Randomized, double-blind, placebo-controlled, parallel-group, 19-week trial	Lamotrigine XR Placebo	239	TEAEs ≥5 % Lamotrigine XR: headache, dizziness, diarrhea, drowsiness nausea, asthenia, tremor	Decreased partial seizure frequency/week: 46 % (p=0.0004 versus placebo) Seizure-free patients (maintenance): 19 % (p=0.0016 versus placebo)
Tompson et al. 2008[34]	Prospective, open-label, 2-period crossover IR-ER switch	Lamotrigine XR Lamotrigine IR	44	Headache most frequent TEAE: Lamotrigine XR: 16 %. Lamotrigine IR: 7 %	Number of seizures/week: Lamotrigine XR: 1.4. Lamotrigine IR: 1.5
Chung et al. 2012[46]	Randomized, double-blind study with historical control,10-week trial	Levetiracetam XR Historical control	228	Most common TEAEs: drowsiness (22 %), headache (20 %), convulsion (15 %)	Levetiracetam XR cumulative exit rate criteria of seizure frequency was significantly lower than historical control
Richy et al. 2009[38]	Meta-analysis of pooled individual patient data from three randomized double-blind, placebo-controlled trials; including placebo arms	Levetiracetam XR Levetiracetam IR	555	Risk difference for Levetiracetam XR versus Levetiracetam IR. CNS disorders: (risk difference –18 %) (p=0.03). Psychiatric disorders: –11 % (p=0.08). Metabolism and nutrition disorders: –3 % (p=0.08)	NR

Table 3: Summary of Studies Examining Extended-release Antiepilepsy Drug Adverse Events, Tolerability, and Efficacy (continued)

Author, Year	Study Design	Treatment Arms	Patients (n)	Adverse Events/Tolerability	Efficacy
French et al. 2013[42]	Randomized, double-blind, placebo-controlled, parallel-group, 16-week trial	Oxcarbazepine XR Placebo	366	Most common AEs: headache, dizziness, drowsiness nausea, vomiting, diplopia	Median percent seizure frequency change: Oxcarbazepine XR (1,200 mg): –38 % (p=0.08 versus placebo). Oxcarbazepine XR (2,400 mg): –43 % (p=0.003 versus placebo). Placebo: –29 %
Doughty et al. 2003[21]	Prospective, open-label, 3-month IR-ER switch	Valproate ER Valproate IR	2,031	Mean side-effect score: Valproate ER: 28.5. Valproate IR: 32.8 (p<0.001). Most significant changes in side-effect profile in tiredness, nervousness, agitation, headache, concentration, and memory	Seizures-free: Valproate ER: 69 % Valproate IR: 46 % (p<0.001)
McCabe et al. 2006[37]	Prospective, open-label, 5-month, IR-ER switch	Valproate ER Valproate DR	41	Decreased TEAEs with Valproate ER (tremor, weight gain, nausea/vomiting)	Seizures/28 days: Valproate ER: 3.29 Valproate DR: 3.35
Yu et al. 2011[32]	Prospective, multicenter, 6-month, open-label	Valproate ER	958	6.7 % of patients had increased AEs (weight gain, hair loss, hand tremor, drowsiness) after 6 months	Seizures/month: Endpoint: 1.0 Baseline: 8.56

AE = adverse event; CNS = central nervous system; CR = controlled-release; DR = delayed-release; ER, XR = extended-release; IR = immediate-release; NR = not reported; TEAEs = treatment-emergent adverse event.

due to AEs,[42] while in another study, 67 % of patients (n=694) discontinued treatment at the highest dose of oxcarbazepine IR due to AEs.[48]

However, not all AEDs clearly show an improvement in the tolerability profile with the ER formulation. Mixed results were seen in studies comparing divalproex ER versus divalproex DR (or equivalent).[33,35] In a trial of 41 adult patients with epilepsy who switched from divalproex DR to divalproex ER, no change was found in the AE profile after 6 months, including gastrointestinal disorders and weight gain.[33] The effect of tremors on daily activities and the Archimedes spiral score were also not significantly changed with divalproex ER (p=0.07 and p=0.79, respectively). One should not be too surprised to see no significant difference in the AE profile of two formulations of an AED that are designed to reduce AEs associated with the IR formulation of that drug. Though the DR valproate formulation is not 'extended' release to the extent the ER formulation is, nonetheless, it is more 'extended' than the IR formulation, thus reducing the difference in the impact of the slower-absorption formulations (DR and ER) on AEs.

Of interest, the ER formulation of lamotrigine does not appear to have an improved AE and tolerability profile compared with the IR formulation. In a pooled analysis of three clinical trials evaluating the long-term safety and tolerability of lamotrigine ER (n=662), 69 % of patients reported one or more AEs, which led to premature withdrawal in 7 % of patients, similar to previous reports with lamotrigine IR.[41]

Simplicity of Regimen and Convenience of Dosing

Studies that have evaluated the relationship between dosing frequency and adherence in patients with epilepsy suggest that increased dosing frequency usually contributes to decreased medication adherence.[17,49] Based on the results of a questionnaire answered by 661 patients, there was a 27 % increase in the odds of missing a dose of AED for each increase in the number of times per day the AED was taken (p=0.09).[17] In a separate study, the effect of dosing frequency of AEDs on adherence over a period of 3,428 days was evaluated using a medication event monitoring system.[49] Adherence rates increased as the number of daily doses decreased from four times a day to once daily (39 %, 77 %, 81 %, and 87 %, respectively). However, in a recent study of 108 patients by Bautista et al., better adherence (higher mean medication possession ratio) was observed with thrice- and twice-daily dosing compared with once-daily dosing (1.02 and 0.93, respectively, versus 0.86; p<0.001).[50]

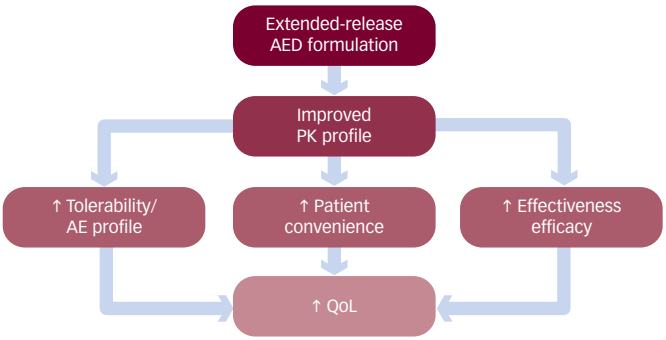
Increase in Effectiveness and Efficacy

While effectiveness may refer to the totality of effects produced when considering all factors of a product following its administration to patients, including efficacy, safety, tolerability, pharmacokinetics, and ease of use, efficacy refers to the ability of a product to produce a desired effect. Therapeutic plasma drug concentrations of ER-AEDs are more stable, which may lead to enhanced effectiveness through improved seizure control (see *Table 3*).[21,30,32–47]

In a double-blind crossover study by Canger and colleagues, a significant decrease in seizure frequency from 9.3 to 6.3 (p=0.013) was seen with carbamazepine ER compared with carbamazepine IR in 48 patients after 1 month of optimal therapy.[40] Similarly, in a retrospective chart review of 61 patients with up to 1 year of follow-up after switching from carbamazepine IR to carbamazepine ER, 46 % of patients had a ≥50 % decrease in seizure frequency after switching and 27 % became seizure-free.[36] However, seizure frequency per month was comparable with that prior to the switch.

In a trial where 2,031 patients with epilepsy were switched from an IR to ER valproate formulation, improved adherence was observed that was accompanied by a 23 % increase in the proportion of patients who were seizure-free. Importantly, this improvement was also accompanied by a statistically significant decrease (19 %; p<0.001) in the proportion of patients experiencing one or more seizures per month.[21] Furthermore, in a comparison of two open-label trials (n=63) comparing outcomes following a divalproex DR to divalproex ER medication switch, a significantly smaller proportion of patients experienced seizures during treatment with divalproex ER (19 % versus 32 %; p=0.02).[35]

Figure 1: Potential Factors Associated with Increased Patient Adherence and Preference of Extended-release Antiepileptic Drug Formulations



AE = adverse event; AED = antiepileptic drug; PK = pharmacokinetics; QoL = quality of life.

However, in some studies with divalproex, comparable or only slightly improved efficacy was seen for a given ER formulation compared with other formulations of divalproex. A small head-to-head comparative trial of divalproex DR versus divalproex ER was conducted in 43 adolescent and adult patients with generalized seizures that were well controlled on a stable dose of divalproex or valproate.[39] These patients had a lengthy history of treatment success prior to the switch, with 91 % seizure-free in the previous year. During the 12 weeks of treatment after switching to divalproex ER, no statistical difference in seizure control was seen with divalproex ER (93 %) compared with divalproex DR (95 %; p=0.564). These results may be associated with the slow release of the DR formulation, as described above. In a 6-month, open-label prospective study in adult patients with epilepsy, patients reported a nonstatistically significant decrease in monthly seizure frequency (0.7 versus 0.85; p=0.14) with divalproex ER treatment versus divalproex IR.[33] At study end, a higher percentage of patients taking divalproex ER were seizure-free (42 %) compared with baseline divalproex IR treatment (32 %), although these improvements did not reach statistical significance (p=0.06).

Because of the enhanced tolerability of ER AEDs, clinicians may potentially safely prescribe higher therapeutic doses in patients who require them clinically (e.g., those experiencing breakthrough seizures). Breakthrough seizures may be reduced by maintaining higher minimum plasma drug concentrations, thereby decreasing the potential for concentrations to fall into the subtherapeutic range.[13,51] Some support for this concept has been described in an investigation of five patients experiencing breakthrough seizures who were able to tolerate higher doses of valproate after being switched to the ER formulation, with no increase in AEs.[37] Four of the five patients had not been able to tolerate similar increases of their valproate IR formulation. One patient became seizure-free and three patients had decreased seizure frequency.

Improved Quality of Life

As with any drug regimen that must be maintained over a long period of time, the tolerability, complexity, and convenience of AED therapy can have a profound impact on patient QoL. Such QoL concerns include limitations on the ability of the patient to drive, socialize, and work as well as effects on their physical and mental state. Relatively few investigations have examined QoL in patients with epilepsy (see *Table 2*),[21,27–34] particularly comparing ER and IR formulations. In one such study, the QoL of patients before and after switching from IR to ER oxcarbazepine were compared. A significant improvement in QoL (as measured by Quality of Life in Epilepsy [QOLIE]-10) was observed (p<0.001), with 23 of 27 patients reporting improvements.[31] In the results from a separate prospective open-label investigation whereby patients were switched from IR to ER carbamazepine (n=453), a significant improvement in QOLIE-31 scores, from 62.8 to 68.3, was found (p<0.001).[30]

Conclusion

In general, patients preferred and were more adherent to the ER (XR) formulations, probably because of decreased AEs, increased tolerability, dosing convenience, increased efficacy, and improved QoL (see *Figure 1*). This increased patient preference for and adherence to ER formulations, however, may differ depending on the given AED, which may reflect differences in the AEDs. For example, while AEs have generally been reported to be reduced with the ER formulation of carbamazepine,[30,36,40] no difference was seen between the ER and IR formulations of lamotrigine.[41]

There are times when physicians may prefer the IR formulation. Concerns exist that the 'forgiveness' period, or time period one can delay taking the prescribed dose, is shorter with ER versus IR formulations.[25] On the contrary, we believe that if patients forget to take their once-daily AED in the morning, they have the whole day to take it before going to bed. Likewise, if they forget to take their once-daily bedtime dose, they can take it upon awakening. We strongly recommend the use of a pill-box (with a schedule) for all patients to readily discover whether a particular dose was forgotten. Also, some physicians believe that the ER formulation does not provide complete therapeutic coverage throughout the dosing interval.[25] It is in this situation that we recommend full use of the therapeutic range by making the necessary modest increases in the dose since the lesser peak–trough fluctuations in plasma concentrations make such adjustments with ER formulations more permissible. While it is easy to assume that XR formulations provide low C_{max} (hence less side effects) and higher minimum concentration (C_{min}) (hence less breakthrough seizures theoretically) compared with IR formulations, some XR formulations showed a slightly lower C_{min} (i.e., lamotrigine, levetiracetam, and divalproex) than IR counterparts. This could be partly due to the fact that not all XR formulations are bioequivalent to IR formulations milligram for milligram. One should refer to the manufacturer's instructions for dosage conversions when switching patients from IR to XR formulations of the same AED. This may not be a factor when a healthcare provider starts a patient on an XR formulation *de novo*.

Overall, it is extremely important that the patient is educated on his/her treatment options. When discussing AED regimens with patients, it is important for physicians to give patients options and encourage them to communicate their concerns, problems, and preferences regarding their medication regimen. In doing so, the individual treatment strategy may be tailored for each patient and may thereby result in better long-term adherence. Epilepsy therapy is not 'one size fits all,' and many patients require individualized medication regimens.

Extended-release AEDs offer several potential advantages over IR counterparts. In addition to benefits in tolerability and the potential for improved efficacy, they may also include improved QoL, and, ultimately, better patient satisfaction. Consequently, these improved attributes can lead to better patient adherence. ■

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