The Dependence Potential of Short Half-Life Benzodiazepines: A Meta-Analysis

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ABSTRACT

Objectives. The dependence potential of benzodiazepine medications is now widely recognized, but uncertainty exists as to whether use of short half-life vs long half-life drugs results in greater dependence. The present study reports a meta-analysis of the extant research to evaluate the dependence potential of different types of benzodiazepines.

Method. Seven studies were found that specifically compared long half-life and short half-life benzodiazepines and allowed statistical comparison by their homogeneous dependent variables. Drugs in these studies were used as daytime sedatives.

Results. Substantial evidence was found for differential effects of short vs long half-life drugs at withdrawal. In all studies, dropouts were higher among short half-life subjects. In the random-assignment short-term use studies, Hamilton Anxiety Scale scores showed higher incidence of rebound among subjects who used the short half-life drugs.

Conclusions. The present meta-analysis confirms clinical impressions of the greater dependence potential of short vs long half-life benzodiazepines. Doctors, patients, and policymakers need to be informed so as to avoid harm to the public health through unintended drug dependence. (*Am J Public Health.* 1993;83:1300–1304)

Introduction

The potential of benzodiazepine medications to produce physical and/or psychological dependence is now widely recognized.[1,2] Benzodiazepines are among the most widely prescribed drugs, and, within the United States, they account for over 50% of all psychotropic drug prescriptions.[3] To the extent that benzodiazepines produce dependency, they represent medically sanctioned addiction and have profound implications for the cost and quality of health care treatment. A central issue is whether the significance of dependence reactions varies among types of benzodiazepines. The goal of the present study was to assess extant evidence of the relationship between physical and psychological dependence and benzodiazepine half-life.

A 1990 report from the American Psychiatric Association[2(p12)] concluded that prescribing benzodiazepines does not present "any great public health problems." The report noted, however, that sufficient data about newer benzodiazepines are not available and that data about long-term use and dependence may alter present conclusions. According to Salzman,[4] chair of the American Psychiatric Association task force, while "no research data are available to confirm these clinical observations," short half-life, high potency benzodiazepines are more likely to produce dependence than their low potency, long half-life counterparts. Although conclusive data are not available, substantial research has evaluated the effects of different benzodiazepines. The present study focused on these available studies and used meta-analytic statistical techniques to integrate their results in order to evaluate differential addictive problems among benzodiazepines.

Background

Since the early 1960s, investigators have been interested in the withdrawal effects of benzodiazepines. Sleep researchers, in particular (see Kales et al.[5] and Gillin et al.[6]), have investigated the influence of drug half-life on the phenomenon they termed "rebound insomnia." Widespread knowledge and acceptance of the dependence potential of benzodiazepines is, however, relatively recent. The 1986 report of Busto et al. in the *New England Journal of Medicine* seems to mark recognition of the benzodiazepine withdrawal syndrome. The report claimed to provide "unequivocal evidence" of a clinically important syndrome of benzodiazepine withdrawal after daily use of a benzodiazepine for at least 3 months. The Busto et al. study also underscored the observation by clinicians and researchers that patients who attempted to withdraw from short half-life benzodiazepines experienced a more rapid onset of uncomfortable symptoms. These patients were also less likely to comply with withdrawal protocols than those taking long half-life benzodiazepines, and they were much more likely to relapse to drug use.

Advantages of short half-life drugs have been scientifically confirmed, most notably their lack of a "hangover effect." Ray et al.[7] found that short half-life benzodiazepines were less likely to result in

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falls and hip fractures among the elderly than their long half-life counterparts. These findings supported practice guidelines to avoid prescribing long half-life drugs to elderly patients and other patients who wish to avoid residual grogginess. The implied message was that the "safer" alternative was to prescribe short half-life benzodiazepines. Coupled with the introduction and aggressive marketing of the newer short half-life, high potency drugs alprazolam (Xanax) and triazolam (Halcion), there is a clear need for information on the potential for increased drug dependence.

Present Investigation

There is both a great deal of clinical experience with benzodiazepines and substantial, although not definitive, research data about their use. The present investigation was designed to integrate systematically the evidence from research studies that compared withdrawal effects from short and long half-life benzodiazepines. A comprehensive search of the published literature was conducted to identify the population of comparative half-life studies, and, where possible, meta-analytic[8,9] statistical tests were used to combine results. Because virtually all of the individual studies were limited by a focus on one type of drug from each class and had low statistical power (i.e., small samples), none of them alone could be considered conclusive. There were, however, sufficient similarities in their methodology and line of inquiry to permit aggregation of results across studies.

The hypothesis was that short half-life drugs are more likely to cause dependency than long half-life drugs. Clinically, there is substantial information that drugs that leave the system slowly appear to create fewer withdrawal problems. By integrating the results of studies that have compared at least one exemplar drug within each category (short vs long half-life), the goal was to assess the validity of these clinical observations.

Method

A meta-analysis was developed to assess the differential dependency effects of short vs long half-life benzodiazepines. Described below are the criteria for selecting studies, the characteristics of these studies, and the statistical analyses.

Selection of Studies

All articles that met the broad criterion of "studies examining length of use, dependency, or withdrawal from benzodiazepines that compare different drug half-life or potency" were examined from an automated Medline search for the period 1983 through 1991. *Dissertations Abstracts International* was also searched, but no relevant papers were found. Additional articles were obtained from reference lists of the articles found in the Medline search. Articles or book chapters published prior to 1980 were not used because of concerns about differences in design and drug availability.

Seven studies comparing anxiolytics (daytime tranquilizers) and five studies comparing hypnotics (sleeping tablets) were obtained from this search. All of the sleep studies[10–14] were dropped from the present review because published results did not include individual subject information or standard deviations for group means, and thus did not allow statistical analyses.

In the seven studies reviewed, subjects used three types of benzodiazepine medication: long half-life, low potency (diazepam [Valium] and clorazepate [Tranxene]); short half-life, high potency (alprazolam [Xanax] and lorazepam [Ativan]); and short half-life, low potency (bromazepam). The initial research hypothesis was that short half-life, high potency drugs would produce greater evidence of dependence than either long half-life, low potency drugs or short half-life, low potency drugs. This hypothesis reflects the "clinical view" suggested by Salzman.[4] However, because so few studies met our criteria, little could be done to test the effects of high vs low therapeutic potency. Consequently, only the effects of short vs long half-life were compared.

Description of Studies

Table 1 lists the chief characteristics of each of the studies. The first four investigations[15–18] were randomized clinical trials; the last three studies[19–21] compared subjects who had used benzodiazepine medication for more than a year and who, in many cases, had used them for 10 years or more. Although each of the studies reported a variety of withdrawal measures, two theoretically important dependent variables were selected for comparison: (1) number of dropouts and (2) rebound anxiety, based on changes in Hamilton Anxiety Scale scores. These two measures were reported in each of the studies.

The Hamilton Anxiety Scale provides a well-tested and widely used psychometric measure of anxiety, while dropout rates provide an interesting proxy for dependence. Presumably, dropouts are not able to tolerate withdrawal and so break the study protocol and return to drug use. In several of the studies,[20,21] this relapse to drug use by dropouts was explicitly reported.

The four randomized trials each used a similar definition for rebound anxiety. All but one of the four used the criterion of a 10% increase over baseline score. The remaining investigation[16] used a slightly less stringent criterion of a withdrawal score at least equal to baseline. For example, a subject may have begun the study with a Hamilton Anxiety Scale score of 25. At the end of drug treatment, the subject may have had a score of 12. To meet the criterion of rebound for three of the studies, the subject would have been required to have a score of 27.5 or higher during the withdrawal period; in the Rickels et al. study,[16] a score of 25 would have sufficed. Because these criteria were reasonably similar, the results as reported were grouped together for analysis.

The remaining three anxiety studies did not report the number or percentage of subjects meeting the criterion for rebound anxiety. From the results reported in these studies, it appears that all subjects would have met the 10% over baseline criterion for withdrawal. Because of design issues, and because results were not reported in a fashion consistent with the first four investigations, Hamilton Anxiety Scale scores are simply displayed for these studies.

The Schweizer et al. study was considered questionably appropriate for comparison because the protocol for withdrawal was so different. Not only was the withdrawal period by taper (to which the authors attribute the markedly different results), but protocols allowed subjects to be "partially compliant" and remain in the withdrawal study. The full compliance group adhered to the 25% per week taper schedule and began no supplementary medication during taper. The partially compliant group varied from the protocol in one of the following ways: slowing of the taper rate, supplementary use of antidepressant medications, as-needed use of hypnotics for insomnia, or a combination of these. Sixty-three percent of short half-life drug subjects vs 48% of long half-life drug subjects were partially compliant. Although this difference was not statistically significant, combining it with the higher dropout rate among short half-life drug subjects makes the Hamilton Anxiety Scale score results questionable.

TABLE 1—Overview of Anxiety Studies

Study	Length of Use	Type of Withdrawal	Drug n (dose)	Dropouts	Hamilton Anxiety Scale Score Changes
Fontaine et al.[15]	4 wk	16 abrupt, 14 taper	14 bromazepam (18 mg/d), 16 diazepam (15 mg/d)	Short: 3/14 (21%) Long: 3/16 (19%)	Rebound criterion: ≥ 10% increase over baseline[a] Short: 5/14 (36%) Long: 2/16 (13%)
Rickels et al.[16]	4 wk	Abrupt	28 clorazepate (15–30 mg/d), 26 lorazepam (2–4 mg/d)	Short: 4/16 (25%, all on days 3–6) Long: 2/18 (11%, all after day 7)	Rebound criterion: ≥ baseline level Short: 4/16 (25%) Long: 3/18 (17%)
Roy-Byrne et al.[17]	7 wk, 2-wk taper	Tapered to half of dose, then abrupt	24 alprazolam (4.3 ± 2.8 mg/d), 22 diazepam (56 ± 31 mg/d)	Short: 4/17 (24%) Long: 1/16 (6%) (during taper)	Rebound criterion: ≥ 10% increase over week 1 (placebo washout) Short: 6/13 (46%) Long: 1/15 (7%)
Noyes et al.[18]	8 mo	Taper	25 alprazolam (4.1 mg/d), 19 diazepam (34 mg/d) Short: 16/25 (64%) Long: 11/19 (58%)	Short: 16/25 (69%) Long: 11/19 (58%)	Rebound criterion: ≥ 10% increase over baseline Short: 17/25 (68%) Long: 7/19 (37%)
Rickels et al.[19]	Chronic	Abrupt	22 diazepam or clorazepate, 16 lorazepam or alprazolam	Short: 11/16 (69%) Long: 9/22 (39%)	Base to peak change scores: Short: 45% mean increase over baseline (day 3) Long: 25% mean increase over baseline (day 8)
Rickels et al.[20]	Chronic	Abrupt	14 lorazepam (4 ± 2.5 mg/d), 7 alprazolam (1.6 ± 1.2 mg/d), 16 diazepam (11.6 ± 6.8 mg/d), 16 clorazepate (12.5 ± 7.1 mg/d)	Short: 12/21 (57%) Long: 7/26 (27%)	Base to peak change scores: Short: 65% mean increase over baseline Long: 36% mean increase over baseline
Schweizer et al.[21]	Chronic	Taper	28 lorazepam (4.6 ± 3.9 mg/d), 10 alprazolam (3.5 ± 2.0 mg/d), 20 diazepam (14.6 ± 8.9 mg/d), 5 clorazepate (22.3 ± 12.3 mg/d)	Short: 16/38 (42%) Long: 8/25 (32%)	Base to peak change scores: Short: 31% mean increase over baseline Long: 48% mean increase over baseline

Note. Roy-Byrne et al.[17] provide information about subjects experiencing rebound using totals that exclude dropouts; the other three clinical trials include dropouts in the denominator. Short = short half-life; long = long half-life.
[a]Only subjects from the abrupt withdrawal category experienced rebound.

Statistical Procedures

The DerSimonian and Laird pooled rate difference[22] technique was used to analyze dropout rates in the seven tranquilizer studies. This method allows study data to be pooled while controlling for differences in sample size and variation in each study. Hamilton Anxiety Scale scores were also assessed by this method for the four randomized clinical trials.

Results

Table 1 displays the dropout and Hamilton Anxiety Scale results from the relevant anxiety studies. There were consistently more dropouts among short half-life benzodiazepine users than among long half-life benzodiazepine users. This difference was significant when all studies were combined ($P < .004$; see Table 2), although dropout rates in individual studies were rarely significantly different from one another. The pooled rate difference between groups was .15 with a 95% confidence interval.

The rebound on Hamilton Anxiety Scale scores also was higher for short half-life drug subjects, except in the Schweizer et al. study[21] (see Table 1). Subjects meeting the rebound anxiety criteria in the four clinical trial studies were collectively analyzed for differences by drug group, which were found to be significant (Table 3). Subjects taking short half-life drugs had a .25 greater likelihood of experiencing rebound anxiety than subjects taking long half-life drugs (with a 95% confidence interval).

The three studies exploring withdrawal patterns after chronic use all show very large increases in Hamilton Anxiety Scale scores for both study groups. The two Rickels et al. studies found effects almost twice as great, both on Hamilton Anxiety Scale scores and in dropout rates, for the short half-life drug subjects after abrupt withdrawal. Even in the Schweizer et al. study, dropout rates continued to be higher, and fewer short half-life dependent subjects were able to comply fully with the study protocol.

Discussion

The results of this meta-analytic assessment of withdrawal studies involving short vs long half-life benzodiazepines support the clinical assertion (see, e.g., Salzman[4]) that differences in withdrawal effects between long and short half-life

drugs exist, even at very short periods of use. Rebound anxiety is more likely to occur with short half-life drugs and to occur more rapidly after stopping use of the medication. These results can occur after a treatment period as brief as 4 weeks. Although these withdrawal effects have not been considered clinically significant, the present results suggest otherwise. Patients undergoing withdrawal, particularly with short half-life benzodiazepines, may be exceedingly uncomfortable and less likely to successfully complete withdrawal. The results of this meta-analysis indicate that dependence is differentially problematic based on the type of benzodiazepine used.

The finding of differential withdrawal rates and symptoms appears robust. The same differences in effects persist whether patients are randomly assigned to treatment groups or are chronic users drawn from naturally occurring medical practices. Although not reported here, box score analysis of sleep studies showed a similar trend of rebound insomnia with short half-life drugs.[23] Since results could not be combined statistically, however, it is suggested that further research be done to confirm this pattern of greater dependence with short half-life hypnotics.

The consistently higher dropout rate with short half-life drugs in the present meta-analysis is a particularly strong validation of Salzman's[4] clinical hypothesis for daytime sedatives. Even with the elaborate supports provided in the Schweizer et al. study[21] to help wean patients from their medication, 10% more patients on short half-life benzodiazepines had to withdraw from the study and return to their medication. One tentative hypothesis that can be drawn from these results is that a relatively small percentage of persons are less sensitive than others to the symptoms of benzodiazepine withdrawal. The large number of dropouts may mask differences in scores by leaving these less sensitive people in the study, particularly in the short half-life drug groups (as in the taper studies).

Even if there are important individual differences in reactions, the results of the present study show a consistent trend. Patients who are prescribed benzodiazepines and who try to stop after a period of use would probably not try elaborate tapering schedules, and it would seem somewhat problematic for anxious, unwell patients to devise or follow such schedules. It seems more likely that they would simply try to stop. Since the receptor responsivity with short half-life drugs is swift and intense and is an exaggeration of the problems that prompted them to seek assistance from the doctor in the first place, these studies seem to support the hypothesis of greater dependence potential.

TABLE 2—Pooled Rate Difference: Dropouts

Study	No. of Short Half-life Dropouts	Short Half-life Total	No. of Short Half-life Dropouts	Long Half-life Total	Rate Difference	95% Confidence Interval
Fontaine et al.[15]	3	14	3	16	.027	−.261, .315
Rickels et al.[16]	4	16	2	18	.139	−.118, .396
Roy-Byrne et al.[17]	4	17	1	16	.173	−.061, .407
Noyes et al.[18]	16	25	11	19	.061	−.230, .352
Rickels et al.[19]	11	16	9	22	.278	−.028, .585
Rickels et al.[20]	12	21	7	26	.302	.030, .574
Schweizer et al.[21]	16	38	8	25	.101	−.140, .342
Pooled[a]					.1530	.0523, .2537

[a] $Q = 3.142$; $df = 6$; $\tau^2 = 0$; $Z = 2.979$; $\chi^2 = 8.877$.

TABLE 3—Pooled Rate Difference: Hamilton Anxiety Scale Scores

Study	No. of Short Half-life Drug Subjects Meeting Rebound Criteria	Short Half-life Total	No. of Long Half-life Drug Subjects Meeting Rebound Criteria	Long Half-life Total	Rate Difference	95% Confidence Interval
Fontaine et al.[15]	5	14	2	16	.232	−.067, .531
Rickels et al.[16]	4	16	3	18	.083	−.190, .357
Roy-Byrne et al.[17]	6	13	3	18	.395	.096, .694
Noyes et al.[18]	17	25	7	19	.312	.028, .595
Pooled[a]					.249	.105, .393

[a] $Q = 2.526$; $df = 3$; $\tau^2 = 0$; $Z = 3.389$; $\chi^2 = 11.487$.

All of the studies suffered from small sample sizes that did not allow detection of consistent but small differences. A rationale for conducting meta-analysis is to add power to statistical results by comparing and combining numerous small studies.[8,9,24,25] Valid statistical analysis was limited to studies that could be appropriately combined in terms of their design and reporting results. The present analysis, along with the suggestive results of sleep studies reported elsewhere,[23,26] supports the clinical hypothesis and demonstrates the potential for using research data, even when limited, to answer important questions. Benzodiazepine use is widespread, and, while many suggestions have been made about the need to limit its prescribed usage,[27–29] these discussions have tended to be polarized. Proponents have argued for the benefits to individual patients; opponents have countered with the risks and side effects. What is clear, however, is that the risks—particularly of dependence—may vary significantly by the specific type of benzodiazepine prescribed. Information about differential effects is critical both for physicians and patients who need to make informed decisions about treatment.

The present analysis suggests that prescription policies for benzodiazepines need to be reconsidered. The benefits of short half-life compounds need to be weighed against the problems of dependency and withdrawal. The use of different types of benzodiazepines appears, from these results, to have important implications for patients' quality of life and for the costs and nature of treatment. To the extent that there are clear benefits to prescribing dependence-producing medications, this information must be conveyed to physicians, patients, and policymakers and made a part of the decision-making process. □

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