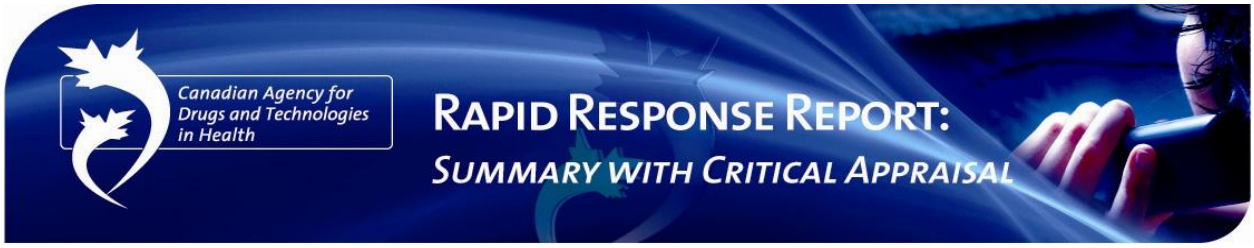

TITLE: Abuse and Misuse Potential of Pregabalin: A Review of the Clinical Evidence

DATE: 24 April 2012

CONTEXT AND POLICY ISSUES

Pregabalin (Lyrica) is an anticonvulsant approved in Canada and the United States (US) since 2005 to treat neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and pain associated with fibromyalgia in adults, and approved by the European Commission in 2006 to treat generalized anxiety disorder.[1,2] The maximum dose of pregabalin depends on its indication but should not exceed 600 mg/day.[3]

Clinical studies including 5500 patients showed that euphoric effects were reported more frequently in pregabalin groups versus placebo (4% vs. 1%, respectively).[4] A clinical abuse liability study in 15 drug and alcohol abusers found that pregabalin and diazepam differentiated from placebo consistently and suggested that pregabalin had a potential for euphorigenic activity in susceptible populations.[5] Therefore, pregabalin was scheduled by the US Drug Enforcement Administration under the Controlled Substances Act as a Schedule V drug, indicating that it had abuse potential.[5] In Canada, it was listed under schedule F, as a 'prescription drug'.[6]

Considering that pregabalin's positive psychic effects were limited and did not continue with time or continued drug use in some clinical trials, and that withdrawal effects of pregabalin were less severe than those with substances currently controlled in Schedule IV, pregabalin was not categorized in Schedule IV in the USA.[7] Although Schedule V drugs are defined as having a low potential for abuse relative to the drugs in Schedule IV, abuse of Schedule V drugs may lead to limited physical dependence or psychological dependence.[3] The Swedish authorities reported abuse liability of pregabalin in an issue of the European Journal of Clinical Pharmacology in 2010.[8] Pregabalin has also been listed as a new recreational psychoactive substance in the relevant EU agencies in 2010.[9] The potential of misuse of pregabalin was not typically mentioned in the prescriber's aids.[9]

Gabapentin was approved by FDA for the adjunctive treatment of complex epilepsy and postherpetic neuralgia in adults and used to reduce withdrawal and rebound symptoms associated with other anti-anxiety agents in psychiatry.[9,10] Gabapentin-induced hypomania and mania as well as gabapentin-associated aggression have been reported.[10] Both pregabalin and

gabapentin are GABAergic, and pregabalin is structurally related to gabapentin.[9] Pregabalin has shown greater potency than gabapentin in preclinical models of epilepsy, pain and anxiety.[10] However, the precise mechanism of action of these two drugs on psychotropic action is still unclear.[9,10].

The purpose of this report is to review the clinical evidence for the potential of abuse and misuse of pregabalin, particularly compared with gabapentin.

RESEARCH QUESTION

What is the clinical evidence for the potential misuse and abuse of pregabalin?

KEY MESSAGE

There is a limited volume of evidence regarding the abuse and misuse potential of pregabalin. Existing evidence is generally of low quality and suggests that certain populations with a history of substance abuse may be at increased risk to abuse pregabalin.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, Ovid PsychINFO, The Cochrane Library (2012, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and an abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and March 23, 2012.

Selection Criteria and Methods

One reviewer screened titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults
Intervention	Pregabalin (trade name: Lyrica)
Comparator	None specified
Outcomes	Drug abuse, illicit use, misuse, drug diversion, addiction
Study Designs	Health technology assessments, systematic review and meta-analyses, randomized controlled trials, non-randomized studies, case studies and case series

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria or were duplicate publications.

Critical Appraisal of Individual Studies

The methodological quality of included studies on pregabalin potential of abuse and misuse was performed using the SIGN50 methodological checklists.[11] Detailed checklist results are not presented. Instead, strengths and limitations of each included study are summarized and described.

A formal quality assessment of non-comparative studies or case reports was not conducted since these study designs are considered to be inferior quality. The quality of these studies will be discussed with other limitations.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 216 citations. Upon screening titles and abstracts, 206 citations were excluded and 10 potentially relevant articles were retrieved for full-text review. One potentially relevant report was identified through grey literature searching. Of the 11 potentially relevant reports, four did not meet the inclusion criteria. The study selection process is outlined in a PRISMA flowchart (Appendix 1). Among the seven articles included in this review, three articles reported abuse liability for pregabalin,[2,5,8] three articles reported pregabalin abuse,[3,12,13] and one reported pregabalin misuse.[9] Two additional references of potential interest on pregabalin overdose use are provided in the Appendix 2.

Summary of Study Characteristics

Study design

Two double-blind, cross-over RCTs,[2,5] one database analysis (data-mining study),[8] one analysis of anecdotal online reports,[9] and three case reports [3,12,13] were included in this review. No health technology assessments, systematic reviews and other observational studies were identified. The seven included articles originated from the United States,[2,3,5] the United Kingdom,[9] Sweden,[8] Turkey,[13] and Germany[12] and ranged in date from 2004[5] to 2012.[2]

Population

Two RCTs reported the abuse potential for pregabalin for 16 healthy volunteers[2] and 15 drug and alcohol abusers[5], respectively. The Swedish database analysis investigated the abuse liability in 16 patients with unknown indication, non-specified anxiety or non-specified pain and generalized anxiety disorder between 1980 and 2009.[8] The analysis of online reports summarized the information on recreational misuse of PGB, compared with gabapentin, from 108 websites monitored on a regular basis between Jan. 2008 and Aug. 2010.[9] Three case reports described pregabalin abuse for one patient with neuropathic abdominal pain syndrome under pain treatment and repeated use of opioid drugs,[3] one patient with epilepsy and bipolar disorder and clonazepam abuse,[13] and one patient with a history of alcohol and cannabis abuse as well as heroin dependence,[12] respectively.

Interventions

One cross-over RCT investigated 75mg pregabalin, 150mg pregabalin, 10mg Oxycodone, and 75mg pregabalin combined with 10mg Oxycodone, compared with placebo.[2] The other cross-over RCT investigated 450mg pregabalin compared with 30mg diazepam or placebo at a single dose.[5] Swedish database analysis reported pregabalin 300 to 4200 mg per day, mostly taken as single doses[8]. The analysis of online reports provided the comparison of misuse between pregabalin and gabapentin with different doses and administrations.[9] Three case reports described that pregabalin was increased to 7500 mg/day [12], 3000mg on six or seven occasions in a two month span,[13] and 88,500 mg within 28 days [3].

Outcomes

Subjective effects, including overall liking and wanting (to receive PGB again) and euphorigenic activity were evaluated in two RCTs.[2,5] The potential of pregabalin abuse, addiction, dependence, diversion, or withdrawal were evaluated in the analyses and case reports.[3,8,9,12,13] The study characteristics are summarized in Appendix 3.

Summary of Critical Appraisal

Because the reported details for one cross-over RCT was limited,[5] one cross-over RCT[2] was appraised in this review. The study had clearly described research questions, inclusion and exclusion criteria, interventions, and outcome measures. Double-dummy methods and a one-week wash-out period between any two experimental conditions were applied in the study. Repeated-measures analysis of variance was used to analyze effects. However, the study did not provide the methods of randomization, and allocation concealment, as well as baseline characteristics of subjects between groups. Both RCTs were self-described as double-blind, but no method for blinding outcome assessors was described. The sample size of the studies was limited and the generality of the study findings is limited to the acute doses investigated and non-drug-abusing volunteers tested. A summary of the strength and limitations of the eligible study are summarized in Table 2.

Table 2: Summary of Critical Appraisal

First Author, Publication Year, Country	Strengths	Limitations
Zacny,[2] 2012 USA	• The research question is clearly focused. • This randomized cross-over trial was conducted in a departmental laboratory with double-dummy method and at least one week wash-out period between any two experimental conditions. • Healthy adult volunteers were involved in the study without a history of psychiatric or substance use disorders or any significant medical conditions. • PGB 75mg, PGB 150mg, Oxycodone 10mg, PGB 75mg	• The study does not provide information about the methods of randomization • Allocation concealment is not reported • Blinding of outcome assessors is not reported • Baseline characteristics of subjects between groups were not provided. • Missing data or drop outs and related methods to handle them were not provided. • Small sample size (n=16) • The generalizability of the

First Author, Publication Year, Country	Strengths	Limitations
	combined with Oxycodone 10mg, and placebo were investigated based on previous research. • Five forms and five tests were used to measure subjective effects and psychomotor and physiological outcomes, respectively, to ensure a standard, valid and reliable measurement • Repeated-measures analysis of variance was used to compare peak (highest value obtained) or trough (lowest value obtained) effects. • This study was supported in part by the National Institute on Drug Abuse	study findings is limited to the acute doses investigated and non-drug-abusing volunteers tested.

Summary of Findings

One cross-over RCT shown no increased ratings of abuse liability-related effects (e.g. drug liking or wanting) with 75mg and 150mg pregabalin per day in healthy volunteers. The combination of 75mg pregabalin and 10mg oxycodone increased ratings of having pleasant /unpleasant bodily sensations, taking the drug again and coasting (feeling spaced out) compared with placebo, while each drug alone did not alter subjective effects.[2]

The other cross-over RCT reported that participants taking 450mg pregabalin had more 'drug-taking behavior' (e.g. good drug effect and high) than diazepam 30mg in drug and alcohol abusers and the effect of pregabalin had a one hour delayed onset compared with diazepam.[5].

The Swedish database analysis identified 16 reports concerning pregabalin out of 198 reports indicative of abuse or addiction to any drug between 1980 and 2009. Thirteen of the 16 reports of pregabalin abuse indicated a history of past or current substance abuse, and two patients sold their prescribed medication. No case indicative of abuse or addiction to gabapentin was identified.[8]

The analysis of anecdotal online reports revealed the recreational misuse potential for pregabalin compared with gabapentin. Pregabalin misusers were profiled as individuals with a history of recreational polydrug misuse; different dosages of pregabalin were associated with a vast range of effects and most dosages were reported in excess of the clinically advisable maximum level 600mg (up to 5g); misuse mostly occurred orally but intravenous, rectal, and 'parachuting' administration was also reported; time to onset of effect was between 10 minutes and 2 hours, depending on the route of administration; tolerance was developed rapidly and wore off quickly after drug cessation which led to self-administered increase of dosage. Among gabapentin misusers, heavy sedative and psychedelic effects were also noticed. Tolerance of gabapentin was also developed very rapidly which led to self-administered increase of dosage. However, the dosage of pregabalin to achieve the same recreational high was far less than that of gabapentin, and the observations in the analysis were consistent with the fact that pregabalin

was characterized by higher (2.5 times) potency, quicker absorption rates, and greater bioavailability levels than gabapentin.[9]

One case study reported that the patient felt euphoria on high doses of PGB.[13] One patient who had a history of opioid-seeking behavior showed similar drug-seeking behavior with pregabalin.[3] One patient who repeatedly complained of a heavy craving for pregabalin, discontinued detoxification treatment prematurely, and relapsed immediately at home by taking high dose pregabalin.[3] A summary of the findings is presented in Appendix 4.

Limitations

Because pregabalin is not recognized as a drug with high-abuse potential, data on pregabalin abuse and addiction are lacking.[3] Although there are some clinical trials regarding pregabalin treatment for patients with chronic pain (non-drug-abusers), it is difficult to interpret some outcomes related to abuse liability in these studies. For example, measures as drug liking and desire to take the drugs again could increase, not necessarily due to positive subjective effects such as euphoria, but due to the pain-relieving properties of the drugs.[2] In the absence of high quality evidence, observational studies, including case studies, were included in this review.

The quantity of evidence on the potential for abuse and misuse of pregabalin is limited to two cross-over RCTs,[2,5] one database analysis,[8] one analysis of anecdotal online reports,[9] and three case reports[3,12,13] in this review. The quality of the evidence is generally low. The sample sizes of the two cross-over RCTs are small (n = 15 and n = 16) and the generalizability of one study findings is limited to the acute doses investigated and non-drug-abusing volunteers tested,[2] while the information reported by the other study is so limited that the study appraisal could not be conducted.[5] The non-comparative- database analysis and online report analysis only provides signals, but not evidence of, abuse liability for pregabalin and further study is needed.[8,9]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Pregabalin does not have abuse liability-related subjective effects at the acute doses in non-drug-abusing volunteers.[2] Pregabalin has a potential for euphorigenic activity in susceptible populations[5] and may be associated with an abuse liability.[8] Pregabalin was described in a review of online reports as an 'ideal psychotropic drug' for recreational purposes to achieve specific mindsets, e.g. alcohol-like effects mixed with euphoria, and it seemed easier to achieve a recreational high than gabapentin.[9] Although pregabalin may be abused for its euphoric effects, these effects are weak and not sustained during long-term use and a history of other drug addiction may be important in the reward effect of pregabalin.[3,12,13]

Although pregabalin appears to have low potential for abuse, certain populations may be more liable to abuse or misuse. Further psychopharmacological studies with pregabalin are needed, including assessing its abuse liability across a range of doses in sedative abusers, as well as testing the drug in combination with other CNS-active drugs and alcohol within the same subject population.

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REFERENCES

1. Pregabalin (Lyrica): suicidal ideation and attempt. Canadian Adverse Reaction Newsletter [Internet]. 2010 Jul [cited 2012 Apr 23];20(3):1-2. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n3-eng.pdf

2. Zacny JP, Paice JA, Coalson DW. Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers. Pharmacol Biochem Behav. 2012 Jan;100(3):560-5.

3. Filipetto FA, Zipp CP, Coren JS. Potential for pregabalin abuse or diversion after past drug-seeking behavior. J Am Osteopath Assoc. 2010 Oct;110(10):605-7.

4. Highlights of prescribing information: Lyrica [Internet]. New York (NY): Pfizer, Inc.; 2011 Jun. [cited 2012 Apr 18]. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=561

5. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Lyrica (pregabalin) capsules. Company: Pfizer, Inc.. Application No.:21-446. Rockville (MD): Food and Drug Administration; 2004 [cited 2012 Apr 18]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021446_Lyrica%20Capsules_medr.pdf.

6. Drug product database [Internet]. Ottawa (ON): Health Canada; 2009 -. Drug Product Database online query; 2012 [cited 2012 Apr 23]. Available from: http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

7. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: placement of pregabalin into schedule V. Final rule. Fed Regist. 2005 Jul 28;70(144):43633-5.

8. Schwan S, Sundstrom A, Stjernberg E, Hallberg E, Hallberg P. A signal for an abuse liability for pregabalin--results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol. 2010 Sep;66(9):947-53.

9. Schifano F, Offizi S, Piccione M, Corazza O, Deluca P, Davey Z, et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom. 2011;80(2):118-22.

10. Frye MA, Moore KM. Gabapentin and pregabalin. In: Schatzberg AF, Nemeroff CB, editors. The American Psychiatric Publishing textbook of psychopharmacology (4th ed.). Arlington, VA: American Psychiatric Publishing, Inc.; US; 2009. p. 767-77. Chapter 38.

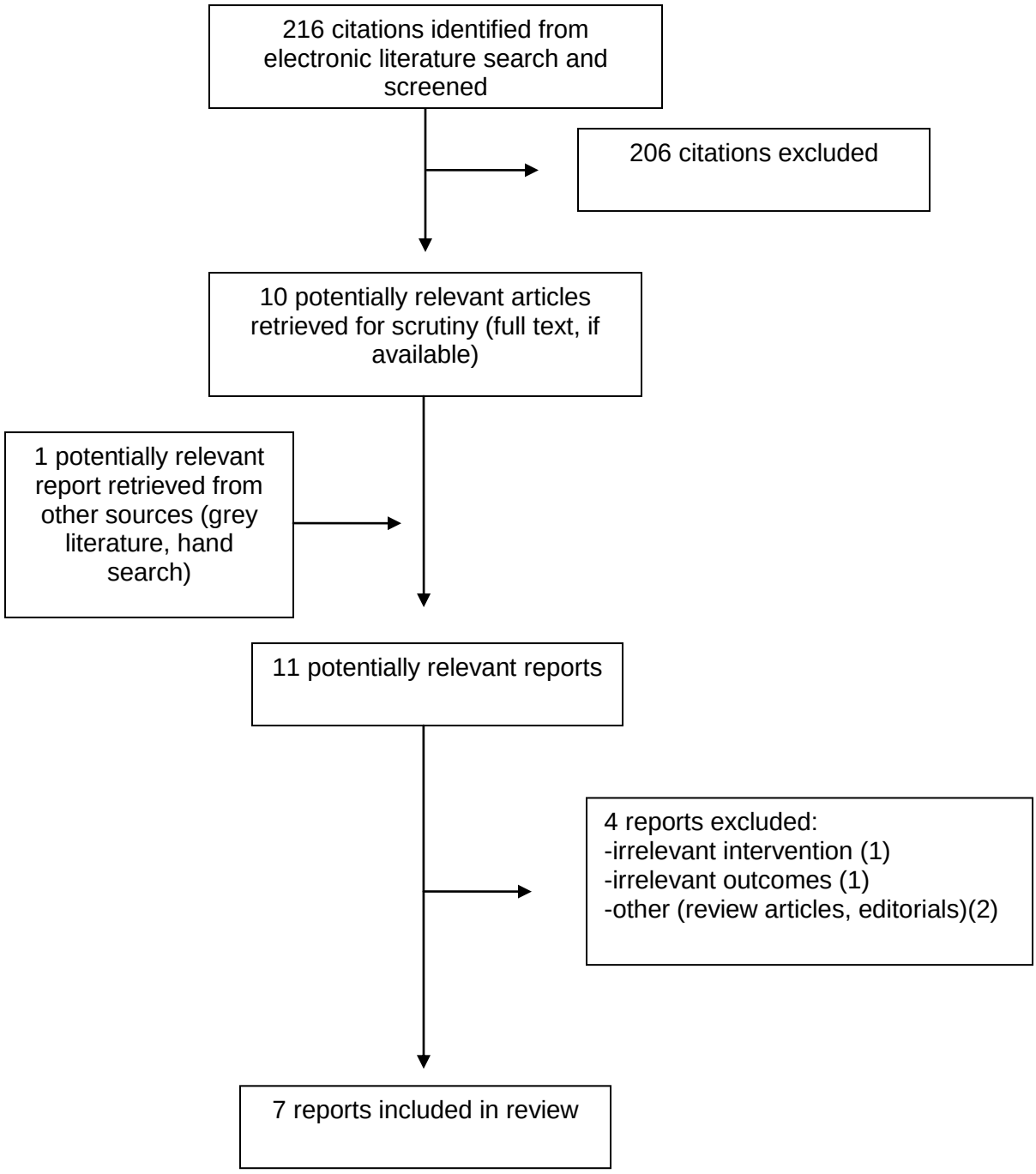
11. Annex C: critical appraisal - notes and checklists [Internet]. In: SIGN 50: a guideline developer's handbook. Edinburgh (UK): Scottish Intercollegiate Guidelines Network; 2011 Nov [cited 2012 Apr 18]. Available from: http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html.

12. Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, et al. Pregabalin abuse, dependence, and withdrawal: a case report [letter]. Am J Psychiatry. 2010 Jul;167(7):869.

13. Yargic I, Ozdemiroglu FA. Pregabalin abuse: a case report. Klinik Psikofarmakoloji Bulteni/ Bulletin of Clinical Psychopharmacology. 2011;21(1):64-6.

14. Product monograph: Lyrica© [Internet]. Kirkland (QC): Pfizer Canada, Inc.; 2010 Jun. [cited 2012 Apr 18]. Available from: http://www.pfizer.ca/en/our_products/products/monograph/141

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional Articles of Potential Interest

1. Spiller HA, Bratcher R, Griffith JR. **Pregabalin** overdose with benign outcome. Clin Toxicol (Phila). 2008 Nov;46(9):917.
PubMed: PM18668385

2. Braga AJ, Chidley K. Self-poisoning with lamotrigine and **pregabalin**. Anaesthesia. 2007 May;62(5):524-7.
PubMed: PM17448068

APPENDIX 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Clinical Outcomes
Zacny,[2] 2012 USA	Double-blind, randomized, placebo-controlled, double-dummy, crossover trial	Healthy volunteers (age 21 to 39 years) Mean age(±SEM): 26.9±5.0 years 8 males /8 females N=16	PGB 75mg; PGB 150mg; Oxycodone 10mg; PGB 75mg and Oxycodone 10mg	Placebo*	Subjective effects: including overall liking and wanting (to receive PGB again)
Abuse liability study ('098'),[5] 2004 USA^	Double-blind, randomized crossover trial	Drug and alcohol abusers N=15	PGB 450mg single dose[§]	Diazepam 30mg single dose[§]; Placebo	Euphorigenic activity
Schwan,[8] 2010 Sweden	Database analysis	Patients with unknown indication, non-specified anxiety or non-specified pain and GAD (age 18 to 51 years) Median age: 29 years 9 males/7 females N=16 (1980 to 2009)	PGB 300 to 4200 mg/day (median 1000 mg), mostly taken as single doses	None	IC, derived from a Bayesian data-mining algorithm, for pregabalin and reports of abuse and addiction in SWEDIS[†]
Schifano,[9] 2011 UK	Analysis of anecdotal online reports	108 websites monitored on a regular basis for recreational misuse of PGB (Jan. 2008 to Aug. 2010); 32 websites identified as relevant to the misuse of gabapentin (and clonazepam)	PGB	Gabapentin	Dosages taken; Routes of administration; Tolerance; Use in combination with other substances
Yargic,[13] 2011 Turkey	Case report	A 37-year-old male with a history of epilepsy, bipolar disorder and clonazepam abuse	PGB 300 mg/day added on to control anxiety; PGB 3000mg on 6-7 occasions in 2	None	Potential of abuse

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Clinical Outcomes
			months after starting PGB		
Filipetto,[3] 2010, USA	Case report	A 35-year-old female with 2-year history of neuropathic abdominal pain syndrome under pain treatment and repeated use of opioid drugs	PGB 88,500 mg /28 days	None	Potential of abuse or diversion
Grosshans,[12] 2010 Germany	Case report	A 47-year-old male with a history of alcohol and cannabis abuse as well as heroin dependence	PGB increased to 7500 mg/day with alcohol and cannabis at irregular intervals within 2 years	None	PGB abuse, dependence and withdrawal

IC = information component; GAD = generalized anxiety disorder; PGB = pregabalin;

*All 16 subjects were exposed to the five conditions: placebo, pregabalin 75mg and 150mg, Oxycodone 10mg, pregabaline 75mg followed 1 hour later by oxycodone 10mg.
^The brief introduction of this study was identified in FDA medical review but no further detailed information is available.
§Dose information is extracted in Pregabalin product monograph[14]
† SWEDIS = Swedish national register of adverse drug reactions

APPENDIX 4: Summary of Individual Study Findings

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
Zacny,[2] 2012, USA	There were no increased ratings of abuse liability-related effects with either dose of PGB (e.g. elated, having pleasant bodily sensations, like drug, take again); 10 instances in combination of PGB 75mg and oxycodone 10mg increased ratings of having pleasant /unpleasent bodily sensations, taking again and coasting (spaced out) relative to placebo, while each drug alone did not alter subjective effects; Oxycodone increased drug liking ratings but the addition of PGB 75mg did not increase the rating any further	"PGB does not have abuse liability-related subjective effects, at least at the acute doses tested, in non-drug-abusing volunteers, and it does not potentiate self-reported liking of oxycodone effects at the doses tested." (p564) "Further psychopharmacological studies with PGB are warranted, including a study assessing its abuse liability across a range of doses in sedative abusers, as well as testing within the same subject population the drug in combination with other CNS-active drugs such as benzodiazepines and alcohol." (p564)
Abuse liability study ('098'),[5] 2004 USA^	PGB 450mg had more 'drug-taking behavior' (e.g. good drug effect and high) than did diazepam 30mg. The effect of PGB had a one hour delayed onset compared with diazepam	"PGB has a potential for euphorigenic activity in susceptible populations." (p5)
Schwan,[8] 2010 Sweden	• 16 reports concerned PGB of 198 reports indicative of abuse or addiction to any drug • IC = 3.99 (3.21-4.59) on the basis of the 16 reports • Feelings of becoming "high", "a nice benzodiazepine effect, an "amphetamine trip" with euphoria and hospitalization for detoxification reported • 13 patients with history of past or current substance abuse and 2 patients selling their prescribed medication • No case indicative of abuse or addiction to gabapentin in SWEDIS*	"PGB is likely to be associated with an abuse liability and that further studies are urgently needed to characterize its extent and nature." (p952-953)

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
Schifano,[9] 2011 UK	<u>PGB misuse</u> • PGB misusers profiled as individuals with a history of recreational polydrug misuse • Different dosages of PGB associated with a vast range of effects and most dosages reported in excess (up to 5g) of the clinically advisable maximum level 600mg • Misuse of PGB mostly occurred orally plus intravenous, rectal, and 'parachuting' • Time of effect onset between 10 minutes and 2 hours, depending on the route of administration • Tolerance developed rapidly and worn off quickly after drug cessation • Self-administered increase of dosage due to rapid development of high tolerance levels <u>PGB vs. gabapentin misuse</u> • Heavy sedative and psychedelic effects also noticed among gabapentin misusers • Tolerance of gabapentin also developed very rapidly • Self-administered increase of dosage also for gabapentin • Far less dosage of PGB to achieve the same recreational high compared with gabapentin • Concurrent administration of PGB with gabapentin or other sedatives (e.g. benzodiazepines)	• "PGB was described as an 'ideal psychotropic drug' for recreational purposes to achieve specific mindsets, including alcohol /GHB /benzodiazepine-like effects mixed with euphoria." (p118) • The observations of the analysis are consistent with the fact that "PGB is indeed characterized by higher (2.5 times) potency, quicker absorption rates, and greater bioavailability levels than gabapentin" (p120) • "As with any centrally active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of anticonvulsant misuse." (p121)

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
Yargic,[13] 2011 Turkey	Patient felt euphoria on high doses of PGB and did not have any blackouts or disturbing behaviors. Patient did not have any signs of drug abuse when taking valproate and PGB regularly at recommended doses for six months after the episodes of PGB abuse	"PGB is likely to be abused for its euphoric effect. Its GABA-ergic effects may cause positive reinforcement in some patients; however these effects are weak and not sustained during long-term use." (p65) "The case cautions the doctors to be cautious when using PGB in treating patients with a history of drug or alcohol dependence." (p65)
Filipetto,[3] 2010, USA	PGB may be a readily available substitute for drugs with higher abuse potential, such as opioids and benzodiazepines. The patient who had a history of opioid-seeking behavior, was suspected of substance use disorder after she showed similar drug-seeking behavior with PGB	"Physicians should exercise caution when prescribing PGB, particularly in a patient with past substance abuse or drug-seeking behavior," even though "PGB has a very low potential for abuse." (p607) "Further epidemiologic research regarding the incidence of PGB abuse should be considered in an effort to more accurately assess its incidence." (p607)
Grosshans,[12] 2010 Germany	The patient developed tolerance and withdrawal symptoms. During detoxification, PGB were slowly reduced to 2 capsules a day within 12 days. The patient repeatedly complained of a heavy craving for PGB, discontinued the treatment prematurely, and relapsed immediately at home by taking 20 capsules of PGB per day and continued this dosage.	"PGB might have a potential for abuse" and a history of drug addiction may be "important in the reward effect of PGB". (p869) The authors recommended "being especially cautious when using PGB to treat patients with a history of drug or alcohol dependence." (p869)

PGB = pregabalin;
* SWEDIS = Swedish national register of adverse drug reactions; Data on gabapentin were not shown.
^The brief introduction of this study was identified in FDA medical review but no further detailed information is available.