Review

The importance of drug titration in the management of patients with epilepsy

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A B S T R A C T

The variable response to antiseizure medication (ASM) treatment and the numerous drug- and patient-related factors that must be considered when initiating therapy make drug titration to an optimal and tolerable dose an essential component in the pharmacologic treatment of patients with epilepsy. When initiating a new ASM, a “start low, go slow” titration approach is generally recommended and has been shown to reduce the risk of severe idiosyncratic reactions with certain medications and improve tolerability with regard to many frequently occurring central nervous system-related adverse effects (e.g., somnolence, dizziness). Many patients with epilepsy will require medication changes due to lack of efficacy or intolerability of the initial regimen. When this occurs, patients may be switched from one monotherapy to another or receive adjunctive therapy. When transitioning a patient from one ASM to another (referred to as monotherapy conversion or transitional polytherapy), there are several strategies for tapering the baseline ASM depending on the clinical scenario. Regardless of the particular strategy, the goal should be to discontinue the baseline ASM in order to prevent increased toxicity due to drug load. When adding on ASM therapy, flexible titration of the new ASM and adjustment of concomitant ASMs to achieve disease control with the lowest possible drug load (lowest numbers and lowest doses) may help improve tolerability of the add-on therapy. Communication with patients during the initiation of a new therapy may help patients adhere to the titration schedule, allowing them to reach their optimal maintenance dose.

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1. Introduction

Antiseizure medications (ASMs) are the predominant management strategy for patients with epilepsy, [1,2] with the treatment goal being the achievement of seizure freedom (100% seizure reduction) with no or minimal adverse effects [3–5]. However, despite the introduction of 20 ASMs over the past several decades, many patients with newly diagnosed epilepsy do not achieve this goal with their first ASM regimen (monotherapy) [6]. Medication changes are frequently necessary because of a lack of efficacy or tolerability to initial treatment. Because of the interindividual response to ASMs, titration to an optimal and tolerable dose is generally recommended [7]. Many available ASMs include a manufacturer-recommended initial drug titration phase, ranging from weeks to months (Table 1 [8–14]), with the purpose of minimizing the risk of serious adverse effects and/or improving tolerability, so that the patient may reach a target dose or dose range that is associated with optimal efficacy based on the results of clinical studies. However, pivotal clinical studies of ASMs are designed to meet regulatory requirements, including fixed-dose titration and rigorous inclusion/exclusion criteria. In the real world, the treatment of epilepsy is highly individualized, and clinical practice may differ from randomized clinical trials in regard to ASM initiation and optimization, particularly in patients receiving polytherapy. This article focuses on the role of dose titration when initiating ASM treatment, including the rationale for a “start low, go slow” approach, pharmacokinetic and pharmacodynamic factors, and additional considerations when adding on an ASM for monotherapy conversion (also referred to as transitional polytherapy) or as adjunctive treatment (polytherapy).

Abbreviations: ASMs, antiseizure medications; CNS, central nervous system; DRESS, drug-related rash with eosinophilia and systemic symptoms; FDA, Food and Drug Administration; TEN, toxic epidermal necrolysis; SJS, Stevens–Johnson syndrome.

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2. “Start low, go slow” titration

Newer ASMs are generally associated with a better safety and tolerability profile than first-generation ASMs; however, all ASMs are associated with a risk of adverse effects that may result in treatment discontinuation and reduced quality of life and may contribute to non-adherence [1,15,16]. Adverse effects can also prevent or delay the attainment of potentially optimal treatment dosages [15,17].

ASM-associated adverse effects vary widely in their frequency, type (e.g., idiosyncratic, pharmacological, drug interactions), and severity depending on the drug, patient characteristics, and concomitant medications [15]. A “start low, go slow” titration approach is often used to reduce the risk of serious adverse effects and tolerability issues, allowing patients to safely reach an optimal maintenance dose, which may improve adherence for some patients, as demonstrated among patients treated with antidepres-
sants [18]. This approach may not be suitable for all patients, for instance, those requiring emergency treatment or those with severe, debilitating, or high-frequency seizures for which prompt treatment with a therapeutic dose is preferred.

2.1. “Start low, go slow” titration to reduce the risk of immune-mediated idiosyncratic adverse effects

ASMs are associated with rare, but potentially life-threatening idiosyncratic adverse effects, including immune-mediated hypersensitivity reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-related rash with eosinophilia and systemic symptoms (DRESS). High starting doses and rapid rates of titration are contributing factors to the risk of severe cutaneous adverse reaction with several ASMs, including carbazepine, lamotrigine, and phenytoin [19,20]. Starting treatment at a low dose with gradual dose increases may decrease the risk of these adverse reactions via desensitization [19,21].

Lamotrigine provides one of the most well-known examples of the relationship between dose, titration rate, and rash. Data from early monotherapy studies of lamotrigine in adults showed a 20.5% risk of rash with starting doses between 62.5 and 125 mg/day compared with a risk of 6.1% with doses <31 mg/day [22]. Co-administration of valproic acid with lamotrigine was also associated with an increased risk of cutaneous reactions, via inhibition of glucuronidation, the metabolic pathway for lamotrigine [22,23]. Following the recommended use of lower starting doses, including specific dosing guidance for patients taking concomitant valproic acid, and slower titration rates, the risk of rash was 5.7% [23]. Rash involving hospitalization, including SJS, occurred with an incidence as high as 1:100 in children and 1 in 300 in adults during early clinical use of lamotrigine [24]. After dosing recommenda-
tions changed, the estimated risk of SJS/TEN among new users of lamotrigine decreased to 3.8 in 10,000 [25].

“Start low, go slow” titration is also recommended for cenobamate. Early in its clinical development, three confirmed cases of DRESS were reported among the first 953 patients exposed to cenobamate, including one death [26]. These cases occurred during a higher starting dose (50 mg/day or greater) and a faster titration regimen (weekly or faster) than the Food and Drug Administration (FDA)-approved starting dose and titration schedule. Support for the FDA-approved dosing regimen came from a long-term, phase 3, open-label safety study that used a starting dose of 12.5 mg/day and an 11-week titration phase to reach a target dose of 200 mg/day. No cases of DRESS occurred among 1339 patients who received cenobamate, including 1110 patients treated for 6 months [26].

2.2. “Start low, go slow” titration to reduce the risk of pharmacological adverse effects

Pharmacological (type A) adverse effects are common and are associated with the ASM’s mechanism of action, with an onset typically at the start of therapy or at dose escalation [15]. Central nervous system (CNS) effects (e.g., drowsiness, dizziness, fatigue, blurry or double vision, gait and balance disturbances, cognitive impairment) are the most frequently occurring pharmacological adverse effects with ASMs and are a common cause of treatment failure and poor quality of life [15,27]. Many of these adverse
effects can be minimized using low starting doses and slow titration, allowing pharmacodynamic tolerance or adaptation to the adverse effect to occur over time [15,28]. For instance, real-world analyses of perampanel have shown reduced overall rates of adverse events with slower titration [29,30]. In one analysis, the rate of adverse events was 51.1% with weekly titration compared with 32% with titration every 3 to 4 weeks [30]. According to a retrospective analysis, a slower titration rate (every 4 weeks) and lower initial target (6 mg/day) were effective for many patients (50% responder rates of 51.9% and 81.8% at 6 months for patients with focal and generalized epilepsy, respectively) and the 6-month retention rate was 78.4% [31].

ASMs that act on voltage-gated sodium channels (e.g., eslicarbazepine, lacosamide, oxcarbazepine) are frequently associated with vestibulocerebellar adverse effects, including dizziness, ataxia, and balance disturbance [27]. An integrated analysis of several pivotal phase 3 studies of eslicarbazepine as adjunctive therapy for focal seizures found that among patients assigned to the 800 and 1200 mg/day maintenance groups, respectively, the rates of discontinuation due to treatment-emergent adverse events were lower among patients who started treatment at a dose of 400 mg (12% and 21%) compared to those that started at 800 mg (20% and 27%) [32].

Among newer ASMs, topiramate is associated with a higher risk of cognitive adverse effects, including attention difficulties, confusion, psychomotor slowing, and effects on verbal function and language [14,15]. Early clinical trials, which utilized higher starting doses (100 mg), rapid titration (100–200 mg/day increases in weekly increments), and higher than currently recommended target doses (600–1000 mg/day), were associated with high incidences of cognitive-related adverse events [33,34]. Lower starting doses and slower titration improved tolerability and retention [35,36]. In a comparison of titration regimens, a starting dose of 50 mg/day with titration in weekly increments of 50mg/day was associated with a significantly lower cumulative incidence of treatment-emergent adverse events leading to changes in topiramate therapy (i.e., dose reductions, interruptions) compared with a starting dose of 100 mg/day with titration in weekly increments of 100–200 mg/day (p=0.048) [36]. Interruptions or discontinuations of topiramate therapy due to adverse events occurred in 22% of patients in the faster titration group compared with 11% of patients in the slower titration group (p=0.040) [36]. In another analysis, a slower titration approach resulted in substantially lower cognitive-related adverse events than were reported from an earlier study with a faster titration rate (psychomotor slowing 2% vs 20% for 200 mg/day target dose groups, respectively) [34,35].

2.3. “Start low, go slow” titration in elderly patients

In general, lower initial doses of ASMs and slower titration rates should be used in elderly patients [16,37]. Elderly patients often respond with lower than recommended treatment doses [29,38,39], so assessment at a lower target dose is recommended.

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3. Pharmacokinetic and pharmacodynamics factors

Several ASMs, particularly older ASMs, act as CYP enzyme inhibitors (e.g., valproate) or inducers (e.g., phenytoin, phenobarbital, carbamazepine, and primidone) and have the potential for pharmacokinetic drug–drug interactions that can adversely affect treatment outcomes when used concomitantly with other agents [47]. Phenytoin is an important example, as it induces the metabolism of other drugs and is subject to the effects of metabolic inhibition or induction. Its non-linear elimination pharmacokinetics means that small changes in dose may lead to substantial increases in serum concentration [48]. Phenytoin also has a narrow therapeutic index in which there is a small range for therapeutic effect without toxicity. Thus, the metabolism of the add-on ASM must be considered when used concomitantly with phenytoin or other hepatic enzyme inducers or inhibitors in order to avoid potential adverse effects and drug–drug interactions. If transitioning from an enzyme inducing/inhibiting ASM monotherapy to another ASM that is susceptible to its effects, titration should be closely monitored, as the new ASM may need additional up- or down-titration once the baseline ASM is removed depending on the length of overlap. Patients with epilepsy also have an increased prevalence of comorbidities compared with the general population [49]. Therefore, additional concomitant medications may also need to be adjusted once the enzyme inducing/inhibiting ASM is discontinued.

Combination therapy can also result in pharmacodynamic interactions, leading to alterations in activity and tolerability [50]. When initiating and titrating add-on therapy note that the effective and tolerable dose may be different depending on the concomitant ASM.

4. Titration when adding on ASM during monotherapy conversion or polytherapy

4.1. Monotherapy conversion

Initial treatment with ASM monotherapy is standard; however, ASM conversion may be required when the initial drug fails, either due to lack of efficacy or tolerability [48,51]. Although the benefits of substitution over add-on therapy are still a matter of debate [17,52–55], a trial with one or more additional monotherapies is common before starting chronic polytherapy.

For monotherapy conversion, a period of transitional polytherapy is recommended where the new ASM overlaps with the baseline ASM. If the patient tolerates the first ASM, but the drug fails to achieve efficacy, experts recommend tapering the baseline ASM after an efficacious dose of the new ASM is reached. Earlier and faster reduction of the baseline ASM may be needed should adverse effects occur during titration of the new ASM [51]. In patients who are already experiencing adverse effects with the first drug, slowly reducing the dose of the first drug before adding a second drug has been recommended to help avoid potential worsening side effects from overmedication [48,56]. Earlier dose reductions of baseline ASMs with long half-lives, such as clobazam, may also be beneficial to prevent toxicity, [57] as it can take 1 or more weeks for drug levels to decrease and possible side effects to resolve. Keep in mind that the goal with monotherapy conversion is to remove the already established ineffective or intolerable ASM. There is a tendency among some clinicians to prematurely discontinue the newly added ASM therapy when intolerable dose-related pharmacological adverse effects such as dizziness and sedation occur; however, these symptoms are mediated by the combination of drugs and should not be solely attributed to the new therapy [51]. Doing so may result in discontinuation of the new therapy before an adequate assessment period.
Unfortunately, this may lead to future avoidance of what could be a potentially useful treatment under the right dosing conditions.

4.2. Polytherapy

Despite the evidence that the likelihood of additional seizure control diminishes with each subsequent ASM regimen, [6] many patients with drug-resistant epilepsy receive polytherapy, often with high doses that increase the burden of toxicity and negatively affect quality of life [58,59]. Among patients with drug-resistant epilepsy, adverse effects from medications are a stronger predictor of quality of life than seizures [59]. Treatment complexity and polytherapy are also associated with lower rates of adherence in patients with epilepsy [60].

When adding on ASM therapy, titration and adjustment of concomitant ASMs to achieve disease control with the lowest possible drug load (lowest numbers and lowest doses) is essential to avoid overtreatment. Studies have shown little benefit of adding more than 3 ASMs [6,17]. In fact, evidence has shown that reducing the number of ASMs in patients with drug-resistant epilepsy can decrease adverse events without an increase in seizure frequency [61].

Many of the same principles of transitional polytherapy also apply when adding adjunctive therapy, including titration of the new add-on therapy along with adjustment of the concomitant medications based on tolerability. Flexible dose-titration with allowable adjustment of concomitant ASMs has been demonstrated in several open-label and observational studies of ASMs, including lacosamide, topiramate, zonisamide, cannabidiol, perampanel, and cenobamate [30,57,62–66]. In patients with rare epilepsies refractory to current ASM therapy, a slow titration of cannabidiol to a target dose of 10 mg/kg/day over at least 1 month, with additional gradual increases over 6 months to a maximum of 20 mg/kg/day, was associated with an improved safety profile, a low withdrawal rate due to adverse events, and similar efficacy compared to previous studies using a shorter titration schedule (2–4 weeks) [64]. Concomitant medication reductions or suspensions occurred in 37.6% of patients; reductions involved mainly clobazam, valproic acid, and topiramate [64]. Results from a post hoc analysis of a subset of patients from the phase 3, open-label, safety study of cenobamate in patients with uncontrolled focal seizures found that patients who continued cenobamate treatment tended to have greater reductions in concomitant ASM doses than those who discontinued [57]. Dose decreases of phenytoin, phenobarbital, clobazam, valproate, and lacosamide occurred earliest during the study [57].

Evaluation of prospective titration strategies for adjunctive ASMs are limited. One prospective open-label study in patients with uncontrolled focal epilepsy evaluated the efficacy and safety of lacosamide added as adjunctive therapy to patients receiving levetiracetam, with down-titration and discontinuation of other sodium channel blockers over a 9-week cross-titration phase [67]. The cross-titration strategy was found to be effective, with favorable tolerability and improvement in quality of life [67].

5. Other considerations for ASM titration

While there is a concern for breakthrough seizures during the titration phase, evidence from several studies suggests that the timeframe for seizure recurrence after the first unprovoked seizure is generally within the first 3–6 months [68,69]. Therefore, many patients with newly diagnosed epilepsy would likely be able to undergo a “start low, go slow” titration without a negative impact on seizure activity. For patients with established refractory epilepsy, a thorough seizure history may provide a general guide for the timeframe of seizure frequency. Many patients with uncontrolled seizures may begin to see some improvement with doses that are lower than the maintenance target doses used in pivotal clinical studies. This has been observed in studies of patients with focal seizures treated with perampanel [29,70], zonisamide [71], topiramate [35], and cenobamate [72,73].

Many common dose-related CNS adverse effects, including sedation and dizziness, occur early during treatment and then decrease over time [71,74–76]. Communication and managing patient expectations during titration may help patients adhere to the titration schedule and reach their individualized maintenance dose, where they are more likely to experience optimal seizure control. Adherence to ASMs has been shown to positively correlate with quality of life in patients with epilepsy [77]. Although increased healthcare costs associated with additional clinic visits/monitoring [78] and increased prescription costs (may exceed insurance coverage limits) may occur during titration, there is the potential for overall cost savings with titration associated with improved adherence and better seizure control. Both non-adherence to ASMs and uncontrolled disease account for a disproportionate amount of the economic burden associated with epilepsy [79]. Titration may also lower the risk of potential adverse events from ASMs, which have been associated with higher total drug costs in the outpatient setting and higher total costs of outpatient visits [80].

6. Summary

Epilepsy is a chronic disease that often requires life-long medical treatment, including medication changes and polytherapy for many patients. Titration is an essential component of treatment individualization with ASMs. A “start low, go slow” initiation has been shown to improve the tolerability of many agents. When converting patients from one monotherapy to another or when adding on an adjunctive therapy, flexible dose titration and adjustment of the other medication(s) may help prevent drug toxicity from overtreatment. Patients should be part of the shared-decision making process during epilepsy treatment. Communication during the initiation of a new therapy should include a discussion of expectations during drug titration.

Declaration of Competing Interest

LGS: has served as an advisory board member for Greenwich Biosciences, SK Life Science, Inc., and UCB Pharma and is a current Speaker Bureau member for Greenwich Biosciences, SK Life Science, Inc., Sunovion, and UCB Pharma.

GSC: has served as an advisory board member for SK Life Science, Inc.

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References

[1] Perucca P, Scheffer IE, Kiley M. The management of epilepsy in children and adolescents. Med J Aust 2018;208(5):226–33.
[2] Golyala A, Kwan P. Drug development for refractory epilepsy: the past 25 years and beyond. Seizure 2017;44:147–56.
[3] Clauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guererro C, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epilepsy seizures and syndromes. Epilepsia 2006;47(7):1094–120.
[4] Brandon Westover M, Cormier J, Bianchi MT, Shafi M, Kilbridge R, Cole AJ, et al. Revising the “Rule of Three” for inferring seizure freedom. Epilepsia 2012;53(2):368–76.
[5] Clauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guererro C, Källvainen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epilepsy seizures and syndromes. Epilepsia 2013;54(3):551–63.
[6] Chen Z, Brodie MJ, Liew D, Kwan P. A treatment outcome study. JAMA Neurol 2018;75(3):279. https://doi.org/10.1001/jamaneurol.2017.3940.
[7] Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol 2011;10(5):446–56.
[8] NCORPA® (clobazam tablets), for oral use, CV [prescribing information]. Paramus, NJ: SK Life Science, Inc.; April, 2021.
[9] VIMPAT® (lacosamide) film coated tablet, for oral use, CV, VIMPAT® (lacosamide) injection, for intravenous use, CV, VIMPAT® (lacosamide) oral solution, CV [prescribing information]. Smyrna, GA: UCB, Inc.; November, 2020.
[10] APTIOM® (eslicarbazepine acetate) tablets, for oral use [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; March, 2019.
[11] LAMICTAL® (lamotrigine) tablets, for oral use. LAMICTAL OD (lamotrigine) chewable dispersible tablets, for oral use. LAMICTAL OD (lamotrigine) orally disintegrating tablets, for oral use [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; October, 2020.
[12] KEPPRA® (levetiracetam). 250 mg, 500 mg, 750 mg, and 1000 mg tablets. 100 mg/mL oral solution [prescribing information]. Smyrna, GA: UCB, Inc.; October, 2019.
[13] FYCOMPA® (perampanel) tablets, for oral use. CV, FYCOMPA® (perampanel) oral suspension, CV [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; September, 2021.
[14] TOPAMAX® (topiramate) TABLETS, for oral use. TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES, oral use [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; June, 2020.
[15] Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol 2012;11(9):792–802.
[16] St. Louis EK. Minimizing the adverse effects of epilepsy therapies: principles and practice. In: St. Louis EK, Ficker DM, O’Brien TJ, editors. Epilepsy and the elderly: comparing clinical characteristics with younger patients. Acta Neurol Scand 2014;129(5):283–93.
[17] Stefani H, May TW, Pflauff M, Brandt C, Füratsch N, Schmitz B, et al. Epilepsy in the elderly: optimizing management. Acta Neurol Scand 2011;124(4):305–11.
[18] Pozzi J. Management of epilepsy in the elderly. Neuropsychiatr Dis Treat 2007;3:723–8.
[19] Acton EK, Feldman MA, Hennessy S, Xu SX, Pollard JR, Kasner SE, et al. Trends in oral anticoagulant co-prescription with antiepileptic drugs among adults with epilepsy, 2010–2018. Epilepsy Behav 2020;113:107550. https://doi.org/10.1016/j.yebeh.2020.107550.
[20] Chen, Stecker E, A, V, Warden B. Direct oral anticoagulant use: a practical guide to common clinical challenges. JAHA 2020;9(13). https://doi.org/10.1161/JAHA.120.017559.
[21] FLAVAX® (clonipogrel tablets) for oral use [prescribing information]. Bay Shore, NY: Sanofi-Aventis U.S. LLC; March, 2021.
[22] COUMADIN® (warfarin sodium) tablets, for oral use; COUMADIN® (warfarin sodium) injection, for intravenous use [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company October, 2011.
[23] ELIQUIS® (apixaban) tablets, for oral use [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; November, 2019.
[24] XARELTO® (rivaroxaban) tablets, for oral use [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; November, 2019.
[25] Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006;61(3):246–55.
[26] Garnett WR, St. Louis EK, Henry TR, Bramley T. Transitional polytherapy: tricks of the trade for monotherapy to monotherapy AED conversions. Curr Neuropsychopharmacol 2009;7:83–95.
[27] Ruiz-Giménez J, Sánchez-Álvarez JC, Cañadas-Hidalgo F, Serrano-Castro PJ. Antiepileptic drug treatment in patients with epilepsy and other comorbidities. Seizure 2010;19(7):375–82.
[28] Verrotti A, Latzaun S, Brigo F, Zaccara G. Pharmacodynamic interactions of antiepileptic drugs: From bench to clinical practice. Epilepsy Behav 2021;117:107844. https://doi.org/10.1016/j.yebeh.2021.107844.
partial epilepsy failing on a single drug: a multicentre, randomised, pragmatic controlled trial. Epilepsy Res 2003;37(1):1–13.
[50] Schmidt D. Strategies to prevent overtreatment with antiepileptic drugs in patients with epilepsy. Epilepsy Res 2002;52(1):61–9.
[51] Rosenfeld WE, Aboz-Khalil B, Abouammar S, Bhatia P, Biton V, Krauss GL, et al. Post hoc analysis of a phase 3, multicenter, open-label study of clobrodate for treatment of uncontrolled focal seizures: Effects of dose adjustments of concomitant antiepileptic medications. Epilepsia 2021;62(12):3016–28.
[52] Perucca E, Kwan P. Overtreatment in epilepsy: how it occurs and how it can be avoided. CNS Drugs 2005;19(11):897–908.
[53] Luoni C, Buolli F, Canevini MP, De Sarro G, Fattore C, Galimberti CA, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia 2011;52(12):2181–91.
[54] O’Rourke G, O’Brien JJ. Identifying the barriers to antiepileptic drug adherence among adults with epilepsy. Seizure 2017;45:160–8.
[55] Dash D, Aggarwal V, Joshi R, Padma MV, Tripathi M. Effect of reduction of antiepileptic drugs in patients with drug-refractory epilepsy. Seizure 2015;27:25–9.
[56] Bauilac M,oulb M, Coty D, McShea C, De Backer M, Bartolomei F, et al. Adjunctive losartan for focal epilepsy: an open-label trial evaluating the impact of flexible titration and dosing on safety and seizure outcomes. Epileptic Disord 2017;19(2):186–94.
[57] Steinhoff BJ, Someville ER, Van Paesschen W, Ryvlin P, Schelstraete I. The SKATe study: an open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy. Epilepsy Res 2007;76(1):6–14.
[58] D’Onofrio G, Kuchenbuch M, Machon-Le Camus C, Desnoues B, Staath V, Napuri S, et al. Slow titration of cannabidiol add-on in drug-resistant epilepsies can improve safety with maintained efficacy in an open-label study. Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.00829.s001.
[59] Naritoku DK, Hulihan JF, Schwarzman LE, Kamin M, Olson WH. Effect of cotherapy reduction on tolerability of epilepsy add-on therapy: a randomized controlled trial. Ann Pharmacother 2005;39(3):418–23.
[60] Dodson WE, Kamin M, Kraut L, Olson WH, Wu S-C. Topiramate titration to response: analysis of individualized therapy trials (TRAITs). Ann Pharmacother 2003;37(5):615–20.
[61] Bauilac M, Byrnes W, Williams P, Borghs S, Webster E, De Backer M, et al. Lacosamide and sodium channel-blocking antiepileptic drug cross-titration against levetiracetam background therapy. Acta Neurol Scand 2017;135(4):434–41.