

ROLE OF BENZODIAZEPINES IN THE TREATMENT OF ANXIETY DISORDERS IN 2014

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SUMMARY

Background: This article aims at determining the place of benzodiazepines in the current treatment of anxiety disorders in opposition to antidepressants, neuroleptics and anticonvulsants. Belgium and France are the only two European countries which prescribe the most benzodiazepines despite the dissuasion of the international guidelines (NICE) issued in the nineties concerning the high risk of dependence of these molecules. What about the respect of these guidelines and the use of benzodiazepines in general practice in 2014?

Methods: Review of the literature with the following key words «anxiety disorder, benzodiazepines, anxiolytic, treatment» in the international database of PubMed, Medline, PsycINFO, PsycARTICLES and consulting of various reference books.

Results: No class of molecules could measure up to benzodiazepines until now, neither from the point of view of efficiency, nor from the point of view of cost-efficiency. This is why the guidelines (NICE) discourage the few available alternatives in the general practice. International figures from Belgium and France show a continuous increase in the use of benzodiazepines in the treatment of anxiety disorders, even after the nineties. Given the fact that benzodiazepines differ from one another at the level of their action profile (graphical representation in “stars”) and are therefore able to relieve several symptoms simultaneously, these molecules still respond nowadays to many expectations of the clinical practitioners.

Conclusions: The divergence between the guidelines and the practice confirm the irreplaceability of benzodiazepines at the present time. Nevertheless, the expectation of new molecules with fewer side effects should be investigated in further research.

Key words: anxiety disorder – benzodiazepines – anxiolytic - treatment

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INTRODUCTION

Anxiety disorders form the most frequent psychiatric disorder of our population: their prevalence varies between 10.4% and 28.8% according to different studies (Cadet-Taïrou et al. 2012, 14.5% in Bernier & Simard 2007, 25% in Kessler et al. 1994 in Epstein et al. 2005). Theoretically, SSRI antidepressants represent the treatment of choice in the long term (Gourion 2003, Zdanowicz et al. 2008). However, the most used pharmacological class to achieve quick and effective relief for the patients is that of the benzodiazepines (BZD) (Gourion 2003, Bernier & Simard 2007). It is therefore advisable, ideally, to use anxiolytics only to cover the period when the antidepressant has not yet reached its full effectiveness, or the first two to four weeks of therapy (Bernier & Simard 2007). To do this, 22 BZD or related compounds are currently commercialized in France, including ten available as anxiolytics (Berthes et al. 2013, Cavalié et al. 2012). In 2010, anxiolytics represented more than half (50.2%) of BZD sold (Cavalié et al. 2012). However, their place should remain fairly limited given their many side effects and should be provided only in the management of severe, disabling anxiety disorders and for short periods (Berthes et al. 2013, Cavalié et al. 2012, Gourion 2003).

Despite these guidelines of good clinical practice, we know that the use of BZD is very high for many years, both in France (AFSSAPS 2012) and in Europe (The ESEMeD/MHEDEA 2011). In 2001, the prevalence of BZD use was 18% in France, against 10% for

the other five European countries (Germany, Belgium, Spain, Netherlands, Italy) (AFSSAPS 2012). The total consumption of BZD and related compounds has decreased overall in France between 2000 and 2010. In 2009, France ranked second in the consumption of anxiolytics in Europe (Belgium and Italy excluded) after Portugal and second in the consumption of hypnotics after Sweden (AFSSAPS 2012, Berthes et al. 2013, Cavalié et al. 2012).

This work has been motivated by our clinical sense that BZD (anxiolytics or hypnotics) have been prescribed excessively to inpatients. Moreover, as the NIHDI (National Institute for Health and Disability Insurance) of Belgium does not identify BZD given the non-repayment for these molecules, it seemed important to obtain representative figures.

The purpose of this study is to evaluate the use of BZD (all together, and in particular anxiolytics) and the prevalence of anxiety disorders in the hospitalized population. Moreover, we will highlight the number of different molecules consumed by the patient, and the type of molecules most used. Thereafter, we will compare these results with data from the literature.

SUBJECTS AND METHODS

Outside the bibliographic research, we were also interested in consumption of BZD in our hospital (Mont-Godinne University Hospital), the latter being a university hospital consisting of 413 beds and including all medical services. We reviewed the consumption of

all patients together who were hospitalized at the University Hospital of Mont-Godinne from 01/01/2013 to 31/12/2013 and which were administered BZD (regular or occasional treatment combined). These data were compared with those of the literature.

Review of the literature on the role of BZD in anxiety disorders today. The literature review has been selected in the international database of PubMed, Medline, PsycINFO, PsycARTICLES with the following key words: anxiety disorder, benzodiazepines, anxiolytic, treatment.

RESULTS

Hospital data

Consumption of BZD

The census of the BZD consumption shows that among 16.821 hospitalizations, 56.5% (9.502) of the patients received any type of BZD (occasionally or regularly): anxiolytic, hypnotic or related. If we take into account patients who consume anxiolytic BZD, we get a result of 50.0% (8.342) of all inpatients in 2013, or 87.8% of the inpatients being identified as having consumed BZD.

If we assume that anxiolytic BZD are prescribed exclusively in the treatment of anxiety disorders and if we consider that the population admitted to our hospital represents approximately the general population, we obtain a prevalence of anxiety disorders of 50.0%.

If we focus on the number of BZD consumed simultaneously by each patient, we arrive at the following results: more than half of the patients (57.0%) consume only one BZD, almost a third (29.9%) consumes two, and the remainder (13.1%) more than two BZD (between three and nine BZD) (Table 1).

Table 1. Number of BZD consumed per patient

Number of BZD	Number of patients	Percentage
1	5412	57.00%
2	2845	29.94%
3	888	9.35%
4	249	2.62%
5	67	0.71%
6	29	0.31%
7	8	0.08%
8	3	0.03%
9	1	0.01%

By doing the same for anxiolytics only, we get somewhat different proportions: 70.2% of patients consume only one anxiolytic BZD, 22.3% take two, and the remainder (7.5%) receive more than two BZD (between three and eight BZD) (Table 2).

Table 2. Number of anxiolytic BZD consumed per patient

Number of anxiolytics	Number of patients	Percentage
1	5852	70.15%
2	1862	22.32%
3	449	5.38%
4	125	1.50%
5	38	0.46%
6	12	0.14%
7	3	0.04%
8	1	0.01%

Type of consumed BZD

The eighteen BDZ (ten of which are anxiolytics) used are listed in table 3.

Table 3. Type and percentage of molecules used (BZD all together and related)

BZD	Number of molecules used	Percentage
Alprazolam (Xanax®)	5262	34.26%
Lorazepam (Temesta®, Tavor®)	2280	14.84%
Prazepam (Lysanxia®)	2074	13.50%
Lormetazepam (Loramet®)	1753	11.41%
Zolpidem (Stilnoct®)	1644	10.70%
Diazepam (Valium®)	906	5.90%
Clonazepam (Rivotril®)	462	3.01%
Clorazepate, dipotassium ((Uni-)Tranxène®)	375	2.44%
Bromazepam (Lexotan®)	330	2.15%
Zopiclone (Imovane®)	126	0.82%
Flurazepam (Staurodorm®)	64	0.42%
Triazolam (Halcion®)	48	0.31%
Clobazam (Frisium®)	21	0.14%
Flunitrazepam	9	0.06%
Cloxazolam (Akton®)	2	0.01%
Clotiazepam (Clozan®)	2	0.01%
Loprazolam (Dormonoct®)	1	0.01%
Brotizolam (Lendormin®)	1	0.01%
Total	15360	100%

The undoubtedly most used anxiolytic is alprazolam (34.3%), followed by lorazepam (14.8%) and prazepam (13.5%). Alprazolam and lorazepam together are therefore the most prescribed molecules (49.1%).

Distribution by hospital service

In addition, it is also interesting to examine the distribution of our patients in the different departments of the general hospital.

Among the 7.447 patients being on BZD, 6.1% (455) of the listed patients were hospitalized in the service of Psychosomatic Medicine, against 93.9% (6.992) in another department of the general hospital. However, the terms „anxiety“, „anguish“ or „anxious“ only appear in 306 hospital reports, and that, only among patients hospitalized in our Psychosomatics Unit. Of these 455 patients, 67.3% are actually carrying a diagnosis of anxiety disorder.

Considering this time only anxiolytics, we get out of a total of 6.714 patients very similar figures: 6.3% (420) of the patients being on anxiolytics were hospitalized in Psychosomatic Medicine, against 93.7% (6.294) in all other services combined. Among patients hospitalized in the department of Psychosomatic Medicine and taking anxiolytics, 67.4% (283) of the hospital reports contain the term „anxiety“, „anguish“ or „anxious“ (and optionally the diagnosis of an anxiety disorder).

Literature confrontation

Prevalence of anxiety disorders

Recall that the prevalence of anxiety disorders varies between 10.4% and 28.8% according to different studies (Cadet-Taïrou et al. 2012, 14.5% in Bernier & Simard 2007, 25% in Kessler et al. 1994 in Epstein et al. 2005).

Data from the ESEMeD study (Gasquet et al. 2005) demonstrate the high consumption of benzodiazepines in patients with anxiety disorders.

Diagnosis of anxiety disorders

According to the study ESEMeD (Gasquet et al. 2005) also, a number of patients use these medications without an established anxiety disorder (Gasquet et al. 2005, Grolleau et al. 2008, Norton et al. 2009): in fact, 14.7% of the patients having presented no trouble in their lifetime had used anxiolytics in the year. More surprisingly, this study shows that 45.6% of anxiolytic and hypnotic users never fulfilled the diagnosis of anxiety or depressive disorder during their lifetime.

Association of BZD

According to the study of Cavalié et al. (2012), 21% of the patients had a combination of two BZD during treatment. 30% of the patients had two BZD associated, anxiolytics or hypnotics. The author makes it clear that the combination of several BZD increases the risk of addiction (Cavalié et al. 2012).

Prescribed molecules

So far, no study has demonstrated the superiority of a BZD particularly in the treatment of anxiety disorders.

However, we prefer molecules with intermediate half-life, such as alprazolam and lorazepam (Bernier & Simard 2007, Gourion 2003). Moreover, clonazepam demonstrated its effectiveness in certain anxiety disorders, even if it has not yet received its authorization to market in France (Cavalié et al. 2012, Gourion 2003).

Comparison of national consumption

The exact BZD consumption in Belgium is difficult to assess but is similar to that of France (Cavalié et al. 2012).

DISCUSSION

First, we note that there is a strong discrepancy between the prevalence of anxiety disorders in our study (50%) and the literature (between 10.4% and 28.8%). If we consider that anxiolytics were prescribed appropriately, namely only when an anxiety disorder exists, our prevalence is too high. The fact that, as the literature describes, a number of patients use anxiolytics without an established disorder may partially explain our divergent results (first bias). A second bias of this overestimation of the prevalence of anxiety disorders could be the quantification of the number of patients in the sample: indeed, in the first part of the results, each hospitalization corresponds to a different patient, while the same patient might have been hospitalized several times (for the same or different reasons) during the year 2013. Another bias to mention in these calculations is the approximation that we have made about the superposition of hospitalized population and general population. Indeed, patients in the institution are a priori ill and otherwise, are of a certain age. However, anxiety disorders usually occur in young people who are probably not directly treated.

As already stated above, the diagnosis of an anxiety disorder is sometimes not established although anxiolytics are prescribed. In fact, recall that there are only 67.4% of the patients hospitalized in the department of Psychosomatic Medicine and on anxiolytics who received the diagnosis of anxiety disorder. Note, however, that the hospital reports made in other services rarely take into consideration the mental or psychological aspect of the patient and therefore do not mention «anxiety» in the hospital report although they prescribe anxiolytics.

Moreover, we can also assume that not all BZD delivered in hospital are prescribed only for anxiety disorders. It could be a one-off prescription during hospitalization given the circumstances in which patients are at that time.

Moreover, the accumulation of different BZD consumed per patient in our study is challenging (up to nine BZD associated).

In comparing the use of the sum of alprazolam and lorazepam together in our study with the literature, we find a slightly different percentage: 49.1% in our study, against 61% in the literature.

Note also that clonazepam is still very little prescribed (3.9%) in our hospital, despite the evidence of its effectiveness in anxiety disorders.

Finally, note also that we compare Belgian data to French data, two countries whose drug legislation differs a lot from each other, since BZD are not registered in Belgium having regard to the non-repayment and non-prescription requirement of these molecules. This last point must be a non-negligible bias.

CONCLUSIONS

In conclusion, this study demonstrates the overconsumption of BZD, whether they are anxiolytics or hypnotics.

This study sheds light also on the complexity of the use of BZD today, despite the numerous recommendations of the literature on their prudent use in view of their side effects. Inappropriate, abusive and uncontrolled use of these drugs requires a more rigorous control for the prescription of these molecules. There are currently a lot of data in this direction. Recall that these drugs should only be prescribed in disabling and severe anxiety disorders and in the short term (to avoid side effects). Ideally, they should be used to cover the period when the antidepressant has not yet reached its full effectiveness (the first two to four weeks of therapy). However, our clinical practice shows that, once the BZD is introduced, it is very difficult to remove (quickly) such an efficient molecule which the patient continues to request.

In addition, also note the almost complete absence of therapeutic alternatives to BZD. We expect the development of other molecules relieving patients as effectively and quickly as BZD, but which do not have the side effects of the latter.

This study leaves many avenues open and offers a glimpse of other research opportunities in this area. We were able to include data concerning the association of antidepressant treatments and duration of treatment, but the development of these was beyond the scope of our study.

It would be desirable to extend this research in several hospitals in Belgium, ours being only representative of a rural place, and also across other countries.

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