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of pregabalin in the treatment of DPN. The only other FDA drugs approved for DPN are Capsaicin Cream (Zostrix) and duloxetine (Cymbalta).

BACKGROUND

Pregabalin is structurally related to the inhibitory transmitter gamma aminobutyric acid (GABA). However, it does not bind directly to GABA receptors but has a high affinity for the α_2 -delta site, an auxiliary subunit of voltage-gated calcium channels. Although the exact mechanism of action is unknown, it is believed that this binding may reduce excitatory neurotransmitter release and thereby reduce the symptoms of nerve pain.¹ Pregabalin has a similar pharmacological profile to its developmental predecessor gabapentin. Gabapentin is approved for the treatment of partial seizures and postherpetic neuralgia.²

REVIEW OF PREGABALIN (LYRICA) FOR THE TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY (DPN)

by

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Pregabalin (Lyrica) was approved by the Food and Drug Administration (FDA) in December 2004 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia, and as adjunctive therapy for adult patients with partial onset seizures.¹

This review will focus exclusively on the safety and efficacy

METHODS

The evidence used in this review is limited to published randomized controlled clinical trials (RCTs) and to the FDA reviews of pregabalin data submitted to the agency by the drug's sponsor prior to its approval.

Studies and articles published in medical journal supplements, throwaway journals, and published abstracts were excluded. Evidence suggests that RCTs published in journal supplements are generally of inferior quality compared with articles published in the parent journals.³ Throwaway journals are characterized as those that contain no original investigations, are provided free of charge, have a high advertisement-to-text ratio, and are non-society publications. They have been found to be lower in methodologic and reporting quality than journals containing original investigations.⁴ Published abstracts are also excluded from review as only approximately one half of all studies initially presented in abstract form may subsequently be published as full-length reports.^{5,6}

The FDA reviews are included as they may offer the only objective information about a new drug at the time of its approval. These reviews often contain unpublished RCTs and it is no longer possible to conduct an independent evaluation of the therapeutic value of a new drug without the examination of FDA review documents.

The National Library of Medicine's PubMed data base was searched for published randomized controlled trials involving pregabalin. The search was limited to the terms pregabalin, randomized controlled trials, English, and human studies. A total of four reports were found testing pregabalin in patients with DPN.⁷⁻¹⁰

EFFICACY

Five efficacy studies were reviewed by the FDA prior to the approval of pregabalin for DPN. A sixth trial was also included in the application; however, it was prematurely terminated and was not considered in evaluating the efficacy of the drug. The designs of the five studies evaluated by the FDA are summarized in Table 1.

A number of efficacy endpoints were to be used in these studies. An extensive list as well as results to these secondary parameters is available in Appendix A.

Table 1 below summarizes the design of the five trials submitted to the FDA by the sponsor.

Protocol	Design	No. of Subjects	Treatment Duration	PGB Dose
014	Trial of 2 doses of PGB given as a TID regimen	PBG: 161 Placebo: 85	Titration: 2 wks Fixed Dose: 6 wks	150 mg/day 600 mg/day
029	Trial of 3 doses of PGB as TID regimen vs amitriptyline	PGB: 240 Placebo: 97	Titration: 1 wk Fixed Dose: 4 wks	75 mg/day 300 mg/day 600 mg/day
040	Trial of 1 dose pregabalin given as TID regimen vs amitriptyline	PGB: 86 Placebo: 81 Amitriptyline: 87	Titration: 2 wks Fixed Dose: 6 wks Withdrawal: 1 wk	600 mg/day
131	Trial of 1 dose PGB as TID	PGB: 76	Fixed Dose: 8 wks	300 mg/day

Protocol	Design	No. of Subjects	Treatment Duration	PGB Dose
	regimen vs amitriptyline	Placebo: 70		
149	Trial of 3 doses of PGB as BID regimen vs amitriptyline	PGB: 299 Placebo 96	Titration: 1 wk Fixed Dose: 11 wks	150 mg/day 300 mg/day 600 mg/day

Table 2 below compares the sponsor’s results for the five trials to the FDA’s analysis. Two of the five studies 040 and 149 did not support the efficacy of pregabalin in the management of DPN.

Protocol	Primary Outcome Measure	Applicants Results	Agency Results
014	Final weekly mean pain score	600 mg/day was significantly better than placebo	150 and 600 mg/day were significant
029	Mean pain score	300 and 600 mg/day significant, 150 mg/day not significant	300 and 600 mg/day significant
040	Mean pain score	600 mg/day was no more significant than placebo, amitriptyline was	Agency did not reanalyze data, agreed with applicant
131	Final weekly mean pain score	300 mg/day was significant	300 mg/day was significant
149	Final weekly mean pain score	150 and 300 mg/day not significant, 600 mg/day significant	150, 300, and 600 mg/day were not significant

Studies 014, 029, and 131 have been published. Studies 031 and 014 were published in the *Journal of Pain* in 2004 and 2005, respectively. Study 029 was published in the *Journal of Neurology* in 2004.¹²⁻¹⁴ Two studies, 040 and 149, remain unpublished, both of which produced results unfavorable to the use of pregabalin in DPN.

Four of the studies included amitriptyline as an active comparator, however, only study 040 included amitriptyline in the final analysis. Study 040 found that 600 mg per day of pregabalin was not

statistically different compared to placebo but amitriptyline was.

The maximum recommended dose for pregabalin in DPN is 100 mg three times daily. The label states that higher doses do not provide additional benefit, but do increase adverse effects.¹ Out of these five studies, only two showed 300 mg per day to be effective in the primary efficacy outcome. In conclusion, pregabalin has shown inconsistent efficacy in the treatment of diabetic peripheral neuropathy.

SAFETY

Deaths

In controlled studies in patients with DPN, four deaths were reported. The FDA safety officer noted that all of those patients were

treated with pregabalin. Three of these patients died while taking the drug during the trial, while the other patient died after prematurely discontinuing pregabalin during the trial. These cases are summarized in Table 3.¹⁵

Body System	Cause of Death	No. of Patients
Body as a whole	Sudden Death	1
Cardiovascular	Myocardial Infarction	1
	Heart Failure	1
Pulmonary	Pulmonary Congestion	1

Dropouts

From the data reported, it was determined that more pregabalin-treated subjects withdrew due to

adverse events (9%) compared to that of placebo (4%). Twice as many placebo subjects withdrew due to lack of efficacy compared to pregabalin treated patients.¹⁶

Patient Status	Placebo (n=459)	Pregabalin (n=979)
Completed	365 (79.52%)	732 (74.77%)
Reason for Discontinuation:		
Adverse Event	17 (3.70%)	86 (8.78%)
Lack of Efficacy	27 (5.88%)	33 (3.37%)
Lack of Compliance	4 (0.87%)	10 (1.02%)
Lost to Follow-up	1 (0.22%)	0 (0.0%)
Other*	45 (9.80%)	118 (12.05%)
*Other = withdrawal of consent, loss to follow-up, and early termination per the FDA or failure to meet prequalification criteria		

The most common adverse events associated with premature discontinuation from the study of pregabalin-treated patients, occurring at a frequency of less than 1 percent were: dizziness, somnolence, and headache.¹⁶

percent in the pregabalin and placebo groups respectively.

Serious Adverse Events (SAEs)

The number of dropouts in the pregabalin clinical trials for DPN was relatively high, 75 percent and 80

It was reported that 3.9 percent (38/979) of pregabalin-treated patients and 2.4 percent (11/459) of placebo treated patients experienced at least one SAE in the DPN controlled trials. No SAE was

reported occurring at a frequency of greater than 1 percent in patients

treated with pregabalin.¹⁷

Body System	SAE	Placebo (n=459)	Pregabalin (n=979)
Body as a whole	Chest pain	1 (0.22%)	5 (0.51%)
	Accidental injury	0 (0.00%)	4 (0.41%)
	Infection	1 (0.22%)	3 (0.31%)
Respiratory system	Pneumonia	1 (0.22%)	3 (0.31%)
	Dyspnea	0 (0.00%)	2 (0.20%)
Cardiovascular	CHF	1 (0.22%)	3 (0.31%)
	MI	0 (0.00%)	3 (0.31%)
	Angina pectoris	0 (0.00%)	2 (0.20%)
	CVA	0 (0.00%)	2 (0.20%)
Metabolic/Nutritional disorders	Hypoglycemia	0 (0.00%)	2 (0.20%)
Digestive system	Vomiting	0 (0.00%)	2 (0.20%)

Serious Adverse Events (SAEs) of Interest

There were several SAEs that the FDA found remarkable that required further investigation. Those included adverse events related to the eyes, skin, and metabolic disorders.¹⁷

Skin-Related

Because patients with DPN are at significant risk of skin ulcers, the adverse event database was queried to identify reports of dermatological adverse events in diabetic patients to see if this is suggestive of skin abnormalities that would place this population at even

higher risk of developing this type of adverse event. Rash was the most common skin-related AE, occurring in greater frequency than placebo (8/459, 1.74%) versus treatment at all doses (10/979, 1.02%). Otherwise, for all other skin-related adverse effects, there was effectively no difference between the placebo and pregabalin treatment groups.¹⁷

Since skin ulceration is of greatest concern in the DPN patient population, a closer review of the six patients (6/1438; 0.4%) experiencing this AE in controlled trials was done. These events are summarized in Table 6.¹⁷

Subject Number	Treatment Assignment/ Dose (mg/day) at AE onset	Serious AE?	Study Day of AE Onset
029-030009	Placebo	No	37
040-073-005	Amitriptyline 75 mg	No	43
040-112016	Pregabalin 600 mg	No	48

Subject Number	Treatment Assignment/ Dose (mg/day) at AE onset	Serious AE?	Study Day of AE Onset
173-336010	Pregabalin 300 mg	No	4
149-356024	Pregabalin 150 mg	Yes	36
149-391010	Placebo	No	10

Because the incidence of skin ulcer in the placebo group was 0.4 percent (2/459) and 0.3 percent (3/979) in the pregabalin treatment group, there is an unlikely association with pregabalin and a greater risk of skin ulceration. However, the controlled trials were relatively short (≤ 12 weeks) and may not accurately capture the incidence of skin ulceration in DPN patients treated with pregabalin.¹⁷

Eye-Related

In both controlled and uncontrolled trials, many patients

reported having visual adverse effects including the following: abnormal vision, amblyopia (“blurry vision”), diplopia, or visual field defect. More subjects experienced these adverse effects in the pregabalin treatment group than those taking placebo, which suggests that pregabalin is probably the cause.¹⁷

In DPN studies, blurred vision and vision abnormalities occurred at a higher frequency in pregabalin-treated patients than those in the placebo group. It is believed that these adverse events may be dose-dependent as well.¹⁷

Adverse Effect	Placebo (n=459)	All Pregabalin (n=979)	Total pregabalin daily dose (mg/d)		
			150 mg/day (n=212)	300 mg/day (n=321)	600 mg/day (n=369)
Abnormal vision	1 (0.22%)	11 (1.12%)	1 (0.47%)	4 (1.24%)	5 (1.36%)
Amblyopia	7 (1.53%)	35 (3.58%)	3 (1.42%)	9 (2.80%)	21 (5.69%)
Diplopia	0 (0.00%)	8 (0.82%)	2 (0.94%)	4 (1.24%)	1 (0.27%)
Visual field defect	5 (1.09%)	6 (0.61%)	3 (1.42%)	1 (0.31%)	2 (0.54%)

Metabolic Adverse Events: Hyperglycemia and Hypoglycemia

In DPN controlled trials, there were 17 reports of hyperglycemia, one of which was serious, but unlikely drug-related. There were 22 patients that experienced 36

episodes of hypoglycemia. Two of those were serious, and not believed to be related to the study drug. As seen in Table 10 below, there is a greater risk of glucose abnormalities with pregabalin compared to placebo.¹⁷

Adverse Effect	Placebo (n=459)	Total pregabalin daily dose			
		All PGB* (n=979)	150 mg/day (n=212)	300 mg/day (n=321)	600 mg/day
Hyperglycemia	3 (0.65%)	14 (1.4%)	4 (1.9%)	5 (1.6%)	5 (1.4%)
Hypoglycemia	5 (1.1%)	17 (1.7%)	7 (3.3%)	5 (1.6%)	4 (1.1%)

*Includes 75 mg/day

Peripheral Edema

For all indications in controlled trials, the overall incidence of peripheral edema was higher in the pregabalin treated groups compared to placebo: 6.1 percent vs. 1.8 percent respectively. In DPN studies alone, there was a 9.4 percent

frequency of this adverse effect. This AE led to the discontinuation of study medication in less than 1 percent of patients, most of which were DPN or post-herpetic neuralgia. Also of note in DPN, patients between the ages of 65-74 were found to be at a higher risk for developing this adverse effect.¹⁷

Placebo (n=459)	Pregabalin Total Daily Dose in mg/day (BID and or TID)						
	150 mg/day (n=212)	200 mg/day	300 mg/day (n=321)	400 mg/day	450mg /day	600 mg/day (n=369)	Any dose (n=979)
11 (2.4%)	13 (6.1%)	-	30 (9.3%)	-	-	46 (12.5%)	92 (9.4%)

The risk of peripheral edema was six times greater for pregabalin patients taking a thiazolidinedione (TZD), such as pioglitazone (Actos) and rosiglitazone (Avandia), compared to placebo patients taking a TZD (19% vs 3%). Among pregabalin treated patients, more patients taking a TZD reported peripheral edema and congestive heart failure compared to pregabalin treated patients who were not taking a TZD.¹⁸

The FDA concluded that the concomitant treatment of pregabalin and TZDs appears to result in an additive effect, and possibly a synergistic effect, on peripheral edema. Concomitant treatment may

also increase the risk of congestive heart failure.¹⁸

Controlled Substance Scheduling

Pregabalin is a Schedule V controlled substance. The FDA originally suggested that the drug be considered for inclusion in Schedule IV of the Controlled Substances Act. However, Pfizer argued that pregabalin did not fit the criteria for scheduling and presented their case opposing scheduling to the FDA. While there was agreement by both the FDA and Pfizer on the data used, there was considerable difference about how to interpret that data.¹⁹

The FDA summarized the evidence in the following manner. The data suggests that pregabalin possesses a substantial potential risk for abuse. However, evidence does not support the placement of pregabalin into Schedule IV, but rather, Schedule V.

Pregabalin has a rapid loss of euphoric effect, matching the rapid decline in self-administration rate, and fewer withdrawal effects following discontinuation than other Schedule IV drugs. Pregabalin is also not related pharmacologically to other products with known abuse liability. Placement of pregabalin into Schedule V will not reduce the ability to detect abuse should it occur in post-marketing, and to react accordingly.²⁰

Conclusion

Pregabalin should not be used as a first line treatment for diabetic peripheral neuropathy but may be used for refractory cases. The drug is a controlled substance with risk for abuse. Other concerns are the relatively short duration of clinical trials, less than 12 weeks; inconsistent efficacy data at the recommended maximum dose of 300 mg/day as well as the comparative data versus amitriptyline.

Pregabalin's adverse effects of visual changes and peripheral edema need to be considered especially in this population in which the drug is likely to be prescribed. The six fold increase in peripheral edema seen in patients taking

pregabalin in combination with a TZD is troublesome.

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THE BEERS LIST: BUPROPION INDUCED SEIZURES IN THE ELDERLY

by

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The Beers List is one of the most widely used set of criteria for safe medication use in elderly patients. The list was developed using expert opinion from nationally recognized specialists in geriatric care, clinical pharmacology, and psychopharmacology. Few randomized controlled trials have

been undertaken in patients 65 years and older. Therefore, gaps in medical knowledge must be filled by substituting expert opinion for clinical trial evidence.¹

Bupropion (Zyban, Wellbutrin, Wellbutrin SR, and Wellbutrin XL) lowers seizure threshold and was added to the Beers List because of this potential adverse drug reaction.

The risk of seizure while on bupropion is not only dose-related but is also based on patient factors such as clinical situation and concomitant medications. Patient factors to consider before prescribing bupropion are those that may increase the risk of seizure such as history of head trauma or previous seizure, central nervous system tumor, and severe hepatic cirrhosis. Clinical situations that may increase the risk of seizure include excessive use of alcohol or sedatives, addiction to opiates, cocaine, or stimulants, use of over the counter stimulants, and diabetes treated with oral hypoglycemics or insulin. Other medications that lower the seizure threshold include antipsychotics, theophylline, systemic steroids, and other antidepressants. Also, bupropion is excreted by the kidneys, and so accumulation and potential toxicity may be greater in patients with impaired renal function.²

Fleet et al. evaluated clinically significant adverse reactions to bupropion in a study involving 1,310, patients. A total of 1,153 received bupropion at doses ranging from 15 to 1200 mg per day. These patients

were compared to 196 patients receiving a tricyclic antidepressant (TCA) at doses ranging from 25 to 300 mg per day and 177 patients who received placebo. Major motor seizures occurred in two normal volunteers and eight patients taking bupropion at doses 450 mg per day or higher. None of the patients experiencing a seizure were over the age of 60. There were no seizures in patients taking placebo or TCAs. Electroencephalograms (EEGs) were also measured in this study; however, no clinically significant changes were seen.³

The relationship between seizures and bupropion use was studied using manufacturer's adverse event reports. This review included 4,259 patients who received doses of bupropion ranging from less than 150 mg per day to 900 mg per day. Seizures occurred in 34 of these patients. Table 1 below summarizes seizure frequency with bupropion use by age group. No significant differences were seen between each of these groups.⁴

Age in years	< 18	18-29	30-39	40-49	50-59	60-69	≥ 70
Seizure Frequency (%)	0.0	1.1	1.1	0.9	0.2	0.2	0.0

In a study by Johnston et al, 3,277 patients were followed in a prospective, multicenter evaluation of the safety of bupropion. Patients included in this study ranged from 17 to 88 years of age, and 451 (14%) were 60 years of age or older. Of these patients, 13 patients experienced seizures while taking bupropion at daily doses ranging from 300 mg to 450 mg. This corresponds with a seizure rate of approximately 0.4 percent. Only one of these patients was over the age of 60 years. However, this patient developed hyponatremia, a predisposing factor to seizures. The development of this patient's hyponatremia appeared to be caused by an unusual diet which was started two weeks before the seizures occurred.⁵

This article is not an extensive review of the literature relating to the association of bupropion and seizure. The references used in this article were chosen primarily to provide readers with literature documentation of seizures occurring in patients 65 years of age or older taking bupropion. As with many other medications on the Beers List, evidence from randomized controlled trials is limited. There is no clear evidence indicating whether or not bupropion is safe to use in the elderly. Although a gap in the literature on this topic exists, it would be reasonable to consider this antidepressant as unsafe to use in the elderly population.

Because bupropion is metabolized by the liver and excreted by the kidneys, physiologic changes that occur as people age may lead to toxic adverse effects. If possible, other antidepressants should be considered in this age group. Because bupropion poses an unnecessarily high risk in persons who are older and with a seizure disorder and there are safer alternatives available, this medication has been placed on the Beers List and should be avoided in the geriatric population at risk for seizures.

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COMMENTARY WHAT HAPPENED TO CONGRESSIONAL OVERSIGHT OF THE FDA?

Today, Congressional oversight of the Food and Drug Administration (FDA) is almost nonexistent. This was not always the case. Beginning in late 1959

hearings conducted by Senator Estes Kefauver that ultimately led to the requirement that drugs are both safe and efficacious before marketing through the mid-1960s and much of the 1980s Congress regularly investigated the pharmaceutical industry and probed the regulatory histories of dubious drugs in careful detail, uncovered FDA weaknesses and ordered corrections.

Congressional oversight of the FDA and the pharmaceutical industry began to languish in the late 1980s. Oversight spiraled precipitously downward in 1992 with passage of the Prescription Drug User Fee Act (PDUFA). This Act allows the industry to pay so-called user fees as a way to speed FDA approval of new drugs (see *The Drug Information Letter* October 2005).

The Constitution grants no formal, express authority to Congress to oversee or to investigate the executive or federal agencies such as the FDA. Congress's oversight authority derives from its "implied" powers in the Constitution, public laws, and House and Senate rules. It is an integral part of the American system of checks and balances and is a vital part in ensuring that the public has access to safe and efficacious drugs.

There has been only one serious Congressional investigation of the FDA since the late 1980s. This hearing was held on November 18, 2004 by Senator Charles Grassley, chairman of the Senate Finance Committee. The star witness was

FDA physician and medical epidemiologist David Graham who told the lawmakers that rofecoxib (Vioxx) caused between 88,000 and 139,000 cardiovascular events while on the market with 40 percent of these events leading to death. "Vioxx could possibly be the single, greatest drug safety catastrophe in the history of this country," he said. "I strongly believe this should have been and largely could have been avoided, but it wasn't. Over 100,000 Americans have paid dearly for this failure. In my opinion the FDA has let the American people down."

A remarkable aspect of the Grassley rofecoxib hearing was that the Senate Finance Committee does not have jurisdiction over the FDA. The Finance Committee's primary responsibility is the financial oversight of the Medicare program. Grassley reasoned that rofecoxib had needlessly cost Medicare millions of dollars and that Congressional hearings were in order. He was criticized by some colleagues for overstepping his authority.

Senator Grassley has said that his committee will continue to hold hearing until they get to the bottom of the rofecoxib issue. After 19 months these hearings have yet to materialize.

The Senate committee with jurisdiction over the FDA is Health, Education, Labour, and Pensions (HELP). So far, the HELP committee has been of no help in regard to FDA oversight.

There is ample ammunition for Congress to conduct additional FDA oversight hearings. The story returns to rofecoxib and FDA epidemiologist David Graham. According to a sealed transcript of videotaped testimony taken for rofecoxib litigation of his remarks obtained by Bloomberg News Graham said "I experienced threats, intimidation and actually what, in my view, appears to have been a very organized and orchestrated campaign to smear and discredit me," and that FDA officials worked "hand in glove" with Merck, the manufacturer of rofecoxib, to tarnish his reputation.

A chilling comment in Graham's testimony that has implications for drugs other than rofecoxib is that FDA employees who try to block a drug's approval or limit its marketability are "severely reprimanded, pressured, criticized and threatened."

Even if David Graham is overstating the case against rofecoxib the questions left from the Grassley hearings and these latest allegations required Congressional oversight. Congress are the only ones who can get to the bottom of the story.

Is there an answer to the question "What happened to Congressional oversight of the FDA?" Not without Congress. A plausible answer at this time is "pharmacopolitics"

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