Drug and Alcohol Dependence 128 (2013) 206–213

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

# Acute cognitive effects of high doses of dextromethorphan relative to triazolam in humans

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ARTICLE INFO

*Article history:*
Received 17 April 2012
Received in revised form 21 August 2012
Accepted 23 August 2012
Available online 16 September 2012

*Keywords:*
Dextromethorphan
Triazolam
Cognitive
Memory
Robitussin
Coricidin

ABSTRACT

*Background:* Although concerns surrounding high-dose dextromethorphan (DXM) abuse have recently increased, few studies have examined the acute cognitive effects of high doses of DXM. The aim of this study was to compare the cognitive effects of DXM with those of triazolam and placebo.
*Methods:* Single, acute, oral doses of DXM (100, 200, 300, 400, 500, 600, 700, 800 mg/70 kg), triazolam (0.25, 0.5 mg/70 kg), and placebo were administered p.o. to twelve healthy volunteers with histories of hallucinogen use, under double-blind conditions, using an ascending dose run-up design. Effects on cognitive performance were examined at baseline and after drug administration for up to 6 h.
*Results:* Both triazolam and DXM produced acute impairments in attention, working memory, episodic memory, and metacognition. Impairments observed following doses of 100–300 mg/70 kg DXM were generally smaller in magnitude than those observed after 0.5 mg/70 kg triazolam. Doses of DXM that impaired performance to the same extent as triazolam were in excess of 10–30 times the therapeutic dose of DXM.
*Conclusion:* The magnitude of the doses required for these effects and the absence of effects on some tasks within the 100–300 mg/70 kg dose range of DXM, speak to the relatively broad therapeutic window of over-the-counter DXM preparations when used appropriately. However, the administration of supratherapeutic doses of DXM resulted in acute cognitive impairments on all tasks that were examined. These findings are likely relevant to cases of high-dose DXM abuse.


## 1. Introduction

Dextromethorphan (DXM) is a drug that was approved by the US Food and Drug Administration (FDA) in 1958 as a non-prescription cough medication. Today, DXM is available in the US in over 125 different over-the-counter (OTC) products and formulations for the treatment of unproductive cough (FDA Briefing Information, 2010). Current common trade names of DXM-containing products include Robitussin (liquids and capsules) and Coricidin (capsules; Bem and Peck, 1992). In addition, DXM can be legally purchased in the US currently as an unfinished drug product (i.e., as a bulk powder); however, such formulation is not approved for medical use (H.R., 1259 (111th): Dextromethorphan Distribution Act of 2009). Although DXM is available OTC and is not scheduled under Federal Law, DXM has liability for abuse (Banken and Foster, 2008; Reissig et al., 2012; Romanelli and Smith, 2009; Schutz and Soyka, 2000; Soyka et al., 2000; Zawertailo et al., 1998; Ziaee et al., 2005) and the sale of DXM has already been regulated or restricted by several States in the US (Erowid, 2012). Epidemiological studies have documented cases of DXM abuse that have been reported to the National Poison Data System in the US (Wilson et al., 2011). Recently, there has been an increasing concern surrounding DXM abuse as studies have reported an increase in the number of cases of DXM abuse from 2000 to 2006, although the frequency of these cases appears to have been stable from 2006 to 2010 (Wilson et al., 2011).

The therapeutic dose range for cough suppression for DXM is 10–30 mg. In contrast, doses of DXM that are used recreationally often exceed several hundred mg (e.g., 600–900 mg/70 kg, Boyer, 2004; 75–2700 mg/70 kg, Ziaee et al., 2005). At high concentrations, DXM binds to *n*-methyl-D-aspartate (NMDA) receptors as an antagonist (Church et al., 1994) in a manner similar to that of phencyclidine (PCP; Morris et al., 2005; Newell et al., 2007) and ketamine (Sinner and Graf, 2008). In addition, the primary active metabolite of DXM, dextrorphan, binds to NMDA receptors with greater

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http://dx.doi.org/10.1016/j.drugalcdep.2012.08.025

affinity than DXM and functions as an antagonist (Franklin and Murray, 1992; Parsons et al., 1995; Werling et al., 2007). It is likely that most of the cases of DXM abuse, sometimes referred to as "Dexing" or "Robotripping," are the result of a user seeking effects similar to those produced by classic hallucinogens, which occur at very large doses of DXM (Reissig et al., 2012). Cognitive impairments associated with these high doses of DXM might contribute to the reports of adverse events and toxicity that have been reported in recent years.

Part of the rationale for this investigation is that few studies have examined the effects of DXM in human participants within the range of doses that are frequently abused (i.e., 400–1000 mg/70 kg; Steinberg et al., 1996; Zawertailo et al., 1998). In studies that have examined the effects of supratherapeutic doses of DXM, effects on cognitive functions such as attention and memory processing were not evaluated (Schutz and Soyka, 2000; Soyka et al., 2000; Steinberg et al., 1996; Zawertailo et al., 1998). Given the increasing concern surrounding high-dose DXM abuse, it is important to know if and how high-dose DXM abuse might affect cognitive functioning. Thus, one of the aims of this study was to examine the acute dose effects of high doses of DXM on a variety of different cognitive measures. A second aim was to extend previous findings from our laboratory on the comparative pharmacology and the differential profiles of the cognitive effects of benzodiazepines such as triazolam (Carter et al., 2006, 2007, 2009; Mintzer and Griffiths, 2002, 2005) and NMDA antagonists such as ketamine (Carter et al., 2012; Lofwall et al., 2006). On the basis of the results from these previous studies, we hypothesized that the effects of DXM on participants' subjective ratings of drug effects and of their own cognitive performance impairment would be greater than those of triazolam, whereas the cognitive impairments observed after administration of triazolam would be greater than those observed after DXM.

## 2. Materials and methods

A brief description of the general methods is provided below. This report describing the cognitive effects of DXM and triazolam comes from a larger study in which additional measures of physiological effects, psychomotor performance, subjective effects, and hallucinogen-like effects were examined. A more detailed description of those measures and the complete study methods can be found in a prior publication (Reissig et al., 2012).

### 2.1. Participants

Twelve adult volunteers (9 males) completed this study. Participants ranged in age from 20 to 40 years (mean 27.5 years), were medically and psychologically healthy, and had a history of hallucinogen use. Ten participants were Caucasian (83%), one was African-American, and one was Asian-American. All volunteers reported past use of LSD (range: 2–500 lifetime uses, mean: 58.2 uses) and psilocybin (range: 4–60 lifetime uses, mean: 21 uses). Seven of the twelve volunteers had used DXM previously for recreational purposes (range: 1–10 lifetime uses, mean of these seven volunteers: 4.8 uses), and three of the twelve had experience with either PCP or ketamine. Individuals were excluded from participation if they had a history of substance dependence according to DSM-IV-TR criteria (excluding nicotine or caffeine), were pregnant or nursing, had a current significant medical condition or had a contraindication to receiving sedatives or anesthetics. A detailed psychiatric history was taken during the screening interview to exclude individuals with a personal or immediate family history of schizophrenia, bipolar affective disorder, delusional disorder, paranoid disorder, or schizoaffective disorder. The Johns Hopkins University School of Medicine Institutional Review Board approved this study and it was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all applicable U.S. Laws. Participants gave their written informed consent before beginning the study and were paid for their participation.

### 2.2. General procedures

During the study, participants could receive a maximum of 11 different conditions over 11 experimental sessions (placebo, 0.25 and 0.5 mg/70 kg triazolam, and 100, 200, 300, 400, 500, 600, 700 and 800 mg/70 kg DXM). Consecutive sessions for each participant were separated by a minimum of 48 h and the median number of days between sessions for all participants was 6. The order of the three types of conditions (triazolam, DXM, and placebo) was counterbalanced across participants. Within each drug condition, the sequence of the doses was ascending, and dosing with triazolam or DXM was completed before proceeding to another type (e.g., both doses of triazolam were administered before proceeding to DXM dosing and vice versa). The ascending sequence was used to determine the maximum dose of DXM that could be safely tolerated by individual participants and to avoid adverse events that might result if an individual was particularly sensitive to DXM. As described elsewhere (Reissig et al., 2012), all participants received placebo, both doses of triazolam (0.25 and 0.5 mg/70 kg), and at least four doses of DXM (100, 200, 300, and 400 mg/70 kg). The highest dose of DXM administered varied across participants (400 mg/70 kg, $n = 2$; 500 mg/70 kg $n = 2$; 600 mg/70 kg, $n = 4$; 700 mg/70 kg, $n = 2$; 800 mg/70 kg, $n = 2$). Seven volunteers reached their stop point because of significant behavioral impairment. Two volunteers reached their stop point because the investigators judged administration of higher doses to be inadvisable. One volunteer reached a stop point because the participant stated that he/she did not want to receive that dose of drug again.

Prior to the first experimental session, participants practiced the experimental tasks to achieve a stable level of performance. Participants were asked to refrain from using any drugs other than non-prescription pain relievers, tobacco, and caffeinated products while enrolled in the study. They were asked to consume their usual amounts of tobacco or caffeine and a low fat breakfast before arriving for each session. At the beginning of each experimental session participants' urine was tested for the presence of cocaine, benzodiazepines, and opioids using an EMIT system (Syva Co., Palo Alto, CA, USA) and expired air was tested for the presence of alcohol using a breathalyzer test (Alco-Sensor IV, Intoximeters, Inc., St. Louis, MO); urine was not screened for the presence of THC or THC metabolites. Female participants were asked to take a pregnancy test at the beginning of each session and were only allowed to continue in the study with the provision of a negative result.

### 2.3. Drugs

Drugs and placebo were orally administered in size 0 aqua colored opaque capsules with approximately 200 ml of water. Four identical capsules were administered during each experimental session. Capsules were filled with lactose monohydrate (placebo; Ruger Chemical Company, Linden NJ, USA); powdered dextromethorphan hydrobromide (Spectrum Chemical, Gardena CA, USA) and lactose; or commercially available crushed triazolam tablets (Halcion; The Upjohn Company, Kalamazoo, MI, USA) and lactose. All doses were adjusted for participant body weight. Doses of dextromethorphan are expressed as the salt.

### 2.4. Cognitive measures

Participants completed the digit-symbol-substitution task, divided attention task, and working memory task before capsule administration (baseline or pre-drug) and at 120, 240, and 360 min after capsule administration. Tasks assessing episodic memory and metacognition were administered as described below.

*2.4.1. Digit-symbol-substitution task (DSST).* This task was a computer version of the digit-symbol-substitution task (McLeod et al., 1982), which is a measure of focused attention and pattern recognition. Dependent measures were the number of trials attempted and the proportion of trials completed correctly within 90 s.

*2.4.2. Divided attention.* In this task, which has been previously described in detail (Kleykamp et al., 2010), participants were presented with a diamond stimulus that moved back-and-forth horizontally in the center of the computer screen, in addition to five non-moving single digit integers with one digit presented in each of the four corners of the screen in white font and one digit presented in the center of the bottom of the screen in green font. Participants were instructed to concurrently track the moving diamond stimulus using the computer mouse, which controlled a crosshair depicted on the screen (tracking), and to click the computer mouse whenever one of the four digits in the corners of the screen matched the green digit at the center of the bottom of the screen (monitoring). The primary dependent measure associated with the tracking component was tracking deviation (distance in pixels between the diamond stimulus and cross hair). The primary dependent measure associated with the digit monitoring component was proportion correct (number of times a mouse press was made when the target digit was presented in the corner of the screen out of a total possible of 24).

*2.4.3. Working memory.* The working memory task that was used is a variant of the classic Sternberg task (Sternberg, 1969) and was administered using procedures similar to those described by Mintzer and Griffiths (2007). During each experimental session, standardized instructions were read to the participants before the task and practice trials were presented before the experimental trials to ensure that the participants understood and performed the task correctly. A memory set consisting of 7 randomly selected and randomly ordered consonant letters (e.g., ZHFKDXW) was presented on the screen followed by a probe consisting of a lower case letter–digit pair (e.g., f–4), and participants were asked to decide whether the probed letter had appeared in the memory set in the ordinal position represented by the digit (e.g., 4 = 4th position in the memory set). Participants completed 36 trials consisting of 12 trials in each of the three conditions: non-memory control (i.e., the memory set remained on the screen during probe presentation), 0 s delay (between memory set and probe presentation), and 12 s delay. The order of presentation of trials from the