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ORIGINAL INVESTIGATION

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Zolpidem and memory: a study using the process-dissociation procedure

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Abstract *Rationale:* There is a dearth of studies which have employed sophisticated paradigms to investigate the effects of zolpidem on memory. *Objectives:* To explore anterograde cognitive deficits induced by acute oral doses of zolpidem by means of the process-dissociation procedure (PDP). *Methods:* The present study followed a placebo-controlled, double-blind, parallel-group design. Young, healthy females were randomly allocated to one of three treatments with 12 subjects each: placebo, 5 mg and 10 mg zolpidem. Two word-stem completion tasks were carried out close to theoretical peak-plasma concentration: a) direct inclusion task with cued recall, in which participants had to try to use words seen at study to complete stems; and b) direct exclusion task, in which words seen at study were to be avoided as completions. The PDP was applied to the results in these tasks to yield indices of explicit/controlled (C) and implicit/automatic (A) memory. Classical psychometric tests were also carried out. *Results:* Zolpidem 10 mg led to cognitive effects similar to benzodiazepines (except for the atypical lorazepam), including impairment of exclusion, but not inclusion-task performance. Results of the application of the PDP were inconclusive but concurred with the pattern established in previously published work on benzodiazepine effects, i.e. that zolpidem (10 mg) impaired C. *Conclusions:* Zolpidem leads to cognitive effects similar to most benzodiazepines. Although the application of PDP in drug studies may be counterproductive in view of methodological difficulties that are discussed, the pattern of effects on the stem-completion tasks involved in this paradigm is potentially useful in the investigation of cognitive effects of psychoactive drugs.

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Introduction

Research on the cognitive effects of benzodiazepines (BZ) in healthy subjects usually involves administering acute doses, with testing occurring close to theoretical peak plasma concentration of drugs. Studies conducted using these methods to investigate the effects of the imidazopyridine zolpidem, a non-benzodiazepine hypnotic agent that acts at the benzodiazepine omega$_1$ receptor subtype, show that this drug has similar cognitive effects to those of BZ, including anterograde episodic memory impairment, i.e. impairment in remembering episodic information to which subjects were exposed while under the effects of the drug (Patat et al. 1994; Rush and Griffiths 1996; Lobo and Greene 1997; Mintzer et al. 1997; Greenblatt et al. 1998; Mattila et al. 1998; Rush et al. 1998; Mintzer and Griffiths 1999; Patat et al. 2001). Although it is widely assumed that zolpidem, like most BZ, does not impair repetition priming (facilitation in processing a stimulus after having been previously exposed to it; Ochsner et al. 1998), to date only one study has investigated such effects (Mintzer and Griffiths 1999). In this study, indirect word and picture fragment-completion tests were used and no zolpidem-induced changes in performance were noted.

Repetition priming in BZ studies is mostly measured through tasks that involve completion or identification of "incomplete" stimuli (e.g. fragment or stem completion, and identification of fragmented pictures). The stem-completion task is by far the most commonly used. This test involves showing subjects words (during the "study" or "encoding" phase) and then instructing them to complete three-letter word-stems ("test phase"). In general, half the stems can be completed with words that were previously shown (studied words), while the remaining stems complete words that were not seen (non-studied words) and that are used to determine base-rate completion. Memory is measured by the difference in completions between studied and non-studied words.

The most common instruction in repetition priming tests is "indirect", in which there is no mention of the relation between study and test (see Johnson and Hasher 1987). In the case of stem-completion, the classical instruction is that stems be completed with the first word that comes to mind. This, in principle, leads subjects to use mainly implicit mnemonic strategies (repetition priming). This type of task, however, is not considered an ideal measure of priming, for it is widely accepted that subjects may use both priming and explicit memory while carrying it out (Richardson-Klavehn and Bjork 1988).

Equivalent versions of the stem-completions task can be used to evaluate explicit, episodic memory by changing the instruction type from indirect to direct (see Johnson and Hasher 1987). In this case, the task is classically known as "cued-recall" in which instead of subjects completing stems with the first word that comes to mind, they are required to do so with words seen at study. Here again, though, repetition priming may contaminate results and be responsible for part of the success in completing stems to form previously shown words. Alternative means must therefore be employed in order to determine the contribution of episodic memory and priming to performance in tasks that are not pure measures of specific types of memory.

The "process-dissociation procedure" (PDP) (Jacoby 1991, 1998; Jacoby et al. 1993) constitutes a paradigm for studying the intra-task contributions of different types of long-term memory and yields alternative measures of explicit, "conscious" or "controlled" recollection (C) and implicit, repetition priming or automatic (A) memory. In the case of stem-completion tasks, these indices are considered independent and are calculated on the basis of the proportion of stems completed with words seen at study in two types of direct tasks:

1. Inclusion task (equivalent to classic direct stem-completion or cued-recall), in which subjects are instructed to use stems to retrieve stimuli seen during a previous learning episode. Performance in this task thus reflects use of studied words due to explicit/conscious strategies (C) plus that of implicit/automatic memory (A) when C fails (1–C) [Inclusion=C+A(1–C)]. For example, performance of a pure amnesic patient, whose explicit/conscious memory is in principle totally impaired, would be solely due to automatic memory [0+A(1–0)].
2. Exclusion task, in which subjects are instructed to avoid completing stems with stimuli seen before. In this case, responses with studied stimuli are associated with automatic memory when conscious recollection (voluntary or involuntary) fails [Exclusion=A(1–C)]. In other words, responses with previously shown stimuli are contingent upon implicit or automatic memory, for if subjects have conscious or explicit recollection of these items, they do not use them as completions. Thus, an amnesic patient's performance in this task would also be due exclusively to use of automatic memory [A(1–0)].

The index "C" can be calculated by subtracting exclusion-test performance, in which completions with studied words reflect implicit memory, from scores in the inclusion test, in which both explicit and implicit type memories can be employed [C=Inclusion–Exclusion]. "A" can then be calculated using simple arithmetic [A=exclusion/1–C]. However, the equations above can be applied only if response criteria are found to be constant, such that base-rates in the inclusion and exclusion tasks and the proportion of uncompleted stems are equivalent across experimental manipulations.

The PDP was used to investigate anterograde BZ memory effects in only a few published papers. The studies that evaluated memory alterations while subjects were still under the effect of the drugs showed that lorazepam (Vidailhet et al. 1996) impaired inclusion task performance, while diazepam (Vidailhet et al. 1996) and flunitrazepam (Pompéia et al. 2003a) did not. In contrast, lorazepam did not impair performance in the exclusion task, while diazepam (Vidailhet et al. 1996) and flunitrazepam (Pompéia et al. 2003a) had this effect. These studies, despite methodological limitations that could preclude the application of the PDP (see Discussion), suggest that BZ reduce C and in general do not consistently impair A, except for lorazepam, a BZ known to display atypical effects (see Pompéia et al. 2003b, 2003c).

In order to determine whether zolpidem shows long-term memory effects similar to those of most BZ, the present study evaluated the effects of two clinical doses of this drug in inclusion and exclusion stem-completion and used performance in these tasks to determine A and C memory indices through the application of the PDP. Classical psychometric tests were also carried out as control measures to determine if the doses of zolpidem employed were high enough to elicit cognitive effects.

Materials and methods

Subjects

Subjects were 36 physically healthy, native Portuguese speaking female volunteers, aged 20–30 (mean±SD: 24.4±2.5 years), with average body mass index (weight/height^2: 21.1± 2.5 kg/m^2), more than 12 years of schooling, and trait anxiety scores (STAI: 40.4±6.5) corresponding to normal values for Brazilian University students (Gorenstein et al. 1995). Participants met the usual exclusion criteria for clinical trials (e.g. pregnancy, allergy, chronic clinical or psychiatric disorders), had no history of drug abuse or heavy alcohol drinking, consumed less than 5 units of alcohol per week, did not smoke or use drugs of abuse such as cannabis and cocaine regularly, and were on no medication at the time of the study.

Procedure

This was an independent group-design study using single oral doses of zolpidem. Subjects were randomly allocated to one of three treatments with 12 subjects each: placebo (P), 5 mg zolpidem (Z5), and 10 mg zolpidem (Z10). The Ethics Committee of the institute where the study was conducted (UNIFESP) approved the protocol and all subjects provided informed consent. Subjects were instructed to abstain from alcohol or other drugs for 24 h before and after the experiment. They were tested in the morning after ingesting a light breakfast (with their usual intake of caffeine) provided at the laboratory. Time to reach peak-plasma concentration for zolpidem, when ingested orally, varies from 0.75 h to 2.6 h in different studies (Salvà and Costa 1995), so testing was conducted approximately 80 min after treatment, when theoretical peak should have been reached in most subjects. These tests were conducted only once in order to maintain subjects naive to the tasks. Classical psychometric tests were performed both before treatment and at the end of the experiment (approximately 130 min after ingestion). These included DSST, delayed recall of prose and evaluation of subjective sedation. Further cognitive and neurophysiological tests (EEG, ERP) were also conducted and the results are reported elsewhere (Lucchesi et al., unpublishe data). Different task versions were counterbalanced across subjects and treatments in the case of tests that were carried out more than once. In respect to the stem-completion tasks, word sets and instructions were balanced across subjects and groups.

Treatment

Treatments were formulated in identical capsules containing the active principle (zolpidem) or talcum powder (placebo).

Test battery

Classical psychometric tests

Digit-Symbol Substitution Test (DSST; Wechsler 1955). A paper and pencil test involving coding skills and psychomotor ability: substitution of digits for symbols as indicated on a grid on the answer sheet. Scores were the total number of correct substitutions in 90 s.

Delayed prose-recall (Correa and Gorenstein 1988a, 1988b). A measure of long-term episodic memory. Volunteers were asked for delayed (approximately 20 min) spoken recall of a story of 14 “idea items” presented orally. Scores were based on the number and precision of items recalled (1=perfect recall; 0.5=partial recall or synonym).

Visual-analogue arousal scale. Rating was performed by subjects and the experimenter who marked a point on a 100-mm line that represented the full range of subject’s level of arousal (from “very alert” to “very sleepy”).

Stem completion

Materials. A pool of 84 neutral, five-letter Portuguese words (nouns, adjectives, verbs) with unique three-letter word-stems that could be completed with three to seven common words. Seventy-two of these words were organised into four sets of 18 words. These sets were balanced according to rank among other completions (e.g. if the word was the most common completion, the second most frequent, etc.), number of alternative words that could complete the stem, frequency with which no completions were found for the word, and chance completion (all determined in a pilot study with 69 university students). The remaining 12 stimuli were buffer words to control for primacy and recency effects (not scored). Two study lists were constructed by randomly combining two sets of words plus three primacy and recency items. Test lists were comprised of the four sets of stimuli, two of which corresponded to stems of studied words, and the other two to words not seen (non-studied) that were used to determine chance completion. Subjects completed stems of two sets of studied and non-studied words following inclusion instructions, and the remaining sets of studied and non-studied words following exclusion instructions. Thus, memory could be established by subtracting completions with studied words in the inclusion and exclusion task from completions with non-studied words.

Study/encoding phase. Words from a “study” list were shown on a computer screen at the rate of one word every 5 s (Arial font no. 60, uppercase, bold, black over white background). Subjects were instructed to say each word aloud and rate how much each word was liked on a 5-point scale (semantic encoding). Subjects responded aloud and the experimenter recorded their responses.

Tests. Each stem was presented on the computer screen for a maximum of 25 s, in the same lettering as the one used during the study phase. Direct retrieval instructions were employed (e.g. subjects were asked to use a word stem as a cue to recall a studied word that fits the stem) to ensure that C and A operated independently (Jacoby 1998): stems accompanied by the word “old” were to be completed with words seen before (inclusion instruction) while those accompanied by the word “new” should be completed with words that had not been seen at study (exclusion instruction). “Old” and “new” were written in lowercase above each stem. In the latter case, subjects were told that stems should be left blank if no alternative word to the word seen at study came to mind. If they could not remember a word seen before when following the inclusion task they were instructed to complete the stem with the first word that came to mind. The direct retrieval instructions used in the present study differ from generate-recognize instructions that involve telling subjects to complete word stems with the first word that came to mind in the inclusion condition, and to check each completion in the exclusion condition to be sure it is not a studied word before giving it as a response (Jacoby 1998). Inclusion and exclusion instructions varied randomly from stem to stem and in both cases subjects were asked to avoid proper nouns and plural words. Subjects responded aloud and the experimenter wrote down their responses. The dependent variables scored were the proportion of stems completed with target words (those that appeared in the word-lists used) and the proportion of stems left blank. Indices A and C were determined as outlined in the introduction: inclusion=C+A(1−C); exclusion=A(1−C); C=inclusion–exclusion; A=exclusion/(1−C).

Results

Analysis of variance (ANOVAs) followed by Tukey *t*-tests for comparisons of means were used in the statistical analysis and will be detailed below. The significance level of 5% was adopted for all statistical comparisons. Variables and comparisons that are not cited below did not show significant effects. Groups did not differ in age, body mass index or trait anxiety.

Classical psychometric tests

The analysis of these variables involved one-way ANCOVAs on post-treatment scores with group as the factor using pre-treatment scores as the covariate. For DSST [$F(2,32)=7.59$; $P<0.003$] and delayed recall of prose [$F(2,32)=13.30$; $P<0.001$] subject in the Z10 were impaired in relation to both those in the Z5 and the placebo treatments ($P<0.002$). For the visual-analogue arousal scale [$F(2,32)=14.31$; $P<0.001$], placebo-treated subjects reported less sedation than those who took both active doses ($P<0.002$) (Table 1).

Table 1 Performance (mean±SD) in the control psychometric tasks pre- and post-treatment, per group. *Z* zolpidem, *P* placebo

Measure	Placebo		Zolpidem (5 mg)		Zolpidem (10 mg)	
	Pre	Post	Pre	Post	Pre	Post
DSST (no. substitutions)*	73.7±11.3	72.7±9.8	71.4±11.9	66.4±11.7	61.4±14.3	52.5±11.0
Delayed recall (no. items)*	7.1±1.2	8.4±2.0	8.6±2.3	7.3±2.7	6.6±2.7	3.5±2.2
Subjective sedation (mm)**	39.1±23.3	42.7±30.0	31.9±21.3	73.4±13.6	21.9±15.7	78.1±14.2

* Z10<Z5 and P, **Z10 and Z5>P ($P<0.002$); post-treatment scores with group as factor covarying pre-treatment scores were used in the analysis

Stem-completion (Table 2, Fig. 1)

Data from each stem completion task was analysed separately using two-way ANOVAs with group (Z10, Z5, placebo) and "familiarity" (familiar/studied, unfamiliar/non-studied) as factors. These analyses involved the proportion of stems completed. Chance completion was analysed through one-way ANOVAs with group as the factor.

Inclusion test

A "familiarity" effect was observed [$F(1,33)=87.18$; $P<0.001$], studied words being completed more often than non-studied ones ($P<0.001$). This indicates that there was memory of words seen at study irrespective of treatment. No differences were found among groups in chance completion [$F(2,33)=1.16$; $P>0.32$].

Exclusion test

A "familiarity" effect [$F(1,33)=31.24$; $P<0.001$], and an interaction of group and "familiarity" [$F(2,33)=7.21$; $P<0.003$] were observed. This interaction showed a memory effect only in the Z5 and placebo treatments, that is, more non-studied words were completed than studied ones in these treatments ($P<0.001$). Zolpidem 10 mg also led to memory impairment by increasing completions with studied words in comparison to the other groups ($P<0.03$). Note that larger scores indicate worse performance. No chance completion differences between groups were observed [$F(2,33)=0.61$; $P>0.54$].

Process-dissociation procedure (PDP)

A two-way ANOVA with group and instruction as factors was employed to determine whether chance completion was equated between experimental manipulations. No statistical differences were found (treatment $P>0.21$; instruction $P>0.11$; interaction $P>0.97$). For stems left blank, group, instruction (inclusion and exclusion) and "familiarity" (studied and non-studied) were taken into account. There was an interaction of "familiarity" and instruction [$F(1,33)=27.02$; $P<0.001$]: studied words in the inclusion task were left blank less often than non-studied ones, and than studied words in the exclusion task ($P<0.001$). This interaction is in agreement with the notion that all types of memory facilitate completions in the inclusion task, making completions with studied words more probable than under all other conditions. It also reflects that subjects' explicit memory for studied words enabled them to follow exclusion task instructions requiring stems to be left blank if they could not generate a completion other than the word seen at study. A secondary analysis was then conducted in order to determine whether the inclusion and exclusion instructions influenced the proportion of stems of non-studied words left blank in each group, for which there could be no memory from the study phase. No significant differences were found ($P>0.10$). Neither was there any difference between groups in the total proportion of stems left blank (Z10=0.11±0.06; Z5=0.16±0.06; P=0.12±0.07; $P>0.16$). Thus, C and A indices were calculated (Table 2; Fig. 1).

For C [$F(2,33)=3.90$; $P<0.04$], performance in the Z10 group was impaired in relation to that of the placebo group ($P<0.03$) (other $P>0.18$). Three volunteers in the placebo group and two in the Z5 group completed zero

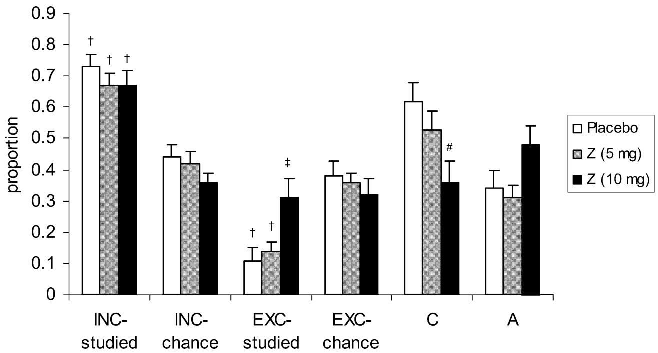

Fig. 1 Proportion (mean±SE) of stems completed with studied and non-studied (chance completion) target words according to instructions at test [inclusion (*INC*) and exclusion (*EXC*)], as well as indices of automatic (*A*) and conscious (*C*) memory, per group (*Z*). There were no chance completion differences between experimental manipulations, nor effects of group or interaction of this factor with familiarity and instruction. †,≠ Non-studied word in the same group and test (memory effect); ‡ zolpidem (10 mg)>placebo and zolpidem (5 mg) in terms of studied words in the exclusion task (memory impairment); # zolpidem (10 mg)<placebo (conscious memory impairment). All $P<0.05$. See text for detailed statistical analysis

Table 2 Proportion (mean±SD) of stems completed with studied and non-studied (chance completion) target words and stems left blank according to instructions at test (inclusion and exclusion), as well as indices of automatic (*A*) and conscious (*C*) memory, per group (see Fig. 1 for statistical effects). *CI* 95% confidence interval

	Measure	Placebo	Zolpidem (5 mg)	Zolpidem (10 mg)
Completed	Inclusion studied	0.73±0.13	0.67±0.15	0.67±0.16
	Inclusion non-studied	0.44±0.12	0.42±0.15	0.36±0.11
	Exclusion studied	0.11±0.13	0.14±0.11	0.31±0.20
	Exclusion non-studied	0.38±0.16	0.36±0.12	0.32±0.16
Non-completed (blank)	Inclusion studied	0.04±0.04	0.05±0.05	0.11±0.06
	Inclusion non-studied	0.16±0.11	0.11±0.08	0.18±0.10
	Exclusion studied	0.21±0.15	0.15±0.11	0.18±0.11
	Exclusion non-studied	0.08±0.05	0.11±0.10	0.15±0.08
Indices	C	0.62±0.21	0.53±0.22	0.36±0.25
	A	0.34±0.19	0.32±0.14	0.48±0.19
	C (grand means)	0.62 (CI 0.57–0.67)	0.53 (CI 0.48–0.58)	0.36 (CI 0.31–0.41)
	A (grand means)	0.29 (CI 0.24–0.34)	0.30 (CI 0.25–0.35)	0.48 (CI 0.43–0.53)

stems with target words in the exclusion task, so there was no A index for these subjects. For the remaining volunteers, despite a tendency for effect to appear [$F(2,33)=2.65$; $P=0.09$], none of the comparisons of mean scores approached significance ($P>0.12$).

C and A were also estimated from grand means collapsed over participants and items (Table 2) because these estimates from the pooled data do not seem to be affected by the exclusion=0 problem (see Curran and Hintzman 1995; Mintzer et al. 2003). For this analysis, pairs of grand means are considered proportions and compared through two-tailed *z*-tests using the standard error of the difference between proportions as the denominator. In addition, following Curran and Hintzman (1995), the standard error of such "proportions" was used to derive a 95% confidence interval around the pooled means in each condition (Table 2). Using this analysis, a paradoxical dissociation occurred: Z10 decreased C in comparison to placebo ($z=7.23$) and Z5 ($z=4.66$) and increased A in relation to the other groups (placebo: $z=-5.34$; Z5: $z=-5.04$) ($P<0.0001$).

Discussion

The present study corroborates previous findings that clinical doses of zolpidem lead to cognitive effects equivalent to those of BZ when classical psychometric tests are conducted close to theoretical peak-plasma concentration (Curran 1991, 2000; Buffett-Jerrott and Stewart 2002), i.e. zolpidem impairs psychomotor performance (DSST), causes anterograde amnesia and subjective sedation (Mintzer and Griffiths 1999).

The use of a more refined paradigm to investigate memory impairment, the PDP (Jacoby 1991), also showed that 10 mg zolpidem affects C, confirming that this drug impairs episodic memory as observed through the application of this same paradigm to data from BZ-treated subjects (Vidailhet et al. 1996; Pompéia et al. 2003a).

Results relative to BZ effects on the A index are not as clear cut. It has been shown that diazepam and flunitrazepam do not impair it (Vidailhet et al. 1996; Pompéia et al. 2003a), while lorazepam does (Vidailhet et al. 1996). Our results for zolpidem add little to this debate. Although effects on automatic memory did not reach significance ($P=0.09$), which would be consistent with the lack of repetition priming effects of this drug in the only other study to evaluate this type of memory (Mintzer and Griffiths 1999), this result may have been due to lack of statistical power, particularly given the fact that a number of subjects scored zero in the exclusion task so no A index could be calculated for them [$A=EXC/(1-C)$]. This occurred despite our efforts in selecting words with high chance-completion in order to make it more difficult for subjects to have perfect performance in this task.

Contrary to Vidailhet et al.'s (1996) findings for lorazepam, Mintzer et al. (2003) showed that midazolam increased A and decreased C, a paradoxical dissociation similar to that obtained in publications that employed manipulations other than drug treatment (e.g. Curran and Hintzman 1995; Russo et al. 1998). When we compared groups using A and C derived from grand means such as used by Curran and Hintzman (1995) and Mintzer et al. (2003), an equivalent paradoxical dissociation was observed, that is, zolpidem 10 mg decreased C and increased A in relation to the other groups. It must be kept in mind, however, that for this analysis subjects and items contribute multiple observations, so they are not independent, a necessary premise for the application of *z*-tests (see Curran and Hintzman 1995). Also, grand means are not proportions. Hence, these results do not contribute a great deal to the understanding of BZ or similar drugs on automatic memory.

Although it is beyond doubt that the paper by Mintzer et al. (2003) was the most thorough study to use the PDP to investigate drug effects, it differs from the present work and other cited papers in the field (Vidailhet et al. 1996; Pompéia et al. 2003a) in that memory was evaluated when subjects were no longer under the effect of the drug and also because levels of processing were manipulated. Thus, Mintzer et al.'s (2003) findings are not directly comparable to the data presented here. The same applies to Fillmore et al.'s (2001) study in which the PDP was used to investigate retrograde memory effects of triazolam.

Difficulties in applying the PDP have by no means been restricted to the present study. There has, in fact, been widespread criticism of this paradigm, even when drugs are not used (e.g. see Baddeley 1997; Hirshman 1998; Russo et al. 1998; Richardson-Klavehn et al. 2002; Mintzer et al. 2003). In addition, although the previous studies on effects of BZ that used the PDP (Vidailhet et al. 1996; Fillmore et al. 2001; Mintzer et al. 2003; Pompéia et al. 2003a) found it acceptable to apply this paradigm, none was devoid of methodological restrictions that made findings inconclusive. These include variation in response criteria and the use of artificial and unorthodox statistical analysis to make the data fit the premises of the PDP.

Recourse to PDP has therefore led to few concrete results in studies of drugs that bind to BZ receptors, and may be counterproductive when considering the difficulty in matching response criteria among conditions and the loss of data of subjects who score zero in the exclusion task. Thus, although there is no doubt that BZ and zolpidem impair episodic memory, even if results of C are inconclusive, investigations into zolpiden's automatic memory or priming effects are warranted and would benefit from the use of other paradigms in which little or no contamination by explicit memory occurs, such as perceptual identification tests (see Hirshman et al. 1999).

Zolpidem's effects on inclusion and exclusion tasks were more revealing in terms of comparing them to those of BZ and less contentious concerning possible methodological flaws. Despite the impairment in delayed prose recall, zolpidem did not decrease performance in the "explicit memory" direct/inclusion stem-completion task, as would be expected of a BZ (Curran 1991, 2000; Buffett-Jerrott and Stewart 2002). Although impairment in this type of task has been reported for lorazepam (File 1992; Bishop and Curran 1995; Stewart et al. 1996; Vidailhet et al. 1996; Buffett-Jerrott et al. 1998a; Pompéia et al. 2000) and oxazepam (Stewart et al. 1996; Buffett-Jerrott et al. 1998a, 1998b), no effects have been shown for other BZ, including diazepam (Vidailhet et al. 1996), flunitrazepam (Pompéia et al. 1996, 2000, 2003a), and nitrazepam (Pompéia et al. 1996) in doses that led to impairment of other measures of episodic memory. This may reflect the small task demands imposed by this test (Pompéia et al. 1996).

Despite a lack of effects in the inclusion task, 10 mg zolpidem impaired performance in the exclusion task, a pattern of effects previously observed for diazepam (Vidailhet et al. 1996), and flunitrazepam (Pompéia et al. 2003a). This similarity in effects of drugs that bind to BZ receptors suggests that these results do not reflect casual variations or a methodological artefact. Impairment of exclusion and not inclusion stem-completion may be ascribed to task sensitivity since exclusion tasks are more difficult to carry out and BZ tend to have greater effects under higher test demands (see Pompéia et al. 1996). Why lorazepam would show the opposite effects (impairment of performance in the inclusion task only) is still unclear. This may in some way reflect its atypical effects (see Pompéia et al. 2003b, 2003c). Alternatively, BZ and BZ-like substances such as zolpidem may alter the way in which subjects respond to task instructions rather than, or in addition to, memory changes themselves. Subjects treated with placebo and 5 mg zolpidem completed less stems with target words following the exclusion instruction than by chance, suggesting that they may have employed generate-recognize strategies to complete stems despite our having used direct-retrieval instructions to ensure that C and A operated independently (see Jacoby 1998). Subjects may nevertheless use generate-recognize strategies in which case words that are automatically generated by a stem are recognized as studied and then excluded, precluding the application of the PDP because A and C are thus no longer independent (Jacoby 1998). The treatment with 10 mg zolpidem may have rendered subjects unable to use generate-recognize strategies, possibly due to unspecific drug effects such as sedation. This potential difference in retrieval strategies, however, does not seem to be responsible for the pattern of effects in the completion tasks because Vidailhet et al. (1996) showed no evidence that subjects employed generate-recognize strategies. These authors still found that diazepam impaired performance in the exclusion task and not in the inclusion task.

In conclusion, zolpidem seems to display a similar pattern of anterograde cognitive effects to BZ (excluding the atypical lorazepam) even though results of the application of the PDP were somewhat inconclusive. Despite this, there are two important implications in using the stem-completion tasks involved in this paradigm. Firstly, the pattern of effects in the inclusion and exclusion tasks when comparing BZ and zolpidem, on the one hand, and lorazepam, on the other, may illuminate the atypical effects of lorazepam. Secondly, although rarely employed in the literature, the exclusion task is potentially useful as a means of easily determining psychoactive drug effects since it was found to be highly sensitive to the ingestion of zolpidem and BZ.

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References

Baddeley A (1997) Recollective and implicit memory. In Human memory: theory and practice, revised edition, Psychology Press, Hove, pp 351–371

Bishop KI, Curran HV (1995) Psychopharmacological analysis of implicit and explicit memory: a study with lorazepam and the benzodiazepine antagonist flumazenil. Psychopharmacology 121:267–278

Buffett-Jerrott SE, Stewart SH (2002) Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des 8:45–58

Buffett-Jerrott SE, Stewart SH, Teehan MD (1998a) A further examination of the time-dependent effects of oxazepam and lorazepam on implicit and explicit memory. Psychopharmacology 138:344–353

Buffett-Jerrott SE, Stewart SH, Bird S, Teehan MD (1998b) An examination of differences in the time course of oxazepam's effects on implicit vs explicit memory. J Psychopharmacol 12:338–347

Correa DD, Gorenstein C (1988a) Bateria de testes de memória. Parte 1: Critérios de elaboração e avaliação. Arq Bras Psicol 40:24–35

Correa DD, Gorenstein C (1988b) Bateria de testes de memória. Parte 2: Teste de homogeneidade e análise das funções mnêmicas. Arq Bras Psicol 40:42–53

Curran HV (1991) Benzodiazepines, memory and mood: a review. Psychopharmacology 105:1–8

Curran HV (2000) Psychopharmacological perspectives on memory. In: Tulving E, Craik FIM (eds) The Oxford handbook of memory. Oxford University Press, Oxford, pp 539–556

Curran T, Hintzman DL (1995) Violations of the independence assumption in process dissociation. J Exp Psychol [Learn Mem Cognit] 21:531–547

File SE (1992) Effects of lorazepam on psychomotor performance: a comparison of independent-groups and repeated-measures designs. Pharmacol Biochem Behav 42:761–764

Fillmore MT, Thomas HK, Rush CR, Hays L (2001) Retrograde facilitation of memory by triazolam: effects on automatic processes. Psychopharmacology 158:314–321

Gorenstein C, Pompéia S, Andrade L (1995) Scores of Brazilian university students on the Beck Depression and the State-Trait Anxiety Inventory. Psychol Rep 77:635–641

Greenblatt DJ, Harmatz JS, von Moltke LL, Ehrenberg BL, Harrel L, Corbett K, Counihan M, Graf JA, Darwish M, Mertzanis P, Martin PT, Cevallos WH, Shader RI (1998) Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. Clin Pharmacol Ther 64:553–561

Hirshman E (1998) On the logic of testing the independence assumption in the process-dissociation procedure. Mem Cognit 26:857–859

Hirshman E, Passannante A, Henzler A (1999) The effect of midazolam on implicit memory tests. Brain Cognit 41:351–364

Jacoby LL (1991) A process dissociation framework: separating automatic from intentional use of memory. J Mem Lang 30:513–514

Jacoby LL (1998) Invariance in automatic influences of memory: towards a user's guide for the process dissociation procedure. J Exp Psychol [Learn Mem Cognit] 24:3–26

Jacoby LL, Toth JP, Yonelinas AP (1993) Separating conscious and unconscious influences of memory: measuring recollection. J Exp Psychol [Gen] 122:139–154

Johnson MK, Hasher L (1987) Human learning and memory. Annu Rev Psychol 38:631–668

Lobo BL, Greene WL (1997) Zolpidem: distinct from triazolam? Ann Pharmacother 31:625–632

Mattila MJ, Vanakoski J, Kalska H, Seppala T (1998) Effects of alcohol, zolpidem, and some other sedatives and hypnotics on human performance and memory. Pharmacol Biochem Behav 59:917–923

Mintzer MZ, Griffiths RR (1999) Selective effects of zolpidem on human memory functions. J Psychopharmacol 13:18–31

Mintzer MZ, Frey JM, Yingling JE, Griffiths RR (1997) Triazolam and zolpidem: a comparison of their psychomotor, cognitive, and subjective effects in healthy volunteers. Behav Pharmacol 8:561–574

Mintzer MZ, Hirshman E, Griffiths RR (2003) A paradoxical dissociation in the effects of midazolam on recollection and automatic process in the process dissociation procedure. Am J Psychol 116:213–237

Ochsner KN, Chiu C-YP, Schacter DL (1998) Varieties of priming. In: Squire LR, Kosslyn SM (eds) Findings and current opinion in cognitive neuroscience. MIT Press, Cambridge, Mass., pp 99–104

Patat A, Naef MM, van Gessel E, Forster A, Dubruc C, Rosenzweig P (1994) Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. Clin Pharmacol Ther 56:430–436

Patat A, Paty I, Hindmarch I (2001) Pharmacodynamic profile of zaleplon, a new non-benzodiazepine hypnotic agent. Hum Psychopharmacol 16:369–392

Pompéia S, Gorenstein C, Curran HV (1996) Benzodiazepine effects on memory tests: dependence on retrieval cues? Int Clin Psychopharmacol 11:229–236

Pompéia S, Bueno OFA, Lucchesi LM, Manzano GM, Galduróz JCF, Tufik S (2000) A double-dissociation of behavioural and event-related potential effects of two benzodiazepines with similar potencies. J Psychopharmacol 14:288–298

Pompéia S, Bueno OFA, Galduróz JCF, Tufik S (2003a) Stem-completion tasks (indirect, direct inclusion and exclusion) are differently affected by equipotent doses of lorazepam and flunitrazepam. Hum Psychopharmacol 18:1–9

Pompéia S, Bueno OFA, Tufik S (2003b) Lorazepam should no longer be used as a prototypical benzodiazepine. Psychopharmacology 169:211–212

Pompéia S, Manzano GM, Galduróz JCF, Tufik S, Bueno OFA (2003c) Lorazepam induces an atypical dissociation of visual and auditory event related potentials. J Psychopharmacol 17:31–40

Richardson-Klavehn A, Bjork RA (1988) Measures of memory. Annu Rev Psychol 39:475–543

Richardson-Klavehn A, Gardiner JM, Ramponi C (2002) Levels of processing and the process-dissociation procedure: elusiveness of null effects on estimates of automatic retrieval. Memory 10:349–364

Rush CR, Armstrong DL, Ali JA, Pazzaglia PJ (1998) Benzodiazepine-receptor ligands in humans: acute performance-impairing, subject-rated and observer-rated effects. J Clin Psychopharmacol 18:154–165

Rush CR, Griffiths RR (1996) Zolpidem, triazolam, and temazepam: behavioural and subject-rated effects in normal volunteers. J Clin Psychopharmacol 16:146–157

Russo R, Cullis AM, Parkin AJ (1998) Consequences of violating the assumption of independence in the process dissociation procedure: a word fragment completion study. Mem Cognit 26:617–632

Salvà P, Costa J (1995) Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clin Pharmacokinet 29:142–153

Stewart SH, Rioux GF, Connolly JF, Dunphy SC, Teehan MD (1996) Effects of oxazepam and lorazepam on implicit and explicit memory: evidence for possible influence of time course. Psychopharmacology 128:139–149

Vidailhet P, Kazès M, Danion J-M, Kauffmann-Muller F, Grangé D (1996) Effects of lorazepam and diazepam on conscious and automatic memory processes. Psychopharmacology 127:63–72

Wechsler DA (1955) Manual for the Wechsler Adult Intelligence Scale. National Foundation for Educational Research, London