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Cognitive Effects of Long-Term Benzodiazepine Use

A Meta-Analysis

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Abstract

Introduction: While benzodiazepines are the most widely used psychotropic drugs, there are relatively few studies that have examined deficits in cognitive functioning after long-term use. The literature that is available is difficult to interpret due to conflicting results as well as a variety of methodological flaws.

Objective: To systematically evaluate and integrate the available research findings to determine the effect of long-term benzodiazepine use on cognitive functioning using meta-analytical techniques.

Methods: Thirteen research studies that employed neuropsychological tests to evaluate cognitive performance after long-term use of benzodiazepine medication met inclusion criteria. The neuropsychological tests employed in these 13 studies were each categorised as measuring one of 12 cognitive domains. Separate effect sizes were calculated for each of the 12 cognitive categories. Each study was only allowed to contribute one effect size to each cognitive category by averaging together the effect sizes from the same study if more than one type of test was used to measure a particular category. This strategy resulted in equal weight being given to each study per category, regardless of the number of tests in that category.

Results: The overall mean number of patients who were benzodiazepine users was 33.5 (SD ± 28.9) and the mean number of controls was 27.9 (SD ± 19.6). The duration of benzodiazepine use ranged from 1 to 34 (mean 9.9) years. Long-term benzodiazepine users were consistently more impaired than controls across all cognitive categories examined, with effect sizes ranging in magnitude from −1.30 to −0.42. The mean weighted effect size was −0.74 (SD ± 0.25). None of the effect sizes had 95% CIs that spanned zero and, therefore, all of these effects were significant and different to zero.

Conclusion: Moderate-to-large weighted effect sizes were found for all cognitive domains suggesting that long-term benzodiazepine users were significantly impaired, compared with controls, in all of the areas that were assessed. However, this study has several limitations, one being that it includes a relatively small number of studies. Further studies need to be conducted; ideally, well designed, controlled studies that thoroughly investigate certain areas of cognitive functioning and present data in such a way so as to be amenable to inclusion in a meta-analysis. Incorporating the information from these studies into a larger meta-analysis would allow for a more thorough and statistically sound investigation of the effects of moderator variables. The observation that long-term benzo-

diazepine use leads to a generalised effect on cognition has numerous implications for the informed and responsible prescription of these drugs.

Following their introduction in the 1960s, benzodiazepines quickly became the most frequently used class of drugs in the treatment of anxiety disorders.[1,2] Epidemiological data from different countries have indicated that between 0.5% and 5.8% of the adult population use benzodiazepines on a long-term basis of 1 year or more.[3-5] More recently, researchers in The Netherlands reported a prevalence of benzodiazepine use (duration of use defined as >1 year) of 0.6% in their study of over 80 000 general practice patients. Among the population of longterm benzodiazepines users in this study, females outnumbered males by 2 : 1.[6]

Benzodiazepines are widely used in the treatment of anxiety, insomnia and panic disorder, and less widely used to treat a number of other conditions, including psychotic states, depression, social phobia (social anxiety disorder), obsessive-compulsive disorder, drug withdrawal and the adverse effects induced by antidepressants and antipsychotics.[7] Benzodiazepines produce anxiolytic, sedative, hypnotic, skeletal muscle relaxant and antiepileptic effects by acting at the limbic, thalamic and hypothalamic levels of the CNS, and are capable of producing CNS depression ranging from mild sedation through to coma.[8] Benzodiazepines are capable of producing a large and varied number of adverse effects due to the wide distribution of receptors found in a number of areas including the spinal cord, cerebellum, limbic areas and the cerebral cortex.[9]

Although the benzodiazepines were initially thought to have a relatively good safety profile, reports began to emerge as early as 1963 regarding the potential for addiction, abuse and withdrawal difficulties of chlordiazepoxide (one of the first marketed benzodiazepines). It is now well accepted that, even with normal therapeutic doses, benzodiazepines are capable of causing both physiological and pharmacological dependence, as evidenced by a withdrawal syndrome when the drugs are discontinued.[4,10-12] Previously, the main focus regarding the long-term use of benzodiazepines has been on their tolerability and dependency. More recently, however, there has been a growing concern that long-term benzodiazepine use may lead to cognitive impairment.

The limited amount of research published to date examining the cognitive effects of long-term benzodiazepine use is difficult to interpret due to variations in methodology and widely conflicting results. The findings with regard to memory impairments are a particular case in point. In one study of ten long-term users (average 5 years),[13] there was evidence of nonverbal memory impairment, but no influence on short-term verbal memory was found. Other researchers[14] observed significant deficits in both verbal memory and verbal learning in a group of 21 patients who had previously been long-term benzodiazepine users and who remained abstinent at 6 months.

In contrast, some researchers claim little or no memory effect caused by long-term benzodiazepine use. Golombok et al.[15] found no evidence of memory impairment in 50 patients who had used benzodiazepines for >1 year. These authors argued that there was a strong relationship between the sedative and amnesic effects of the drugs, suggesting that as patients become tolerant to the sedative effects of the drugs, memory deficits were no longer apparent. Similarly, Lucki et al.[16] found that any impairment evident in their group of 43 long-term benzodiazepine users appeared to diminish with time after the last dose was increased. These results suggest that memory impairments, if they do occur, may be due to the acute effects of the drug and do not support the hypothesis that long-term benzodiazepine use leads to permanent memory impairment.

Some studies support the notion that long-term benzodiazepine use is associated with significant impairments in concentration[13] and attention.[15,17,18] Other researchers suggest that cognitive skills such as vigilance and attention are not ad-

versely affected by long-term benzodiazepine use, but rather patients' performance is impaired on the more complex tasks requiring the combined use of a number of sensory and fine motor skills.[19]

The suggestion that long-term benzodiazepine use is associated with deficits in visuospatial abilities has arisen from a number of studies. Tata et al.,[14] in a study of 21 patients with a history of long-term therapeutic benzodiazepine use, found significantly impaired visuomotor and visuospatial abilities compared with age- and IQ-matched controls. Similarly, in a well controlled study of past benzodiazepine users, Golombok et al.[15] found long term use to be associated with impaired visuospatial ability. Impairments in visuospatial skills have not previously been noted in studies of short-term users, which may indicate that the deterioration of visuospatial ability develops as a direct and exclusive result of long-term use.[15]

Numerous other areas of cognitive functions have been reported to be impaired with long-term benzodiazepine use, including general intellectual ability,[20,21] motor speed and fine motor co-ordination,[19,22] reaction time,[23,24] arousal,[13] psychomotor speed,[25] conceptual tracking abilities,[14] speed of information processing[17] and critical flicker fusion threshold.[16] Increased cognitive decline in the elderly has also been noted with long-term benzodiazepine use.[26]

There are, of course, opposing views in the literature, including claims that most cognitive skills are not adversely affected[19] and the proposition that long term use of benzodiazepines does not cause risks for cognitive complaints.[27] Lucki and Rickels[2] found that the cognitive function (the areas assessed were psychomotor skills, reaction time, digit span, tapping rate) of 54 long-term benzodiazepine users was not impaired compared with that of a group of drug-free control patients with anxiety. These authors[2] concluded that when benzodiazepines are taken at therapeutically accepted doses, serious psychomotor or cognitive deficits are not produced by long-term use.

The findings from research concerned with the cognitive effects of long-term benzodiazepine use are difficult to compare due to the variability between studies in a number of areas. The most salient of these is the heterogeneity of samples with regard to psychiatric diagnoses, the use of other drugs and/or alcohol, the range of doses used, and a varying definition of what is termed 'long-term' use.[28] Other factors contributing to the difficulty in drawing general conclusions from the literature include the various types of benzodiazepines used and the many different cognitive measures employed.

Most studies in this area tend to be retrospective and cross-sectional, and the between-subjects design of many longitudinal studies introduces error variance requiring the presence of a substantial drug effect in order to be detected.[14,15] Furthermore, many studies do not take into consideration the time since last dose in order to separate the acute and chronic effects observed in long-term users.[2]

The various methods of recruitment or sample selection can also create problems when comparing results across studies. Those who abuse benzodiazepines over a long period, in high doses and in combination with other drugs and/or alcohol are more likely to perform poorly on standardised tests than persons taking therapeutic doses of benzodiazepines. Similarly, sampling bias is likely to be an issue when assessing only those patients who are attending withdrawal clinics because they are concerned about long-term effects, or who have cognitive complaints that they attribute to their use of benzodiazepines.

Another problem inherent in the literature is that few studies take into account the effect of anxiety on test performance. Under conditions of high anxiety, those tasks most susceptible to the disruption caused by anxiety disorders have been reported to be measures of attention and concentration rather than tests of spatial, language or memory skills.[29] However, a number of researchers have reported little or no effect of anxiety on test performance in patients with an anxiety disorder[30] or individuals scoring highly on test anxiety scales.[31] In a well controlled comparison of neuropsychological test performance in anxious drug-free patients and normal controls, no significant difference was observed in performance

on a variety of neuropsychological tests, except for a ball-bearing test of motor co-ordination.[22]

In light of the prevalence of long-term benzodiazepine use,[3-5] it is important to establish whether long-term use leads to cognitive impairment and, furthermore, to tease out the nature of these deficits.[5] Clearly, well controlled, methodologically sound studies are required which involve heterogeneous groups of subjects and multiple measures of cognitive functioning. The feasibility of such large scale studies may be limited.

Another alternative, however, is to use meta-analytical techniques to combine the results of the extant studies to determine overall effect sizes and to examine variations in effect sizes related to subject variables and the measures of cognitive status employed. The aim of the present study was to use meta-analytical techniques to integrate the available information on the cognitive effects of long-term benzodiazepine use and, where possible, to examine the effects of moderators on these measures.

Methods

Selection of Studies

A comprehensive search of the computerised databases Medline and PsycINFO was conducted to identify papers that have assessed the long-term use of benzodiazepines and were published between 1980 and 2000. Key search terms used included 'benzodiazepine', 'benzodiazepines', 'hypnotics' and 'sedatives' paired with 'long-term', 'chronic', 'effects', 'cognitive' and 'deficits'. Only those articles that were written in English and published in peer-reviewed journals were included. Relevant articles were obtained and the bibliographies scanned for additional relevant articles not obtained through the computer-based searches. These articles were then obtained and their reference lists were scanned for additional articles and so on.

Criteria for Inclusion

For an article to be included in the meta-analysis, it was necessary for the following criteria to be met: the studies were required to (i) be published between 1980 and 2000; (ii) be written in the English language; (iii) possess a control group or use a within-subjects design; (iv) conduct a cognitive assessment; (v) have a minimum period of benzodiazepine use of at least 1 year; (vi) report results that were sufficient to allow the calculation of effect sizes; and (vi) be original results or be results that had not been reported elsewhere.

Of the 34 papers identified from the searches, 19 were not eligible for inclusion for the following reasons: (i) one did not use any objective test measures; (ii) five used computed axial brain tomography and no other psychometric tests; (iii) nine did not reach the minimum of 1 year of benzodiazepine use; (iv) two were reporting preliminary results of later studies that were included in the meta-analysis; (v) one was reporting a summary of previous results that were included in the meta-analysis; and (vi) one reported results as correlations between effects and dose, thus it was not possible to transform these data in such a way to allow for calculation of effect sizes.

On two occasions, pairs of articles were combined because they reported results from the same patient group using different tests. This resulted in a final selection of 13 independent studies,[2,13,14,17,19-22,28,32-37] which used a total of 45 tests. Each test and its corresponding area of cognitive function measured was grouped into one of 12 categories corresponding to the broad cognitive area measured according to two neuropsychology text books.[38,39] The 12 cognitive categories and the list of the assessment tools used to measure skills within these categories are included in table I.

Coding of Study Characteristics

Each of the 13 studies that met the inclusion criteria was coded according to certain study attributes. The following variables were extracted and recorded.

- Study attributes: (i) publication year; (ii) journal; and (iii) country in which the study was carried out (see table II).
- Subject attributes: (i) number of long-term benzodiazepine users in each group; (ii) number

Table I. Cognitive function categories and tests assessing skills within those categories that were used in the studies assessed in this meta-analysis to determine the effect of long-term use of benzodiazepines on cognitive function[30,31]

Sensory processing
Seashore rhythm test (auditory perception); Witkins Rod and Frame Test (field dependence)
Nonverbal memory
DCS – A Visual Learning and Memory Test for Neuropsychological Assessment and the Gollin Picture Completion Test (visual memory); Visual Reproduction (visual recall); Bender Gestalt (visuoconstructional ability); Tactual Performance Test (tactile memory); Spatial Recognition Task (visual recognition); Memory for Designs (immediate visuospatial memory)
Speed of processing
Four choice reaction time, Leeds Psychomotor Test Apparatus - Critical Flicker Fusion[a] and Reaction time test (reaction time); Trails B (visual search)
Attention/concentration
Vigilance test paradigm (attention/concentration); d2 (concentration); Cancellation task and the Sensory threshold detection test (visual attention); Trails A (visual conceptual tracking)
General intelligence
Vocabulary/information score and the Wechsler Adult Intelligence Scale score/standardised regression-based change score (general intelligence); National Adult Reading Test (premorbid IQ)
Working memory
Recognition test[a] (recognition memory); Digit span[a] (working memory)
Psychomotor speed
Digit symbol substitution test;[a] Symbol copy
Visuospatial
Little men (spatial orientation); Visual perceptual analysis (visual information processing); Koh's blocks/block design (visuoconstructive skill)
Problem solving
Tower of Hanoi and Wisconsin Card Sorting Test/Bexley-Maudsley Category Sorting Test (problem-solving ability); Category Test (abstract concept formation)
Verbal memory
Selective Reminding Test and Word lists (immediate memory/verbal learning); Logical memory/prose recall/story memory (immediate/delayed recall); Word stem completion/priming task[a] (implicit memory); Paired Associates (associate learning); Paired Associate interference task (procedural learning)
Motor control/performance
Ball-bearing test; Finger tapping/tapping rate; Purdue pegboard (motor control/performance)
Verbal reasoning
Thurstone figure classification test (reasoning); Controlled Oral Word Association Test/word fluency (verbal fluency); synonyms (verbal understanding)

a Tests from which norms and standard deviations were used (which were taken from various studies[40-45]) to determine pooled standard deviations or comparison norms where this information was not provided in the studies involved in the meta-analysis.

of controls in each group; (iii) type of control group used (i.e. anxious or normal); (iv) number of males and females in each group; (v) age (mean, standard deviation and range); (vi) mean level of education; (vii) source of subjects (i.e. general practitioner population, hospital patients); (viii) duration of benzodiazepine use (mean, standard deviation and range); (ix) type of benzodiazepine used; (x) dosage of benzodiazepine; (xi) matching of subjects; (xii) presence of alcohol or other drug use; (xiii) condition benzodiazepines prescribed for (i.e. anxiety, depression, insomnia); and (xiv) time since last dose (if recorded).

- Test information: (i) test used in each study/cognitive areas measured; and (ii) category of cognitive area tested (see table I).
- Outcome measures: (i) exact statistics, means and standard deviation; (ii) results of statistical analysis (i.e. t, p and F values); and (iii) significance levels.

Table II. Publication variables of the studies assessed in this meta-analysis to determine the effect of long-term use of benzodiazepines on cognitive function

Publication year	Country of origin	Publication source	References
1980 and 1989[a]	Sweden	American Journal of Psychiatry and British Journal of Addiction	20,21
1992	Germany	European Review of Applied Psychology	13
1992	England	Journal of Psychopharmacology	32
1999	USA	Journal of Clinical Psychopharmacology	35
1994	England	Psychological Medicine	14
1995	Sweden	Acta Psychiatrica Scandinavia	33
1988	Scotland	Psychopharmacology	17
1994 and 1995[a]	Brazil	International Clinical Psychopharmacology and Journal of Psychopharmacology	24,28
1980	USA	American Journal of Psychiatry	34
2000	Canada	Journals of Gerontology. Series B, Psychological Sciences and Social Sciences	37
1983	England	Psychopharmacology	19
1986	USA	Psychopharmacology Bulletin	2
1992	USA	International Journal of Geriatric Psychiatry	36

a Pairs of studies reporting on the same patient group that were combined.

With regard to the coding of significance levels, a conservative approach was adopted. If the study stated that there was 'no significant difference' or there was 'no difference between the groups', the effect size for that test was set at zero. Similarly, if a study stated that the significance level was, for example, '$p < 0.05$' or '$p < 0.01$', then the p-value used to calculate the effect size was set only marginally lower at 0.049 or 0.0099, respectively.

Separate effect sizes were calculated for each of the 12 cognitive categories. Each study was only allowed to contribute one effect size to each cognitive category by averaging together the effect sizes from the same study if more than one type of test was used to measure a particular category. This strategy resulted in equal weight being given to each study per category, regardless of the number of tests in that category.

The average daily dose of benzodiazepine was converted into a diazepam equivalent dose using conversion tables.[46]

Calculation of Effect Sizes

Effect sizes were calculated following the method set out by Rosenthal[47] using Cohen's *d* as the effect size index. The effect size represents the difference between the patient group and the control group divided by the pooled standard deviation (SD_p). Therefore, a negative effect size indicates that patients were performing worse than controls upon assessment.

When means and standard deviations were not available, p-values were converted to Fisher's *Z*-scores that were then used to calculate the effect size correlation (*r*). To maintain consistency, *r* was converted to *d* using procedures described by Rosenthal.[47]

Where means, but not standard deviations, were available, SD_p was taken as the standard deviation from the test's published norms. This was necessary on a small number of occasions, and a footnote in table I states the tests and studies from which this information was gleaned. The effect sizes included in this meta-analysis were weighted on the basis of their sample size.

The relationships between the study characteristics coded and effect size were examined using Student's t-tests where the variable was categorical, and Pearson correlations where the variable was continuous.

Results

Participant and Study Characteristics

Of the 13 independent studies used in the meta-analysis, all were published in peer-reviewed journals.[2,13,14,17,19-22,28,32-37] Publication variables of these studies are listed in table II.

The overall mean number of patients who were benzodiazepine users was 33.5 (SD ± 28.9; range 10–96; median 21) and the mean number of controls was 27.9 (SD ± 19.6; range 10–56; median 20). Overall, 40.6% of the total 384 participants were male.

Two of the 13 studies employed a within-subjects design and did not include a control group. In the meta-analysis, published norms from various neuropsychological tests were used in order to calculate effect sizes for the tests that were used in these two studies (see footnote in table I). Of the 11 studies that used a control group, eight studies recruited individuals from the general population who had no history of anxiety, one study used previous benzodiazepine users as their comparison control group and one study used both a healthy control group and an anxious control group. In this instance, the healthy control group was used in the calculation of effect sizes. Six of the studies matched benzodiazepine users and controls on at least age and sex, with two studies also matching on education, one on social class, one on marital status and type of work, and another also matched the groups on their scores on the National Adult Reading Test (NART; a premorbid IQ estimation). In two studies, the methods used to match controls were not specified and two studies did not use any method of matching. One study used patients who were not yet withdrawn from benzodiazepines as their control group.

Overall, the mean age of participants was 47.6 years with a range of 21–75 years. Eleven studies (84.6%) recruited patients from those who were admitted to a hospital or clinic for the purposes of withdrawal or investigation of drug dependence. One study used media advertisements, and another recruited nursing home residents. Ten studies specified the following benzodiazepines, listed in order of decreasing frequency of usage, as those used by patients: lorazepam, diazepam, alprazolam, triazolam, dipotassium clorazepate, bromazepam, oxazepam, chlordiazepoxide, flurazepam, temazepam, nitrazepam, clobazepam, clonazepam and flunitrazepam. The average daily benzodiazepine dose (expressed as a diazepam equivalent) was 17.2mg (SD ± 9.86).

The mean duration of benzodiazepine use (specified by 12 of the 13 studies) was 9.9 years. The range of the duration of use (specified by nine of the studies) was between 1 and 34 years. Nine studies specified when psychometric testing was carried out in relation to time since last dose. In five of the studies, testing took place between 1 and 18 days since the patient's last dose. In the remaining four studies, testing took place either just prior to the normal daily administration, or not within 4 hours of taking a normal dose. In those studies that examined the effect of a normal daily dose, the predose data were used in the meta-analysis.

The majority of studies (77%) excluded patients with a history of heavy alcohol or other drug use, two studies did not specify and one study stated that 23% of patients had a history of alcohol use in excess of four standard drinks per day. Seven studies specified the condition for which subjects used benzodiazepines. In five of these studies, patients had used benzodiazepines to treat anxiety or depression and in two studies patients had used benzodiazepines to treat insomnia.

Effect Sizes

The most frequently used test was the digit symbol substitution test, which was used in 53.8% of studies, followed by symbol copy and tapping rate, which were each used in 38.5% of studies. The most frequently measured category was verbal memory, contributing to 19% of the overall effect sizes, followed by working memory (13.7%) and attention/concentration (10.5%).

From 95 initial effect sizes obtained from the 13 studies (see table III), the mean weighted effect size was −0.74 (median −0.68) with a standard deviation of 0.25. Unweighted mean effect sizes, weighted

mean effect sizes and the standard deviations of weighted mean effect sizes are reported in table III for each cognitive category.

Long-term benzodiazepine users were consistently more impaired than controls across all cognitive categories examined, with effect sizes ranging in magnitude from −1.30 to −0.42. Figure 1 shows that none of the effect sizes had 95% CIs that spanned zero and, therefore, all of these effects were significant and different to zero.

The analyses conducted on all moderator variables revealed only one significant correlation, the time since last dose and psychomotor speed (r [11] = 0.97, $p < 0.01$). A number of other trends that approached significance were apparent; however, given the small data set these should be interpreted with caution. Studies published after 1994 tended to have larger effect sizes than those published before 1994 for the categories verbal memory, working memory, speed of processing, mental control and the combined category. Studies whose samples comprised >40% males tended to have higher effect sizes for the categories verbal memory, general intelligence and mental control. Finally, a higher effect size was observed for verbal memory in those patients who had been using benzodiazepines for an average of at least 8 years.

Discussion

In this study, meta-analytical techniques were used to integrate the available information on the cognitive effects of long-term benzodiazepine use. Moderate-to-large effect sizes were found across all categories of cognition. According to Cohen,[48] effect sizes of $d = 0.20$, 0.50 and 0.80 are considered small, medium and large in magnitude, respectively. The effect sizes found in this meta-analysis were consistently significant across all domains and none had 95% CIs spanning zero. The conservative approach to effect size calculation that was adopted in this meta-analysis, combined with the small sample of studies, may have resulted in an underestimation of the true effect size.

The studies included in this meta-analysis were all published in peer-reviewed journals. Rosenthal[47] has argued that because studies that obtain nonsignificant results are less likely to be published, extracting data from only published results is likely to bias results in favour of a significant mean effect size. This is known as the 'file drawer problem'. To

Table III. Summary statistics for each cognitive function category (listed in order of decreasing weighted effect size) calculated from the studies assessed in this meta-analysis to determine the effect of long-term use of benzodiazepines on cognitive function

Cognitive function category	No. of effect sizes per category[a]	Cohen's *d*	Weighted effect size *d*	SD of weighted *d*
Sensory processing	2	−0.84	−1.30	0.69
Psychomotor speed	5 (11)	−1.10	−0.99	0.67
Nonverbal memory	4 (6)	−1.18	−0.91	0.45
Visuospatial	2	−1.12	−0.86	0.39
Speed of processing	6 (9)	−0.76	−0.72	0.31
Problem solving	2 (5)	−0.63	−0.68	0.16
Attention/concentration	9 (10)	−0.65	−0.67	0.40
Verbal memory	9 (18)	−0.58	−0.66	0.40
General intelligence	5 (7)	−0.70	−0.64	0.28
Motor control/performance	7	−0.45	−0.49	0.36
Working memory	6 (13)	−0.48	−0.48	0.33
Verbal reasoning	3 (5)	−0.21	−0.42	0.29
Overall	**61 (95)**	**−0.72**	**−0.74**	**0.25**

a Where a study used more than one type of test within a particular cognitive category, the effect sizes obtained were averaged so that each study was allowed to contribute only one effect size per category, thus giving equal weight to each study. The figure in parentheses refers to the initial number of effect sizes obtained per category prior to calculating mean effect size.

SD = standard deviation.

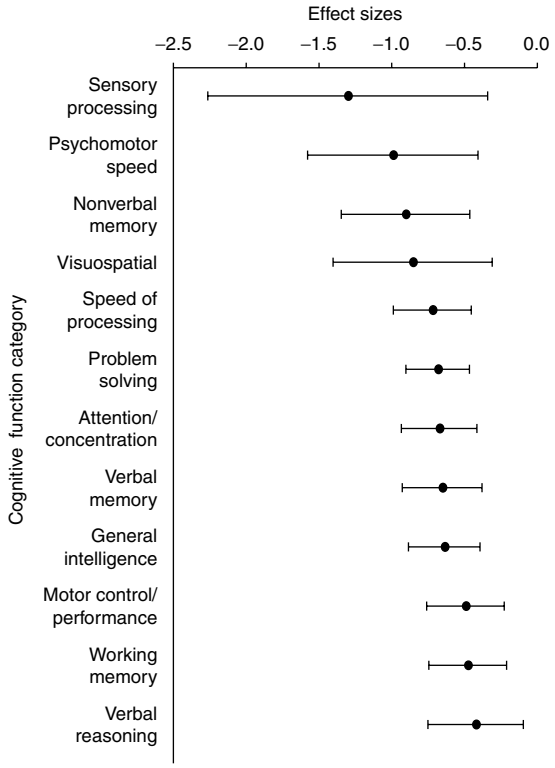

Fig. 1. Weighted mean effect sizes and 95% CIs for the performance of patients who were taking benzodiazepines on tests of various cognitive function categories. A negative effect size indicates that patients were performing worse than controls upon assessment.

determine whether the results of a meta-analysis are susceptible to the file drawer threat, the number of additional unpublished or unretrieved studies that are likely to exist is estimated. Rosenthal[47] has suggested that a conservative estimate for this tolerance level is $5k + 10$, where k is the number of studies retrieved. In the present meta-analysis, the tolerance level is estimated at 5 (13) + 10 = 75. The fail-safe n, which represents the number of studies obtaining null results that would need to be in existence to threaten the significant effect size found, was calculated to be 84 using procedures described by Rosenthal.[47] Since the fail-safe n exceeds the tolerance level, a file drawer problem is considered unlikely.

Weighting for sample size had little impact on the effect size (−0.72 unweighted compared with −0.74 weighted), suggesting that including studies with small samples that yielded large effect sizes did not artificially increase the effect size. An analysis of heterogeneity[49] was considered inappropriate due to the small number of studies that met the inclusion criteria in this meta-analysis, and the limited information provided on relevant characteristics.

The small number of studies included in the meta-analysis also resulted in insufficient data to conduct a thorough investigation of the contribution of moderator variables. The apparent trends, although of interest, should be interpreted with caution. These trends suggest that, for some categories, more recent studies were more likely to obtain a larger effect size than those published prior to 1994. Closer examination of those studies did not reveal any significant differences in any participant or study variables compared with earlier published studies. It may be the case that some real differences do exist that were undetectable given the small sample size.

Studies whose samples comprised at least 40% males tended to have higher effect sizes for a small number of categories, suggesting that males may be more affected by the long-term use of benzodiazepines. Again, while the possibility exists that another explanation was masked by insufficient statistical power, a more detailed comparison of those studies with and without >40% males failed to show any other differences between the groups.

Finally, a higher effect size was observed for the verbal memory category for patients who were users of benzodiazepines for an average of at least 8 years. This finding may suggest that the cognitive effects of benzodiazepines increase as the duration of use increases, which is consistent with previous findings of a cumulative effect of benzodiazepine use[15] – the higher the intake (dose and period of use), the greater the risk of cognitive impairment.

The single significant effect found in the analysis of moderator variables should also be interpreted with caution due to the inflation in type 1 error rates associated with the number of analyses conducted. The significant, positive correlation between time since last dose and the effect size for psychomotor

speed (suggesting that as time since the last dose increases psychomotor speed is less affected), raises the question of the presence of short-term effects compounding the long-term effects of benzodiazepines.

The time following the last dose of medication is an important variable that has been shown to be difficult to control in many clinical studies due to the varying medication schedules of patients.[2] The few studies which have examined the short-term effects of a normal dose in long-term benzodiazepine users have found a lack of acute effects on psychomotor measures[28,32] and conflicting results on measures of memory. Curran[32] reported no change in performance on memory measures (except for increased susceptibility to proactive interference), while others found evidence of memory impairment occurring for a brief period of time in long-term users following a benzodiazepine dose.[2,16,28] Short-term effects compounding long-term effects are an unlikely explanation of the findings in this meta-analysis as five of the nine studies that reported the time since last dose carried out assessments between 1 and 18 days since the last dose, with the remaining studies assessing either just prior to, or not within 4 hours, of a dose.

Considering that some of the studies carried out cognitive functioning assessments a number of days into the withdrawal period, raises the possibility that improvements following the discontinuation of benzodiazepines had already began to occur in some patients. Birzele[13] reported a positive withdrawal effect on memory functions over a number of weeks, while Sakol and Power[17] observed improvements in cognitive functioning after 4 weeks' withdrawal, as measured by a reaction time task and a sensory detection threshold task. Other studies supporting the notion of cognitive improvements following discontinuation, were inclined to report such improvements after longer periods of at least 1 year post-withdrawal.[33,50]

The moderate-to-large effect sizes found across all cognitive areas studied in this quantitative review suggests that long-term benzodiazepine users are impaired across many cognitive areas. Most investigations of the effects of the long-term use of benzodiazepines tend to focus on one or two specific areas of cognition; however, integrating all of the available evidence indicates that it may be the case that long-term benzodiazepine users are affected in a generalised rather than specific manner, with some areas being more affected than others.

Conclusion

In order to fully investigate the nature of impairment after long-term use of benzodiazepines, much larger-scale studies, which examine many areas of cognition, are needed. Clearly, this is not feasible and a more likely scenario is one that involves conducting many smaller, well designed studies that thoroughly investigate certain areas of cognitive functioning and present data in such a way so as to be amenable to inclusion in a meta-analysis. Incorporating this information into a larger meta-analysis would allow for a more thorough and statistically sound investigation of the effects of moderator variables – an obvious shortcoming of the current investigation associated with the dearth of appropriate literature available.

A small number of the studies included in this meta-analysis also conducted psychometric testing at some point post-withdrawal. The issues of improvement, residual impairment or persistence following discontinuation warrant a similar analysis on the available follow-up data. Although such an analysis would, of course, be subject to even more of the restrictions associated with a small number of studies than the current meta-analysis and may seem somewhat premature, integrating the available data could provide more valuable information than simply relying on the results of single studies.

In conclusion, the observation that long-term benzodiazepine use leads to a generalised effect on cognition has numerous implications for the informed and responsible prescription of these drugs. This is undoubtedly an important issue given the current level of use of benzodiazepines and the degree of uncertainty that surrounds the risks of long-term benzodiazepine therapy.

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