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The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis

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Abstract

Objective: This study presents an updated meta-analysis of the effects of benzodiazepines on cognitive functioning in long-term, current users of these agents, those who have recently withdrawn and on those who have successfully abstained following withdrawal. The study represents an update of the previous meta-analyses published by our group.
Method: A comprehensive search of the computerized databases Medline and PsycINFO was undertaken to identify studies that assessed the cognitive effects of benzodiazepines published up to 28 November 2016 (the date of the last update). Nineteen studies (eight studies published since the previous meta-analyses and 11 studies included in the previous studies) were included.
Results: The results of the analysis for current users revealed statistically significant, negative effects for the cognitive domains of working memory, processing speed, divided attention, visuoconstruction, recent memory, and expressive language. For those who had withdrawn and successfully abstained following withdrawal, deficits were observed for the domains of recent memory, processing speed, visuoconstruction, divided attention, working memory, and sustained attention.
Conclusions: The results of the study are important in that they corroborate the mounting evidence that a range of neuropsychological functions are impaired as a result of long-term benzodiazepine use, and that these are likely to persist even following withdrawal. The findings highlight the residual neurocognitive compromise associated with long-term benzodiazepine therapy as well as the important clinical implications of these results.

Keywords: Benzodiazepines; Meta-analysis; Cognitive effects; Sleep disorders; Anxiety disorders

Introduction

The benzodiazepines were introduced in the latter half of the 20th century to treat anxiety, insomnia, and panic disorders (Coleman, 1985). While these medications are useful in the short-term, the published evidence indicates that when they are used for longer periods, they often culminate in significant harm. This is of particular concern, as they continue to be amongst the most widely prescribed psychotropic medications across the globe (Crowe & Barker, 2007). The short-term cognitive effects of these agents include decreased alertness, impaired psychomotor performance, and memory dysfunction (Deckersbach, Moshier, Tuschen-Caffier, & Otto, 2011).

Barker, Greenwood, Jackson, and Crowe (2004a, 2004b, 2005) conducted a series of meta-analyses and an empirical study examining the longer-term affect of these agents. The results indicated that current long-term benzodiazepine users were significantly impaired in all of the cognitive domains measured (Barker et al., 2004a) including sensory processing, psychomotor speed, non-verbal memory, visuospatial processing, speed of processing, problem-solving, attention/concentration, verbal memory, general intelligence, motor control/performance, working memory, and verbal reasoning.

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A subsequent meta-analysis (Barker et al., 2004b) investigated whether the cognitive function of long-term users would improve following their withdrawal and whether previous long-term users would still be impaired at follow-up as compared to controls or normative data. The findings indicated that long-term benzodiazepine users significantly improved in many cognitive areas when they discontinued (i.e., visuospatial, attention/concentration, general intelligence, psychomotor speed, and non-verbal memory). However following withdrawal, significant impairment in many areas of cognition (i.e., verbal memory, psychomotor speed, speed of processing, motor control/performance, visuospatial processing, general intelligence, attention/concentration, and non-verbal memory (Barker et al., 2004b), persisted).

Definitively characterizing the residual effects of benzodiazepine use has been complicated however, as the effects of these agents are confounded by the presence of the clinical condition for which the drug had originally been prescribed (Deckersbach et al., 2011). In the context of these methodological issues, our group conducted an empirical evaluation of the functioning of previous long-term benzodiazepine users (Barker et al., 2005). Five of the cognitive areas identified in the follow-up meta-analysis as having moderate to large effect sizes (i.e., attention/concentration, motor control/performance, non-verbal memory, verbal memory, and visuospatial skills) were chosen for further assessment. Twenty previous long-term benzodiazepine users of more than 1 year's duration, who had remained abstinent for over 6 months, were each matched closely to two control groups (with and without anxiety) for age, sex, and education.

The results indicated that after at least 6 months of abstinence, previous long-term benzodiazepine users, continued to display cognitive deficits as compared to matched controls with moderate to large effect sizes for verbal memory, motor control/performance and non-verbal memory when comparing the previous benzodiazepine users and the normal controls. Significant differences were also found on these measures between previous benzodiazepine users and the anxious control group.

The observation that the anxious control group and the normal control group performed similarly on most measures and both groups performed significantly better than did the previous benzodiazepine users, implicates long-term benzodiazepine use as the most plausible explanation for these differences. Since the publications of these studies, there has been considerably more research into the cognitive effects of benzodiazepines.

In addition to the effects of these agents on the index condition as indicated earlier, their pharmacokinetic properties, such as their half-life are also important determinants of the residual effects of these drugs on cognitive functioning (Greenblatt, Shader, Divoll, & Harmatz, 1981). Helmes and Østbye (2015) examined the association between benzodiazepine use and neuropsychological test scores in older adults and found that the short half-life benzodiazepines were not associated with neuropsychological impairment, whereas the intermediate and long half-life benzodiazepines were both associated with deficits on the Token test. In addition, the participants who took intermediate half-life benzodiazepines were more likely to exhibit impairments on comprehension tests, and long half-life benzodiazepine use was associated with impaired performance on a word recall test (Helmes & Østbye, 2015). When the chronically benzodiazepine-medicated patients were compared to patients with panic disorder who were not chronically medicated as well as normal controls, it was found that the impairments observed in the domains of non-verbal memory and visuoconstruction performance was larger for the chronically medicated participants (Helmes & Østbye, 2015).

The variability in the drug response for patients is multifaceted, and is influenced by environmental, genetic, and disease determinants that can each affect the absorption, distribution, metabolism, and excretion of a given drug (Wilkinson, 2005). Pharmacogenomics is concerned with how genes can influence responses to drugs and is considered to be one of the most immediate clinical applications of the Human Genome Project with its potential to reduce adverse drug reactions (Phillips, Veenstra, Oren, Lee, & Sadee, 2001). Specifically, "adverse drug reactions could be reduced by modifying drug selection or dosing in patients with poor ability to metabolize a drug because of genetic variation in their drug metabolizing enzymes or by developing drugs a priori that will avoid metabolic pathways with adverse genetic variability" (Phillips et al., 2001, p. 2270).

Within the benzodiazepines grouping, large differences exist with regard to their pharmacokinetic properties and metabolism (Breimer, Jochemsen, & Von Albert, 1979). Some are eliminated from the body at a relatively slow rate (e.g., diazepam) while others are metabolized rather rapidly (e.g., oxazepam, temazepam, triazolam) (Breimer et al., 1979). The Cytochrome P450 (CYP) enzymes (which are predominantly expressed in the liver but also produced in the small intestine, placenta, and kidneys) are essential for the metabolism of many medications, including benzodiazepines (Lynch & Price, 2007; Slaughter & Edwards, 1995). This class has more than 50 enzymes, with the most significant ones being CYP3A4 and CYP2D6, of which over 40 allelic variants have been discovered thus far (Bradford, 2002; Lynch & Price, 2007). Variability in these enzymes may directly influence a patient's responses to certain drugs (Lynch & Price, 2007, p. 391). More specifically, CYP enzymes can be inhibited or induced by drugs, resulting in clinically significant drug interactions that can cause unanticipated adverse sequelae (Lynch & Price, 2007). The CYP2D6 is the enzyme that has been the most studied. While this particular enzyme accounts for <2% of the total CYP liver enzyme content, it is involved in the metabolism of a large number of

psychotropic medications, including many antipsychotics and antidepressant, β-blockers, anti-arrhythmic agents, opiates, and most benzodiazepines (Bradford, 2002).

Indeed, research suggests that there are also ethnic differences with respect to the response to medications such as benzodiazepines due to the relative activity levels of the CYP enzymes, which are typically categorized into functional, non-functional, and reduced function groups (Bradford, 2002). A specific gene encodes the CYP enzymes, with single genetic alleles being inherited from each parent (Lynch & Price, 2007). Alleles are classified either as "wild type" (the most commonly occurring in the general population) or "variant," (Lynch & Price, 2007). An individual is considered to be an "extensive" (normal) metabolizer if they inherit two copies of wild type alleles, whereas "poor" metabolizers are those individuals who have inherited two copies of the variant alleles (Lynch & Price, 2007). The proportion of people who are poor metabolizers differs in different ethnic groups. For example, 5%–10% of Caucasians are reported to be poor metabolizers whereas on only 2%–7% of African Americans and Asians are poor metabolizers (Lynch & Price, 2007).

The rationale for undertaking this updated meta-analysis was to incorporate studies published since the previous meta-analyses to provide an up to date review of the residual cognitive effects of the benzodiazepines in current users, those who have recently withdrawn and characterizing the long-term residual effects of those who have successfully abstained following withdrawal taking into consideration the unique features of the drug class itself as well as of that of the patients who are prescribed these agents.

Method

Literature Search and Inclusion Criteria

A search of the computerized databases Medline and PsycINFO was conducted to identify studies that assessed the cognitive effects of benzodiazepines published up to 28 November 2016 (the date of the last update). Key search terms used included "benzodiazepine*", "hypnotics", and "sedatives" paired with the terms "long-term", "chronic", effect*, "Cogniti*", Neuropsych* (*indicating the search terms and its derivatives were used). Searches were conducted using all possible combinations of these terms and were limited to papers written in English.

For a study to be included in the meta-analysis, it was necessary for the following criteria to be met. The studies had to:

(i) be published in a peer-reviewed journal between 2003 and 2016,
(ii) be written in English,
(iii) be either a randomized control trial that included a control or placebo group and a patient group or be a randomized crossover trial,
(iv) include a control group consisting of healthy adults with no pre-existing sleep disorders, mental health, substance abuse, or other disorder that may have affected cognition,
(v) involve participants who were current users of benzodiazepines or previous users of benzodiazepines who were experiencing short-term withdrawal (<3 months), medium (3–12 months), or long-term withdrawal (i.e., greater than 12 months drug free),
(vi) incorporate standardized neuropsychological and cognitive tests as indicated by their inclusion in neuropsychological test compendia such as Lezak, Howieson, Bigler, and Tranel (2012) and Strauss, Sherman, and Spreen (2006), and
(vii) reported results that were sufficient to allow the calculation of effect sizes.

The initial search yielded 8,251 search results. Of these, 78 papers were selected for further analysis as to whether they met the inclusion criteria, based upon their title and abstract. Of these, 70 papers were excluded for the following reasons; three had an inappropriate study design, eight did not provide sufficient data to allow for the calculation of effect sizes, eight did not incorporate a healthy control group, eight did not incorporate any objective cognitive testing measures, two were not empirical research studies, and 41 included participants who were not current or previous long-term users of benzodiazepines. This selection process identified eight new studies, which were not included in the previous meta-analyses. No additional papers were found when scanning the reference lists. In addition to these studies, 11 papers from the previous meta-analyses conducted by Barker and colleagues (Barker et al., 2004a, 2004b) that met the inclusion criteria were also included.

Coded Variables

For the included studies, the following information was coded:

(a) Participant variables: (i) study N, (ii) age, (iii) gender, (iv) method of participant recruitment, (v) method of participant recruitment, (vi) benzodiazepine medication, and (vi) dose and frequency
(b) Test information: (i) neuropsychological test used and (ii) cognitive domain tested.
(c) Outcome variables: (i) means and standard deviations and (ii) results of statistical analyses.

Statistical Analyses

Analysis was undertaken using the Comprehensive Meta-Analysis (CMA) software. A random effects model was employed, as the distribution of effect sizes is often heterogeneous due to the use of different participants, designs, and cognitive measures (Harvey & Taylor, 2010). Hedges' *g* effect sizes were calculated for each cognitive domain and were used as the principal summary measure. These values were calculated in a multi-stage process. The first stage involved calculating effect sizes for each score for each test used by each individual study, as per the methods outlined by Rosenthal (1995). These represent the difference between the benzodiazepine group and control group data divided by the pooled standard deviation. Thus, a positive effect size indicated better performance of the benzodiazepine group and a negative effect size indicated that the control group performed better than did the benzodiazepine group. However, in cases where a higher score indicated greater impairment than a lower score (e.g., number of errors or reaction time), the direction of the effect sizes for these scores was transformed so that a negative effect size still indicated greater impairment in the benzodiazepine group.

The majority of the studies used multiple outcome measures. As with other meta-analyses (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Harvey & Taylor, 2010; Hutchinson & Mathias, 2007; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; Stranks & Crowe, 2014; Stranks & Crowe, 2016), effect sizes were averaged for measures within the same cognitive domain to produce a single effect size per study for each cognitive domain.

An analysis of homogeneity, publication bias, and moderator analysis was also undertaken. In order to examine the extent of homogeneity, *Q*-statistics were calculated for each effect size for each cognitive domain in order to assess whether the variance exhibited by the effect sizes was due to sampling error alone (Cooper, 2010). Statistically significant values indicate that the variation in effect sizes was too great to be explained by sampling error alone; that is, some other factor was likely to be contributing to the variance in effect sizes (Cooper, 2010). Publication bias was assessed through the calculation of Fail-safe *N*s, which indicate the number of unpublished studies with non-significant results that would need to exist in order to call the observed significant findings into question. The formula developed by Orwin (1983) was used to calculate these values.

As different tests were used with varying frequency, it was decided that the Fail-safe *N*s should be greater than the number of published studies that had used the test (Hutchinson & Mathias, 2007). Finally, a moderator analysis using Pearson's correlations investigated the relationships between certain of the coded study characteristics and the effect sizes for each study. The variables included in the moderator analysis were: total number of study participants, number of participants in the benzodiazepine groups and control groups, mean age of study participants, number of males and females, time (in months) since benzodiazepine withdrawal and number of years of benzodiazepine use.

Results

Nineteen studies were included in this meta-analysis. Each neuropsychological test in each study was classified into 1 of 11 categories (see Table 1) corresponding to the broad cognitive ability that each test was considered to measure, The results of the neuropsychological tests extracted were pooled according to the cognitive domain being assessed (see Daffner et al., 2015; Strauss et al., 2006; Barker et al., 2004a, 2004b for a review of neuropsychological tests and their assignment to cognitive domain). The cognitive domains assessed and the specific neuropsychological tests employed in each study are listed in Table 1. Table 2 presents the summary statistics for all studies. Table 3 details the types of disorder the patients were being treated for, the specific benzodiazepine medications and their doses and details of any cumulative ratings of medical illnesses used for each included study (where applicable).

Table 1. Cognitive function categories and tests assessing skills within those categories that were used in the studies included in this meta-analysis

Domain of cognition	Neuropsychological test
Sustained Attention	Mental Control subtest (WMS-R), CPT, TMT – Part A
Executive Function	Tower of Hanoi, Wisconsin Card Sorting Test, Similarities
Working Memory	Visual Memory Span, Digit Span (forward and Backward)
Recent Memory	BVRT, Logical Memory (immediate and delayed recall), CVLT, WMS-R, Story recall subtest from WMS-R, RAVLT, Buschke recall, Paired Associate Learning Task, Verbal Paired Associates, Visual Reproduction, RCFT (recall), Visual Spatial Learning Test
Visuoconstruction	Mental Rotation test, RCFT (copy), Symbol Copy test, Block Design
Expressive Language	COWAT, verbal fluency
Receptive Language	Vocabulary, Token Test, Comprehension
Processing Speed	DSST, Simple and Complex reaction time task, Cancellation task
Perceptual Motor	Purdue Pegboard Test
Immediate Memory	BSRT
Divided Attention	TMT – Part B
Visual Perception	Benton Judgment of Line Orientation

Note: WMS-R = Wechsler Memory Scale-Revised; WAIS-R = Wechsler Adults Intelligence Scale-Revised; BVRT = Benton Visual Retention Test; CVLT = California Verbal Learning Test; RCFT = Rey Complex Figure Test; COWAT = Controlled Oral Word Association Test; WMS-R = Wechsler Memory Scale-Revised; RAVLT = Rey Auditory Verbal Learning Test; DSST = Digit Symbol Substitution Test; BSRT = Buschke Selective Reminder Test; CPT = Continuous Performance Test; TMT = Trail Making Test.

Table 2. Summary descriptive statistics

Variable	$N_{studies}$	Mean (*SD*)	Range
No. of participants	19	118.8 (330.8)	20–1,482
Benzodiazepine users, *N*	17	29.4 (31.4)	10–136
Controls, *N*	17	99.7 (321.3)	10–1,346
Benzodiazepine age	11	54.5 (15.8)	39.1–83
Control age	11	53.9 (18.1)	33–89
Overall study age	7	48.3 (10.6)	37.7–70.7
Female, *N*	17	22.8 (11.9)	13–57
Male, *N*	17	18.9 (11.4)	5–49
Time since withdrawal (months)	6	7.7 (16.8)	0.5–42
Length of abstinence at follow up	2	8 (2.8)	6–10
Years of benzodiazepine use	16	8.1 (4.2)	1–13.5

Note: *SD* = standard deviation.

Cognitive Deficits of Current Benzodiazepine Users

As can be seen in Table 4, statistically significant negative effect sizes were found for the cognitive domains of working memory, processing speed, divided attention, visuoconstruction, recent memory, and expressive language. A small positive effect size was found for the receptive language domain of functioning for individuals who were currently using benzodiazepines.

Cognitive Deficits of Benzodiazepine Users Who Have Recently Withdrawn From Benzodiazepines

As can be seen in Table 5, the cognitive deficits associated with benzodiazepine use persisted following withdrawal from the medication, and statistically significant negative effect sizes were found for all cognitive domains except for the domain of executive function.

Cognitive Deficits of Benzodiazepine Users at Follow Up

When benzodiazepine users were followed up after withdrawal (i.e., a maximum of 42 months post-withdrawal), cognitive deficits persisted as indicated by the statistically significant negative effect sizes being found for all cognitive domains except for the domain of sustained attention (Table 6).

An analysis of homogeneity was undertaken to test the assumption that sampling error alone could account for the variation between the study effect sizes. *Q*-values were used as the measure of the extent of heterogeneity, or variability between

Table 3. Tyes of disorders, benzodiazepine medication and dose and cumulative ratings of medical illness utilized in each study

Study	Mental disorder	Benzodiazepine medication and dose	Measures used to determine cumulative ratings of medical illness
Barker et al. (2005)	Anxiety Disorder	Mean diazepam equivalent was 33.1 mg	None specified
Bergman, Borg, Engelbrektson, and Vikander (1989)	No illness	Not specified	None specified
Birzele (1992)	No illness	Bromazepam (mean dose 14.5 mg) Diazepam (mean dose 21.6 mg) Flunitrazepam (mean dose 10 mg)	None specified
Curran (1992)	No illness	Diazepam (mean dose 8.6 mg) Lorazepam (mean dose 8 mg) Chlordiazepoxide (mean 7.5 mg)	None specified
Deckersbach et al. (2011)	Panic Disorder	80% of participants used Clonazepam (average dose 1.3 mg) 20% of participants used Alprazolam (average dose 3 mg)	Clinical Global Impression Score
Giersch and Vidailhet (2006)	No illness	Lorazepam (mean dose 1.8 mg)	None specified
Gorenstein, Bernik, and Pompeia (1994)	Anxiety Disorder	Diazepam (mean dose 13.6 mg)	None specified
Gorenstein, Bernik, Pompéia, and Marcourakis (1995)	Anxiety Disorder	Diazepam (mean dose 13.6 mg)	None specified
Helmes and Østbye (2015)	No illness specified	Not specified	None specified
Lucki and Rickels (1986)	Anxiety	Diazepam (mean dose 17.5 mg) Lorazepam (mean dose 4.1 mg) Clorazepate dipotassium (mean dose 10 mg) Alprazolam (mean dose 3.4 mg)	None specified
McAndrews et al. (2003)	Sleep Disorder	Diazepam (mean dose 11 mg)	None specified
Pétursson, Gudjonsson, and Lader (1983)	Anxiety Depression Personality Disorder with Anxiety	Diazepam (mean dose 15.2 mg) Lorazepam (mean dose 4.6 mg) Clobazam (mean dose 30 mg) Oxazepam (mean dose 90 mg)	None specified
Pomara et al. (2015)	General Anxiety Disorder Major Depression Disorder Panic Disorder Bipolar Disorder Insomnia Adjustment disorder with anxiety	Lorazepam (mean dose 1.4 mg)	None specified
Rickels et al. (1999)	General Anxiety Disorder Major Depression Disorder Panic Disorder	Diazepam (mean dose 12.7 mg) Lorazepam (mean dose 2.4 mg) Alprazolam (mean dose 2 mg)	None specified
Salzman et al. (1992)	Sleep Disorder	Triazolam (mean dose .125 mg) Temazepam (mean dose 30 mg) Clonazepam (mean dose 0.5 mg) Lorazepam (mean dose 0.5 mg) Oxazepam (mean dose 20 mg)	None specified
Tata, Rollings, Collins, Pickering, and Jacobson (1994)	Anxiety Disorders	Diazepam (mean dose 41.9 mg)	None specified
Uhlenhuth et al. (2006)	Panic Disorder	Alprazolam (mean dose 1 mg)	None specified
Vignola, Lamoureux, Bastien, and Morin (2000)	Insomnia	Lorazepam (mean dose 1.6 mg)	
Voshaar, Verkes, van Luijtelaar, Edelbroek, and Zitman (2005)	Generalized Anxiety Disorder Dysthymia Social Phobia Panic Disorder	Oxazepam (mean dose 30 mg)	

Table 4. Summary statistics for the effects of current benzodiazepine use (listed in order of decreasing weighted negative effect size) on each domain of cognitive functioning

Cognitive domain	$N_{studies}$	Hedges' *g*	95% CI lower	95% CI upper	*Q*-statistic	Fail-safe *N*
Working Memory	6	−0.78*	−0.96	−0.60	241.4*	29
Processing Speed	7	−0.76*	−0.91	−0.61	632.2*	34
Divided Attention	3	−0.67*	−1.05	−0.29	2.1	13
Visuoconstruction	4	−0.25*	−0.36	−0.14	78.0*	9
Sustained Attention	4	−0.22	−0.45	0.02	5.2	8
Recent Memory	7	−0.18*	−0.25	−0.10	1,141.2*	13
Immediate Memory	1	−0.15	−0.64	0.34	N/A	2
Expressive Language	2	−0.12*	−0.24	−0.01	32.0*	3
Executive Function	3	−0.10	−0.21	0.01	58.5*	5
Perceptual Motor	2	−0.10	−0.35	0.16	9.8*	3
Receptive Language	1	0.21*	0.15	0.28	N/A	0

*Significance at the .05 level.

Table 5. Summary statistics for the effects of recent benzodiazepine withdrawal (listed in order of decreasing weighted negative effect size) on each domain of cognitive functioning

Cognitive domain	$N_{studies}$	Hedges' *g*	95% CI lower	95% CI upper	*Q*-statistic	Fail-safe *N*
Perceptual Motor	1	−1.35*	−1.69	−1.00	N/A	8
Recent Memory	4	−1.19*	−1.37	−1.01	3,541*	28
Visual perception	1	−1.05*	−1.71	−0.39	N/A	6
Divided Attention	2	−0.72*	−1.21	−0.23	0.75	9
Visuoconstruction	5	−0.63*	−0.89	−0.38	19.5*	21
Sustained Attention	3	−0.63*	−1.01	−0.24	1.0	12
Processing Speed	7	−0.61*	−0.82	−0.40	154.0*	29
Working Memory	4	−0.47*	−0.71	−0.23	74.5*	13
Executive Function	1	−0.28	−0.90	0.35	N/A	2

*Significance at the .05 level.

Table 6. Summary statistics for the effects of benzodiazepine withdrawal as measured at follow up (listed in order of decreasing weighted negative effect size) on each domain of cognitive functioning

Cognitive domain	$N_{studies}$	Hedges' *g*	95% CI lower	95% CI upper	*Q*-statistic	Fail-safe *N*
Recent Memory	2	−1.40*	−1.69	−1.12	472.6*	16
Processing speed	2	−1.24*	−1.53	−0.89	111.7*	14
Visuoconstruction	1	−1.11*	−1.67	−0.55	N/A	7
Divided Attention	1	−0.72*	−1.34	−0.09	N/A	5
Working Memory	2	−0.71*	−1.00	−0.42	131.1*	9
Sustained Attention	1	−0.34	−0.95	0.27	N/A	3

*Significance at the .05 level.

study effect sizes. The majority of the *Q*-statistics were statistically significant, indicating that the variation in effect sizes was not due to sampling error alone. Furthermore, as the Fail-safe *N* values for the cognitive domains were for the most part greater than the number of studies that measured a cognitive domain, it was determined that relative confidence could be placed in the results obtained. Finally, the moderator analysis revealed no significant correlations. A comparison between the current study and the previous studies undertaken by the group are presented in Tables 7 and 8.

Discussion

For current long-term benzodiazepine users, the greatest deficits were found in the areas of working memory, processing speed, divided attention, visuoconstruction, recent memory and expressive language. These findings largely support the studies that has been published since the previous meta-analysis (Deckersbach et al., 2011; Helmes & Østbye, 2015; Pomara et al., 2015; Uhlenhuth et al., 2006; Voshaar et al., 2005). The results of the study are somewhat different to those of previous meta-analyses. Within the current meta-analysis, the magnitude of the negative effect size observed for the domain of working memory for current long-term users of benzodiazepines (−0.78) was larger than that found in the previous meta-analysis

Table 7. Summary of Hedges' *g* values calculated in the current study for current users, previous users who have recently withdrawn, and previous users measured at follow up

Cognitive domain	Current users	Recent withdrawal	At follow up
Working Memory	−0.78	−0.47	−0.71
Processing Speed	−0.76	−0.61	−1.24
Divided Attention	−0.67	−0.72	−0.72
Visuoconstruction	−0.25	−0.63	−1.11
Sustained Attention	−0.22	−0.63	−0.34
Recent Memory	−0.18	−1.19	−1.40
Immediate Memory	−0.15	N/A	N/A
Expressive Language	−0.12	N/A	N/A
Executive Function	−0.10	−0.28	N/A
Perceptual Motor	−0.10	−1.35	N/A
Receptive Language	0.21	N/A	N/A
Visual Perception	N/A	−1.05	N/A

Table 8. Summary of Cohen's *d* values calculated in the previous studies conducted by Barker and colleagues for current users, previous users who have recently withdrawn, and previous users measured at follow up

Cognitive domain	Current users	Recent withdrawal[a]	At follow up
Sensory processing	−1.30	0.37	0.26
Psychomotor Speed	−0.99	0.50	−0.78
Non-verbal Memory	−0.91	0.34	−0.26
Visuospatial	−0.86	0.70	−0.49
Speed of processing	−0.72	0.32	−0.76
Problem Solving	−0.68	0.64	−0.11
Attention/concentration	−0.67	0.69	−0.43
Verbal memory	−0.66	0.36	−1.50
General intelligence	−0.64	0.62	−0.47
Motor control/performance	−0.49	0.21	−0.62
Working Memory	−0.48	0.15	−0.58
Verbal Reasoning	−0.42	0.06	−0.02

[a]Effect sizes addressing the improvement following discontinuation represent the difference between the patient group at initial assessment and their performance at follow-up assessment. Therefore, a positive effect size indicates improvement of function from initial assessment to follow-up.

(−0.48) (Barker et al., 2004a). Moreover, the negative affect observed on performance on tests of memory (−0.18) is substantially less than what had been reported in the previous MA (−0.91 and −0.48 for non-verbal and verbal memory, respectively) (Barker et al., 2004a). In addition to attributing the differences in the meta-analyses' findings to different results obtained in studies published since 2004, these inconsistencies can also partly be attributed to the different categorizations of certain tests employed for the respective meta-analyses as well as the breakdown of different cognitive domains. For instance, the domain of recent memory in the current meta-analysis incorporated both verbal (i.e., Logical Memory) and non-verbal (i.e., Visual Reproduction) memory tasks whereas previously these were separated into separate cognitive domains (Barker et al., 2004a, 2004b). Other findings, such as the negative effect on processing speed performance (−0.76) were comparable across the meta-analyses (−0.72) (Barker et al., 2004a).

For users who had withdrawn from long-term benzodiazepine use, they were still significantly impaired in all areas of cognitive function (perceptual motor, recent memory, visual perception, divided attention, visuoconstruction, sustained attention, working memory, and processing speed) except for the domain of executive function. Again, these overall findings are consistent with results from individual studies published since the last meta-analyses as well as those included in the previous meta-analyses (Barker et al., 2004a, 2004b; Gorenstein et al., 1994, 1995; McAndrews et al., 2003; Pétursson et al., 1983; Rickels, Lucki, Schweizer, Garcia-Espana, & Case, 1999; Salzman et al., 1992, Tata et al., 1994). However, whilst a previous meta-analysis demonstrated an improvement in cognitive function following withdrawal (Barker et al., 2004b), the findings of the current meta-analysis did not note this, as evident by the statistically significant negative effect sizes observed among individuals who had recently withdrawn from benzodiazepine use. This trend is also observed at follow-up (i.e., among those individuals who had been successful in remaining abstinent following withdrawal from benzodiazepines). It is important to note that of those studies that included data that allowed for the calculation of effect sizes to determine the cognitive functions of benzodiazepine users at follow-up after withdrawal (Gorenstein et al., 1995; Tata et al., 1994), the maximum period between

cessation and the collection of data at follow up was 10 months. These results are indeed significant, for they challenge earlier findings that benzodiazepine users who are successful in withdrawing from benzodiazepine can expect recovery in cognitive functioning (Barker et al., 2004b).

It is useful to consider the nature of the proposed neurophysiological mechanism driving these neurocognitive changes. Pharmacological interference has the potential to disrupt normal neurotransmission in those brain regions responsible for both amnestic and non-amnestic cognitive functioning (Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 2012). It is the case that the benzodiazepines are safe and effective in short-term administration, as their therapeutic uses predominantly result from the enhancement of the central neurotransmitter gamma-aminobutyric acid (GABA) (Ashton, 1986). Benzodiazepines "act as γ-aminobutyric acid A (GABA-A) receptor agonists, which allosterically modulate GABA-A receptors by increasing their affinity for GABA" (Chung et al., 2016, p. 1029). The inhibitory γ-aminobutyric acid A (GABA-A) may also be implicated in modulating cognitive performance (Tannenbaum et al., 2012). When taken chronically however, benzodiazepines are capable of producing a large number of adverse effects due to the wide distribution of GABA-A receptors in a number of areas of the central nervous system including the spinal cord, cerebellum, limbic areas and the cerebral cortex, areas critical for intact cognitive function (Crowe & Barker, 2007). The commonly observed adverse cognitive effects of benzodiazepines, such as anterograde and retrograde amnesia likely occur as a result of GABAergic agonism (Chung et al., 2016; Tannenbaum et al., 2012). Another critical component in a discussion of mechanisms for neurocognitive changes in benzodiazepine use is the cholinergic system, which is connected to the cortex and hippocampus and implicated in memory storage and retrieval in addition to arousal, perception, and attention (Tannenbaum et al., 2012). Research indicates that the cholinergic system in addition to the histaminergic, GABAergic, and opioid receptor pathways are most commonly implicated in cognitive abilities such as learning, memory, attention, and executive function (Tannenbaum et al., 2012).

The moderator analysis revealed no statistically significant relationships within the data. However, it must be noted that only a small number of studies met the inclusion criteria for this analysis, thus it may be the case that some or all of these factors may significantly influence the effect sizes but were undetectable given the relatively small number of studies included in the analysis. Finally, as the fail-safe *N* values for most cognitive domains were for the most part greater than the number of studies that measured a particular cognitive domain, it was determined that relative confidence could be placed in the results obtained.

The results of this study should be interpreted with a consideration of several important limitations. After careful scrutiny of the studies that met the inclusion criteria as outlined in the methods section, only 19 studies were included after the evaluation and exclusion procedure. The authors recognize that this limits the ability of the study to evaluate potential covariates including participant demographics. It is also noted that many of the studies did not perform comprehensive neuropsychological examinations; with the majority using neuropsychological tests which indexed only a limited number of cognitive domains. It is interesting to note that there appears to be an increased focus within the literature on the acute effects of benzodiazepines on participants who are not long-term users of benzodiazepines; 41 studies were excluded because of this reason. This reinforces the need to ensure future researchers who investigate the cognitive effects of benzodiazepines favor the recruitment of long-term users, whose cognitive function and recovery are arguably of most concern for both clinicians and researchers. Nevertheless, future research might usefully compare the cognitive effects of acute benzodiazepine use among once-off or short-term users with that of long-term users.

In conclusion, the results of this meta-analytic study are important in that they corroborate the mounting evidence that a range of neuropsychological functions are impaired as a result of long-term benzodiazepine use, and that these are likely to persist even following withdrawal. Furthermore, the findings highlight the problems associated with long-term benzodiazepine therapy as well as the important clinical implications of these results. More specifically, it is clear that the residual neuropsychological sequelae must be considered when making treatment decisions for these patients.

Conflict of interest

None declared.

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References denoted with (*) were included in the meta-analysis and were studies published since the previous meta-analyses; References denoted with (§) were studies included in previous meta-analyses.

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