

## Effect of a Single Dose of Dextromethorphan on Psychomotor Performance and Working Memory Capacity

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### ABSTRACT

**Background:** Previous studies show that the prolonged use of dextromethorphan produces cognitive deterioration in humans. **Aim:** The aim of this study was to investigate the effect of a single dose of dextromethorphan on psychomotor performance and working memory capacity. **Materials and Methods:** This is a randomized, double-blind, controlled, and prospective study. Thirty-six (17 women, 19 men) medical students enrolled in the study; half of them (7 women, 11 men) were given placebo, while the other half (10 women, 8 men) received dextromethorphan. The choice reaction time, critical flicker fusion threshold, and *N*-back working memory task were measured before and after 2 h of taking the drugs. **Results:** Dextromethorphan showed a significant deterioration in the 3-back working memory task ( $P < 0.05$ ). No significant changes were seen as regards the choice reaction time components (total, recognition, motor) and critical flicker fusion threshold ( $P > 0.05$ ). On the other hand, placebo showed no significant changes as regards the choice reaction time, critical flicker fusion threshold, and *N*-back working memory task ( $P > 0.05$ ). **Conclusion:** A single dose of dextromethorphan has no effect on attention and arousal but may significantly impair the working memory capacity.

**Key words:** Choice reaction time, critical flicker fusion threshold, *N*-back working memory task

### INTRODUCTION

Dextromethorphan is an agent used to control cough associated with influenza or cold. It has the cough-suppressing effect similar to that of its distantly related family – the opiates – but does not produce the significant effects on the central nervous system as opiates do.<sup>[1]</sup> When used at therapeutic or recommended doses, dextromethorphan

does not produce respiratory depression or other significant side effects that are common with most opiates. Cough syrups sold over the counter often have dextromethorphan as one of the key ingredients.<sup>[2]</sup>

As a sigma-1 receptor agonist and *N*-methyl-D-aspartate (NMDA) receptor antagonist, dextromethorphan has a pharmacodynamics effect similar to that of lysergic acid diethylamide, ketamine, or psilocybin.<sup>[3]</sup> Dextromethorphan therefore belongs to the group of substances with a psychoactive (dissociative) effect.

Dextromethorphan has been suggested to prevent the induction of long-term potentiation *in vivo*.<sup>[4]</sup> In addition, investigators have demonstrated that dextromethorphan impair passive avoidance in rats.<sup>[5]</sup> Similarly, dextromethorphan has been reported

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to impair spatial learning in the Morris water maze in a dose-dependent manner in rats.<sup>[6]</sup> Previous studies show that the prolonged use of dextromethorphan produces cognitive deterioration in humans.<sup>[7]</sup>

The aim of this study was to investigate the effect of a single dose of dextromethorphan on psychomotor performance and working memory capacity in healthy volunteers.

## MATERIALS AND METHODS

### Study design

This is a randomized, double-blind, parallel group, and comparative study conducted from April to May 2011 on healthy students of medical college. An independent scientific committee revised and approved the study, and oral consent was obtained from the participants. Randomization was done by using a computer-generated random list. After randomization, the participants were divided into two groups, a total of 18 students were allocated to drug A and another 18 were allocated to drug B. Dextromethorphan tablets (10 mg) were obtained from the local market and placed in capsules that is similar to capsules containing placebo (sucrose). These capsules were coded by a third person and administered to medical students. Psychomotor performance and working memory capacity were measured before and after 2 h of taking the drugs.

### Subjects

Thirty-six (17 women, 19 men) were randomly selected from third-stage medical students.

### Inclusion criteria

Healthy, young volunteers aged 21–23 years were included in the study.

### Exclusion criteria

Patients with eye disease, smokers, diabetic patients, hypertensive patients, patients with a history of drug therapy in the last 7 days and those who were taking beverages within 8 h prior to the study were excluded from the study. Matching the age and educational level in such studies is important because psychomotor performance and working memory capacity were affected by age and intelligence levels.<sup>[8,9]</sup>

### Instruments

Leeds psychomotor tester (Leeds Psychomotor Services, York) is an instrument used to measure choice reaction time (CRT) and critical flicker fusion threshold (CFFT).

To calculate CRT participants are required to place the index finger of their preferred hand on a central

starting button in the tester and are instructed to extinguish one of six equidistant red lights, illuminated at random, by pressing the response key in front of the light as quickly as possible. The CRT components (total, recognition, and motor) are repeated five times by the participants and then the mean is calculated and recorded. Recognition reaction time is the recorded time between the onset of the stimulus (appearance of random red light) and the lifting of the finger of the participant from the start button. Motor reaction time indicates the movement component of this task and is the time between the participant's lifting of his finger from the start button and touching the response button. Total reaction time is the sum of recognition reaction time and motor reaction time.

The CFFT is measured by asking the subject to concentrate on four illuminated sites and to respond when the illuminated site changed from steady state to flickering and vice versa. The median of five trials of flicker descending (i.e., from steady to flickering) is called flicker threshold, while the median of flicker ascending (i.e., from flickering to steady) is called fusion threshold.

*N*-back computerized task is a test that uses the visual working memory task of that used by Jaeggi *et al.*,<sup>[10]</sup> where squares at eight different locations were presented sequentially on a computer screen at a rate of 3 seconds (stimulus length, 500 ms; interstimulus interval, 2500 ms). A response was required whenever one of the presented stimuli matched the one presented *n* positions back in the sequence.

In the *1-back* condition, the target was any square position that is identical to the square position immediately preceding it. In the *2-back* condition, the target was the square position similar to another square position two trials back. The *3-back* condition is square position identical to another square position three trials back. Participants made responses manually by pressing on the letter 'A' of a standard keyboard with their left index finger for visual targets. The computer automatically measured the accuracy rate (number of successful responses).

The above tests were validated and found to be reliable in testing arousal (CFFT),<sup>[11]</sup> attention (CRT),<sup>[12]</sup> and working memory capacity (*N*-back task).<sup>[13]</sup>

### Statistical analysis

Statistical analysis was done by using SPSS (version 11.5) software, and an independent sample *t* test was used with a significance level of 95%. All the data are presented as mean ± SD.

**Table 1: Dextromethorphan and placebo effects on CRT components (total, recognition, motor reaction time)**

	Total reaction time (ms)		Recognition reaction time (ms)		Motor reaction time (ms)	
	Before	After	Before	After	Before	After
Dextromethorphan	611.5±80.5	607.4±80.1	383±54.8	394±61.7	228.4±84.3	213.3±69.7
Placebo	601.8±81.2	593±59.7	380.4±56.7	370.8±39.6	221.4±47.9	216.6±35.9
<i>P</i> value	0.721	0.544	0.887	0.188	0.759	0.863

Values are presented as mean±SD

## RESULTS

Thirty-six participants completed the study: 18 students in the placebo group (7 women, 11 men), with the mean age being 21.8±0.2 years; and the other 18 students in the dextromethorphan group (10 women, 8 men), with the mean age being 21.6±0.8 years.

As regards the CRT components (total, recognition, motor reaction time), the present study show no significant difference between the placebo and dextromethorphan groups before and after taking the drugs ( $P>0.05$ ). Table 1 shows *P* values for the differences between both groups.

The CFFT shows no significant changes within placebo and dextromethorphan groups before and after taking the drugs ( $P>0.05$ ) [Table 2].

In the working memory capacity test (*N*-back), the placebo group demonstrated no significant difference before and after placebo taking the drugs ( $P>0.05$ ). Interestingly, the dextromethorphan group reveals a significant deterioration in the 3-back working memory task after 2 h of taking the single dose ( $P<0.05$ ) [Table 3].

## DISCUSSION

In the present study, dextromethorphan tablets (10 mg) cause no significant difference as regards the CRT (attention) and CFFT (arousal). On the other hand, dextromethorphan given to normal volunteers deteriorate working memory capacity (3-back).

There is controversy regarding the effect of dextromethorphan on cognitive and motor functions.<sup>[14]</sup> Dextromethorphan is regarded as weak NMDA receptor antagonist; in high dose, it blocks these receptors, leading to impairment in learning and memory processes.<sup>[15]</sup> In addition, dextromethorphan in high dose metabolized to dextrophan, which is a strong NMDA receptor antagonist that causes further deterioration in learning and memory.<sup>[16]</sup>

In the present study, dextromethorphan causes a significant impairment of the 3-back working memory

**Table 2: Dextromethorphan and placebo effects on CFFT**

	Fusion threshold (Hz)		Flicker threshold (Hz)	
	Before	After	Before	After
Dextromethorphan	31.8±3.6	31.4±3	31.9±3.5	32.2±3.5
Placebo	32.1±3.1	32.6±1.3	31.9±3.6	31.4±3.1
<i>P</i> value	0.875	0.163	0.974	0.530

Values are presented as mean±SD

task. Previous studies show that the 3-back working memory test requires more executive attention than do other *N*-back tests<sup>[17]</sup>; therefore, the deterioration in this test may be explained by the following: first, working memory is a delicate central nervous system mechanism that requires an optimum level of dopamine and activity of glutamate receptors; any changes in these may cause deterioration in the working memory capacity.<sup>[18]</sup> Second, the dopamine function on working memory represents U-shaped paradigm; any increase or decrease below the optimum level may deteriorate the working memory capacity.<sup>[19]</sup> It has been found that dextromethorphan enhances dopamine release in the central nervous system; this may explain the deterioration in memory in our study.<sup>[20]</sup> Third, NMDA receptor blockage may also deteriorate working memory as shown in previous studies.<sup>[21]</sup>

Dextromethorphan discloses no significant effect on CRT (attention) or CFFT (arousal) in comparison with placebo; this is compatible with previous literature, which demonstrated that dextromethorphan at recommended doses for antitussive therapy (10–30 mg) had no or rare central nervous system depressive effects.<sup>[22,23]</sup>

Our study is regarded as a preliminary study because of the small sample size; therefore, further studies will require a larger sample size. In addition, further studies are required to show the effect of the dose–response relationship of dextromethorphan on psychomotor performance and working memory capacity.

## CONCLUSION

A single dose of dextromethorphan has no effect on attention and arousal but may significantly impair the working memory capacity.

**Table 3: Dextromethorphan and placebo effects on working memory capacity using N-back task**

	1-Back (%)		2-Back (%)		3-Back (%)	
	Before	After	Before	After	Before	After
Dextromethorphan	98.6 ± 4.2	96.2 ± 12.4	82.6 ± 18.6	81.8 ± 25.7	62.2 ± 13.7	51.4 ± 14.7
Placebo	98.1 ± 5.7	99.1 ± 4.1	83.9 ± 19.3	83.5 ± 19.1	63.1 ± 12.4	69.5 ± 19.5
P value	0.741	0.346	0.834	0.821	0.829	0.003*

Values are presented as mean ± SD. \*Significant ( $P < 0.05$ ) using independent sample t test

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