High-Dose Benzodiazepine Use among Long-Term Users: When Will We Ever Learn?

Julie M. Zito

University of Maryland, Baltimore, Baltimore, Md., USA

In this issue, Cloos et al. [1] present a population-based study on high-potency benzodiazepine (BDZ) use in Luxembourg, a nation with universal coverage, thus allowing a longitudinal analysis of utilization across the years 1995 through 2007. The study categorized those with one or more BDZ dispensings according to the duration of exposure, namely: (1) short-term (less than a 3-month quantity); (2) intermediate (multiple dispensings with at least a 1-year interruption), and (3) continuous use (>3-month quantity with no interruption). In addition, a second characteristic, high-dose use (HDU), was examined within each exposure group. HDU was defined as exceeding the usual therapeutic maximum daily adult dose as recommended by major compendia, i.e. Martinale and Micromedex.

When BDZ anxiolytic and hypnotic users were identified according to the use of BDZ for anxiety or insomnia and combined across the two drug groups, the data revealed that:

- Among total Luxembourg enrollees, 16% had one or more BDZ dispensings yearly, with females being 38% more likely than males to have a BDZ dispensing (unadjusted prevalence ratio).
- Overall, among the three exposure groups, 18.4% were continuous users, although the female-to-male difference was less pronounced in this group.

- HDU grew according to the length of exposure such that HDU was less than 1% among low-exposure use, 3.4% in intermediate exposure while HDU was 20.3% among continuous users. The data support the authors' decision to conduct subsequent analysis targeting the group most at risk, i.e. the 39,324 continuous users wherein HDU was most prevalent.

In the subsequent analysis of continuous users, a multivariable logistic regression using a generalized estimating equations analysis was undertaken to account for persons with repeated BDZ dispensings across the years, stratified according to age at first BDZ intake. The authors present the adjusted odds separately for drugs primarily used as anxiolytics and those primarily used as hypnotics. It should be noted that in the absence of diagnostic information, there are proportions of outpatient use for seizure disorders and other nonpsychiatric conditions which presumably did not vary across the years. Finally, the reference group was diazepam for both anxiolytics and hypnotics. The rationale for the choice of diazepam as the comparator presumably relates to its medium potency, rapid onset and long length of action to avoid the problems high-potency, short-duration products have presented in terms of difficulty in withdrawal, dose escalation and dependence [2]. The analysis revealed that:

- Among anxiolytics, only two products had significantly increased odds of HDU compared with reference diazepam, and both of these occurred among the 69- to 105-year-olds at first BDZ intake: alprazolam and prazepam. The increased risk with prazepam is not consistent with the theory that high-potency, short-acting products are most likely to produce HDU, but could be an artifact.
- By contrast, hypnotics showed a strikingly different risk assessment: The odds of HDU compared with diazepam were significantly greater regardless of the age at first BDZ intake. In the 69- to 105-year-olds, 7 of the 8 products assessed had significantly greater odds of HDU than diazepam, the reference compound. Greatly increased odds were found for both brotizolam and triazolam with HDU twice as common among triazolam users. Study data on the triazolobenzodiazepines corroborate prior findings that short-acting high-potency products are particularly prone to long-term use problems, e.g. withdrawal syndrome and dependence. These can lead to serious adverse events, e.g. severe anterograde amnesia [3]. The data add support for recommendations for clinical guidelines and health payment systems to restrict inappropriate use.

In general, the strengths and limitations of administrative claims data are carefully documented by the authors. The opportunity to examine data longitudinally over 12 years in a large cohort of users is particularly impressive. More information on the distribution of BDZ days of use among continuously exposed persons would have added further strength, and addressing the extent of HDU as a function of both age and continuity of use adds a novel method to assess these clinically important patterns of use.

Implications for Policy and Practice

Of course, the external validity of data in a national health registry gives great credence to the implications for clinical education of practitioners and patients and for enhanced oversight by payers. For example, the sudden growth of antipsychotic use in very young children for nonpsychotic conditions, e.g. attention deficit hyperactivity disorder, has prompted numerous state Medicaid systems to require peer review of requests for such use [4]. In terms of improving clinical prescribing behavior, while HDU appears relatively restricted in these Luxembourg population data, avoidance of both long-term anxiolytic and hypnotic use in elders, particularly triazolo products, seems resistant to voluntary clinical guidelines.

Wide geographic variability in BDZ use is apparent from the summary of published studies the authors reviewed. Comparing national prevalence studies shows that Luxembourg usage is 3 times greater than in the US [5]. By contrast, Luxembourg is comparable to the most recent high-usage European countries, e.g. Portugal and Spain. Moderate-usage countries include France, Italy, Switzerland and Denmark. This wide spectrum of prescribing patterns for BDZ invites hypotheses about why US patterns differ from those of many European countries. For example, US prescription reimbursement policy for Medicare beneficiaries (usually elders > 65 years and persons with disabilities) did not include BDZ under part D outpatient prescription drug coverage until January 2013 [6].

Future Research Directions

Among the possible explanations of low prevalence of BDZ use to treat anxiety in the US is that antidepressants of the selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor class have often been preferred [7]. Despite early enthusiasm for the selective serotonin reuptake inhibitors, a new molecular entity in the late 1980s, new knowledge has arisen from meta-analyses, studies of unpublished data, and concerns about suicide and other serious events [8–11]. Thus, the prominent discrepancy in treatment patterns between Europe and the US invites a call for a head-to-head comparative trial on the short-term benefit/risk of BDZ versus antidepressants for the treatment of anxiety [12]. Moreover, it is critical to integrate nonpharmacologic interventions with drug therapy to assure outcomes that validate comprehensive interventions.

In addition, observational follow-up research in a population-based data source with clinician-reported diagnostic data would be welcome. Moreover, the growth of psychiatric comorbidities [13] makes a case for a study of comparative trends in the drug treatment of depression, anxiety and both comorbid depression with anxiety. Trends on medication class use, alone or in concomitant patterns for these conditions, would help to confirm the hypothesized discrepancies in use of BDZ and antidepressants in US versus European treatment settings. Finally, establishing outcomes in large cohorts of community-treated populations would shed light on the role of social and economic factors in influencing treatment outcomes [14] – a particular challenge to successful treatment of mental disorders.

Challenges to Changing Prescribing Practices

As a pharmacoepidemiologist, I have observed trends in prescription drug use for nearly 30 years, moving up from case observation at a pharmacy counter to using very large population-based administrative data. My interactions with prescribing doctors are mainly here in the US. My observations vary principally by whether the system is privately or publicly oriented and I have seen few easy ‘fixes’ to assure appropriate (evidence-based) prescribing decisions. I have learned to appreciate the interplay of critical stakeholders, principally the prescriber, the patient, the payer and the impact of the pharmaceutical industry marketers. Since the 1960s, the government agency overseeing policy on drug approval, labeling, and revision has played a major role, but in the current deregulatory environment [15], change to assure a public health perspective for optimal treatment is more challenging than ever.

Prescribers often exhibit high expectancy effects when new products, particularly new molecular entities, arrive. Initial information is based on proprietary trials in selected populations. Comparative information on active drug to placebo indicated p was <0.05 for short-term efficacy and reports of harms were minimal and so prescriptions will be written. We patients, too, can overexpect and have been prone to search for the ‘magic pill’,

particularly since nonpharmacologic therapy demands more time, financial commitment and the will to engage in therapy. Over time and as the intensity of marketing new, patented products proceeds, clinicians may gradually observe benefits/risks in community populations that do not comport with the data of the initial trials. At that point, outcomes research in community treatment settings could provide the needed information on long-term tolerability, risks and effectiveness [16].

The carefully detailed analysis Cloos et al. [1] present here pinpoints the continuing risk associated with use of products known for more than 25 years, particularly regarding long-term HDU in the elderly. As researchers, their data remind us that clinical psychopharmacology is an evolving science with the benefit/risk of any drug subject to change over time and as new large populations are treated. But, because there is no major sustained effort for innovative outcomes research on these prescribing practice patterns that can provide feedback to clinicians of benefits and risk over time, I am not optimistic that we *will* ever learn.

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