

Clinical Methodology Matters in Epidemiology: Not All Benzodiazepines Are the Same

Fiammetta Cosci^a Jenny Guidi^b Richard Balon^{c, d} Giovanni A. Fava^{b, e}

^aPsychology and Psychiatry Unit, Department of Health Sciences, University of Florence, Florence, and ^bDepartment of Psychology, University of Bologna, Bologna, Italy; Departments of ^cPsychiatry and Behavioral Neurosciences and ^dAnesthesiology, Wayne State University, Detroit, Mich., and ^eDepartment of Psychiatry, State University of New York at Buffalo, Buffalo, N.Y., USA

In 1977, at a time when psychiatric epidemiology was not as fashionable as it is today, Whitlock [1] outlined its aims and limitations. He criticized a narrow view of psychiatric epidemiology as concerned with the incidence, prevalence and distribution of mental disorders in the general population. He found ‘the pursuit of investigations of this kind a singularly sterile activity, largely because it is difficult to see what possible purpose such enterprises have [...]. Head counting to establish prevalence norms is tedious and can rarely be carried out in any comprehensive fashion by those trained to recognize and treat mental disorders’ [1, p. 11]. Studies concerned with prevalence rates, however, achieved a prominent role in the subsequent decades [2]. Even though such studies were not driven by financial conflicts of interest, they served an important commercial purpose. Expanding the target of psychotropic drug prescription to potentially universal consumption is facilitated by showing that psychiatric illness is widespread, undetected and undertreated [3]. Epidemiological studies are generally conducted using lay or poorly trained interviewers who cannot translate obtained data into clinical context and do not have the skills to judge whether the symptoms they elicit are severe enough to cause clinically significant distress or impairment [3]. There are very few exceptions to this rule [4].

Whitlock [1] emphasized the importance of specifying and testing explicit hypotheses in clinical epidemiology, particularly if such hypotheses might lead to practical measures to prevent and treat mental disorders. Pharmacoepidemiology, with particular reference to benzodiazepines, may illustrate the value of Whitlock’s considerations.

For a long time benzodiazepines have provided an effective treatment for anxiety disorders [5], sleep disorders and a variety of medical conditions such as epilepsy and alcohol withdrawal [6]. Their large number of prescriptions raised many concerns and attempts at limiting their use [5]. The introduction of second-generation antidepressant and antipsychotic drugs has provided more expensive modalities of addressing anxiety disorders [7]. Substituting benzodiazepines with selective serotonin reuptake inhibitors (SSRI) and serotonin-noradrenaline reuptake inhibitors (SNRI) clearly appeared the commercial way to go. Such a road would have been difficult when new medications had to be compared to a gold standard, since direct comparisons clearly indicated higher efficacy and tolerability of benzodiazepines over antidepressants [8]. However, when such superiority was no longer required by regulatory agencies, alternative routes appeared. One was to perform comparisons by meta-analytic methods that are liable to manipulation instead of head-to-

head comparisons [9]. The other complementary strategy was to magnify the side effects of benzodiazepines. Since these negative aspects are actually very limited [5–8], the potential for dependency, toxicity and abuse had to be pictured dramatically, despite the fact that the percentage of recreational abuse is uncommon and the abuse is really low in relation to the number of people using them [10]. The reinforcing effects of benzodiazepines vary and are considerably weaker than those of other drugs of abuse such as other sedative hypnotics, stimulants and opiates [10]. On the other hand, the reinforcing effects are stronger than those of drugs recognized as having little abuse potential such as chlorpromazine [10].

In addition, similar [11], if not worse [12, 13], problems of dependence may ensue with SSRI and SNRI. The ghost of Alzheimer's disease was evoked in observational studies [14] despite a lack of supporting evidence [15]. Correlational methods in these investigations, however, appear to entail the risk of yielding spurious results when using highly heterogeneous constructs and populations. A very instructive example is provided by the alleged benefits of hormone replacement therapy in postmenopausal women as to coronary artery disease, which were reported by observational studies and contradicted by randomized controlled trials [16].

Clinical methodology matters in pharmacoepidemiology, and the study by Cloos et al. [17] provides an illustration of this point. Two distinct yet ostensibly related strategies were used. First, instead of grouping all benzodiazepines together, as is commonly done [14, 18], each medication was considered on its own. Second, the study tested a specific hypothesis formulated by Chouinard [19] in 2004, as suggested by Ciraulo et al. [20] and Schmauss et al. [21], namely, the presence of major clinical

differences among benzodiazepines based on the joint consideration of relative lipid solubility, binding affinity and half-life. Drugs like triazolam and alprazolam, which have high lipid solubility, would be associated with higher dependence liability, cognitive impairment and anterograde amnesic effects [19]. On the contrary, benzodiazepines with low affinity for the benzodiazepine receptor and lipid solubility, such as clonazepam, would be associated with less dependence liability and amnesic potential [19].

In the 12-year national registry study performed in Luxembourg, about 4 out of 5 people who received a benzodiazepine were short-term or intermittent users [17]. Continuous use, not necessarily associated with dose escalation, occurred in the remaining cases. The initial pharmacological hypothesis was confirmed: alprazolam and triazolam were related to continuous and high-dose use, whereas clonazepam and clobazam were not [17]. Thus, it seems obvious that not all benzodiazepines are the same. The findings of the study by Cloos et al. [17] support the importance of a specific benzodiazepine selection based on a number of pharmacological aspects [22, 23]. Unlike undifferentiated studies that provide little information to the clinician [18], the results indicate that certain benzodiazepines such as alprazolam and triazolam that are widely prescribed should be carefully used or simply avoided.

The type of pharmacoepidemiology portrayed in the study by Cloos et al. [17] provides a link between large-scale and anecdotal clinical observations related to the side effects of medications [22, 23]. It also calls for a more careful appraisal of the subtle psychological effects of various medications, including behavioral toxicity and iatrogenic comorbidity [24].

References

- 1 Whitlock FA: Psychiatric epidemiology: its uses and limitations. *Aust NZ J Psychiatry* 1977;11:9–18.
- 2 Kessler RC, Demler O, Frank RG, Olsson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM: Prevalence and treatment of mental disorders, 1990–2003. *N Engl J Med* 2005;352:2515–2523.
- 3 Batstra L, Frances A: Holding the line against diagnostic inflation in psychiatry. *Psychother Psychosom* 2012;81:5–10.
- 4 Faravelli C, Abrardi L, Bartolozzi D, Cecchi C, Cosci F, D'Adamo D, Lo Iacono B, Ravaldi C, Scarpato MA, Truglia E, Rosi S: The Sesto Fiorentino study: background, methods and preliminary results. Lifetime prevalence of psychiatric disorders in an Italian community sample using clinical interviewers. *Psychother Psychosom* 2004;73:216–225.
- 5 López-Muñoz F, Alamo C, García-García P: The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: half a century of anxiolytic drugs. *J Anxiety Disord* 2011;25:554–562.
- 6 Lasagna L: The role of benzodiazepines in nonpsychiatric medical practice. *Am J Psychiatry* 1977;134:656–658.
- 7 Balon R, Fava GA, Rickels K: Need for a realistic appraisal of benzodiazepines. *World Psychiatry* 2015;14:243–244.
- 8 Offidani E, Guidi J, Tomba E, Fava GA: Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. *Psychother Psychosom* 2013;82:355–362.

- 9 Fava GA: Statistical alchemy for drug treatment of generalized anxiety disorder: a commentary on the meta-analysis by Baldwin et al. [BMJ 2011;342:d1199]. *Psychother Psychosom* 2011;80:261–263.
- 10 Task Force Report of the American Psychiatric Association: Benzodiazepine Dependence, Toxicity, and Abuse. Washington, American Psychiatric Association, 1990.
- 11 Nielsen M, Hansen EH, Goetzsche PC: What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin reuptake inhibitors. *Addiction* 2011;107:900–908.
- 12 Fava GA, Gatti A, Belaise C, Guidi J, Offidani E: Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom* 2015;84:72–81.
- 13 Chouinard G, Chouinard VA: New classification of selective serotonin reuptake inhibitor withdrawal. *Psychother Psychosom* 2015;84:63–71.
- 14 Billiotti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Bégaud B: Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* 2014;349:g5205.
- 15 Salzman C, Shader RI: Benzodiazepine use and risk for Alzheimer disease. *J Clin Psychopharmacol* 2015;35:1–3.
- 16 Lawlor DA, Davey Smith G, Ebrahim S: Commentary: the hormone replacement-coronary heart disease conundrum: is this the death of observational epidemiology? *Int J Epidemiol* 2004;33:464–467.
- 17 Cloos JM, Bocquet V, Rolland-Portal I, Koch P, Chouinard G: Hypnotics and triazolobenzodiazepines – best predictors of high-dose benzodiazepine use: results from the Luxembourg National Health Insurance Registry. *Psychother Psychosom* 2015;84:273–283.
- 18 Olfson M, King M, Schoenbaum M: Benzodiazepine use in the United States. *JAMA Psychiatry* 2015;72:136–142.
- 19 Chouinard G: Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry* 2004;65:7–12.
- 20 Ciraulo A, Barnhill JG, Greenblatt DJ, Shader RI, Ciraulo AM, Tarmey MF, Molloy MA, Foti ME: Abuse liability and pharmacokinetics of alprazolam in alcoholic men. *J Clin Psychiatry* 1988;49:333–337.
- 21 Schmauss C, Apelt S, Emrich HM: The seeking and liking potentials of alprazolam. *Am J Psychiatry* 1988;145:128.
- 22 Teboul E, Chouinard G: A guide to benzodiazepine selection. Part I. Pharmacological aspects. *Can J Psychiatry* 1990;35:700–710.
- 23 Teboul E, Chouinard G: A guide to benzodiazepine selection. Part II. Clinical aspects. *Can J Psychiatry* 1991;36:62–73.
- 24 Guidi J, Fava GA: Emerging trends in clinical psychology. *Riv Psichiatr* 2014;49:227.