CORRESPONDENCE

The Problems of Long-Term Treatment with Benzodiazepines and Related Substances Prescribing Practice, Epidemiology, and the Treatment of Withdrawal

by PD Dr. rer. pol. Katrin Janhsen, Prof. Dr. med. Patrik Roser, Dr. med. Knut Hoffmann in issue 1–2/2015

Severe Collateral Damage

The magnitude of the health problem caused by doctors prescribing benzodiazepines and non-benzodiazepine agonists (1) in an uncritical way or to do patients a favor is revealed by this review. If 50% of the 230 million daily doses of these drugs are prescribed privately, even for patients who have statutory health insurance, it has to be assumed that the proportion of patients whose intake is problematic and lasts longer than four weeks is significantly underestimated with 20%. Unfortunately, of the many negative effects, the authors only address the problem of dependence.

A study by a Canadian working group recently published in the British Medical Journal demonstrated a clear association between the prolonged intake of benzodiazepines and symptoms of Alzheimer's disease among elderly patients (2). Thus it could well be that, besides the common mistake of not recognizing arteriosclerotic encephalopathy, this explains the epidemic increase in the number of people being diagnosed with Alzheimer's disease—a reason that has nothing to do with extended life expectancy. It would not be the first time that an extensively researched idiopathic disease turns out to be a massive iatrogenic collateral damage.

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Conflict of interest statement

The author declares that no conflict of interest exists.

Additional Information to Increase Accuracy

The fact that only very few studies on the long-term treatment with benzodiazepines have been published in medical journals so far combined with the very large number of private prescriptions shows that this is a sensitive issue. Therefore, I am all the more grateful that the authors have addressed this topic and described the problem and the management of benzodiazepine abuse appropriately.

To increase accuracy, I would like to add two points:

In the summary, the switch to an “intermediate or long-acting” benzodiazepine is recommended to assist with withdrawal treat-

ment. However, the problem with treating elderly patients with long-acting benzodiazepines such as diazepam is that their phase I metabolism can be slowed down to such an extent that in extreme cases it can take up to six weeks before a steady state is reached. Because of the associated accumulation of the drug, withdrawal treatment can trigger an intoxication with an insidious onset. As the result of the benzodiazepine accumulation, prolonged intake may lead to high-dose dependency from what was presumed to be a low-dose dependency. Therefore, elderly patients on a low-dose regimen can develop severe withdrawal symptoms that one would only expect from a high-dose treatment. Consequently, oxazepam which is mentioned in the reduction dosing scheme (*Figure*) is a good choice (only phase II metabolism, i.e. direct glucuronidation) (2).

When focusing on the problems that led to benzodiazepine abuse in the first place (e.g. insomnia or anxiety), psychotherapy is a useful modality; however, it is not helpful if the focus is on benzodiazepine consumption in general. In a Canadian study, the group receiving psychotherapy even performed significantly worse compared with the control group with a defined medication taper program; the authors thought that the lack of such a program in the psychotherapy group was responsible for this outcome (3).

Successful withdrawal from benzodiazepine hypnotics without negative impact on quality of life and with improvement of neuropsychological functions can also be achieved in general practice, provided a medication taper program is in place, including information about potential rebound symptoms and their temporary nature, as well as a strong doctor-patient relationship, including an emergency contact point; an English study with patients aged 70 years and older has provided impressive evidence of this (4).

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The Use of Antidepressants in Patients With Benzodiazepine Dependence

Janhsen and colleagues describe the disturbing proportions of benzodiazepine use and speak of 230 million defined daily doses (DDD) prescribed per year to patients covered by statutory

health insurance (1). With 1341 million DDDs in 2013, antidepressants are prescribed even more frequently (2).

With regard to the common practice of prescribing both substance groups concomitantly, there is only the brief statement: "The use of antidepressants is recommended only in patients with comorbid depressive symptoms." Here, reference is wrongly made to a study (3) evaluating the use of an antidepressant on benzodiazepine withdrawal in explicitly non-depressive patients. This recommendation of Janhsen et al. is not helpful since almost all patients with addiction show depressive symptoms as part of their illness.

The Drug Commission of the German Medical Association (AkDÄ) has recently issued a detailed statement on the problem of identifying a depressive disorder in patients with alcohol dependence and treating it with pharmacotherapy (4). These recommendations can essentially be applied to patients with benzodiazepine dependence as well. Key messages include: Symptoms such as lack of energy, social withdrawal, insomnia, and a sense of guilt are in most cases associated with addiction and not related to an independent mood disorder. A depressive disorder can only be reliably diagnosed after at least two to four weeks of abstinence. Stringent treatment of addiction is crucial, also to improve depressive symptoms. Along with strict abstinence, depressive symptoms frequently improve.

Prescribing antidepressants will inevitably reinforce ideas typically associated with addiction, such as the assumption that the oral intake of substances is the only way to control the mental state. Physicians should be self-critical and ask themselves whether they take this approach only to avoid the unpleasant discussion about addiction. It remains unclear whether and how antidepressants are acting when concomitantly addictive substance are continuously consumed.

The same recommendations are made in the S3 guideline/National Disease Management guideline Unipolar Depression.

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Prof. Bschor has received conference fees and reimbursement of travel expenses by Lundbeck and Astra Zeneca. He has received lecture fees from Lilly, BMS, esparma (Aristo), Servier, Astra Zeneca, Sanofi, and Lundbeck.

In Reply:

Dr. Wolter rightly points out that, above all in the elderly, the pharmacological characteristics of the medication require special attention and that well-established processes in other patient populations may need to be modified. Given the high prevalence of benzodiazepine dependence among elderly patients, this is an important issue. Further studies are needed to establish the impact of the potential additional risks brought up by Dr. Reuther. Currently, the available data is insufficient. Billiotiti et al. (1) phrase their proposition as a question (quote: "Is there really a link between benzodiazepine use and the risk of dementia?").

Prof. Bschor addresses a fundamental problem: the treatment of substance dependence with a substance. This discussion went on for years with regard to disulfiram. The addiction-specific tendency of those affected to externalize problems and needs and to prefer presumably simple "substance-related" solutions always involves the risk of a substance shift with all potential consequences. However, whether the statements made in the recommendations of the Drug Commission of the German Medical Association (2) can be directly applied to patients with benzodiazepine dependence, as suggested by Prof. Bschor, remains to be seen. Likewise, the guideline Unipolar Depression (3) ultimately addresses comorbidities only in relation to alcohol dependence. Although it is certainly correct that a valid evaluation of affective symptoms can only be performed after period of time where no substance is taken, it is likely that the time required in patients with benzodiazepine dependence is rather longer than that in alcohol dependence. It is rather obvious that further research is needed to reveal the specific links between benzodiazepine dependence and mood disorders.

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