

Gabapentinoids for Chronic Pain: Do the Harms Outweigh the Benefits?

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Received date: December 3, 2018; Accepted date: December 12, 2018; Published date: December 19, 2018

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Abstract

Gabapentinoids, pregabalin (LyricaTM) and gabapentin (NeurontinTM) are anticonvulsants that have been approved for chronic pain conditions such as diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and are also widely prescribed off-label for chronic low back pain. Prescriptions for gabapentinoids have increased rapidly in the last five years, however, the evidence for its efficacy can be conflicting and will be analyzed for each of these chronic pain conditions. The adverse event rates and safety profile will be examined, including case reports of the occurrence of serious adverse events, to ascertain whether gabapentinoids have the potential to cause harm above the benefit of providing effective pain relief. Further case reports documenting serious withdrawal syndromes will add to the body of evidence to weigh the benefits over the risks and will identify areas where research is lacking. From the analysis of evidence on efficacy, adverse events and withdrawal there will be resulting recommendations for practice when considering gabapentinoid treatment for chronic pain.

Keywords: Lyrica; Gabapentin; Pregabalin; Anticonvulsants

Introduction

Chronic neuropathic pain, which is stated to persist over three months, affects at least 10% of the population worldwide and is a major burden to healthcare and the community [1]. A study conducted by Gaskin and Richard estimated the United States healthcare expenditure on chronic pain in addition to the added cost due to loss of productivity totals \$635 billion dollars each year, exceeding the amount for heart disease, cancer and diabetes [2]. The International Association for the Study of Pain defines neuropathic pain as a disease or injury to the central nervous system resulting in hyperexcitability of conducting somatosensory neurons within pain pathways [3]. This differs from nociceptive pain mechanisms that occur from thermal or mechanical tissue damage, such as that seen in acute pain from injury or surgery [4].

In a multi-modal approach to treating chronic pain, gabapentinoid anticonvulsants, including pregabalin (LyricaTM, manufactured by Pfizer Inc, New York, USA) and gabapentin (NeurontinTM, manufactured by Pfizer Inc, New York, USA) have become a favorable option to treat neuropathic pain mechanisms, being recommended as first-line pharmacotherapy by the National Institute for Health and Care Excellence [5], the Canadian Pain Society [6] and the Neuropathic Pain Specialist Interest Group [7]. Gabapentin and pregabalin are approved for use in postherpetic neuralgia, while pregabalin is additionally approved to treat diabetic peripheral neuropathy, fibromyalgia and central neuropathic pain [8]. Both are also currently widely prescribed off-label for chronic low back pain [9].

Although pregabalin has been approved for use in chronic pain for almost 15 years its popularity is rapidly increasing. Pregabalin is currently ranked 8th in government drug spending in both the United States [10] and Australia [11]; while gabapentin prescriptions have increased by 350% in the United Kingdom in the last five years [12]. With gabapentinoid therapy on the rise, it would be pertinent to review

the literature around its efficacy for both on and off-label conditions. A look into the reporting of adverse events will provide an opportunity to examine the benefits against the potential harm. A final review of evidence that demonstrates cases of withdrawal upon cessation of gabapentinoids will identify a major gap in research on this topic.

Background

Prevalence

Within English-speaking nations, the increasing pattern of pregabalin prescriptions has been remarkably similar. In the United States, pregabalin prescriptions doubled between 2012 and 2016 [13], also increasing by 150% in the United Kingdom from 2013 to 2018 [14], and increasing by two and a half times in Australia from 2013 to 2016 [15]. There may be multiple influences for this trend, though primarily the reluctance in primary care to prescribe opioids due to concerns about addiction, dependence, and misuse is a contributing factor [16,17]; only fueled by the intensifying opioid crisis in the United States, with the Centre for Disease Control and Prevention reporting over 33,000 deaths involving an opioid in 2015, 5000 more than the previous year [18].

When considering the increase in prescriptions, the incidence of the chronic pain conditions for which gabapentinoids are approved should be considered. The worldwide incidence of fibromyalgia is stated to be around 2.7% (range 0.5%-4%) [19,20], postherpetic neuralgia is said to occur in 20%-30% of the population that develops the herpes zoster rash [21], also known as shingles; while 50% of all diabetics are said to suffer from diabetic peripheral neuropathy ten years post-diagnosis [22], making these conditions extremely widespread in current chronic pain management. In fact, pregabalin was the first drug to receive FDA approval for diabetic peripheral neuropathy and postherpetic neuralgia [23] providing the only established medication option for this hard to treat population.

In addition to the broadening of regulatory approval of pregabalin for chronic pain conditions, up to 75% of prescriptions have been attributed to off-label conditions, primarily non-specific chronic low back pain [9]. There is an age-related association with the incidence of chronic low back pain as demonstrated in the systematic review of 28 studies by Meucci et al. that stated 4.2% of the population under forty is affected, which increases to 19.6% up to those aged fifty-nine, and 25.4% of adults over the age of sixty [24]. The Global Burden of Disease Study ranked low back pain the highest cause of disability, activity limitation and work absence than any other condition [25].

Mechanism of action and pharmacokinetics

Neuropathic pain results from disease or injury to the somatosensory system causing neural excitability and increased synaptic efficacy in central and peripheral pain pathways [26]. Both pregabalin and gabapentin hold chemical similarity to Gamma-Aminobutyric Acid (GABA) neurotransmitters, however, do not act on any GABA receptors or synapses [27]. There are a couple of potential mechanisms which account for the analgesic effects of gabapentinoids; these center around the reduction of pre-synaptic neurotransmitters including glutamate, dopamine, norepinephrine, serotonin and substance P which are responsible for initiating and sustaining neuropathic pain states [28]. This is achieved as gabapentinoids bind to the alpha-2-delta subunit of voltage-gated calcium channels which inhibit glutamate release [27]. Pregabalin has also been shown to target sodium-dependent ion channels significantly reducing the functional response of glutamate; as well as modulating potassium channels inhibiting the release of substance P in the spinal cord [23]. These mechanisms provide pain relief by reducing the rapid nerve firing that occurs in neuropathic pain states.

While pregabalin and gabapentin have a similar mode of action and chemical structure [29], pregabalin binds to receptors more efficiently, has greater bioavailability of up to 90%, and is more readily absorbed making it four times more potent than gabapentin [30], thus requires significantly lower treatment doses. Additionally, properties including pregabalin's negligible protein binding and linear dosing kinetics limit drug-drug interactions which have major advantages in combination therapy that chronic pain patients often require [31]. Gabapentin is prescribed less in primary care [11], possibly due to its short half-life and immediate release formulation making a less convenient three divided dose regime necessary, combined with decreased drug absorption and bioavailability as the dose increases. Pregabalin is rapidly absorbed in the gastrointestinal tract, reaching peak plasma within 60 to 90 minutes after administration in fasted subjects [4]. The half-life is six hours and a steady state is achieved within two days of regular dosing; with both being primarily excreted through the kidneys, with renal impaired patient's requiring a 50% dose reduction [32]. In a multi-modal approach to treating chronic pain, gabapentinoids are regarded as safe and have gained popularity in pharmaceutical combination therapy to target neuropathic pain.

Evaluation

To evaluate the harms against the benefits of utilizing gabapentinoids for chronic pain there will be analysis into three themes. Efficacy will examine the benefits, while adverse events and withdrawal will define potential harms. Through analysis of these themes, recommendations for practice and further research will be identified.

Efficacy

With prescriptions trends rapidly increasing, it is judicious to look into the evidence for the efficacy of gabapentinoids, most importantly for the approved pain disorders of fibromyalgia, postherpetic neuralgia, and diabetic peripheral neuropathy. The Initiative on methods, measurement, and pain assessment in clinical trials group regarding a 50% pain reduction in participants from treatment as clinically relevant, and ultimately, an effective pharmacotherapy; though 30% pain reductions are often also benchmarked for analysis [33].

Fibromyalgia is characterized by chronic widespread pain and stiffness in at least 11 of 18 specific tender points in the body which usually accompany other symptoms such as fatigue and restless sleep [4], as well as mood disorders including anxiety and depression [31]. Originally, fibromyalgia was thought to be a rheumatologic condition affecting the musculoskeletal system but it is now believed to be a neurological condition which affects pain pathways [34]. This led to pregabalin becoming the first approved drug to treat fibromyalgia prompting a series of clinical trials often with conflicting findings. A meta-analysis by Straube et al. reported the results from five high-quality randomized trials (n=3808) to conclude pregabalin is effective and safe in treating this chronic condition [35]. However, when examining the data, only 21% (300mg daily dose) and 24% (600 mg daily dose) of participants achieved 50% pain relief. Furthermore, 14% and 15% of participants attained the same level of pain relief with placebo, demonstrating the possibility that only a further 10% of participants received 50% pain relief due to the pregabalin. A similar result was achieved with around 40% of participants having a 30% pain reduction with pregabalin, where 28% achieved this outcome with placebo, again achieving a result for a further 12% of participants. For both outcomes, it could be argued that the result for pregabalin is significant though not when compared to the high amount of placebo responders. Ultimately, the results showed only 10%-12% of participants gained pain relief above those who responded to placebo, though it is impossible to determine exact efficacy rates caused exclusively by pregabalin.

The 2016 revised European League against Rheumatism guidelines does not support the prescribing of gabapentinoids for fibromyalgia despite the approval for use in neuropathic pain by the European Medicines Agency [36]. This guideline was strongly influenced by a Cochrane review published by Uceyler et al. that reported the supporting evidence as weak. Interestingly, this review has since been withdrawn due to competing and financial interests of the lead author [37]. However, the 2017 current Cochrane systematic review by Derry et al. analyzed eight studies with 3283 participants and reported that only 1 in 10 people with moderate to severe neuropathic pain had a significant drop in pain by 30%-50%; although, 80%-90% experienced adverse effects such as dizziness, drowsiness, weight gain and peripheral edema [38]. While the evidence to support the current European guidelines is withdrawn the available evidence continues to substantiate the recommendations against gabapentinoids for fibromyalgia.

Postherpetic neuralgia is a common neuropathic pain condition caused by the re-activation of the varicella virus which causes the herpes zoster rash known as shingles. The herpes roster infection affects the peripheral and central nervous system, causing inflammatory neuron damage leading to the occurrence of postherpetic neuralgia in about half of these patients [39]. This manifests as pain described as burning, throbbing, paraesthesia and

itching in the affected region which can persist for several years following the rash [39]. The research is divided on the efficacy of gabapentinoids for postherpetic neuralgia. One systematic review by Edelsberg et al. benchmarked results based on an atypically low 25% reduction in pain, which found that 21% responded to gabapentin and 22.4% responded to pregabalin, being outperformed by other pharmacologic therapies that included antidepressants and opioids [40]. This directly contrasts to a systematic review by Snedecor et al. that pooled data from seven studies to state pregabalin at or above 300mg daily was the most effective pharmacotherapy to provide 30% and 50% reductions in pain scores [relative risk vs. placebo=2.44 and 2.13, respectively] [41]. A meta-analysis Zhang et al. included eleven trials to conclude gabapentin significantly reduced pain intensity compared to placebo [MD=-0.91, 95% CI -1.32 to -0.51, $P<0.00001$] [42]. While the evidence is conflicting, the efficacy rates of gabapentinoids for postherpetic neuralgia are above those for other neuropathic pain conditions.

Diabetic Peripheral Neuropathy (DPN) occurs in around a quarter of all diabetic patients with the prevalence increased to 50% for diabetics who have suffered the disease for over 25 years [43]. DPN involves neuropathic pain accompanied by loss of proprioception or temperature perception, caused by loss of nerve fibers, affecting the feet 96% of the time [43]. There are a plethora of studies that state pregabalin provides effective pain relief to these sufferers where inadequate treatment options were previously available [44-50]. Yet again, the effective pain relief of pregabalin that is reported typically occurs in only a small percentage of participants above placebo. Furthermore, the number of positive studies that have been sponsored by Pfizer, or conducted by consultants affiliated with Pfizer, brings a question of validity and bias over this body of evidence. It has been conferred that there is a major flaw in industry-funded research, which has been shown to produce more positive results over government-sponsored studies [51,52], conceivably due to bias in the choice of hypotheses tested, alterations with study designs and selective publication [53].

There are two reviews conducted by Parson et al., [54] and Zhang et al., [43] that add to the body of evidence that supports pregabalin for DPN, both state that between 300 mg and 600 mg daily dose produces a significant reduction in pain scores. Though once again, over three-quarters of all the studies included in these reviews were sponsored by Pfizer. The meta-analysis by Zhang et al., showed pregabalin had significantly lower mean point pain scores than placebo [MD=-0.79, 95% CI -1.11 to -0.48, $P<0.00001$] evidenced through the duel analysis model of both random-effect and fixed-effect. However, five of the included studies contrasted their analysis conclusion that pregabalin was effective over placebo at achieving 50% pain reduction [43]. Zhang et al., [43] criticized the unfavorable pregabalin research in the analysis, stating population bias and study design flaws; including Ruack et al., [55] participants recognizing through informed consent that the chance of placebo was only two out of seven whereby participants assume a high chance of receiving the treatment drug potentially altering pain scores. Ruack et al., [55] recognized that their data of placebo outperforming pregabalin for DPN was largely unsupported by further research and were ultimately unable to determine whether the drug, or trial, failed. The following year, however, a large independent RCT ($n=398$) conducted by Smith et al., [56] showed similar findings that pregabalin did not significantly alter the percentage of pain responders from that of placebo.

A Cochrane systematic review by Moore et al., [57] compared the efficacy of pregabalin with postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia. These results, displayed in the figure (Figure 1), demonstrate the percentage of participants that reported 50% reductions in pain with daily doses of 150 mg, 300 mg and 600 mg against placebo. The analysis showed that there is little benefit of 150 mg against placebo in all three pain conditions, with placebo outperforming 150 mg in fibromyalgia. Furthermore, the evidence showed only a small quantity of people will benefit from pregabalin for fibromyalgia at any dose, which is consistent with the aforementioned Cochrane review findings [38]. The 600 mg daily dose of pregabalin provides 50% pain relief to an additional 30% of patients with postherpetic neuralgia and 22% of patients with diabetic peripheral neuropathy above placebo. However, both Moore et al., [57] and Zhang et al., [43] have demonstrated the number of patients that benefit from 600 mg, above a daily dose of 300 mg, is atypically small, bringing the dose of 600 mg/day into serious question.

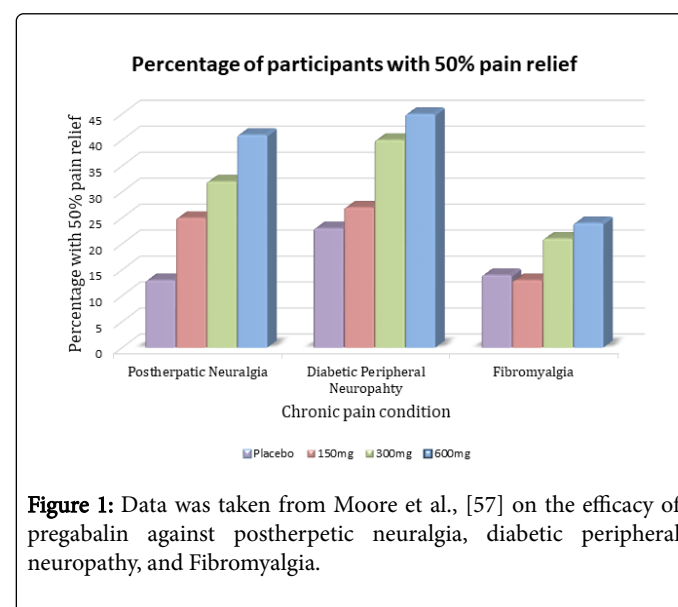


Figure 1: Data was taken from Moore et al., [57] on the efficacy of pregabalin against postherpetic neuralgia, diabetic peripheral neuropathy, and Fibromyalgia.

Chronic Low Back Pain (CLBP) was found by Giladi et al., [9] to be the most prevalent indication, accounting for up to 30%, of off-label prescriptions of pregabalin. Recently there have been three high-quality systematic reviews by Chou et al., [58], Enke et al. [59], and Shanthanna et al., [60] that reported on the efficacy of gabapentinoids for CLBP. All three papers included an array of different studies due to the reviewer's inclusion and exclusion criteria, however, all three systematic reviews concluded that there was no evidence to support gabapentinoids for CLBP. Recent randomized controlled trials conducted on participants with CLBP strengthen this body of evidence with Atkinson et al., [61] reporting gabapentin having no effect on pain scores; and Maitheson et al., [62] found no reduction in pain intensity with pregabalin. A commonly cited study by Baron et al., [63] stated when comparing pregabalin to placebo there was no difference in time to loss of therapeutic effect, which was calculated by a one-point increase in weekly mean pain scores. There is an ever-increasing body of evidence against gabapentinoids for CLBP with a growing number of prescriptions indicating a trend against the current best evidenced-based practice that needs to be addressed.

Adverse Events

The most consistently reported Adverse Events (AE) that occur from gabapentinoids are dizziness, somnolence, peripheral edema and weight gain, followed by dry mouth, blurred vision and ataxia [64-68]. Generally, it is stated that these AE's occur in the early stages of initiating medication with side effects that resolve without the need to cease treatment [66,67]. Small variations in adverse event incidence arise with a review of industry-funded RCT's by Freynhagen et al., [67] that reported rates of dizziness at 24%, somnolence 22%, and weight gain at 6%; with Semel et al., [69] review along with the European Medicines Agency both reporting dizziness occurred in 31% and somnolence in 22% of participants [70]. There is a consensus in reporting that the rate of AE's is dose-related which increases with higher doses [57,67-69]. In a large meta-analysis (n=5,802) by Zaccara et al., [71] there was no clear relationship between AE's to age, and found no differences in the incidence between neuropathic pain conditions; however, there are some conflicting results of minor differences in occurrence rates between neuropathic pain conditions [57,67,68].

There are AE's, that while not having a significant impact on systemic health, can have a massive impact on psychosocial function and quality of life; the most significant being a decline in cognitive function, mood disorders, and suicidal ideation. There has been empirical research that has demonstrated both pregabalin and gabapentin have caused a significant decline in cognitive function [61,72]; though this has not often been studied in the context of the impact on patients quality of life. There has been a significant association with gabapentinoids and memory disorders which were identified as poorly described within the literature [73,74]. The evidence to explain this cognitive decline has been provided by Eroglu et al., [75] that discovered gabapentinoids block the formation of new brain synapses in the central nervous system with pathological changes in synaptic plasticity thought to be responsible for memory defects [76].

For chronic pain patients, the worsening mood can have a large impact on functional ability. Pfizer [8] recommends the monitoring of patients initiating treatment with gabapentinoids for the emergence or worsening of mood disorders including depression and suicidal ideation. Pfizer states from 199 placebo-controlled trials the risk of suicidal ideation was 0.43%, double that of placebo, with four suicides documented with pregabalin and none with placebo. This small incidence contrast to other accounts such as Hall et al., [77] that details five cases of worsening depression and suicidal ideation out of the fifty patients they had on gabapentinoid treatment. All cases had a history of depression, though had been stable at the time of initiating pregabalin, with improvements seen in all cases after treatment ceased. However, Kustermann et al., [78] reported a patient with the first presentation of depression, or any psychiatric disorder, which resulted in a suicide attempt two months after initiating pregabalin. The patient's mental state stabilized and depressive symptoms resolved with discontinuation of treatment. In contrast, reports of gabapentinoids providing improvements in depression further complicate this evidence [79].

Another AE having an impact on quality of life is the occurrence of sexual dysfunction. A large case series observational study (n=75) by Hamed [80] investigated the effect pregabalin has on sexual function to conclude that 32% suffered from anorgasmia, 35% had significant loss of libido and 51% of men suffered from erectile dysfunction. These findings were not dose-related, occurred within weeks of initiating

treatment and improved with discontinuation. Although sexual dysfunction is less reported in studies when assessing AE's, there seems to be a high rate of occurrence above that of the most commonly reported AE's. There have been supporting studies that also report erectile dysfunction caused by pregabalin [81,82], however, further research would strengthen the need for patient assessment on sexual function during treatment with this medication.

Case reports of serious cardiac AE's can be found with Erdogan et al., [83] reporting on a patient with no cardiac history on 300 mg of pregabalin daily for neuropathic pain that presented with peripheral edema, with normal hemodynamic parameters and kidney function. Central edema with dyspnea and chest pain then developed with a computerized tomography scan finding cardiomegaly and pleural effusion. Pregabalin was identified as the culprit and ceased whereby the condition completely regressed. Gabapentin was then commenced, with a similar development of symptoms, and was subsequently ceased. A report by Adar et al., [84] presents an 80-year-old female that suffered recurrent syncope attacks and chest pain with long QT syndrome that was attributed to pregabalin, again the condition completely resolved with cessation of treatment. There are reports of gabapentinoids exacerbating the severity of established chronic heart failure [85,86], though due to the common occurrence of peripheral edema, the potential for the first onset of acute heart failure should not be overlooked.

There are also cases of hemodynamic instability including two case reports by Bozikas et al., [87] and Kino et al., [88] that describe pregabalin induced neutropenia that quickly resolved when the medication was discontinued. This resulted in their recommendations for periodic monitoring of white blood cell counts for patients on high dose regimens. There is also a total of seven case reports [89-95] found detailing comparable accounts of pregabalin-induced liver damage where other causes were excluded. Duration of treatment spanned from two days to four months with doses from as little as 50 mg a day to the max dose of 600 mg. All reports detail worsening liver function tests, at times resulting in jaundice. Liver function was restored with the cessation of medication in all cases.

Withdrawal

To assess further harms, reports of withdrawal will be discussed. The Lyrica monograph provided by Pfizer recommends a one week taper from a regular high dose pregabalin. This was demonstrated by an industry-funded study published by Kasper et al., [96] that reported low-level discontinuation symptoms after 12 and 24 weeks of treatment. Though it could be argued that this ought not to be considered long-term treatment compared to patients whose treatment spans years, even decades. With the longest trial included in this extensive review spanning less than one year, there is a gap of evidence that needs to be addressed for long-term treatment patients regarding the cessation of gabapentinoids.

There are case reports in the literature that demonstrate serious adverse events from patients in hard to treat acute withdrawal. Gahr et al., [97] report on a 38-year-old female patient with borderline personality disorder on 600 mg/day for two months, after the decision was made to wean and cease pregabalin due to no obvious indication for treatment. This was achieved by a reduction of 25 mg a day down to 350 mg/day. The patient quickly developed psychomotor agitation, arterial hypertension, tachycardia and tremor whereby another two-week detoxification regime was needed with inpatient monitoring.

Barrett, Kittler and Singarajah [98] reported on a 61-year-old-male on 300 mg/day of pregabalin for eight months, who then presented to emergency with sudden and severe withdrawal symptoms of extreme combative agitation, diaphoresis, tachycardia, hypertension, tremor and incontinent diarrhea needing ICU admission. The patient had a paradoxical reaction to benzodiazepine and lorazepam, with haloperidol and hydromorphone having little effect on his agitation. Pregabalin was unable to be administered orally due to the patient's confusion and physical inability to keep a nasogastric tube sited. Sublingual clonidine was ultimately the only treatment that provided any reduction in withdrawal symptoms.

Hellwig et al., [99] also published a case report of a 53-year-old woman, who ceased gabapentin due to the inability to ingest medications orally post endoscopy and band ligation. On day three, symptoms of agitation, anxiety, and confusion started with no response to benzodiazepines. The symptoms worsened over the next days with disorientation, headaches and light sensitivity; whereby on day 5 gabapentin was reinitiated; the patients showed significant improvement that evening and was calm, alert and orientated the next morning. Mah and Hart [100] report on a 75-year-old woman who after a ten-day taper from 1800 mg of gabapentin developed hypertension, chills, insomnia, nausea and severe abdominal cramps that were also unalleviated by benzodiazepines with blood tests and scans providing no cause; however, symptoms completely resolved three days after recommencing therapy at a renal adjusted dose.

A serious account by Barrueto et al., [101] saw a 34-year-old male present with status epilepticus, again unresponsive to lorazepam and diazepam, needing intubation plus IV phenobarbitone and phenytoin to stop the ninety-minute seizure. This was thought to be attributed to a rebound release of glutamate involving the NMDA receptors. It is reported by Pfizer that sudden discontinuation of gabapentinoids can cause seizures in epileptics, though this particular patient had no reports of previous seizures. This has been further documented in a case report by Du et al., [102] when a middle-aged woman with diabetic peripheral neuropathy developed acute on chronic renal impairment whereby pregabalin was ceased and not recommended. Four days later the patient suffered her first tonic-clonic seizure with no further seizures after resuming treatment on a renal adjusted dose of 75 mg/day. The possible initiation of seizures when ceasing gabapentinoids is a serious harm that should be taken into consideration when planning cessation of treatment.

Discussion

The efficacy of gabapentinoids varies across different neuropathic pain conditions. There is stronger evidence to support its use in diabetic peripheral neuropathy and postherpetic neuralgia over fibromyalgia, with no evidence for off-label use in chronic low back pain. Although many reported studies find significant results with gabapentinoids there is not a single study included here that have achieved the primary outcome for more than 50% of participants, with some as low as 21% [35,40]. This needs to be considered for practitioners initiating gabapentinoids, where evidence suggests that it is more likely to provide no effectiveness in reducing pain. Careful monitoring of reported pain scores should be performed with cessation of treatment for patients who receive little benefit.

With the lack of strong evidence for the efficacy of pregabalin, especially for CLBP and fibromyalgia, the question of safety should come to the forefront to assess benefit over risk. Adverse events

consistently occurred in all treatment groups over placebo, with up to 69% of patients experiencing at least one side effect [103]. The highest occurring adverse events were universally reported as dizziness, somnolence, peripheral edema, weight gain, dry mouth, blurred vision, and ataxia. However, since efficacy rates can be as low as 25% with higher adverse event rates coupled with the potential for serious adverse events, individual patient assessment should be performed to assess the benefit of continuing treatment with titration to the lowest dose that provides efficacy. While there is an abundance of data on the adverse event profile for short-term treatment, the question of long-term consequences of taking anticonvulsants in the absence of seizures, including but not limited to cognitive function and withdrawal, should be the focus for continued research.

The Australian Pharmaceutical Benefits Scheme [104] reported 43% of patients had only one script of pregabalin filled, which has been supported by a large United States database observational study [105] that claimed the percentage of prescription refills was 52.6% and 56.9% of patients that initiated therapy with gabapentin and pregabalin, respectively. With such a large percentage of patients that discontinued therapy with gabapentinoids, it could be argued that either there was a clear lack of efficacy or cessation occurred due to adverse events. Wettermark et al., [106] conducted a database observational study in Sweden and only 21.5% of the patients taking pregabalin for neuropathic pain continued to fill prescriptions after one year bearing a striking resemblance to many efficacy rates reported in this review [35,38,40,41]. However, this is contrasted to the trend in the United States, Australia and the United Kingdom that see consistently rising prescription rates.

An interesting trend with studies within this review that measured the efficacy of gabapentinoids for chronic pain conditions was the consistently high response rate to placebo [35,55-57]; whereby data showed significant responders to treatment, however, not above those which had a positive response to placebo. This was demonstrated with Straube et al., [35] that showed a mere 10% of responders over that of placebo. The placebo effect in pain management has long been recognized and discussed. Neuro-anatomy of placebo analgesia is said to involve an increase in activity in descending pain modulatory pathways as well as decreased activity in nociceptive pain processing pathways in the dorsal horn of the spinal cord [107]. Possible disease in the peripheral nervous system, such as that in postherpetic neuralgia, could account for lower placebo response rates for these trials over fibromyalgia and diabetic peripheral neuropathy. There are also contextual influences that can trigger the placebo response including doctor-patient relationships, expectations, personal characteristics and even the therapeutic ritual itself which can be challenging to measure and control [108].

Placebo response rates in pain trials were found by Arakawa et al., [109] to be increased by longer trial durations and flexible dose regimens and decreased by increasing age and higher baseline pain intensity; ultimately recommending careful consideration to trial planning and design. A review conducted by Castelnuevo et al., [108] determined that 'the placebo effect' had a moderate impact with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia trials, especially when compared to other pain conditions including complex regional pain syndrome and central neuropathic pain. With the placebo effect so prominent in pain trials it can prove difficult to adequately assess the efficacy of the comparative drug bringing the results into question. Transparency with patients regarding efficacy rates of gabapentinoids for their specific condition

may aid in facilitating lower placebo responses to determine patients who receive true benefit from treatment. This may provide more accurate efficacy rates to aid in establishing a possible benefit for patients.

The growing issue of industry-funded research influencing evidenced-based medicine for the benefit of pharmaceutical companies has been reported in many facets of healthcare. A Cochrane review by Lundh et al., [110] concluded that industry-funded studies provided more favorable results and conclusions than independent research, which correlates to the trend in results discussed in this review. From all the studies included in this review, there are more industry-funded studies than independent. This can be challenging when examining evidence as the poor methodology is not likely to account for the bias that occurs [111]. Though, industry-sponsored research should still be highly scrutinized for the occurrence of bias including a close examination of methods used, data analysis and study design flaws, with pharmaceutical sponsorship itself to be considered a risk of bias [110].

Case reports of serious withdrawal from gabapentinoids [97-101] raise issues with the recommended one week taper. Serious events including acute withdrawal syndromes, intensive care admissions and the onset of new seizures have been published. However, there is a major gap in the literature with no published trials that assess the potential impact that long-term treatment can have when patients face the task of discontinuing these medications, with no clear indication in healthcare for appropriate withdrawal treatment [98]. A large portion of gabapentinoid trials utilize a one-week titration to reach stable treatment doses with a one week taper to discontinue; however, these trials last twenty-four weeks at most, which could be argued as inadequate to correlate this to patients who have been on therapy for many years. Unfortunately, a quantitative trial design to research this issue would prove difficult, including recruiting a very specific population that has been on long-term gabapentinoids that are willing to cease their medication; though, qualitative trials may shed light on the experiences endured by this specific population. Practitioners should recognize that serious complications can arise from gabapentinoid withdrawal and an extended taper with patient monitoring in primary care should be considered for long-term treated patients.

Conclusion

With the use of gabapentinoids rapidly increasing in pain management and the large amount of conflicting evidence to support this trend, it can become difficult for clinicians to align with the current best evidenced-based practice. Gabapentinoids should not be prescribed for chronic low back pain and caution should be used in fibromyalgia, for which there is conflicting evidence. Initiating gabapentinoids for patient's suffering from postherpetic neuralgia and diabetic peripheral neuropathy should be closely supervised, with a focus on the level of pain reduction achieved. There should be swift discontinuation of therapy for patients where gabapentinoids prove not effective. With little evidence to support the efficacy of a 600 mg daily dose of pregabalin, coupled with the high potential for adverse events, practitioners should consider a maximum dose of 300 mg. Close monitoring of less reported side effects throughout long-term treatment should be performed, including, but not limited to, cognitive decline and mood disorder assessment, with cardiac, liver, kidney and sexual function also monitored. A slow monitored taper for patient's that wish to discontinue from long-term treatment should be

performed; with further research in this area desperately needed to inform practitioners on appropriate supportive treatment options for this population. All these aspects need to be considered on an individual basis when assessing the benefit over the risks for the patient's on gabapentinoids.

Conflicts of Interest

The author reports no conflicts of interest in this work.

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