Eur J Clin Pharmacol (2013) 69:2021–2025
DOI 10.1007/s00228-013-1578-5

CLINICAL TRIAL

Pregabalin abuse among opiate addicted patients

Martin Grosshans · Tagrid Lemenager · Christian Vollmert · Nina Kaemmerer · Rupert Schreiner · Jochen Mutschler · Xenija Wagner · Falk Kiefer · Derik Hermann

Received: 13 June 2013 / Accepted: 11 August 2013 / Published online: 30 August 2013

Abstract
Purpose Pregabalin is a novel GABA-analogue approved for the treatment of partial onset seizures, neuropathic pain, and general anxiety disorder. Pregabalin has been classified as a Schedule V drug with a low risk of inflicting abuse or addiction. However, some publications have indicated that pregabalin may have a potential for abuse among patients with past or current opiate addiction. Thus, we hypothesized that pregabalin might be abused by patients who were undergoing an opiate replacement therapy and never had an indication for taking pregabalin on medical grounds.
Methods Urine specimens from 124 patients with opiate dependency syndrome and from 111 patients with other addiction disorders (alcohol, benzodiazepines, cannabis, amphetamines) were screened for pregabalin by means of a mass spectrometer analysis.
Results We found 12.1 % of all urine specimens from patients with opiate addiction to be positive for pregabalin. None of the patients concerned had a medical indication for using pregabalin. In the control group, 2.7 % of the patients were tested positively for pregabalin, due to their taking it regularly for chronic pain or general anxiety.
Conclusions Our data suggest that pregabalin is liable to be abused among individuals with opiate dependency syndrome Thus, vigilance and caution are called for when patients with a past or current opiate dependency are exposed to treatment with pregabalin.

Keywords Pregabalin · Abuse · Opiate replacement therapy · Urine analysis · Mass spectrometry

Introduction

Pregabalin is a novel gamma-aminobutyric acid (GABA) analogue that increases neuronal GABA levels by selectively binding to the alpha2delta subunits of voltage-gated calcium channels and inhibiting the release of excitatory neurotransmitters like glutamate, noradrenaline, and substance P. Pregabalin has been approved for the treatment of partial-onset seizures, neuropathic pain, fibromyalgia, and general anxiety disorders [1–4]. The efficacy of pregabalin in chronic pain conditions like diabetic neuropathy, postherpetic neuralgia and central neuropathic pain has been demonstrated by a Cochrane database review of double-blind randomized controlled trials reporting on the analgesic effect of pregabalin [5]. In addition, pilot studies indicated pregabalin to be effective in the treatment of anxiety in schizophrenia [6], and of the alcohol withdrawal syndrome [7]. Pregabalin is widely used in neurology and psychiatry, and ranked within the 30 most prescribed medications in the US in 2011 [8]. Premarketing trials demonstrated a low potential for abuse and a limited dependence liability of the drug if misused [9]. Therefore, pregabalin has been classified as a Schedule V drug (i.e. with a low potential for abuse) in the U.S. Controlled Substances Act [10].

Nevertheless, there is some evidence suggesting that pregabalin might possess a potential for abuse among patients with past or current drug abuse or addiction. Recently, we

Electronic supplementary material The online version of this article (doi:10.1007/s00228-013-1578-5) contains supplementary material, which is available to authorized users.

M. Grosshans (✉) · T. Lemenager · C. Vollmert · N. Kaemmerer · X. Wagner · F. Kiefer · D. Hermann
Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg/Medical Faculty Mannheim, J5/68159 Mannheim, Germany
e-mail: martin.grosshans@zi-mannheim.de

R. Schreiner
Limbach Medical Laboratories, Heidelberg, Germany

J. Mutschler
Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital Zürich, Zürich, Switzerland

published a case report of a patient who abused pregabalin in extremely high dosage (up to 7,500 mg per day), thereby developing an addiction as indicated by the occurrence of severe symptoms upon withdrawal of the drug [11]. This patient reported a history of heroin dependence and current abuse of alcohol and cannabis, pointing out that "in the (heroin) scene," pregabalin is regarded as a new substance used by some addicts who appreciate it for the "kicks" it produces, particularly in combination with alcohol. Furthermore, Schwan et al. reported data from the Swedish National Register of Adverse Drug Reactions (SWEDIS): until the end of 2009, 16 cases of pregabalin abuse were registered, most of them concerning patients with a history of drug abuse and/or addiction [12]. By the same token, a retrospective evaluation of indicators of drug dependence provided by data from the Global Individual Case Safety Reports Database (VigiBase) of the World Health Organization (WHO) has highlighted pregabalin's dependence potential [13]. Additionally, Dyrkorn et al. published results of a nationwide drug screening in Norway investigating [$n=1{,}854$] urine samples. Pregabalin was detected in 4.5 % of these samples. The authors assumed that pregabalin may be abused as one of several substances not included in the standard test panel for the urinary screening for drugs lending themselves to abuse and addiction [14]. Moreover, in a recent report, the Canadian Agency for Drugs and Technologies in Health published a review of the clinical evidence (until April 2012) available on the abuse potential of pregabalin [15].

On the other hand, in a recent double blind randomized study, Zacny et al. investigated in healthy volunteers whether pregabalin, in the dose of 75 mg or 150 mg alone or in combination with 10 mg oxycodon, would affect parameters indicative of abuse liability. Their results show no difference between pregabalin and placebo [16].

However, the question remains open whether there is a significant abuse of pregabalin—and if so, whether a special group of individuals can be identified as being particularly prone to it. Based on the clinical experience with our pregabalin-addicted patient and his medical history [11] and on the research mentioned above, we hypothesize that subjects with a past or current opiate addiction are liable to abuse pregabalin. To test our hypothesis, we resorted to the patients in our outpatient department undergoing opiate replacement therapy (ORT), and focused on the question of whether pregabalin is abused among these patients. To answer this question, we conducted a pregabalin screening of urine specimens of all patients treated in our outpatient ORT unit. Furthermore, to control the findings gleaned therefrom, we also investigated the illicit use of pregabalin among subjects swayed by addiction to other drugs than opiates. We hence extended the screening to 111 other patients admitted to our department for inpatient detoxification from alcohol, benzodiazepines, cannabis, or amphetamines. To our knowledge, this is the first study set up to trace pregabalin abuse in a defined sample of opiate-dependent patients never exposed to pregabalin for medical reasons.

Methods

Participants

A total of 124 (34 female, 90 male) patients with a mean age of 37.1±8.1 years (range 20–55) were screened for pregabalin. We analyzed only a single urine sample per patient. All patients fulfilled the diagnostic criteria for opiate dependence according to the Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994). In order to be included in our outpatient ORT-program, a patient was required to have been an opiate addict for at least 2 years. All participants received an opiate replacement containing either methadone or buprenorphine. About two times per month, the patients' urine was tested for drugs and substances contraindicated during ORT (heroin, benzodiazepines, cocaine, amphetamines, and barbiturates). Furthermore, alcohol intake was controlled by means of a breathalyzer.

The control group consisted of the above-mentioned 111 patients treated for non-opiate addiction: namely to alcohol ($n=90$), cannabis ($n=11$), benzodiazepines ($n=3$), and amphetamines ($n=1$). The remaining six patients were polydrug abusers. Their urine samples were collected on the day of their admission to our department for inpatient detoxification.

Upon admission, all patients being treated in our ORT unit or in our inpatient department have to declare their written informed consent that urine and/or blood samples may be collected before and/or during treatment, and analyzed for substances of abuse or medication for treatment/quality control or safety. Therefore, a separate approval of the local ethical Committee was not necessary to conduct this drug-screening.

Laboratory analysis

The urine samples for pregabalin analysis were collected under staff observation between 9.00 and 11.30 a.m. as part of the routine urine drug monitoring for the opiate-addicted subjects, and on the day of their admission for the control group. Five milliliters of urine were separated, immediately refrigerated to 4 °C, and sent to the local medical laboratory (Limbach Laboratories, Heidelberg, Germany) for mass spectrometer analysis. It has been demonstrated in a large nationwide multicenter screening in the US ($n>57{,}000$) that mass spectrometry is a reliable and sensitive method of detecting pregabalin in human urine specimens [17].

Fifty microliters of each urine sample was pipetted into Eppendorf tubes (Eppendorf, Hamburg, Germany). The

sediment or peptides were precipitated by adding 500 μl of a solution of 70 % acetonitrile and 30 % methanol, as well as 25 mg/l droperidol. After 1 min of mixing, the tubes were centrifuged at 14,000 rpm for 5 min. The clear supernatant was then transferred to vials that were placed into the autosampler of a high-performance liquid chromatography (HPLC) system (Merck-Hitatchi, Darmstadt, Germany) equipped with a Halo C18 reversed phase column (MZ Analysetechnik, Mainz, Germany). The run time was 4 min; the retention time for pregabalin was 2.1 min (internal standard=droperidol: 2.6 min). For pregabalin detection, we used a mass spectrometer (Quattro Premier, Eschborn, Germany) in a positive electrospray mode.

The analysis showed a linear correlation of the concentration and the signal between 0.1 and 200 mg/l pregabalin, and further a coefficient of variation ranged from 2.3 % to 6 %. The bias varied from 3 % to 5 %. Samples with a higher pregabalin-concentration were diluted with water and then reanalyzed. For external quality control, we used samples of a German quality assessment scheme (GTFCH). No carryover was detected when a blank sample was injected during the validation process after the standard sample containing 200 mg/l pregabalin. However, all samples that were analyzed directly after a sample that contained a pregabalin-concentration above 100 mg/l were reanalyzed. The detection threshold above which pregabalin concentrations were considered to be positive was defined at 0.2 mg/l.

Statistical methods

For the statistical analysis, SPSS 16.0 (SPSS Inc. Chicago, Ill, USA) was used. Pearson's correlation coefficient was resorted to for computing associations between the pregabalin urine concentration and a variety of sample variables and clinical parameters. The level of significance was set at $\alpha < 0.05$. The mean values in our data are presented along with the standard errors of the mean.

Results

ORT sample

At the time of the study, 124 patients (90 men and 34 women) with an opiate dependency were being treated in our ORT unit. The average duration of their addiction amounted to 16.2± 7.7 years, with a range from 3 to 40 years. Prior to the actual treatment, the patients had, on average, passed through 3.0± 4.2 inpatient detoxifications. The treatment was performed with methadone in 78.2 % of the patients, and with buprenorphine in 21.8 %. In Table 1, the data are presented separately for men and women.

Table 1 Sample characteristics of the opiate-dependent patients

	Male (n=90)	Female (n=34)	t/c	p
Age (years)	37.9±7.8	35.1±8.4	t=−1.75	0.08
Duration of dependency (years)	16.6±7.6	15.1±7.8	t=−0.98	0.32
Methadone-treatment	70 (77.8 %)	27 (79.4 %)	c=0.73	0.61
Buprenorphine-treatment	20 (22.2 %)	7 (20.6 %)	c=0.84	0.52
Number of inpatient detoxifications prior to the study	3.0±4.5	2.5±3.2	t=−0.69	0.48
Pregabalin positive	12 (13.3 %)	3 (8.8 %)	c=0.49	0.36

t=t-value; c=chi-square value; p=p value

Urine analysis

Pregabalin is for the most part excreted unchanged in the urine (> 98 %) [18], with a relatively short half-life of 4.6–6.8 h [19]. Pregabalin (in concentrations above the cutoff point of 0.2 mg/l) was detected in 12.1 % (n=15) of the urine samples from opiate-addicted subjects. Of our patients, 13.3 % of males and 8.8 % of females had positive test results for pregabalin. The mean concentration of pregabalin came to 45.0±74.4 mg/l, with the concentration range extending from 0.2 to 293.6 mg/l. To our knowledge, none of the positively tested patients suffered from epilepsy, general anxiety, fibromyalgia, neuropathic pain, or any other disease constituting an indication for applying pregabalin on medical grounds. Furthermore, when confronted with the positive results, most of the patients concerned (n=11 of 15) confirmed that they bought pregabalin from other heroin addicts or from drug dealers, but never received prescriptions of pregabalin from their private physicians or other medical facilities. Four male patients did not believe that their urine contained pregabalin, denying its use. The patients confirming the use of pregabalin reported that they bought pregabalin solely for the sake of kicks, disclaiming self-medication of pain or other symptoms associated with opiate withdrawal. Moreover, all abusers were well aware of the fact that pregabalin was not included in the standard test-panel for drug monitoring applied in our ORT program. Interestingly, a vast majority (78.3 %) of the opiate-dependent patients joining the program reported that pregabalin belonged to many drug dealers' supplies, on account of its kick and euphoriant effects. Additionally, no significant correlations were found between pregabalin use and variables such as age, gender, age at first opiate use, duration of opiate dependence or duration and dosage of opiate replacement.

Control group

We analyzed the urine of 111 Patients (79 men, 32 women) who had been admitted to our department for inpatient

detoxification. Most of these patients were addicted to alcohol (81.1 %), 9.9 % to cannabis, 2.7 % to benzodiazepines, and 0.9 % to amphetamines. The remaining 5.4 % were polydrug users. The age of the control subjects came to an average of 44.7±13.3 years (men 45±1.5 years [range 20–70]; women 43.9±2.4 years [range 20–68]). In the control group, three male alcohol-dependent patients tested positive for pregabalin. They had used it regularly in therapeutic dosages of 150–450 mg/day upon prescription from their physicians; two of them for chronic pain syndromes, the third for general anxiety. All three patients answered the questions about having pregabalin-associated "kick" experiences or feelings of euphoria in the negative. Moreover, they assured us of never having heard of pregabalin being a euphoriant drug or having connections to the drug-scene.

Discussion

The results of the present study revealed that about 12 % of the patients undergoing opiate replacement therapy in our unit were positive for pregabalin. Since there was no medical indication for administering pregabalin to these patients, they were likely to have been using this drug irregularly on their own. So far, the international literature offers only a few reports on the abuse of pregabalin. Filipetto and colleagues (2010) published a case of a female patient from the US with chronic pain due to a prior Guillian-Barré syndrome and with a history of opioid-seeking behavior. Having experienced the rewarding effects of pregabalin, she consulted several doctors within a 3-month period in quest of prescriptions to fulfill her growing need of pregabalin. This patient had abused about 88 g of pregabalin in the course of a few weeks before a medical board disclosed irregularities in her pregabalin prescriptions and referred her to a hospital for detoxification [20]. Recently, we reported a similar case of a former heroin addict [11].

Based on its mechanisms of action as a GABA analogue, there have been concerns about pregabalin's potential for abuse and addiction since the beginning [9].

Preclinical studies with animals did not reveal any abuse liability [9]. By the same token, a clinical trial with a small sample ($n=15$) of alcohol and sedative users demonstrated that pregabalin administered in the therapeutic dose range of 200–450 mg/day is far from producing the response spectrum diazepam is notorious for. Hence, pregabalin failed to show the profile of a prototypic drug of abuse [9]. In premarketing trials, however, euphoria was noted, depending on dosage, as an adverse effect occurring more frequently in pregabalin than in placebo groups (4 % vs. 1 %, respectively) [21].

Notably, it is a well-known weakness of randomized controlled premarketing trials that patients with addiction disorders are excluded. Thus, naturalistic data on newly approved drugs are often lacking. In view of the known but very rare adverse effect of dose-dependent mild euphoria [21], pregabalin may act as a weakly rewarding substance in some subjects who have developed long-term opioid tolerance. That fits in with the outcome of a recent double-blind placebo-controlled study that failed to trace subjective effects associated with abuse-liability, such as a liking for pregabalin, in healthy subjects never afflicted with addiction [16].

All in all, it is impossible to validate these phenomena in standardized premarketing clinical trials for substances whose abuse liability is uncertain. Therefore, documentation of postmarketing clinical experience, surveillance, and naturalistic trials are urgently called for.

On the other hand, although all pregabalin abusers in our sample stated that they intended to get kicks, one might speculate that the illicit use of pregabalin may, at least for some heroin addicts, be due to its alleviating effects on the opiate withdrawal syndrome (OWS). We have not systematically collected data on that issue yet, but some opiate-addicted patients in our outpatient unit have reported anecdotally that in the heroin scene, addicts have been taking pregabalin to control typical opiate withdrawal symptoms such as pain, unrest, and sleeplessness. One of those cases has recently been published by our group [22].

However, data on the application of well-proven anticonvulsants (carbamazepine, topiramate) in the treatment of OWS have suggested their effectiveness in that area of indications [23–25]. That correlates with the outcome of recent research indicating pregabalin to be effective in the treatment of the alcohol withdrawal syndrome during detoxification [7, 26]. Furthermore, in a recent pilot study regarding the maintenance of alcohol abstinence, pregabalin produced similar results in the prevention of relapses as naltrexone [27]. Additionally, pregabalin has been shown to be effective in the withdrawal phase of benzodiazepine detoxification [28]. All in all, with pregabalin a preparation has been coming to the fore and may hold out the prospect of becoming a valuable asset in the pharmacological repertoire of addiction medicine.

Some limitations of the investigation presented here should be mentioned. The screening was conducted in one center only, with the number of participants being small. Additionally, we analyzed only a single urine sample per patient, without integrating pregabalin into the standard test panel. This may have lead to false negatives in our data. Moreover, due to the relatively short half-life of pregabalin, the time frame for detection is brief, which may also have lead to false negatives. Another limitation is that we did not measure urine creatinine.

However, with regard to the lack of naturalistic data on the potential of pregabalin for abuse, systematic research on this topic is urgently needed. In view of the research mentioned above and of our current findings, we conclude that pregabalin displays a potential for abuse among individuals with a history

of chronic opiate intake. Thus, we recommend being vigilant and cautious when administering it to these patients, in particular in the polypharmacological management of complex chronic pain and of anxiety disorders.

Role of funding source This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest The authors declare that they do not have any conflict of interest.

References

1. Tassone DM, Boyce E, Guyer J, Nuzum D (2007) Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther 29(1):26–48. doi:10.1016/j.clinthera.2007.01.013
2. Bandelow B, Wedekind D, Leon T (2007) Pregabalin for the treatment of generalized anxiety disorder: a novel pharmacologic intervention. Expert Rev Neurother 7(7):769–781. doi:10.1586/14737175.7.7.769
3. Boomershine CS (2010) Pregabalin for the management of fibromyalgia syndrome. J Pain Res 3:81–88
4. Brodie MJ (2004) Pregabalin as adjunctive therapy for partial seizures. Epilepsia 45(Suppl 6):19–27. doi:10.1111/j.0013-9580.2004.455004.x
5. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ (2009) Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev (3):CD007076. doi:10.1002/14651858.CD007076.pub2
6. Englisch S, Esser A, Enning F, Hohmann S, Schanz H, Zink M (2010) Augmentation with pregabalin in schizophrenia. J Clin Psychopharmacol 30(4):437–440. doi:10.1097/JCP.0b013e3181e5c095
7. Martinotti G, di Nicola M, Frustaci A, Romanelli R, Tedeschi D, Guglielmo R, Guerriero L, Bruschi A, De Filippis R, Pozzi G, Di Giannantonio M, Bria P, Janiri L (2010) Pregabalin, tiapride and lorazepam in alcohol withdrawal syndrome: a multi-centre, randomized, single-blind comparison trial. Addiction 105(2):288–299. doi:10.1111/j.1360-0443.2009.02792.x
8. (2011) The IMS Institute for Healthcare Informatics. http://www.drugs.com/stats/top100/2011/sales. Accessed 28 Dec 2012
9. EMA (2005) European Medicines Agency (EMA). Lyrica (pregabalin) scientific discussion. Available from: http://www.emea.europa.eu/humandocs/humans/EPAR/lyrica/lyrica.htm
10. Drug Enforcement Administration DoJ (2005) Schedules of controlled substances: placement of pregabalin into schedule V. Fed Regist 70(144):43633–43635
11. Grosshans M, Mutschler J, Hermann D, Klein O, Dressing H, Kiefer F, Mann K (2010) Pregabalin abuse, dependence, and withdrawal: a case report. Am J Psychiatry 167(7):869. doi:10.1176/appi.ajp.2010.09091269
12. Schwan S, Sundstrom A, Stjernberg E, Hallberg E, Hallberg P (2010) A signal for an abuse liability for pregabalin–results from the Swedish spontaneous adverse drug reaction reporting system. Eur J Clin Pharmacol 66(9):947–953. doi:10.1007/s00228-010-0853-y
13. Caster O, Edwards IR, Noren GN, Lindquist M (2011) Earlier discovery of pregabalin's dependence potential might have been possible. Eur J Clin Pharmacol 67(3):319–320. doi:10.1007/s00228-010-0920-4
14. Dyrkorn R, Reimers A, Johannessen L, Spigset O (2011) Do urine tests for drugs of abuse cover the substances of interest? Tidsskr Nor Laegeforen 131(6):570–572. doi:10.4045/tidsskr.10.0368
15. Abuse and Misuse Potential of Pregabalin: A Review of the Clinical Evidence (2012) http://www.cadth.ca/media/pdf/htis/april-2012/RC0348%20Pregabalin%20draft%20report%20Final.pdf. Accessed 28th december 2012
16. Zacny JP, Paice JA, Coalson DW (2012) Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers. Pharmacol Biochem Behav 100(3):560–565. doi:10.1016/j.pbb.2011.10.023
17. Heltsley R, Depriest A, Black DL, Robert T, Caplan YH, Cone EJ (2011) Urine drug testing of chronic pain patients. IV. Prevalence of gabapentin and pregabalin. J Anal Toxicol 35(6):357–359
18. Guay DR (2005) Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? Am J Geriatr Pharmacother 3(4):274–287
19. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, Randinitis EJ, Corrigan BW, Haig GM, Boyd RA, Wesche DL (2010) Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 50(8):941–950. doi:10.1177/0091270009352087
20. Filipetto FA, Zipp CP, Coren JS (2010) Potential for pregabalin abuse or diversion after past drug-seeking behavior. J Am Osteopath Assoc 110(10):605–607
21. Pfizer Inc (2011) Prescribing information: Lyrica. http://www.pfizer.com/products/product-detail/lyrica. Accessed 28 Dec 2012
22. Kammerer N, Lemenager T, Grosshans M, Kiefer F, Hermann D (2012) Pregabalin for the reduction of opiate withdrawal symptoms. Psychiatr Prax. doi:10.1055/s-0032-1305042
23. Zullino DF, Cottier AC, Besson J (2002) Topiramate in opiate withdrawal. Prog Neuropsychopharmacol Biol Psychiatry 26(6):1221–1223
24. Zullino DF, Krenz S, Zimmerman G, Miozzari A, Rajeswaran R, Kolly S, Khazaal Y (2004) Topiramate in opiate withdrawal-comparison with clonidine and with carbamazepine/mianserin. Subst Abus 25(4):27–33
25. Zullino DF, Krenz S, Favrat B, Zimmermann G, Bertschy G, Besson J (2004) The efficiency of a carbamazepine-mianserin combination scheme in opiate detoxification. Hum Psychopharmacol 19(6):425–430. doi:10.1002/hup.610
26. Di Nicola M, Martinotti G, Tedeschi D, Frustaci A, Mazza M, Sarchiapone M, Pozzi G, Bria P, Janiri L (2010) Pregabalin in outpatient detoxification of subjects with mild-to-moderate alcohol withdrawal syndrome. Hum Psychopharmacol 25(3):268–275. doi:10.1002/hup.1098
27. Martinotti G, Di Nicola M, Tedeschi D, Andreoli S, Reina D, Pomponi M, Mazza M, Romanelli R, Moroni N, De Filippis R, Di Giannantonio M, Pozzi G, Bria P, Janiri L (2010) Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial. J Psychopharmacol 24(9):1367–1374. doi:10.1177/0269881109102623
28. Bobes J, Rubio G, Teran A, Cervera G, Lopez-Gomez V, Vilardaga I, Perez M (2012) Pregabalin for the discontinuation of long-term benzodiazepines use: an assessment of its effectiveness in daily clinical practice. Eur Psychiatry 27(4):301–307. doi:10.1016/j.eurpsy.2010.12.004