REVIEW ARTICLE

The Problems of Long-Term Treatment With Benzodiazepines and Related Substances

Prescribing Practice, Epidemiology, and the Treatment of Withdrawal

Katrin Janhsen, Patrik Roser, Knut Hoffmann

SUMMARY

Background: Benzodiazepine abuse and dependence have been recognized and widely discussed for more than 40 years. With more than 230 million daily doses prescribed in Germany per year, the burden of reimbursement on the statutory health insurance carriers is high, albeit with a slight decline from year to year. At present, about 50% of all prescriptions in Germany are issued privately, even for patients who have statutory health insurance.

Methods: We selectively review the literature on the epidemiology and treatment of benzodiazepine dependence and abuse in Germany.

Results: Estimates of the number of benzodiazepine-dependent persons in Germany range from 128 000 to 1.6 million. Most estimates take no account of the large number of private prescriptions (i.e., those that are not reimbursed by the statutory health insurance scheme), while many exclude prescriptions for elderly persons, for whom these drugs are frequently prescribed. For the outpatient treatment of benzodiazepine withdrawal, it is recommended that the drug should first be switched to an equivalent dose of another benzodiazepine with an intermediate or long-acting effect; the dose should then, in general, be reduced weekly. In case of consumption of a high dose (≥ 20 mg diazepam equivalent), hospitalization and the additional administration of carbamazepine or valproic acid are recommended. Flumazenil treatment can improve withdrawal symptoms and leads to higher abstinence rates. Antidepressants should be given only if the patient is depressed. The dependence potential of non-benzodiazepine drugs such as zolpidem and zopiclone must also be borne in mind.

Conclusion: Benzodiazepines are generally highly effective when first given, but they should generally be given only for strict indications and for a limited time. If these drugs still need to be given beyond the short term, timely referral to a specialist is indicated, and possibly also contact with the addiction aid system.

► Cite this as:

Janhsen K, Roser P, Hoffmann K: The problems of long-term treatment with benzodiazepines and related substances—prescribing practice, epidemiology and the treatment of withdrawal. *Dtsch Arztebl Int* 2015; 112: 1–7. DOI: 10.3238/arztebl.2015.0001

Misuse and dependency problems with benzodiazepines have been a familiar phenomenon for about 40 years (1, 2, e1). For this reason, pharmaceutical companies and the German Federal Institute for Drugs and Medical Devices (BfArM) have restricted the standard period of use to 2–4 weeks since the 1980s. However, 4–5% of members of statutory health insurance companies receive at least one prescription for a benzodiazepine (BZD) or benzodiazepine derivative (Z-drugs: zolpidem, zopiclone) per calendar year. Furthermore, in 13–14% of these patients, 90 and more defined daily doses (DDD) are prescribed (3). According to a recent projection by Holzbach, the prevalence of misuse and dependency in Germany is 5% (4). When considering patient related and prescription related parameters, Holzbach determined a proportion of patients whose intake could be described as very problematic of 2.8%, and of patients whose intake could be described as problematic of as high as 17.5% (5). In older users, the proportion whose intake is problematic is higher than 20% (6).

In the outpatient setting, members of statutory health insurance schemes receive prescriptions for an annual 25.6 million DDDs of benzodiazepine hypnotics, 103.7 million DDDs of benzodiazepine tranquilizers, 0.5 million DDDs of clomethiazole, and 3.7 million DDDs of clonazepam (7–9). These prescription figures at the expense of statutory health insurance funds have been falling for years.

In addition to this, 74.6 million DDDs of Z-drugs are prescribed to members of statutory health insurance schemes (6), as are 22.0 million DDDs of tetrazepam, which was mainly used as a muscle relaxant, and whose license approval has been suspended since August 2013 because of severe skin disorders, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, DRESS syndrome, and others (e2, e3). Prescriptions in both groups have increased in recent years, at the expense of the statutory health insurers. Cumulatively, annual prescriptions amount to 230.1 million DDDs. Currently, 90 benzodiazepine-containing preparations—including Z-drugs—are included in the German drug directory (“Rote Liste”; e4), which account for 20 individual substances.

In its main indications—which include the treatment of pre-delirium, delirium tremens, and acute withdrawal

LWL-Klinik Bochum, Department of Psychiatry, Psychotherapy, Psychosomatic and Preventive Medicine, Ruhr University Bochum: PD Dr. rer. pol. Janhsen, Prof. Dr. med. Roser, Dr. med. Hoffmann

Faculty of Health (Department of Medicine), Witten/Herdecke University: PD Dr. rer. pol. Janhsen

TABLE 1

PubMed search algorithm, July 2014

Search question	Pubmed search term	Boolean operator
Epidemiology	"epidemiology" (MeSH terms)	or
	"statistics and numerical data" (subheading)	
		AND
Z-drugs	"Zopiclone*"	or
	"Zaleplone"	or
	"Zolpidem"	or
Benzodiazepines	"Benzodiazepine*"	or
	"Benzodiazepines" (MeSH terms)	
		AND
Misuse/dependency	"tolera*"	or
	"habit*"	or
	"dependan*"	or
	"addict*"	or
	"misuse"	or
	"abuse"	
		AND
Germany	"German*"	

* Joker

symptoms, as well as therapy for states of confusion, agitation, and restlessness in elderly patients with organic brain syndrome—clomethiazole is to be used only in the inpatient setting (e5).

Several studies give rise to the assumption that since the end of the 1990s (at least), benzodiazepines and Z-drugs have been prescribed often, and increasingly also to members of statutory health insurance schemes, by means of a private prescription (9–12). The prescription volume of benzodiazepines fell from 12.7 million packets in 1993 to 2.0 million packets in 2012, but the proportion of private prescriptions in 2012 was 55.3%—in a setting of 87% of members in statutory health insurance schemes in the population. Even more conspicuous was the trend in prescriptions of Z-drugs: the volume increased from 2.2 million packages in 1993 to 8.9 million in 2011 (7.9 million in 2012). In 2011, the proportion of private prescriptions amounted to 49.5% (9).

According to the current law on prescriptions of medical drugs, hypnotics and tranquillizers can be prescribed for up to four weeks at the expense of the statutory health insurers—in individual cases this period can be extended if sound reasons exist. Continued prescription with the cost borne by the statutory health insurers is conceivable in individual cases, where certain criteria are being met (for example, in a setting of existing dependency). However, this is the subject of controversial discussion (13). In principle, it is possible, by using data from the statutory health in-

surers, to identify doctors who issue prescriptions with erroneous indications or who prescribe vast volumes, and to counsel them on their prescribing behavior. But the high proportion of private prescriptions currently substantially hampers such a targeted approach.

The case study accompanying this article describes the course of a complicated case of benzodiazepine withdrawal treatment (*eBox*). Initially prescribed for insomnia, benzodiazepines and clomethiazole had been prescribed to the case patient by her doctor for about 10 years. Ultimately, three months of detoxification treatment on an inpatient basis was required to stabilize the patient. On this background, our article provides an overview of the rates of BZD and Z-drug misuse and dependency. Furthermore, we explain how to carry out the withdrawal treatment and discuss prescription practice.

Methods

In order to obtain information on the epidemiology of the misuse of BZDs and Z-drugs and dependency, we conducted a selective literature search in PubMed (*Table 1*). The search was limited to German-language and English-language publications since 2004.

Studies on how to carry out withdrawal treatment in BZD dependency were searched in PubMed in the category "medical subject headings major topic" (MeSH major topic), using the following search terms: "benzodiazepines/adverse effects" and "substance withdrawal syndrome/therapy". We restricted our search to German-language and English-language publications from the past five years. Both searches were conducted in July 2014.

Results

The selective literature search regarding the epidemiology identified 46 matches, of which four publications were relevant (4, 5, 14, 15). We categorized as relevant studies that contained information about the epidemiology of benzodiazepine dependency. *Table 2* provides an overview of these publications, to which prevalence data were added from the Epidemiological Survey on Substance Abuse (ESA) (16, e6), the German Federal Health Survey (17) and the German Center for Addiction Issues (e7). The data from the 2012 Epidemiological Survey on Substance Abuse show that for the whole population as enumerated in the census 2011 (e8), about 1.1 million persons aged between 18 and 64 years were dependent on hypnotics or tranquillizers by 31 December 2011. According to the data from the German Federal Health Survey 1998, the number of people aged 18–79 with dependency on hypnotics/tranquillizers is as high as 1.6 million (18). Holzbach's group considered clinical aspects by dividing dependency into three phases (3, 4). The volume of problematic drug provision (yellow to black phase—that is, longer than 6 months on 3.33 mg and more diazepam equivalent/day) in Germany is reported to be 800 000 patients. These figures are based on data from prescriptions covered by the statutory health insurers and include

TABLE 2

Selected publications on rates of benzodiazepine/Z-drug misuse or dependency in Germany

Reference	Data source	Population	Results
Linden et al. 2004 (14)	Berlin Aging Study (BASE)	516 participants aged 70 and older, 43 participants each in 12 subgroups by 5-year age groups and sex, sample from Berlin's population register, data collection 1990–93	18.9% users of benzodiazepines; mean period of use: 7.58 years; —of these, 33.8% took benzodiazepines for 1–5 years; —of these, 40.3% took benzodiazepines >5 years.
Hoffmann et al. 2008 (15)	Data from statutory health insurance companies (GKV)	1.47 million members of Gmünder ErsatzKasse (GEK), nationwide, study period 1 July 2004 to 31 December 2004	6959 insured persons with at least 1 prescription for Z-drugs—of these 7.2% with at least 180 DDD of Z-drugs (high-volume use)
Kraus et al. 2012 (e6, 16)	Epidemiological Survey on Substance Abuse (ESA) 2012	9084 participants aged 18–64, sample from nationwide population register, data collected April to August 2012	Misuse of hypnotics: 0.8% of participants or 14.8% of users Hypnotics dependency: 0.8% of participants or 15.3% of users Tranquillizer misuse: 0.8% of participants or 14.8% of users Tranquillizer dependency: 1.4% of participants or 26.1% of users
Knopf et al. 2003 (17)	German Federal Health Survey 1998	7124 participants aged 18–79, sample from nationwide population register, data collection 1997–99	Users of benzodiazepine and/or barbiturate containing drugs: women 4.2%, men 2.0% —of these, used for more than 3 months: women 83.5%, men 81.4%
Glaeske G 2006 (e7)	Data from statutory health insurance companies (GKV), marketing data from pharmaceutical companies	Total population in Germany, projection	1–1.1 million benzodiazepine dependent persons in Germany; 1.3–1.4 million medication dependent persons in Germany
Holzbach et al. 2010 (4)	North German medication monitor (prescribing data from statutory health insurance companies [GKV])	Data from data processing center for pharmacies (NARZ), >16 million persons, inclusion period 1 July 2005 to 30 June 2006, prescriptions followed up for a year until 30 June 2007 at the latest. Data projection for population in Germany. Categorized by clinical phase.	Benzodiazepines and/or Z-drugs: 128 261–1 538 860 patients with very problematic (red-black) to problematic (gray-black) use in Germany 790 475 with problematic (yellow-black) use in Germany
Verthein et al. 2013 (5)	North German medication monitor (prescribing data from statutory health insurance companies [GKV])	Data from data processing center for pharmacies (NARZ), >16 million persons, see Holzbach et al. 2010, data evaluation by federal state. Categorized by clinical phase.	Benzodiazepines and/or Z-drugs: 5.2% of the population of Hamburg with at least one prescription in the study period —of these 13.2% with very problematic (red-black) use —of these 15.6% with problematic (yellow-black) use

prescriptions for older patients. Since the end of the 1990s at least, evaluations of data from statutory health insurance companies have meant that the prescribed amounts are likely to be underestimates because of the high proportions of private prescriptions (10).

Several international guidelines on the therapy of benzodiazepine dependency exist (19–21, e9, and others), which mainly relate to outpatient withdrawal treatment of patients without high-dose consumption. A 2006 Cochrane review (22) was updated in 2013 (e10) and is currently subject to further revision. The German Medical Association's guidance on medical drug dependency (23) and the 2006 guideline by Poser and colleagues (20) provide a detailed overview of the treatment of medication dependency. Holzbach published information on withdrawal treatment (3, 24, e11) that exceeded the scope of the former two publications.

The PubMed search on benzodiazepine withdrawal identified 22 matches, of which seven were relevant.

Three of these dealt with the role of pregabalin (25, e12, e13), two with flumazenil (26, 27), one with cognitive behavioral therapy (e16), and one compared interventions with increased frequency of contacts between doctor and patient (28).

For the purposes of outpatient withdrawal treatment, it is widely recommended that patient's medication is swapped to an equivalent dose of an intermediate-acting to long-acting benzodiazepine, such as oxazepam or diazepam. The dose should be reduced weekly, over 4–10 weeks, by 10–25% of the dose that had been taken for a long period of time (24, 20, e16) (*Figure*). Oude Voshaar and colleagues showed in a meta-analysis (e17) that the recommendations regarding how to proceed in this scenario differ widely—they range from sudden withdrawal of the substance to stepping down intake over a year. In clinical practice, there certainly is an increased risk for withdrawal seizures. It remains doubtful whether concomitant medication with

Flow diagram of benzodiazepine withdrawal, modified from 3, 24, 20, e17

TABLE 3

Benzodiazepine withdrawal symptoms (from 24)

Non-specific symptoms	Frequency (%)
Insomnia	71
Anxiety	56
Mood swings	49
Myalgia/muscle twitching	49
Tremor	38
Headache	38
Nausea/vomiting/loss of appetite	36
Sweating	22
Blurred vision	20
Sensory disturbances	
Hypersensitivity to	
– Noise	38
– Light	24
– Smells	15
– Touch	7
Hyposensitivity to	
– Smells	15
– Taste	4
Qualitative changes	
– Movement	>24
– Vision	>13
– Taste	13
– Hearing	2
– Smells	2
Other	
– Feelings of unreality	24
Complications	
– Psychosis	7
– Epileptic seizures	4

From: Holzbach: Benzodiazepin-Langzeitgebrauch und -abhängigkeit [long term use of benzodiazepines and dependency]. Fortsch Neurol Psychiatr 2010; 78: 425–34. With permission from Thieme-Verlag, Stuttgart

anticonvulsants is able to reduce these to a satisfactory degree.

For patients with high-dose consumption, of a diazepam equivalent dose of 20 mg or higher, inpatient treatment is recommended when starting withdrawal treatment, but additional treatment with carbamazepine or valproate is also advised (24). Potential problems arising in this setting are due to different equivalence data (3). Other concomitant medications—such as buspirone, beta blockers, and clonidine—do not seem to affect withdrawal treatment conclusively (e17). The use of antidepressants is recommended only in patients

with comorbid depressive symptoms (e18). There are indications that flumazenil has a positive effect on withdrawal symptoms and results in a higher rate of abstinence (26, 27, e14). The Figure shows different withdrawal treatment options. Table 3 provides an overview of typical withdrawal symptoms. At this point we wish to remind readers again of a possible rebound effect of previously subclinical underlying psychiatric conditions.

The importance of psychotherapeutic interventions has generally been assessed as positive (28, e15, e17), although Oude Voshaar et al. (e20) found in a

TABLE 4

Effectiveness of different interventions in benzodiazepine dependency

Study	Type	Number of included studies	Intervention	N	End point	Effect
Denis et al. (22)	SR	8	Adjuvant medication	458	Progress of withdrawal Abstinence	No effect: buspirone, progesterone Unclear: propranolol Potentially positive effect: carbamazepine, tricyclic antidepressants
Parr et al. (e15)	MA	24	a) Routine treatment vs. b) short intervention vs. c) gradual reduction vs. d) gradual reduction + psychological intervention e) pharmacological substitution		Abstinence	b) and c) are significantly superior to a) (OR: 5.96 and 4.37) d) is significantly superior to a) and c) (OR: 3.38 and 1.82) e) is significantly inferior to c) (OR: 0.3)
Quaglio et al. (26)	CR		Flumazenil	29	Withdrawal symptoms Abstinence rate	Abstinence rate after 6 months: 53%
Tyrer et al. (e18)	RCT		Dosulepin vs. placebo	87	Withdrawal symptoms	No significant difference (OR: 0.63)
Vincens et al. (28)	RCT		Routine treatment vs. structured intervention vs. manualized intervention	532	Abstinence	Interventions significantly superior (p<0.0001)
Oude Voshaar et al. (e17)	MA	29	a) Routine treatment vs. b) minimal intervention vs. c) structured intervention + imipramine or d) structured intervention + CBT	2115	Abstinence	b), c) are significantly superior to a) (OR: 2.8) c) is significantly superior to a) + b) (OR: 3.1) d) is significantly superior to a) + b) (OR: 5.5)
Oude Voshaar et al. (e20)	RCT		a) Routine treatment vs. b) systematic reduction vs. c) systematic reduction + CBT	180	Predictors of success Abstinence	Independent predictors of success: low consumption, independent dose reduction before start of treatment, no alcohol consumption b) + c) are significantly superior to a) (HR: 2.9 and 2.4) b) is superior to c) but non-significantly

MA, meta-analysis; RCT, randomized controlled trial; CT, controlled trial; CR, case reports; SR, systematic review; OR, odds ratio; HR, hazard ratio; N, total sample size

comparative randomized controlled trial that, after a year, merely reducing the dose in a controlled fashion was superior to a combination with cognitive behavioural therapy in terms of the abstinence rate. However, this difference did not reach significance. *Table 4* provides an overview of the effectiveness of selected interventions.

Conclusion

Although treatment with benzodiazepines has many benefits, it became obvious quite soon after their introduction to the market in the 1960s that the risk of dependency should not be underestimated (3, e11). The fact that this was known not only to the medical profession but also to the wider population found its reflection in diverse culture historical episodes. One example is the 1966 song “Mother’s Little Helper” by British Rock band The Rolling Stones.

It should be pointed out that for a long time, the pharmaceutical industry played down the importance of the risk of addiction—not least again, when the Z-drugs were introduced. Their potential for dependency/addiction has been explicitly emphasized by different parties (3, 29, e21).

It is impossible to imagine certain medical disciplines without these groups of medications—for example, emergency medicine, anesthesiology, but also epileptology, and psychiatric emergencies (30, e22, e23, e24). According to the data of the German Federal Health Survey, users list among the most common reasons for taking these drugs insomnia (50%) and inner restlessness, nervousness, and states of agitation and tension (25.9%) (17). In the case study accompanying this article, the initial prescription was issued for insomnia.

Because of a lack of data, one can only speculate about the motivation for prescribing benzodiazepines and related substances for longer periods than those recommended in the medication guidelines. It can be assumed that the good effectiveness in terms of the target symptoms creates great affinity in patients towards their medication—even before manifest dependency develops. Patients therefore put pressure on their doctors who prescribe the drug to them. Those affected fear that their initial symptoms might return. This is also reflected in the comment that in many cases, prescriptions are issued at patients’ explicitly

expressed wishes (31). Furthermore, most patients are likely to have gone through a prolonged history of suffering before they were given benzodiazepine medication, so they desire rapid intervention and need it too. Since, for example, care in the psychotherapeutic setting is still associated with long waiting times, this means that patients' needs are insufficiently met. Another group of persons includes patients with primary polysubstance dependencies, but no concrete data are available in terms of what proportion this group accounts for.

As early as in 1984, Binder and colleagues reported on 157 cases of benzodiazepine dependency and in this context used the term "epidemic" (32). In addition to adjuvant administration in pain therapy (33, e25), psychiatric diagnoses are the primary indications for benzodiazepine medication. The mechanisms or individual risk factors that determine whether a patient develops high-dose dependency or—with comparatively low dosages of benzodiazepines—low-dose dependency are currently not known. Martinez-Cano and colleagues found in a study of 153 patients with benzodiazepine dependency a particularly high risk for high-dose dependency for triazolam and lorazepam. They explained this mainly on the basis of pharmacokinetic and pharmacodynamic factors (34). High-dose dependency has, however, been documented for all benzodiazepines, including the Z-drugs (12, 35, e26). In persons with high-dose benzodiazepine dependency, addiction-specific comorbidities are apparently less common than in consumers of low-dose benzodiazepines (36, e27).

Without any doubt, doctors are crucially involved in the long-term prescribing of benzodiazepines. It can be assumed that the majority of consumed benzodiazepines were not obtained on the black market but were prescribed by doctors. This problem was identified and made the focus of discussion early on (32, 37, 38, e28, e29), but the consequences are not yet reflected in doctors' prescribing behavior. Even after the prescribing options for different benzodiazepines were restricted, no effect was seen in this regard. For example, for flunitrazepam, prescriptions became possible only with a narcotics prescription. A recent survey among Germany's primary care physicians, which asked questions about their prescribing of hypnotic substances in the shape of private prescriptions, provides interesting insights: the doctors named primarily the regulations of the medication guideline and prescriptions on request as reasons for why they issued private prescriptions to patients who were members in statutory health insurance schemes (31). Furthermore, 80.4% out of 458 survey participants were of the opinion that Z-drugs were more effective and—including their addiction-forming potential—less likely to cause adverse effects than benzodiazepines. The literature does, however, not provide any evidence base for this assumption (39). To date, data on the distribution of persons who are dependent on high-dose benzodiazepines are lacking. Since the prescribing problems are set within a legal

gray area, substantial methodological problems arise—but the need for research is evident.

In our view, the prevention of inappropriate long-term prescribing, motivation for withdrawal, as well as carrying out outpatient or inpatient withdrawal therapy, are necessary measures to prevent inappropriate long-term use and long-term prescriptions. On the one hand, doctors and users will have to be better informed in this context, but sufficient treatment capacity is also required. The German Medical Association in collaboration with the Drug Commission of the German Medical Association in 2007 published guidance for medical practice, entitled "Medikamente—schädlicher Gebrauch und Abhängigkeit [Medical drugs—harmful use and dependency]" (23). The German Medical Association and the Association of Statutory Health Insurance Physicians for Hamburg in February 2011 published joint guidance for prescribing benzodiazepines and their analogues (4). This recommendation should be adhered to, even in situations where a patient forcefully expresses their request for a prescription (40). The Association of Statutory Health Insurance Physicians for Westphalia-Lippe also passes the guidance and comprehensive additional information regarding the prescribing of benzodiazepines to its members. The association also provides details of whom to contact for advice, for patients and doctors. With regard to the prevention and therapy of medication dependency, the current guideline of the German Medical Association explicitly points out that primary care physicians and other specialists in private practice, especially psychiatrists, need to collaborate closely. Here lies a potential that has hitherto been insufficiently used and which might improve healthcare.

Conflict of interest statement

The authors declare that no conflict of interest exists.

Manuscript received on 11 April 2014, revised version accepted on 28 October 2014.

Translated from the original German by Birte Twisselmann, PhD.

KEY MESSAGES

- Benzodiazepines and their analogues are still overprescribed and for periods that are too long.
- Because of the regularly occurring loss in effectiveness after merely a few weeks, the medication is often not stopped in insomnia.
- Several sources containing data on rates of dependency on hypnotics and tranquilizers in Germany are available. However, these individual aspects are not sufficiently robust.
- National and international treatment recommendations on the prevention and treatment of medication dependency are available.
- Options for continuing professional development/continuing medical education for the prevention and treatment of medication dependency should be intensified.

REFERENCES

- Müller-Oerlinghausen B: Prescription and misuse of benzodiazepines in the Federal Republic of Germany. *Pharmacopsychiatry* 1986; 19: 8–13.
- Janhsen K: Die stille Sucht: Medikamentenabhängigkeit ist weiblich. In: Glaeske G, Janhsen K (eds.): GEK-Arzneimittel-Report 2007. St. Augustin: Asgard 2007; 125–39.
- Holzbach R: Benzodiazepin-Langzeitgebrauch und -abhängigkeit. *Fortschr Neurol Psychiatr* 2010; 78: 425–34.
- Holzbach R, Martens M, Kalke J, Raschke P: Zusammenhang zwischen Verschreibungsverhalten der Ärzte und Medikamentenabhängigkeit ihrer Patienten. *Bundesgesundheitsblatt* 2010; 53: 319–25.
- Verthein U, Martens MS, Raschke P, Holzbach R: Langzeitverschreibung von Benzodiazepinen und Non-Benzodiazepinen. Eine prospektive Analyse über 12 Monate. *Gesundheitswesen* 2013; 7: 430–7.
- Lohse MJ, Müller-Oerlinghausen B: Mittel zur Behandlung von Alkohol-folgekrankheiten. In: Schwabe U, Paffrath D (eds.): *Arzneiverordnungs-Report* 2013. Berlin, Heidelberg: Springer 2013; 851–3.
- Schwabe U: Benzodiazepine. In: Schwabe U, Paffrath D (eds.): *Arzneiverordnungs-Report* 2013. Berlin, Heidelberg: Springer 2013; 379–80.
- Lohse MJ, Müller-Oerlinghausen B: Hypnotika und Sedativa. In: Schwabe U, Paffrath D (eds.): *Arzneiverordnungs-Report* 2013. Berlin, Heidelberg: Springer 2013; 641–55.
- Hoffmann F, Glaeske G, Scharffetter W: Zunehmender Hypnotikaverbrauch auf Privatrezepten in Deutschland. *Sucht* 2006; 52: 360–6.
- Hoffmann F, Glaeske G: Benzodiazepinhypnotika, Zolpidem und Zopiclon auf Privatrezept. Verbrauch zwischen 1993 und 2012. *Nervenarzt* 2014; 85: 1402–1409.
- Diemert S, Ganso M, Zagermann-Muncke P: Benzodiazepine und Z-Hypnotika. AMK-Umfrage zum Missbrauch. *Pharm Ztg* 2013; 158: 20–4.
- Hoffmann F, Scharffetter W, Glaeske G: Verbrauch von Zolpidem und Zopiclon auf Privatrezepten zwischen 1993 und 2007. *Nervenarzt* 2009; 80: 578–83.
- Voelker K: Welche Vorgaben gelten für die Verordnung von Benzodiazepinen? *Hamb Arztebl* 2009; 6: 15.
- Linden M, Bär T, Helmchen H: Prevalence and appropriateness of psychotropic drug use in old age: results from the Berlin Aging Study (BASE). *Int Psychogeriatr* 2004; 16: 461–80.
- Hoffmann F, Pfannkuche M, Glaeske G: Hochverbrauch von Zolpidem und Zopiclon. Querschnittsstudie auf Basis von Krankenkassendaten. *Nervenarzt* 2008; 79: 67–72.
- Kraus L, Pabst A, Gomes de Matos E, Piontek D: Kurzbericht Epidemiologischer Suchtsurvey 2012. Tabellenband: Prävalenz der Medikamenteneinnahme und medikamentenbezogener Störungen nach Geschlecht und Alter im Jahr 2012. www.ift.de/fileadmin/literaturliste/ESA_2012_Medikamente-Kurzbericht.pdf (last accessed on 23 July 2014).
- Knopf H, Melchert HU: Bundes-Gesundheitssurvey: Arzneimittelgebrauch. Konsumverhalten in Deutschland. Benzodiazepin- und/oder barbitursäure-haltige Psycholeptika. Berlin: Robert-Koch-Institut 2003; 56–7.
- Soyka M, Queri S, Küfner H, Rösner S: Wo verstecken sich 1,9 Millionen Medikamentenabhängige? *Nervenarzt* 2005; 76: 72–7.
- Mental Health and Drug and Alcohol Office: Drug and alcohol withdrawal clinical practice guidelines – NSW. www0.health.nsw.gov.au/policies/gl/2008/pdf/gi2008_011.pdf (last accessed 24 July 2014).
- Poser W, Böning J, Holzbach R, Schmidt L G: Medikamentenabhängigkeit (Sedativa, Hypnotika, Analgetika, Psychostimulanzien). In: Schmidt L G, Gastpar M, Falkai P, Gabel W (eds.): *Evidenzbasierte Suchtmedizin*. Köln: Deutscher Ärzteverlag 2006; 271–307.
- Frei M, Berends L, Kenny P, et. al.: Alcohol and other drug withdrawal: practice guidelines. 2nd ed. Fitzroy, Victoria: Turning Point Alcohol and Drug Centre 2012.
- Denis C, Fatseas M, Lavie E, Auriacombe M: Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database of Syst Rev* 2006; 3: CD005194.
- Bundesärztekammer in Zusammenarbeit mit der Arzneimittelkommission der deutschen Ärzteschaft: Medikamente – schädlicher Gebrauch und Abhängigkeit. Leitfaden für die ärztliche Praxis 2007. Köln: Deutscher Ärzteverlag 2007.
- Holzbach R: Der Benzodiazepinentzug und dessen Behandlung. *Suchttherapie* 2006; 7: 97–106.
- Rubio G, Bobes J, Cervera G, Teran A, Perez M, Lopez-Gomez V, Rejas J: Effects of pregabalin on subjective sleep disturbance symptoms during withdrawal from long-term benzodiazepine use. *Eur addic res* 2011; 17: 262–70.
- Quaglio G, Pattaro C, Gerra G, et al.: High dose benzodiazepine dependence: description of 29 patients treated with flumazenil infusion and stabilized with clonazepam. *Psychiatry res* 2012; 198: 457–62.
- Saxon L, Borg S, Hiltunen AJ: Reduction of aggression during benzodiazepine withdrawal: effects of flumazenil. *Pharmacol biochem behav* 2010; 96: 148–51.
- Vicens C, Socias I, Mateu C, et al.: Comparative efficacy of two primary care interventions to assist withdrawal from long term benzodiazepine use: a protocol for a clustered, randomized trial. *BMC fam pract* 2011; 12: 23.
- Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W: Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction* 2003; 98: 1371–8.
- Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN): S2-Leitlinie: Therapeutische Maßnahmen bei aggressivem Verhalten in der Psychiatrie und Psychotherapie. S2 Praxisleitlinien in Psychiatrie und Psychotherapie 2010; 2.
- Binder W, Kornhuber HH, Waiblinger G: Benzodiazepin-Sucht, unsere iatrogene Seuche – 157 Fälle von Benzodiazepin-Abhängigkeit. *Öffentliches Gesundheitswesen* 1984; 46: 80–6.
- Manchikanti L, Malla Y, Wargo BW: Comparative Evaluation of the accuracy of benzodiazepine testing in chronic pain patients utilizing immunoassay with liquid chromatography tandem mass spectrometry (LC/MS/MS) of urine drug testing. *Pain Physician* 2011; 14: 259–70.
- Martinez-Cano H, Vela-Bueno A, De Inceta M, Pomalima R, Martinez-Gras I, Sobrino MP: Benzodiazepine types in high versus therapeutic dose dependence. *Addiction* 1996; 91: 1179–86.
- Rappa LR, Larose-Pierre M, Payne DR, Eraikhuemen NE, Lanes DM, Kearnes ML: Detoxification from high-dose zolpidem using diazepam. *Ann Pharmacotherapy* 2004; 38: 590–4.
- Hermos JA, Young MM, Lawler EV, Rosenbloom D, Fiore LD: Long-term, high-dose benzodiazepine prescription in veteran patients with PTSD: influence of preexisting alcoholism and drug abuse diagnosis. *J Traumatic Stress* 2007; 20: 909–14.
- Lader M: Iatrogenic sedative dependence and abuse – have doctors learnt caution? *Addiction* 1998; 93: 1133–5.
- Taylor D: Iatrogenic drug dependence – a problem in intensive care? *Intensive Crit Care Nurs* 1999; 15: 95–100.
- Hoffmann F, Schmiemann G, Windt R: Privat statt Kasse? Einstellungen von Hausärzten und Apothekern zur Verordnung von Hypnotika. *Dtsch Med Wochenschr* 2014; 139: 1153–8.
- Hoffmann F: Perceptions of German GPs on benefits and risks of benzodiazepines and Z-drugs. *Swiss Med Wkly* 2013; 143: w13745.
- Ärztekammer Hamburg, Kassenärztliche Vereinigung Hamburg, Apothekerkammer Hamburg: Verordnung von Benzodiazepinen und deren Analoga. Gemeinsame Handlungsempfehlung von Ärztekammer Hamburg, Kassenärztlicher Vereinigung Hamburg und Apothekerkammer. Hamburg 2011.

Corresponding author

Dr. med. Knut Hoffmann
LWL-Universitätsklinikum Bochum
Klinik für Psychiatrie, Psychotherapie und Präventivmedizin
Ruhr-Universität Bochum
Alexandrinenstr. 1–3, 44791 Bochum, Germany
knut.hoffmann@wkp-lwl.org

For eReferences please refer to:
www.aerzteblatt-international.de/ref0115

eBox:
www.aerzteblatt-international.de/15m0001

REVIEW ARTICLE

The Problems of Long-Term Treatment With Benzodiazepines and Related Substances

Prescribing Practice, Epidemiology, and the Treatment of Withdrawal

Katrin Janhsen, Patrik Roser, Knut Hoffmann

eREFERENCES

- e1. Dieser Bärenkram muss aus dem Verkehr. Der Spiegel 1988; 35: 160–7.
- e2. Günther J: Tetrazepam. In: Schwabe U, Paffrath D (eds.): Arznei-verordnungs-Report 2013. Berlin, Heidelberg: Springer 2013; 756–8.
- e3. Bundesinstitut für Arzneimittel und Medizinprodukte: Ruhen der Zulassungen aller Tetrazepam-haltigen Arzneimittel (z. B. Musaril® Filmtabletten) zum 1. August 2013. www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2013/rhb-tetrazepam.pdf?__blob=publicationFile&v=5 (last accessed on 23 July 2014).
- e4. Bundesverband der Pharmazeutischen Industrie (eds.): Rote Liste. Arzneimittelverzeichnis für Deutschland. Aulendorf: Cantor 1984.
- e5. Fachinformation Distraneurin®, Stand: 2/2011.
- e6. Kraus L, Piontek D, Pabst A, Gomes de Matos E: Studiendesign und Methodik des Epidemiologischen Suchtsurveys 2012. Sucht 2013; 59: 309–20.
- e7. Glaeske G: Psychotrope und andere Arzneimittel mit Missbrauchs- und Abhängigkeitspotenzial. In: Deutsche Hauptstelle für Suchtfragen e.V. (eds.): Jahrbuch Sucht 2006. Geesthacht: Neuland Verlagsgesellschaft 2006; 87–103.
- e8. Statistisches Bundesamt: Vorläufige Ergebnisse der Bevölkerungsfortschreibung 2011 auf Grundlage des Zensus 2011. Zensusdaten mit dem Stand vom 10. April 2014. [www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand.html](http://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Bevoelkerungsstand.html) (last accessed 24 July 2014).
- e9. NHS West Essex: Guidelines for prescribing and withdrawing benzodiazepines and Z-drugs. A recourse for general practitioners. October 2012. www.westessexccg.nhs.uk/Downloads/Your%20NHS/Medicines%20optimisation/Prescribing%20guidance/Benzodiazepine_Resource_Pack.pdf (last accessed 24 July 2014).
- e10. Denis C, Fatseas M, Lavie E, Auriacombe M: Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database of Syst Rev 2013, 6: CD005194. doi: 10.1002/14651558.CD005194.pub3.
- e11. Holzbach R: Jahrelange Einnahme von Benzodiazepinen. Wann ein Entzug notwendig ist und wie er gelingt. MMW Fortschr Med 2009; 151: 36–9.
- e12. Oulis P, Konstantakopoulos G: Efficacy and safety of pregabalin in the treatment of alcohol and benzodiazepine dependence. Expert opin investig drugs 2012, 21: 1019–29.
- e13. Bobes J, Rubio G, Teran A, et al.: Pregabalin for the discontinuation of long-term benzodiazepines use: an assessment of its effectiveness in daily clinical practice. Eur psychiatry 2012; 27: 301–7.
- e14. Gerra G, Zaimovic A, Giusti F, Moi, G, Brewer C: Intravenous flumazenil versus oxazepam tapering in the treatment of benzodiazepine withdrawal: a randomized placebo-controlled study. Addict Biol 2002; 7: 385–95.
- e15. Parr JM, Kavanagh DJ, Young RM, Mitchell G: Acceptability of cognitive-behaviour therapy via the Internet for cessation of benzodiazepine use. Drug alcohol rev 2011; 30: 306–14.
- e16. Ashton H: The diagnosis and management of benzodiazepine dependence. Curr Opinion Psychiatry 2005; 18: 249–55.
- e17. Oude Voshaar RC, Couvée JE, Balkom A van, Mulder P, Zitman FG: Strategies for discontinuing long-term benzodiazepine use. Br J Psychiatry 2006; 189: 213–20.
- e18. Tyrer P, Fergusson B, Hallström C, et al.: A controlled trial of dothiepin and placebo in treating benzodiazepine withdrawal symptoms. Br J Psychiatry 1996; 168: 457–61.
- e19. Lugoboni F, Quaglio G: Exploring the dark side of the moon: the treatment of benzodiazepine tolerance. Br J Clin Pharmacology 2013; 1–3.
- e20. Oude Voshaar RC, Gorgels WJ, Mol AJ, et al.: Predictors of long-term benzodiazepine abstinence in participants of a randomized controlled benzodiazepine withdrawal program. Can J Psychiatry 2006, 51: 445–52.
- e21. Lader M: History of Benzodiazepine Dependence. J Subst Abuse Treat 1991; 8: 53–9.
- e22. Deutsche Gesellschaft für Neurologie (DGN): S1-Leitlinie: Status epilepticus im Erwachsenenalter. 2012. www.awmf.org/leitlinien/detail/II/030-079.html (last accessed 2 December 2014).
- e23. Weltgesundheitsorganisation: WHO Model List of Essential Medicines. 18th list. April 2013. apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf?ua=1 (last accessed 24 July 2014).
- e24. Mavrogiorgou P, Brüne M, Juckel G: The management of psychiatric emergencies. Dtsch Arztebl Int; 108: 222–30.
- e25. Mickel C: 3 things to consider before relying solely on point of care tests for determining benzodiazepine use in chronic pain. Pain Physician 2012; 15: E151–8.
- e26. National Institute for Clinical Excellence: Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. www.nice.org.uk/guidance/ta77 (last accessed 2 December 2014).
- e27. Johansson BA, Berglund M, Hanson M, Pöhlen C, Persson I: Dependence on legal drugs among alcoholics. Alcohol Alcohol 2003; 38: 613–8.
- e28. Faust B: Doctors and detailers: the benzodiazepine scandal. Austr Nurses J 1991; 20: 12–3.
- e29. Lader M: Benzodiazepines revisited-will we ever learn? Addiction 2011; 106: 2086–109.

eBOX

Case report

A 58 year old woman was found unconscious by her husband in their apartment. Because of mixed intoxication with alcohol, bromazepam, and clomethiazole she was treated in intensive care (Glasgow coma score: 3). Laboratory parameters at admission: blood alcohol concentration 2.8‰, creatine kinase (CK): 544 U/L. Drug screening: positive for benzodiazepines; normal: cocaine, opiates, amphetamines, cannabis; serum concentrations were not measured. Neurological examination: cranial nerve areflexia; bilaterally mid-dilated non-reactive pupils; absent corneal reflex; floppy muscle tone; weak bilateral muscle reflexes. ECG and cCT findings were normal. After 24 hours the patient was extubated and transferred to a psychiatric ward. Psychopathological findings at admission: alert, temporally disoriented, notable attention and perception impairments, reduced memory performance, depressed mood, reduced emotional responsiveness, listlessness, inner restlessness and psychomotor agitation, formal thought processes slowed down but mainly ordered, no indications of psychotic experiences, no suicidality. Physical and neurological findings were normal. The patient's history did not report any suicidality.

The patient was known to have had longstanding dependency issues with bromazepam and clomethiazole. Relatives presented private prescriptions that proved continuous outpatient prescriptions of sedative by the primary care physician since 2003 (at the end, 100 bromazepam 6 mg tablets, 200 capsules clomethiazole 192 mg, twice weekly). Additionally, different physicians issued private prescriptions, each for 50 tablets of bromazepam 6 mg, at irregular intervals. The patient collected these prescriptions at 11 different pharmacies. According to the patient's own history, she took a daily dose of 9–12 mg bromazepam and 10 capsules of clomethiazole.

During withdrawal treatment using diazepam 4 × 10 mg/day and, adapted to individual need, up to 4 × 5 mg/day, the patient developed a delirious state on the second day, which manifested as confusion/disorientation, cognitive deficits, formal thought disorders, and visual hallucinations. Additionally she developed psychovegetative decompensation with hypertension, which improved after administration of haloperidol and clonidine. On the fourth day the patient developed a grand mal seizure for the first time. After a second grand mal seizure during the day, with increasing clouding of consciousness, the patient was transferred to a neurological intensive care ward, where she developed a grand mal seizure with a Glasgow coma score of 3. Administration of clonazepam and levetiracetam did not stop this series of seizures, so propofol was administered, successfully. The EEG showed slight general changes without any indications of focal findings or epilepsy-typical potentials. Analysis of cerebrospinal fluid, extracranial and transcranial Doppler and Duplex sonography of the cerebral vasculature did not show any pathological abnormalities, and neither did cranial CT and MRI. The seizure event was therefore categorized as associated to the withdrawal, and the patient was treated with antiepilepsy medication—levetiracetam 1000 mg/day. After 13 days of intensive medical and neurological treatment, the patient was transferred back to Bochum Ruhr University's Hospital Department of Psychiatry, Psychotherapy, and Preventative Medicine.

The subsequent withdrawal treatment proved lengthy; the dosage of diazepam was reduced with extreme caution because of the patient's pronounced psychovegetative withdrawal symptoms (0.5 mg/week). The antiepileptic treatment with levetiracetam remained unchanged. The patient did not experience any more instances of withdrawal delirium or seizures. Three months later, the patient had finished the withdrawal treatment and was discharged to her domestic environment in a sufficiently stable state and without any relevant depressive symptoms.