

A Review of Withdraw Strategies for Discontinuing Antiepileptic Therapy in Epilepsy and Pain Management

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Summary

Purpose (100 words per ASHP)

Pain management is complicated by unacceptable levels of opioid abuse with few safe alternatives. The need exists for analgesic agents with limited abuse potential and recommendations for their safe use. Since the 1960's, antiepileptic drugs have been used as adjunctively in pain management. By virtue of their pharmacokinetic and risk profiles, antiepileptic drugs require more prescriber surveillance compared to other medications. However, there is no standard approach for discontinuing these drugs. The objectives of this review were to summarize the risk profile of tapering antiepileptic drugs used for epilepsy vs. pain management and to identify best practices for safe tapering.

Methods (200 words per ASHP)

A retrospective review was performed of literature addressing discontinuation of antiepileptic drugs. Articles were collected from PubMed and Ovid using keywords: anticonvulsant, antiepileptic, withholding treatment, taper and withdrawal. The limitations included English language only publications, regardless of country of origin, and publication between 1990 and 2013.

Results (200 words per ASHP)

Findings revealed 25 published randomized controlled trials, reviews, case reports and editorials. While no taper guideline was found, many studies used a gradual taper protocol ranging from one month to more than four years for discontinuation. However no consistency was found between protocols. Risks for continuation and inappropriate discontinuation of antiepileptic therapy were aggregated from FDA labeled information and published case reports. This constituted the risk profile. Risks of acute discontinuation in epilepsy and pain management manifest differently. In epilepsy, documentation of acute discontinuation of AEDs results in recurrence of epileptic episode. Tapering therapy to discontinuation in epilepsy results in a higher risk of seizure recurrence in the first six months of withdrawal compared to patients continuing therapy. In pain management, acute discontinuation of AEDs results in a benzodiazepine-like withdrawal syndrome with symptoms such as diaphoresis, agitation and altered mental status. However unlike true benzodiazepine withdrawal, acute discontinuation of AEDs in pain management is unresolved by benzodiazepine administration.

Conclusion (100 words per ASHP)

Tapering antiepileptic drugs when discontinuing therapy in epilepsy is common practice though there is no standard taper regimen documented consistently throughout the literature. Tapering strategies for discontinuing antiepileptic therapy when used in pain management are not well documented. This

review identifies gaps in the literature concerning safe discontinuation of antiepileptic drugs used both for the primary indication as well as pain management. Clinical pharmacists would be greatly benefited by future research into appropriate regimens for tapering patients off of antiepileptic therapy with consideration of the effect removing antiepileptics from the body would have on other drug therapies the patient continues.

Key Words

Antiepileptic drugs, withdrawal, tapering strategies, off-label use, pain management

Introduction:

Pain management is complicated by the levels of unacceptable opioid abuse and few safe alternatives. In 2011, the Institute of Medicine estimated 116 million American adults suffered from chronic pain [1]. In 2008, the CDC declared death from opioid use and misuse to be higher than that of heroin and cocaine combined and drug-related death rates that year to have more than tripled since 1990 [2]. There is a need for analgesic agents with limited abuse potential as well as recommendations for safe and effective use of these pain management therapies. Prescribers have turned to older non-opioid analgesic agents for treating pain including the application of agents not indicated for use in pain. Since the 1960's, anti-epileptic drugs (AEDs) have been used as adjunct pain management in both acute and chronic pain with the purpose of enhancing pain control and minimizing opioid exposure. In the primary indication of epilepsy, long-term use of AEDs is controversial and need only be used chronically in select patients [3, 4]. There is evidence to show cognitive side effects with long-term use [5] as well as literature to demonstrate improvement with discontinuation [5, 6] though there is not a clear standard for discontinuing this therapy.

The prevalence of AED off-label prescribing was recently studied in a 2012 Canadian article noting 99.2% of gabapentin prescriptions were off-label and 66.6% of all anticonvulsant prescriptions were off-label [7]. This same study also showed 99.5% of medications prescribed for neurogenic pain were off-label. Phenytoin, valproate, gabapentin and carbamazepine were the most commonly prescribed AEDs in an epidemiology study in the Georgia Medicaid population looking at off-label use of AEDs. Seventy-one point three percent of these patients with an AED prescription did not have an FDA-indicated diagnosis. There was a high association of AED use in the pain management population however the data were unable to be interpreted to identify the indication for the prescription [8]. The need exists to establish recommendations for discontinuing AED therapy in its different indications because of the prevalence of off-label prescribing in conjunction with the risks associated with use. There is evidence against acute withdrawal of AEDs in pain management patients [9-14] but there has yet to be published a safe tapering guideline on discontinuation of AED in epilepsy or chronic pain management. The objectives of this paper were to summarize the risk profile of tapering antiepileptic drugs used for epilepsy vs. use as adjunctive therapy in pain management and to identify best practices for safe tapering.

Methods:

The strategies employed to locate articles for this review consisted of searching the electronic databases PubMed and OVID using keywords (anticonvulsant, antiepileptic, withholding treatment, taper and withdrawal) as well as a search of articles referenced by the retrieved publications. The date limitation took into consideration the long history of use of these agents but to better reflect patient outcomes was restricted to articles published between 1990 and 2013 to ensure only the most up to date studies were included. There was no limitation to the country of study due to the ubiquitous use of these drugs though there was a restriction to the English language. Abstracts, prospective studies, reviews, editorials and case reports were considered. The abstracts were screened for relevance and full text articles were retrieved when applicable. A summary of the referenced articles were placed in a table with the headings source, title, author, intervention and findings.

Results:

Anti-epileptics - Risk Profiles

Summarizing the risk profile of tapering AEDs requires a look at the risks of inappropriate discontinuation as well as safety and toxicity concerns with continuing therapy in both the epileptic and

pain management populations. The risk profile for AED therapy varies between the populations treated according to published case reports and FDA labeled information.

For example, in epilepsy, continued therapies for many AEDs may result in cognitive impairments, behavioral changes and motor problems [15]. Memory decline, reduced attention and other cognitive impairments have been noted in patients taking various AEDs [5].

However, in pain management, risks have not been documented for long-term use of AEDs.

In epilepsy, the literature focusing on withdrawal of AED therapy noted increased risk for seizure recurrence. This increased risk was highest in the first 6 months of therapy withdrawal and was seen thereafter to approach the same risk of seizure recurrence as therapy continuation [6, 16-24].

On the other hand, in pain management, acute discontinuation of gabapentin has been reported to result in benzodiazepine-like withdrawal syndrome with symptoms such as altered mental status, agitation [9, 13], diaphoresis, nausea, insomnia, elevated blood pressure [12, 14], and even status epilepticus in a patient with no previous history of epilepsy [9]. Inappropriate discontinuation of pregabalin was also reported to be associated with benzodiazepine-like withdrawal symptoms such as diaphoresis, elevated blood pressure, and unrest [10]. In each case report, symptoms did not resolve with benzodiazepine administration but only upon re-initiation of AED.

Tapering Anti-epileptics in Epilepsy

Findings revealed the practice of tapering AEDs in epileptic patients is inconsistent. The literature focuses on risks of relapse following withdrawal, benefits of a successful withdrawal from AEDs as well as the characteristics of a patient's epilepsy that are prognostic factors for adverse events upon withdrawal. However, there is no standard in tapering regimens for discontinuing therapy in epilepsy found in the literature. Table 1 is a summary of the reference articles.

The general concept of treating most epileptic patients with AEDs is to induce a remission, then withdraw the therapy [19, 20]. However, the literature also suggests the epileptologist make withdrawal decisions on a case by case basis, taking into account patient characteristics to determine best practice for each particular patient rather than establish guidelines for groups of patients. In epilepsy, the generally accepted rule is that a patient must be seizure-free for ≥ 2 years before considering withdrawal point [17, 21, 23-26]. Patients need to be evaluated for withdrawal based on risk factors that are associated with increased relapse rates. Potential recurrence predictors are abnormal neurological evaluations, etiology of seizures, abnormal EEG findings at time of withdrawal and family history [3,4] though these characteristics are not all ubiquitously accepted as risk factors.

The literature review revealed the time frame of the taper regimen is not consistent though it is generally accepted that the discontinuation of AEDs in epilepsy does require a taper. The ranges in the literature of a taper regimen vary from 4 weeks [16, 22, 23] to 4 years [23] for complete discontinuation. Discontinuation of AEDs has an increased risk of seizure relapse initially though following the first 6 months, the relapse rates approached the level of that in patients continuing AED therapy [22]. In many of the review articles, there was no standard for tapering AEDs amongst the collected studies (Table 1). A Cochrane review looked directly at taper schedules to determine if a safer and more effective time frame to withdraw AEDs existed but only one article was retrieved that met criteria and it's methodology was weak. The reviewing authors were unable to make any strong conclusions about

differences between tapering schedules (rapid v slow taper) [27]. On the other hand, a study by Ramos-Lizana and colleagues identified a trend of higher relapse rates in the first 6 months in patients with a shorter withdrawal period (4-6 weeks v 4-6 months) but the study was powered to determine a difference in seizure recurrence between a withdrawal group and a non-withdrawal group and not a comparison of two tapering schedules therefore the trend was not determined to be statistically significant [22].

Table 1. Summary of Reference Articles for Antiepileptic Drug Use in Epilepsy

Year published	Authors	Title	Study design	Intervention	Findings	Citation
1991	Medical research council antiepileptic drug withdrawal study group	Randomised study of antiepileptic drug withdrawal in patients in remission	P	Gradual taper over ≥ 6 months. Dose reduction q 4 weeks with patients on polytherapy to discontinue drugs sequentially. Phenytoin 50mg; Carbamazepine 100mg; Valproate 200mg.	Seizure recurrence higher in withdrawal group than in continued therapy group for the first year. Identified risk factors for increased seizure recurrence. Recurrence risk in withdrawal group similar to that of faster withdrawal as noted by other studies.	Lancet. 1991 May 18;337(8751):1175-80.
1996	J. Dooley, Mb Frcp; K. Gordon, Md, Ms, Frcp; P. Camfield, Md, Frcp; C. Camfield, Md, Frcp; And E. Smith, Rn	Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: a prospective study	P	Gradual taper over 4-8 weeks	66% remained seizure free at 1 year at 61% remained seizure free at 2 years	Neurology. 1996; 46: 969-974
1996	American Academy Of Neurology - Quality Standards Subcommittee	A guideline for discontinuing antiepileptic drugs in seizure-free patients-summary statement	R	N/A	Evidence supports 2-5 years seizure free period on AED therapy before discontinuing therapy. No mention of specific techniques for discontinuation.	Neurology. 1996;47:600-602
2001	Joseph Sirven, Michael R Sperling, Dean M Wingerchuk	Early versus late antiepileptic drug withdrawal for people with epilepsy in remission	R	3 month taper; 25% dose reduction q 2 weeks; 4 month taper; 1/3 dose reduction; 6-12 month taper	Evidence supports ≥ 2 years of seizure-free period before discontinuing AED in children. No evidence for timing in adults.	Cochrane database of systematic reviews. 2001; issue 3.
2002	L M Specchio, L Tramacere, A La Neve, E Beghi	Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy	P	25% dose reduction q 3 months	50% relapse in withdrawal group v 28% relapse in patients continuing treatment	J neurol neurosurg psychiatry. 2002;72:22-25
2003	Barrera, Juan-Carlos 1; Harden, Cynthia L.	Tapering of anticonvulsant drugs in two-year seizure-free patients with partial and secondarily generalized epilepsy	P	8-12 week taper	Most patients enrolled meeting criteria did not wish to taper	Epilepsia. 2003: 44 (supplement 9);264

2004	Luigi M. Specchio, Ettore Beghi	Should antiepileptic drugs be withdrawn in seizure-free patients?	R	N/A	The decision of whether to discontinue therapy in seizure-free patients must be patient specific and be made after a discussion between physician and patient. Taper should also be drug specific. No particular schedules mentioned	Cns drugs. 2004; 18 (4): 201-212
2006	Ranganathan Ln, Ramaratnam S.	Rapid versus slow withdrawal of antiepileptic drugs	R	N/A	Only one article fit search criteria: no reliable conclusion for taper period	Cochrane database syst rev. 2006; 19(2):cd005003
2008	Lossius Mi, Hessen E, Mowinckel P, Stavem K, Erikssen J, Gulbrandsen P, Gjerstad L.	Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (akershus study)	P	20% dose reduction in first 6 weeks followed by same dose reduction q2weeks	Increased rate of seizure recurrence in withdraw group at 12 months; RR twice that of non-withdrawal; 19% relapse rate in withdrawal group at 2 years; most seizures occurring by first 6 months after withdrawal; use of carbamazepine associated with reduced relapse rates after withdrawal	Epilepsia. 2008;49(3):455-63
2009	Shih Jj, Ochoa Jg.	A systematic review of antiepileptic drug initiation and withdrawal	R	N/A	25% dose reduction q 3 months. Overall increased risk of seizure recurrence in patients withdrawing from therapy	Neurologist. 2009;15(3):122-31
2010	J. Ramos-Lizana, J. Aguirre-Rodri'Guez, P. Aguilera-Lo'Pez, E. Cassinello-Garci'A	Recurrence risk after withdrawal of antiepileptic drugs in children with epilepsy: a prospective study	P	4-6 month gradual taper changed to 4-6 week taper during study	Shorter withdrawal had higher rate of seizure recurrence in first 6 months; longer withdrawal had higher rate of abnormal EEG	European journal of paediatric neurology. 2010; 14: 116 – 124
2010	Hixson Jd.	Stopping antiepileptic drugs: when and why?	E	N/A	Can benefit some patients but patients need to be selected carefully, weighing costs/benefits of withdrawal	Curr treat options neurol. 2010;12(5):434-42
2011	Chaturbhuj Rathore, Samhita Panda, P. Sankara Sarma, And Kurupath Radhakrishnan	How safe is it to withdraw antiepileptic drugs following successful surgery for mesial temporal lobe epilepsy?	P	Dose reduction q 2 months: carbamazepine 100 mg; oxcarbazepine 150 mg; phenytoin 50 mg; lamotrigine, 25 mg; topiramate, 25 mg; levetiracetam, 250 mg and zonisamide, 50 mg.	> 80% of relapse during taper occurred within 2 months of dose reduction. 25% of patients attempting to discontinue AED relapsed. Reported little reliable recommendations for tapering and timing of tapering.	Epilepsia. 2011; 52(3):627–635

2011	Hessen E, Lossius Mi, Gjerstad L.	Improvement in verbal memory after withdrawal of carbamazepine and valproate in patients with well-controlled epilepsy: a randomized, double-blind study	P	Gradual taper over 12 weeks	Carbamazepine group: significant improvement in delayed recall after withdrawal. Valproate group: significant improvement in immediate recall after withdrawal.	Acta neurol scand. 2011; 123: 385–389
2012	A. Verrotti, C. D'egidio, S. Agostinelli, P. Parisi, A. Spalice, F. Chiarelli, G. Coppola	Antiepileptic drug withdrawal in childhood epilepsy: what are the risk factors associated with seizure relapse?	P	25% dose reduction q 3 months. One drug tapered to discontinuation at a time	28.6% relapse by end of study: higher in polytherapy, highest in first year of discontinuation	European journal of paediatric neurology. 2012; 16: 559 – 604
2012	Tellez-Zenteno Jf, Hernandez-Ronquillo L, Moien-Afshari F.	Discontinuation of antiepileptic drugs after successful surgery: who and when?	R	N/A	Patient characteristics that may decrease seizure recurrence after discontinuation; no taper mechanism elucidated	Epileptic disord. 2012;14(4):363-70
2013	Ettore Beghi, Giorgia Giussani, Salvatore Grosso, Alfonso Iudice, Et. Al	Withdrawal of antiepileptic drugs: guidelines of the italian league against epilepsy	R	N/A	Literature contains tapering periods as little as 1 month and as much as > 4 years. Sudden discontinuation leads to higher risk of relapse. Slow taper should be personalized to patient. The decision whether or not to withhold treatment should not consider drug being used.	Epilepsia. 2013; 54(suppl. 7):2–12

P: prospective study, P* : prospective study - abstract only, R: review, E: editorial, C: case report, N/A: not applicable

Tapering Anti-epileptics in Pain Management

Most of the data involving the tapering of AEDs for the indication of pain management came from case reports and cannot be deemed as high quality evidence. The tapering profiles were inconsistent amongst the reports. These data contribute to the idea that AEDs may require a taper upon discontinuation in pain management. The case reports indicate that patients may experience withdrawal symptoms upon acute withdrawal of therapy after being on the medication for as little as one month [13]. Gabapentin was the drug most commonly reported as eliciting withdrawal symptoms (Table 2). Some case reports give example to the risk of abruptly stopping therapy with gabapentin [9, 13] while others showed an unsuccessful taper that resulted in withdrawal syndrome [12, 14]. The tapers in the case reports were of very short time periods, 5-10 days, which are significantly shorter than the weeks to months of tapering in discontinuing AED therapy in epilepsy. Since there is not much published evidence about discontinuation of AEDs in the pain population other than case reports, it is difficult to determine if the practice of a very short taper has been successful in other scenarios or to estimate the prevalence of its practice. Particularly in the case of pain management, AEDs are typically used as adjunct therapy and because of the effects AEDs can have on the metabolism and pharmacodynamics of other drugs, consideration should be taken of concomitant therapy when discontinuing the AEDs. There is a hole in the literature concerning the specific topic regarding safe discontinuation of AED therapy in pain management patients.

Table 2. Summary of Reference Articles in Antiepileptic Drug Use in Pain Management

Year Published	Authors	Title	Study Design	intervention	Findings	Citation
2002	Troels S. Jensen	Anticonvulsants in neuropathic pain: rationale and clinical evidence	E	N/A		European Journal of Pain (2002) 6 (Suppl. A): 61±68
2002	Fermin Barrueto, Jr., Jonah Green, Mary Ann Howland, Robert S. Hoffman, and Lewis S. Nelson	Gabapentin Withdrawal Presenting as Status Epilepticus	C	N/A	patient was taking gabapentin po 8000mg/day x 9 months and no other medications. Within 3 days of running out of medication, patient presented with status epilepticus	Journal of Toxicology. Vol. 40, No. 7, pp. 925–928, 2002
2005	See S, Hendriks E, Hsiung L.	Akathisia induced by gabapentin withdrawal.	C	N/A	acute withdrawal of gabapentin may have been responsible for akathisia, altered mental status and agitation. Patient was taking gabapentin po 3600mg/day x 1 month at home	Ann Pharmacother. 2011 Jun;45(6):e31.
2010	Linda Mah, Michelle Hart	Gabapentin withdrawal: case report in an older adult and review of the literature	C	N/A	patient was taking gabapentin po 1800mg/day. Tapered off over 10-day period. Experienced abdominal pain, headache, elevated blood pressure, chills, cold sweats, nausea, insomnia, agitation, anorexia. Withdrawal symptoms only resolve with re-initiation of gabapentin and does not improve with benzodiazepine administration	JAGS. 2013 Sep; 61 (9): 1635-1637
2010	Tran KT, Hranicky D, Lark T, Jacob NJ.	Gabapentin withdrawal syndrome in the presence of a taper	C	N/A	patient was taking gabapentin po 400mg BID x 5 years as adjunct therapy in bipolar disorder. Taper by 100mg qd x 5 days then discontinued. Experienced flu-like symptoms without fever, sore throat, body ache, cough, elevated blood pressure, somatic pain, disoriented x 4, slurred speech, weak, insomnia	Bipolar Disord 2005: 7: 302–304
2011	MARTIN GROSSHANS, M.D. JOCHEN MUTSCHLER, M.D. DERIK HERMANN, M.D. OLIVER KLEIN, M.D. HARALD DRESSING, M.D. FALK KIEFER, M.D.	Pregabalin Abuse, Dependence, and Withdrawal: A Case Report	C	N/A	patient was taking pregabalin po 7500mg/day. Self weaning process resulted in sweating, unrest, arterial hypertension, tremor and cravings. Withdrawal symptoms were uncontrolled with benzodiazepines but improved with re-initiation of pregabalin.	Am J Psychiatry 167:7, July 2010

2013	HELLWIG, THADDAUS R. PHARM.D., BCPS; HAMMERQUIST, RHONDA PHARM.D.; TERMAAT, JILL M.D.	Withdrawal symptoms after gabapentin discontinuation.[Report]	C	N/A	patient was taking gabapentin at home but all po meds held in hospital. By day 3, patient began experiencing restlessness, altered mental status, agitation and anxiety. Symptoms uncontrolled with benzodiazepines but responded to re-initiation of gabapentin	American Journal of Health-System Pharmacy. 67(11):910-912, June 1, 2010
2013	Philip J Wiffen, Sheena Derry, R Andrew Moore, et al.	Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews	R	N/A	only two drugs (gabapentin and pregabalin) had good evidence for efficacy in neuropathic pain.	Cochrane Database of Systematic Reviews. 2013, Issue 11.

P: prospective study, P* : prospective study - abstract only, R: review, E: editorial, C: case report, N/A: not applicable

Discussion:

Antiepileptic drugs (AEDs) are commonly used off-label for indications such as modulating pain therapy in non-epileptic patients, bipolar disorder, neurogenic pain syndromes along with other diagnoses that exclude epilepsy. In the case of pain management in particular, AEDs are quite often used as adjunct therapy and are in the body in the presence of many other agents at unapproved dosages; this of course leads to an increased potential for significant drug interactions as well as a practice of medicine with no clear strategies for appropriately managing or discontinuing therapies. The various different factors of pharmacokinetics and pharmacodynamics need to be considered when trying to understand the complexity of the drug interactions and how to taper the medications in a way that results in the safest and most effective withdrawal of therapy along with safe and effective continuation of other therapies. This review took a thorough look of the literature with the idea of establishing best practices for tapering AEDs once the prescriber and patient have decided to discontinue this pain management therapy. The evidence is not very clear for a standardized taper schedule for these agents in their use for FDA indicated epilepsy disorders and there is even less evidence for means of discontinuation in unlabeled indications. The risk profiles for the individual agents in the class are still being elucidated decades after their approval in the way of case reports, however, their neuropsychological and psychomotor side effects with chronic use are documented in the literature. The aspect of the drugs that is still being reported as adverse events is the withdrawal syndrome of these medications, perhaps most importantly in the context of their use off-label where there is even less evidence to guide a physician's practice. Eguale and colleagues noted in their 2012 epidemiology study that the estimated use of AEDs is more commonly in off-label than in government-approved indications [7] which indicates that the physicians are less able to practice with a strong evidence base for these patients. The side effects of the medications themselves can be reason enough to lead a patient to discontinuation of therapy as can the practice of using these medications as temporary therapies rather than chronic. However, the adverse events that can occur with inappropriate discontinuation such as abruptly withdrawing or too quickly tapering a patient can be particularly severe themselves. It may then be quite common that some patients are left to continue AED therapy only for the inadequate evidence on a safe way to discontinue it. Clinical pharmacists would be greatly benefited by future research into appropriate regimens for tapering a patient off of AED therapy with consideration of the effect the removal of the AEDs from the body would have on other drug therapies the patient will continue. For instance, their pharmacokinetics are not as predictable as other common medications though this has not seemed to decrease their use, perhaps only the longevity of their use in a patient. As AEDs are not innocuous drugs, it is important to be confident in the ability to discontinue the therapy when

appropriate. This includes how and when to discontinue while also taking into consideration the use of concomitant therapies.

Conclusion:

Tapering antiepileptic drugs when discontinuing therapy in epilepsy is common practice though there is not a standard taper regimen documented consistently throughout the literature. The literature exposes an enormous amount of variation in specific tapering strategies in these patients. Tapering strategies for discontinuing antiepileptic therapy when used in pain management are not well documented. This review identifies gaps in the literature concerning safe discontinuation of antiepileptic drugs used both for the primary indication as well as pain management. Clinical pharmacists would be greatly benefited by future research into appropriate regimens for tapering patients off of antiepileptic therapy with consideration of the effect removing antiepileptic drugs from the body would have on other drug therapies the patient continues.

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