Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern?

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ABSTRACT: Gabapentin is widely used in the United States for a number of off-label indications, often as an alternative to opioid therapy. Increasing evidence has emerged suggesting that gabapentin may not be as benign as once thought and may be associated with substance abuse in concert with opioids. With concerns for safety mounting, it is prudent to examine the efficacy of gabapentin across its many uses to understand the risk-benefit balance. Reviews on off-label indications such as migraine, fibromyalgia, mental illness, and substance dependence have found modest to no effect on relevant clinical outcomes. This high-quality evidence has often been overshadowed by uncontrolled studies and limited case reports. Furthermore, the involvement of gabapentin in questionable marketing schemes further calls its use into question. Overall, clinicians should exercise rigorous appraisal of the available evidence for a given indication, and researchers should conduct larger, higher-quality studies to better assess the efficacy of gabapentin for many of its off-label uses.

KEYWORDS: Treatment outcome, off-label use, marketing of health services, substance-related disorders, pain

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Introduction

Gabapentin functions as a γ-aminobutyric acid (GABA)-mimetic agent, binding to the alpha-2-delta subunit of the voltage-gated calcium channels, purportedly inferring antinociceptive, anticonvulsant, and anxiolytic properties.[1] Gabapentin was originally approved by the US Food and Drug Administration (FDA) in 1993 for epilepsy and later, postherpetic neuralgia. Owing to the multiple actions of the GABA system, gabapentin has subsequently been used for a wide variety of conditions, with up to 95% of gabapentin today prescribed for off-label indications.[2,3] Prescribers are often unaware of gabapentin's approved indications and their prescribing of gabapentin is largely guided by informal discussion with colleagues or professional meetings, as opposed to prescribers' evaluation of its merits for a given indication.[2]

Although gabapentin has been on the market for many years, prescribing in the United States increased 64% from 2012 to 2016.[4] Although the root of this increased utilization is multifactorial, a major influence is the current opioid abuse epidemic, which has led clinicians and policymakers to seek new therapeutic approaches to chronic pain management to reduce opioid prescribing.[5] Unfortunately, effective pharmacologic alternatives to opioids are limited, though one such option commonly prescribed, particularly for neuropathic pain, is gabapentin. Likely owing to several factors (cost, familiarity, noncontrolled status at the federal level, relatively benign adverse effect profile), clinicians view gabapentin as a safe alternative.[6,7]

However, in recent years, reports of recreational gabapentin abuse or intentional misuse have increased at an alarming rate,[1] along with reports of associated harm.[1,8] The risk of adverse effects appears to be particularly prevalent when combined with other central nervous system depressants, such as opioids. A recent systematic review described 31 publications documenting gabapentin abuse, and though the likelihood of abuse was relatively low in the general population, annualized data revealed a rapidly rising trend.[1] Furthermore, the rate of gabapentin abuse among patients with known substance use disorders was found to be markedly higher, in the range of 15% to 22%.[1] A subsequent study of a US commercial insurance claims database found a direct relationship between all-cause and drug-related inpatient hospital and emergency department utilization and increasing degrees of gabapentin overuse.[8] Patients with prolonged overuse of concomitant gabapentin and opioids were significantly more likely to experience an all-cause or drug-related inpatient hospital stay and, more specifically, an inpatient hospital stay or emergency department visit for altered mental status or respiratory depression.[8]

Due to the heightened concern regarding recent trends in the abuse and misuse of gabapentin, the risk profile of gabapentin may be higher than previously realized. As a result, it is

worth reconsidering whether there is sufficient evidence of efficacy to justify the public health risk that might arise from the aforementioned prescribing patterns. Accordingly, the goal of this review is to examine the history of gabapentin, relevant data on efficacy across nonapproved indications, and ethical considerations that should be considered regarding its use, to assist health care providers in applying a more stringent assessment of the risk-benefit balance of prescribing gabapentin for various off-label indications.

History

In 1993, the FDA approval of Neurontin, the original branded gabapentin, was for use as an adjunctive medication to control partial seizures.[9] Over the next several years, the manufacturer, Parke-Davis, a subsidiary of Warner-Lambert, engaged in a large marketing campaign to increase off-label prescribing of Neurontin for pain.[4] By the mid-1990s, it was well known that antiseizure medications also improved neuropathic pain not responsive to traditional medications like opioids. Due to a comparatively favorable safety profile, gabapentin posed limited risks to patients alongside effective pain management; accordingly, by 2001, 83% of gabapentin prescriptions were for nonseizure conditions.[10] Although research suggested analgesic effects, evidence was deemed only sufficient enough to justify approval by the FDA for postherpetic neuralgia in 2002. Indications for neuropathic pain in general are prevalent internationally,[11,12] but the FDA opted not to grant such a broad indication without evidence supporting efficacy of the drug across all or most etiologies of neuropathic pain, shown to be mitigated by similar disease processes.[13] With such a high barrier to approval, the company did not pursue extension of the label. However, by this time, a number of off-label uses for gabapentin had been reported, including bipolar disorder (BPD), diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome (RLS), trigeminal neuralgia, periodic limb movement disorders (PLMDs) of sleep, premenstrual syndrome, migraine headache, and drug and alcohol withdrawal seizures.[14,15] Later in 2004, the Neurontin patent expired and gabapentin became available as a generic with multibillion dollars in sales.

Widespread prescribing for gabapentin continues today, particularly for pain; in 2016, gabapentin was the 10th most commonly prescribed medication in the United States with 64 million prescriptions dispensed, an increase from 39 million in 2012.[4] Recent guidelines from the Centers for Disease Control and Prevention (CDC) recommend that other medication classes be considered before beginning opioids for chronic noncancer pain, which includes a recommendation of gabapentin as a first-line agent for neuropathic pain.[5]

Data on Efficacy

A wealth of literature has been published concerning the efficacy of gabapentin. To assemble this evidence, the Cochrane Library was first searched for systematic reviews/meta-analyses focused on gabapentin efficacy. Second, PubMed/MEDLINE and Embase were used to identify other systematic reviews/meta-analyses and primary literature using search terms "gabapentin" or "Neurontin" along with respective off-label indications. Off-label indications without systematic reviews/meta-analyses were evaluated based on largest body of primary literature available. Those indications in which a Cochrane review was available did not undergo an additional search in PubMed/MEDLINE or Embase; the secondary search instead focused on indications where gabapentin is most commonly used in clinical practice, based on author experience.

Cochrane reviews

A total of 5 high-quality, gold standard systematic reviews from Cochrane focused on gabapentin efficacy are available, for indications including acute postoperative pain,[16] migraine prophylaxis,[17] drug-resistant partial epilepsy,[18] fibromyalgia,[19] and neuropathic pain.[20] These reviews provide both favorable and equivocal evidence regarding gabapentin's efficacy, dependent on the indication (Table 1). Straube et al[16] identified 4 unpublished studies evaluating single-dose gabapentin for acute postoperative pain, including 3 for dental surgery and 1 in orthopedic surgery. Gabapentin was statistically superior to placebo, but the magnitude of effect was limited and comparable with other analgesics.[16] Among 6 trials for migraine prophylaxis, Linde et al[17] found small effects in favor of gabapentin in 2 studies, but pooled estimates failed to identify any differences in comparison with placebo either for raw reduction in headache or proportion of responders. Al-Bachari et al[18] evaluated 11 trials for gabapentin regarding seizure prophylaxis, establishing efficacy over placebo, increasing with higher doses. However, studies were limited to short-term follow-up in the adjunctive treatment setting.[18] Very limited evidence was found by Cooper et al[19] for fibromyalgia-related pain, including only 1 trial with low-quality data. In contrast to the other reviews in size, Wiffen et al[20] reviewed trials totaling nearly 6000 patients for neuropathic pain indications and found moderate effects for pain reduction at daily doses of 1800-3600 mg among patients with postherpetic neuralgia and diabetic neuropathy. This evidence supports one of gabapentin's main FDA indications.

Additional systematic reviews, meta-analyses, or other primary literature

Evidence from the literature of known off-label indications is generally lacking, based on modest to no effect on relevant clinical outcomes, with the exception of RLS (Table 2). Berlin et al[21] recently conducted a systematic review on gabapentin across several psychiatric disorders. For depression, use mainly comprised adjunctive treatment, and assessment was based on one small retrospective chart review of 27 participants. Restless

Table 1. Cochrane reviews focused on gabapentin efficacy.

AUTHOR (YEAR)	PARTICIPANTS	STUDIES	INDICATION	DOSE RANGE, MG	SELECTED OUTCOME MEASURES	FINDINGS (WITH 95% CI)	FAVORS GABAPENTIN
Straube et al (2010)[16]	370	4	Single dose for established acute postoperative pain	250-500	⩾50% maximum possible total pain relief Summed pain intensity difference	RB: 2.5 (1.2 to 5.0) NNT: 11 (6.4 to 35)	Yes (weak)
Linde et al (2013)[17]	1009	6	Prophylaxis of episodic migraine	900-2400	Headache frequency ⩾50% reduction in headache frequency	MD: –0.44 (–1.43 to 0.56) OR: 1.59 (0.57 to 4.46)	No
Al-Bachari et al (2013)[18]	2125	11	Add-on for resistant partial epilepsy	600-1800	⩾50% reduction in seizure frequency Treatment withdrawal	RR: 1.89 (1.40 to 2.55) RR: 1.05 (0.74 to 1.49)	Yes (weak)
Cooper et al (2017)[19]	150	1	Fibromyalgia pain	2400	⩾50% reduction in pain over baseline	49% (gabapentin) vs 31% (placebo)	Unknown
Wiffen et al (2017)[20]	5914	37	Chronic neuropathic pain	⩾1200	Substantial pain relief (⩾50% over baseline or very much improved on PGIC) Moderate pain (⩾30% relief over baseline or much/very much improved on PGIC)	Postherpetic neuralgia: RR: 1.8 (1.5 to 2.1) NNT: 6.7 (5.4 to 8.7) RR: 1.8 (1.6 to 2.0) NNT: 4.8 (4.1 to 6.0) Diabetic neuropathy: RR: 1.9 (1.5 to 2.3) NNT: 5.9 (4.6 to 8.3) RR: 1.4 (1.3 to 1.6) NNT: 6.6 (4.9 to 9.9)	Yes

Abbreviations: CI, confidence interval; MD, mean difference; NNT, number needed to treat; OR, odds ratio; PGIC, Patient Global Impression of Change; RB, risk benefit; RR, risk ratio.

Table 2. Other reviews[a] or literature detailing gabapentin efficacy.

AUTHOR (YEAR)	PARTICIPANTS	STUDIES	INDICATION	DOSE RANGE, MG	SELECTED OUTCOME MEASURES	FINDINGS (WITH 95% CI)	FAVORS GABAPENTIN
Berlin et al (2015)[21]	282	5	BPD	600-4800	YMRS, HDRS, CGI-BP, HARS, PSQI	Likely to be ineffective (either as add-on or monotherapy)	No
	28	2	Depression	300-1800	Change in CGI-Severity, GAF, or SOFAS Outcome status at end of treatment	Significant improvement in CGI-S, GAF, and SOFAS About 37% considered "responders" at endpoint; 18.5% "transient responders"	Yes (weak)
	69	1	Social phobia	900-3600	Change in LSAS, BSPS, MMFQ, SPIN, HAM-D, and HAM-A	Significant reductions in social phobia symptoms per clinical- and patient-rated scaled	Yes (weak)
	103	1	Panic disorder	600-3600	Change in PAS	No significant difference from placebo	No
	934	6	Conditional anxiety[b]	300-1200	Change in STAI, visual analogue scale, or verbal anxiety score	Gabapentin better than placebo at 4 wk ($P = .005$) and 8 wk ($P < .005$) for postchemotherapy Gabapentin better than hydroxyzine ($P = .023$) and placebo for perisurgical anxiety, no different from melatonin	Yes
	40	1	OCD	600-900	Change in Y-BOCS and CGI	Significant improvement at week 2 No difference at weeks 4, 6, and 8	No
	33	4	PTSD	300-3600	Change in subjective reporting	Improvement in sleep, nightmares, and flashbacks	Yes (weak)
	338	2	PTSD prophylaxis	900-1200	Change in PTSD Checklist-Civilian or Military	No difference from placebo	No
Pani et al (2014)[22]	269	5	Alcohol dependence	600-1500	Heavy alcohol use	MD: −0.45 (−0.75 to −0.15)	Yes (weak)
Minozzi et al (2015)[23]	235	3	Cocaine dependence	1600-2400	Report/evidence of use	RR: 1.07 (0.87 to 1.31)	No
Atkin et al (2018)[24]	513	6	Sleep[c]	200-1800	Polysomnographic changes (SE, SOL, WASO, SWS, TST) and SPQ	Consistent improvement in SWS Heterogeneous changes on other polysomnographic variables	Yes (weak)
Liu et al (2017)[25]	4684	26	Sleep[d]	600-3600	Pittsburgh sleep quality index global score, sleep interference score, Epworth Sleepiness Scale, polysomnographic changes	Increased efficacy vs placebo in pooled analysis of eight trials, with conflict in three trials	Yes (weak)
Shanthanna et al (2017)[26]	185	3	Chronic low back pain	300-3600	Pain relief via NRS Treatment success	MD: −0.22 (−0.5 to 0.07) RR: 0.95 (0.6 to 1.49)	No
Bordeleau et al (2010)[27]	66	1	Hot flashes	900	Proportion of patients preferring gabapentin over venlafaxine in an 8-wk cross-over trial	Preference: none (n = 2), gabapentin (n = 18), venlafaxine (n = 38)	No

Table 2. (Continued)

AUTHOR (YEAR)	PARTICIPANTS	STUDIES	INDICATION	DOSE RANGE, MG	SELECTED OUTCOME MEASURES	FINDINGS (WITH 95% CI)	FAVORS GABAPENTIN
Saadati et al (2013)[28]	60	1		900	Intensity (VAS score), duration (minutes), and frequency (per week) of hot flashes after 3 mo of treatment vs placebo	Mean (SD) at follow-up: Intensity: gabapentin (2.06 [0.78]) vs placebo (4.7 [1.2]), $P < .001$ Duration: gabapentin (0.91 [1.31]) vs placebo (2.2 [1.4]), $P < .001$ Frequency: gabapentin (4.2 [4.8]) vs placebo (13.06 [4.3]), $P < .001$	Yes
Pinkerton et al (2014)[29]	600	1		1800	Frequency (per week) and severity (mild [1] to severe [3]) of hot flashes after 3 mo of treatment vs placebo	Frequency MD: −1.14, $P < .001$ Severity MD: −0.19, $P = .012$	Yes
Adler (1997)[30]	8	1	RLS	300-2400	RLS rating scale	4 of 8 patients had beneficial response, 3 of those 4 had almost complete resolution	Yes (weak)
Thorp et al (2001)[31]	16	1		200-300	RLS rating scale	11 of 16 patients responded to gabapentin but not placebo ($P < .006$)	Yes
Garcia-Borreguero (2002)[32]	24	1		600-2400	RLS rating scale, CGI, pain analogue scale, PSQI	Significant improvement on RLS rating scale mean (SD) of gabapentin (9.5 [1.35]) vs placebo (17.9 [1.35]), $P < .001$	Yes
Happe et al (2003)[33]	16	1		300-1200	RLS rating scale, ESS, PSQI, polysomnographic changes	Significant improvement on RLS rating scale at week 4 ($P = .018$) and months 6-10 ($P = .017$) and on polysomnography PLMD ($P < .03$)	Yes
Micozkadioglu et al (2004)[34]	15	1		200	RLS rating scale, SF-36, PSQI	Significant improvement in RLS symptoms ($P < .001$), and sleep quality, latency, and disturbance	Yes
Saletu et al (2010)[35]	80	1		300	RLS rating scale, PSQI, QLI, and ESS	More pronounced improvement on sleep parameters than RLS symptoms	Yes (weak)
Razazian et al (2015)[36]	87	1		200	RLS rating scale, PSQI, and ESS	Significant improvement in RLS symptoms vs levodopa ($P = .016$) and sleep parameters	Yes

Abbreviations: BPD, bipolar disorder; BSPS, Brief Social Phobia Scale; CGI, Clinical Global Impressions Scale; CGI-BP, Clinical Global Impressions Scale for Bipolar Illness; CGI-S, Clinical Global Impressions Severity Scale; CI, confidence interval; ESS, Epworth sleepiness scale; GAF, Global Assessment of Functioning; HAM-A/HARS, Hamilton Rating Scale for Anxiety/Hamilton Anxiety Rating Scale; HAM-D/HDRS, Hamilton Rating Scale for Depression, Depressed Mood substance/Hamilton Depression Rating Scale; LSAS, Liebowitz Social Anxiety Scale; MD, mean difference; MMFQ, Marks-Mathews' Fear Questionnaire; NRS, numerical rating scale; OCD, obsessive-compulsive disorder; PAS, Panic and Agoraphobia Scale; PLMD, periodic limb movement disorder; PSQI, Pittsburgh Sleep Quality Index; PTSD, posttraumatic stress disorder; QLI, Quality of Life index; RLS, restless legs syndrome; RR, risk ratio; SD, standard deviation; SE, sleep efficiency; SF-36, Short-Form 36; SOFAS, Social and Occupational Functioning Assessment; SOL, sleep onset latency; SPIN, Social Phobia Inventory; SPQ, sleep problems questionnaire; STAI, Spielberger Strait-Trait Anxiety Inventory; SWS, slow wave sleep; VAS, visual analog scale; WASO, wake after sleep onset; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; YMRS, Young Mania Rating Scale.

[a]May include reviews from the Cochrane Library where gabapentin was not the focus of the publication and subset results are presented.

[b]Includes postchemotherapy anxiety and perisurgical anxiety.

[c]Includes primary insomnia, insomnia as comorbid diagnosis, or occasional disturbed sleep.

[d]Studies focused on RLS, neuropathic pain, alcohol dependence, hot flashes, fibromyalgia, phantom limb pain, HIV neuropathies and BPD but the review assessed sleep outcomes.

legs syndrome moderately favored gabapentin use, the lack of prospective, controlled trials across an adequate sample renders insufficient evidence to recommend gabapentin in the treatment of depression.[21] The review also identified 5 studies (including 4 randomized controlled trials) evaluating the impact of gabapentin as both adjunctive and monotherapy for BPD, which failed to demonstrate efficacy.[21] The authors noted the significant influence of marketing and uncontrolled, noncomparative reports which have worked to promote gabapentin's efficacy for this indication, despite the existing high-quality evidence stating otherwise.[21]

Berlin et al[21] also assessed gabapentin in various anxiety disorders including social phobia, panic disorder, posttraumatic stress disorder (PTSD), conditional anxiety (perisurgical or postchemotherapy), and obsessive-compulsive disorder (OCD). The strongest support was for conditional anxiety, where gabapentin significantly reduced symptoms across all studies except one and demonstrated greater improvement compared with hydroxyzine and placebo.[21] The major limitation of these studies was that more often than not, baseline anxiety scores were not assessed and compared between treatment groups, limiting interpretability. The one study that did not achieve statistical significance did measure baseline anxiety scores and thus gabapentin did not statistically lower anxiety scores at follow-up as compared with baseline. Social phobia displayed favorable results as well in one study of 69 participants where various symptoms were significantly improved.[21] However, given the lack of attempt to replicate these results, it is unclear whether gabapentin would continue to demonstrate favorable results in larger trials. The use of gabapentin in panic disorder and OCD was unable to demonstrate efficacy compared with placebo, and the use of gabapentin to prevent PTSD development was also not effective.[21] However, 2 small studies assessed gabapentin in the treatment of PTSD, and although results were largely based on subjective reporting, there were consistent reports of improved sleep with decreased nightmares and flashbacks. It is unclear whether these findings were a result of placebo effect.

Two additional Cochrane systematic reviews by Pani et al[22] and Minozzi et al[23] did not focus on gabapentin but evaluated the effects of a host of anticonvulsants on alcohol and cocaine dependence, respectively. The review on alcohol dependence identified 25 studies across 2641 participants, of which gabapentin was evaluated in a minority, primarily against placebo. Although modest positive effects were seen for reductions in heavy drinking, no differences were seen for cravings or abstinence, and the sample size remained too limited in most comparisons to draw any conclusions regarding efficacy.[22] The review on cocaine dependence identified 20 studies with 2068 participants, including gabapentin in 3 studies against placebo; gabapentin failed to result in any significant changes in cocaine use.[22] Accordingly, evidence for gabapentin in these 2 areas of substance abuse is limited to none. However, gabapentin is a second-line recommendation in the Veterans Affairs and Department of Defense 2015 clinical practice guideline for alcohol use disorder and/or withdrawal.[37]

Atkin et al[24] performed a review of gabapentin for insomnia; however, only 1 trial assessed primary insomnia, whereas the remaining 5 involved insomnia as a comorbid diagnosis, or in healthy subjects. Overall, the most consistent finding was the ability for gabapentin to improve slow wave sleep, often referred to as "deep sleep," consistent with additional 2 studies involving patients with occasional disturbed sleep and healthy subjects.[24] In the study of patients with primary insomnia, sleep efficiency and wakefulness after sleep onset each significantly improved.[24] However, these findings were not consistent among the other studies where either no change or negligible change was observed. Of note, 2 studies of insomnia as a comorbid diagnosis noted a significant improvement in sleep overall, and patients with occasional disturbed sleep experienced a significant increase in total sleep time. Again, these findings were not consistent. In a large meta-analysis of adults with sleep disturbances by Liu et al,[25] gabapentin demonstrated efficacy over placebo in 5 out of 7 composite end points. However, tolerability was comparatively lower than placebo and included studies only assessed sleep changes secondary to other indications (such as neuropathic pain and RLS).

Shanthanna et al[26] conducted a review of randomized controlled trials of at least 3 months duration for gabapentinoids and chronic lower back pain. A total of 8 studies were included in the systematic review and 6 studies for meta-analysis evaluating pain relief as the primary outcomes. Gabapentin demonstrated minimal improvement in pain compared with placebo but was accompanied by significant increases in adverse effects, including dizziness, fatigue, mental difficulties, and visual disturbances.[26]

Bordeleau et al[27] and Saadati et al[28] conducted studies of similar size to evaluate preference of gabapentin versus venlafaxine or placebo and changes in frequency, duration, and severity of hot flashes, respectively. In the cross-over trial by Bordeleau et al,[27] a higher portion of patients preferred venlafaxine over gabapentin due to greater reduction in hot flash severity and frequency with fewer adverse effects and less frequent dosing. Saadati et al[28] found gabapentin to produce significantly greater reductions of hot flash frequency, severity, and duration as compared with placebo after 3 months of therapy, with these results corroborated by Pinkerton et al[29] in a larger trial of 600 participants. Despite the heterogeneous evidence, the American Association of Clinical Endocrinologists and American College of Endocrinology consider gabapentin to be an effective treatment for hot flashes among patients with breast cancer without regard to presence of tamoxifen.[38]

Finally, gabapentin is likely used for RLS or PLMD in lieu of the costly, brand-name-only gabapentin enacarbil (Horizant),[39] despite package recommendations stating that these agents are not interchangeable due to varying pharmacokinetic properties.[39] Prior to market availability of gabapentin enacarbil, which does carry an FDA-approved indication for RLS, gabapentin was studied in a few small studies consisting of 8 to 87

participants.[30–36] Gabapentin consistently displayed significant reductions in RLS symptoms with improved sleep. Gabapentin performed similar to ropinirole in one study,[33] slightly worse than ropinirole but still effective in another study,[35] and either similar to or better than levodopa in another 2 studies.[34,36] Despite the various studies being small in nature, the consistent reporting of favorable results after treatment with gabapentin is promising and likely supports use in this population.

Ethical Concerns

Beyond the clinical data, there is additional information regarding gabapentin that should be considered. Despite the lack of robust data for off-label indications, gabapentin was aggressively and illegally marketed for numerous unapproved uses, including indications that were reviewed and rejected by the FDA.[40] This marketing strategy, carried out by Parke-Davis, included targeting physicians who frequently prescribed anticonvulsants, had the potential to influence their peers, and had an influential affiliation with a major academic medical center.[40] Residents and trainees were also targeted 2-fold to influence the physicians in which they work under and to establish familiarity with gabapentin as they entered into their own practice.[40]

Aside from the commercial marketing, gabapentin was promoted via a "seeding" clinical trial called the *Dosing to Efficacy with Neurontin: Study of Titration to Effect, Profile of Safety (STEPS)* trial.[41] Seeding trials ultimately aim to promote medications that are either under FDA review or recently FDA-approved by allowing recruited prescribers to participate as investigators in a clinical trial.[42] These trials are typically poorly designed and loosely regulated, with complex inclusion and exclusion criteria that limit external validity.[41] Physician participants are usually underqualified with nearly absent oversight on investigation sites.[41] The STEPS trial met these criteria which undermined the quality of data and scientific validity.[41] In addition, analysis of prescribing rates among trial investigators before and after trial completion was conducted, finding both increased prescribing rates and higher doses prescribed, although the intent to analyze prescribing patterns was not disclosed to investigators.[41] Despite the façade as a clinical trial, Parke-Davis repeatedly referenced this as the "best tool" in its marketing strategy to promote gabapentin.[41]

These marketing tactics came at a settlement price of US $430 million in criminal and civil liability charges in 2004,[40,43] but led to a tremendous growth in gabapentin prescriptions for off-label use from the early 1990s to early 2000s,[40] a trend that has now shaped modern practice.[44] After the settlement, use of gabapentin for off-label indications persisted, albeit to a lesser degree,[44] as prescribers were more likely to continue patients on gabapentin rather than de-prescribe as a result of legal scrutiny.[45] In addition, prescribers still have access to industry-funded literature that promotes gabapentin for off-label use.[43] Furthering gabapentin-related unethical practices, Pfizer, who bought Parke-Davis in 2000, agreed to pay US $190 million in April 2014 as part of a settlement that alleged the company took steps to delay market entry of generic versions of gabapentin.[46] After 6 weeks, Pfizer also agreed to pay US $325 million after they were accused of defrauding insurers and health care benefit providers via off-label marketing of gabapentin.[47]

Conclusions

Gabapentin has several potential therapeutic uses and may represent a safer option versus alternative agents in some of these indications, so the intent of this analysis is not to condemn its use. However, it is prudent to recognize that gabapentin has seen high rates of off-label use and increased prescribing in recent years, which fails to align with current evidence regarding efficacy. Indeed, most of the evidence for off-label use is limited to a few small, low-quality studies, often with data only weakly supporting use. Higher quality evidence, which indicates gabapentin nonefficacy, is often lost in the shuffle. Given the increasing reports of abuse and evidence of potential harms associated with gabapentin use, it is important to realize the potential risks associated with this medication and weigh these risks against this lack of reliable evidence purporting its efficacy for many of its off-label uses. Thus, we urge clinicians to apply a more stringent appraisal of the available evidence for a given indication when prescribing gabapentin off-label and call for larger, higher-quality studies to be conducted to better assess the efficacy of gabapentin for many of its off-label uses.

Author Contributions

All authors contributed to the conceptualization, research, writing and review of the manuscript. JRC provided leadership and oversight for the writing team.

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