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A laboratory study of patients with chronic allergic rhinitis: Antihistamine effects on skilled performance

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Twenty-four patients with chronic allergic rhinitis participated in a study of antihistamine effects on skilled performance. They were tested while experiencing symptoms and when they were free of symptoms. Within each symptom condition, they attended two sessions; each patient received a placebo capsule at one session and a 50 mg diphenhydramine capsule at the other. Subjects performed a battery of skilled performance tests, which included the Divided-Attention, Visual Backward Masking, Stimulus Response Conflict, and Vigilance tests. They rated the treatments and their performance. Affective states were assessed with the Profile of Mood States. Symptoms did not affect performance. Diphenhydramine impaired vigilance performance and measures of Divided Attention and Stimulus Response Conflict. Visual Backward Masking performance was not affected. The largest performance changes occurred when diphenhydramine was administered to subjects when they were free of symptoms. (J ALLERGY CLIN IMMUNOL 1994;93:716-24.)

Key words: Allergy, allergic rhinitis, antihistamine, attention, diphenhydramine, performance, symptom condition, vigilance

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Medications, either prescription or over-the-counter, can adversely affect a patient's performance of various tasks. Safety is compromised whenever the medications degrade skills that are essential to the safe performance of such activities as driving and work- or home-related operation of machinery.

Abbreviations used

MART: Maximum allowable response time

RT: Reaction time

Concern about increased risk of accidents has led to laboratory study of the kind and magnitude of deficits associated with therapeutic doses of a variety of potentially impairing drugs.¹⁻⁴ However, most studies have been conducted with healthy subjects, and important questions concerning effects on patients' performance remain unanswered. A medication that adversely affects healthy subjects may not have the same effects in the presence of the disorder for which it is prescribed. It is possible that a patient's relief from symptoms will offset negative performance changes.⁵⁻⁷

A laboratory study was carried out to examine a drug's effects on performance in patients with chronic allergic rhinitis. They were tested with and without treatment when they were experiencing symptoms and when they were free of symptoms.

METHODS

Subjects

Twenty-four men and women, aged 18 years and older, participated in a balanced, crossover design experiment. Patients with chronic allergic rhinitis who presented at an allergy clinic for treatment were evaluated and referred for participation if they met study criteria.

The primary study criterion was a positive skin test result for allergens. Also, if the patient had been in immunotherapy for 6 months or longer, the therapy was to be continued throughout the study. Patients were not eligible if they had a known hypersensitivity to antihistamine or had taken nasal steroids, nasal cromolyn, antihistamines, or nasal decongestants within 1 week or if they had taken astemizole within the past 4 weeks.

Twenty-five patients met the criteria and were enrolled as subjects. One female subject completed only two sessions. Twenty-four subjects participated in all conditions, as outlined in Table I.

The referring physician rated a patient's allergic rhinitis symptoms on two occasions: once when the patient was experiencing symptoms and once when he or she was free of symptoms. Symptoms were rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The symptomatic condition required the presence of two or more symptoms with a total score of 4 or greater. The asymptomatic condition was defined as an absence of symptoms.

The study protocol and informed consent were reviewed and approved by Southern California Research Institute's institutional review board.

Treatment

The active drug treatment was 50 mg of diphenhydramine. Placebo capsules contained no active ingredient but appeared identical to the drug capsules. Single-dose packages of active or placebo capsule were labeled only with subject and session number.

Twelve subjects entered the study while they were free of symptoms, and the condition order of their sessions was asymptomatic-symptomatic. The other 12 subjects entered the study while experiencing symptoms and participated in the opposite condition order.

Treatment order within each condition order group was determined by random procedures. Six subjects in each group ($n = 12$) were assigned to receive treatments in the order, placebo-diphenhydramine and six to receive treatment in the order, diphenhydramine-placebo. Subjects and research assistants who conducted the behavioral testing were blinded to treatment order.

Performance tests

A battery of tests was selected on the basis of what is known about the study drug and its expected effects.^{4, 6, 7} Because performance impairment by diphenhydramine is due at least in part to drowsiness, the battery included tests that are sensitive to sedation. Because of potentially large individual differences in symptom condition and response to the active drug treatment, the battery included tests with a range of task demands. For example, mild sedation was expected to be offset by complex, stimulating tasks but to be measurable with less demanding tasks. Performance tests included Divided Attention (D-A), Vigilance, Visual Backward Masking (VBM), and Stimulus Response Conflict; Performance Evaluation and Treatment Identification scales were included to assess subjects' responses to symptoms and treatments.

Procedures

Subjects were trained to perform the tests during two training days, held during the week preceding the first treatment session. Research assistants followed a standardized protocol for instructions and demonstrations. If persistence of a subject's symptoms caused more than a 2-week lapse between symptom conditions, refresher training was given when testing resumed.

Subjects were instructed to consume no food or stimulants during the 2 hours preceding a session. They were transported to the laboratory by taxi, and all of a subject's sessions began at the same time. The drug treatment was given shortly after arrival, and testing began 60 minutes after the dose was given.

RESULTS

Subjects' mean age was 27 years, 9 months (range, 19 to 50 years). Body weight varied from 50 to 141 kg. The 50 mg diphenhydramine dose yielded a mean dose of 0.7 mg diphenhydramine/kg body weight (range, 0.355 to 1.000

TABLE I. Conditions of the study

Condition	Treatment	
	Placebo	Drug
Asymptomatic	Baseline	Drug effect
Symptomatic	Symptom effect	Treated symptom effect

TABLE II. Performance test scores

Tests, measures	Placebo		Diphenhydramine	
	AC	SC	AC	SC
Divided attention				
Tracking error	18.26 ± 7.32	17.79 ± 7.37	20.99 ± 7.40	19.43 ± 7.56
RT without	3.02 ± 0.58	3.11 ± 0.67	3.12 ± 0.63	3.08 ± 0.69
MART (sec)				
RT with MART	3.11 ± 0.69	3.18 ± 0.76	3.28 ± 0.80	3.18 ± 0.81
(sec)				
Z scores (tracking +	48.89 ± 7.97	49.03 ± 7.00	51.78 ± 8.69	50.16 ± 7.89
RT ÷ 2)				
Response errors	1.4 ± 1.9	1.9 ± 1.6	2.3 ± 3.0	1.8 ± 1.9
VBM (no. of letters				
correct)				
ISI 33 msec	1.74 ± 0.47	1.80 ± 0.52	1.64 ± 0.45	1.67 ± 0.44
ISI 66 msec	2.63 ± 0.65	2.75 ± 0.56	2.70 ± 0.60	2.75 ± 0.57
ISI 100 msec	3.01 ± 0.60	3.08 ± 0.55	3.08 ± 0.56	3.02 ± 0.63
Mean, all ISI	2.46 ± 0.53	2.54 ± 0.48	2.47 ± 0.47	2.48 ± 0.46
Vigilance				
RT without	0.95 ± 0.32	0.91 ± 0.30	1.06 ± 0.42	1.08 ± 0.40
MART (sec)				
RT with MART	1.87 ± 1.01	1.95 ± 1.01	2.60 ± 1.07	2.55 ± 1.11
(sec)				
Correct responses	25.3 ± 6.4	24.1 ± 7.1	19.9 ± 8.2	20.1 ± 8.0
(no.)				
SRC				
Place	0.478 ± 0.062	0.479 ± 0.076	0.497 ± 0.087	0.496 ± 0.091
Same meaning	0.748 ± 0.095	0.756 ± 0.102	0.790 ± 0.115	0.791 ± 0.122
Opposite meaning	0.989 ± 0.169	1.003 ± 0.167	1.013 ± 0.147	0.968 ± 0.128
All conditions	1.139 ± 0.257	1.151 ± 0.215	1.172 ± 0.246	1.139 ± 0.213

Scores are expressed as means ± SD.
AC, Asymptomatic condition; SC, symptomatic condition; VBM, Visual Backward Masking; ISI, inter-stimulus interval; SRC, Stimulus Response Conflict.

mg/kg). Despite the wide range, test scores were not related to the effective dose as demonstrated by statistically nonsignificant Spearman rank difference correlation coefficients (range, -0.113 to 0.382).
Table II summarizes the performance test data. Figs. 1 to 5 graph selected measures. Statistically significant F ratios from analyses of variance appear in Table III, and paired *t* comparisons appear in Table IV.

Symptom effects

Symptoms of chronic allergic rhinitis were not associated with significant performance impairment. This finding cannot be attributed entirely to measurement failure because three tests were included in the battery specifically because they had been shown to be sensitive measures of skill-specific, relatively small effects of diphenhydramine.¹⁻⁴ Although it is possible that symptoms of chronic allergic rhinitis will impair other skills,

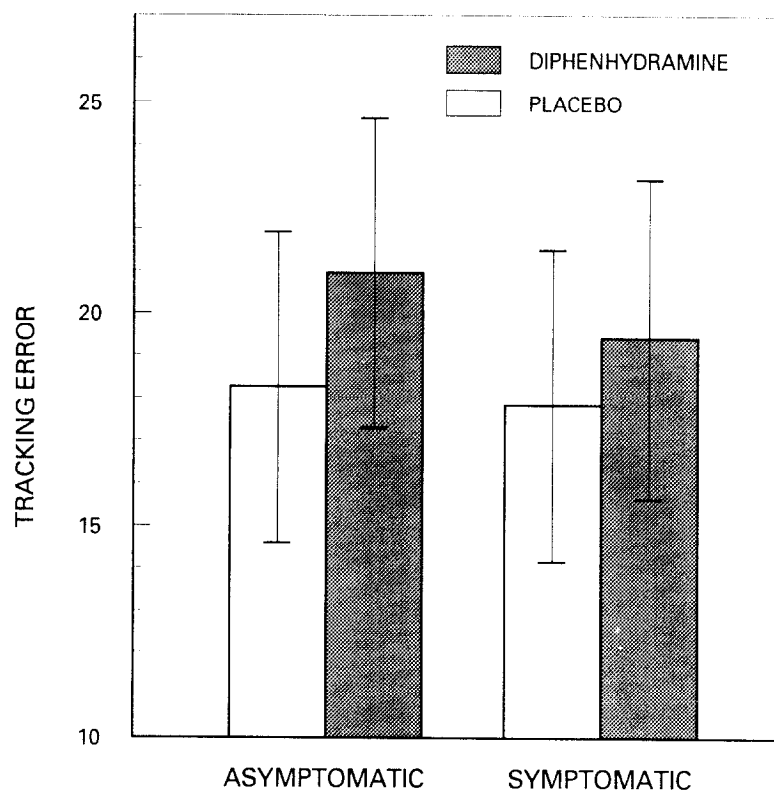


FIG. 1. Divided Attention Performance. Tracking error in 24 patients with chronic allergic rhinitis.

they did not impair divided attention, selective attention, vigilance, or information processing as measured in this experiment.

The finding that symptoms were nonimpairing also requires consideration of their severity. The physician used an objective symptom checklist to evaluate patients. The minimum score for the symptomatic condition was 4. As can be seen in Table V, the mean ratings were 8.0 for patients with symptoms and 1.0 for patients who were free of symptoms ($t = -14.315$, 23 df, $p < 0.001$).

Some subjects appeared to be experiencing obvious discomfort during the symptomatic sessions, but others displayed only minor symptoms. Overall, it is concluded that subjects' symptoms were moderate, and the finding that symptoms were not associated with performance impairment should not be generalized to patients with very severe symptoms.

Treatment effects

The drug treatment significantly affected seven performance measures. Divided attention is a complex and difficult task, which requires subjects to monitor multiple sources of visual information simultaneously. Error from the tracking task in the central visual field increased significantly with

diphenhydramine. The concurrent task, a search for signals in the peripheral visual field, was not affected by the drug.

Tracking error and Visual Search response times were combined as Z scores to obtain a measure of total Divided Attention performance. This index was only slightly degraded (0.3% change) by untreated symptoms. When symptoms were treated with diphenhydramine, there was a slightly larger deficit (2.6%).

Visual backward masking was not affected by the treatment. Because this task measures the rate of information processing, the finding is of some consequence. It demonstrates that diphenhydramine's effects on other tasks are not the consequence of a generalized slowing such as that which occurs with a central nervous system depressant.

The Stimulus Response Conflict test measures the ability to selectively attend to critical information and to screen out distracting information. Typically, selective attention is improved by stimulant drugs and impaired by depressants.

Stimulus words (right, left, up, down) were presented in a 4-position matrix on a computer screen. The relevant dimension of the words was defined by blocks of trials as the "location" of the

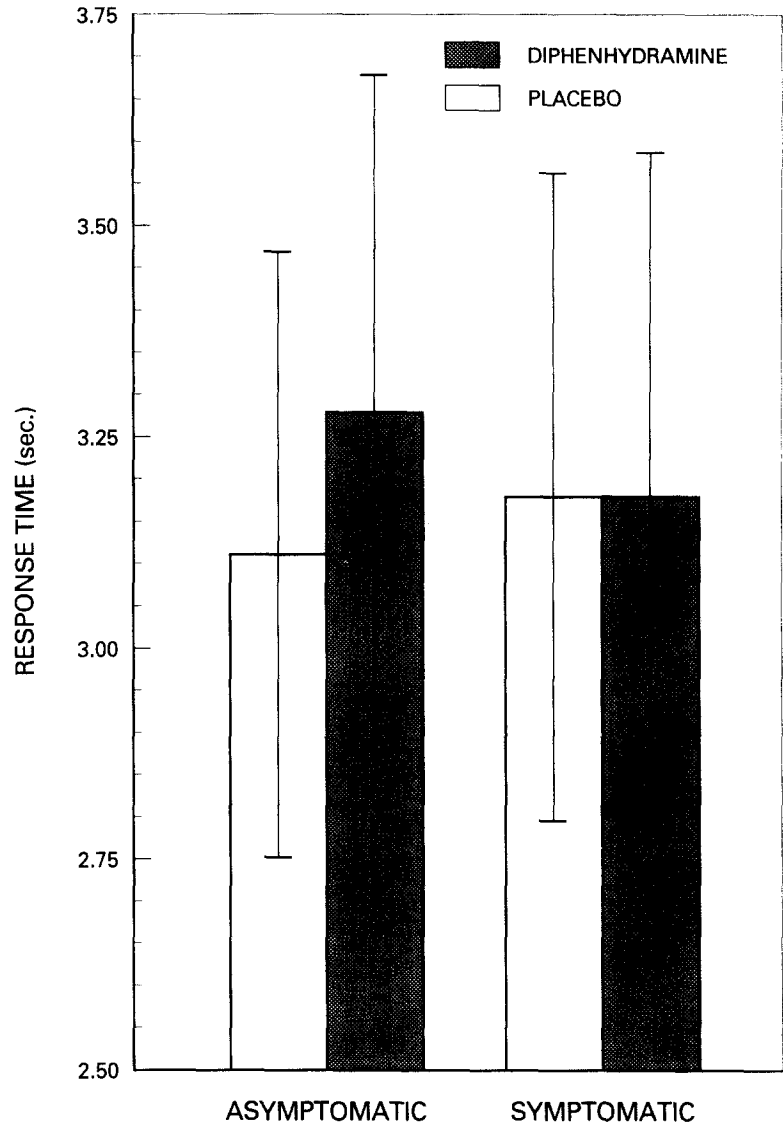


FIG. 2. Divided Attention Performance. Response Time to visual signals with adjustment for missed signals in 24 patients with chronic allergic rhinitis.

word within the matrix, the “meaning” of the word, or the “opposite meaning” of the word. Subjects responded with the four directional arrows on the computer keyboard. Performance was affected by diphenhydramine only when the relevant dimension was the “meaning” of the word.

A sustained attention task, vigilance, was presented with a Mackworth clock. Subjects monitored a cursor moving around a 24-position clock face at the rate of 2 jumps per minute. The signal, a skip of one position, occurred 32 times during

a 40-minute trial. The monotonous visual environment is nonstimulating and conducive to drowsiness.

Vigilance mean reaction time (RT) without maximum allowable response time (MART), which is a simple RT to a single signal, was longer with diphenhydramine (71% of the trials). RT with MART adds an allowance of 5 seconds for each missed signal; RTs were longer in 90% of the trials with diphenhydramine. A failure to observe signals is interpreted as an index of increased drowsiness.

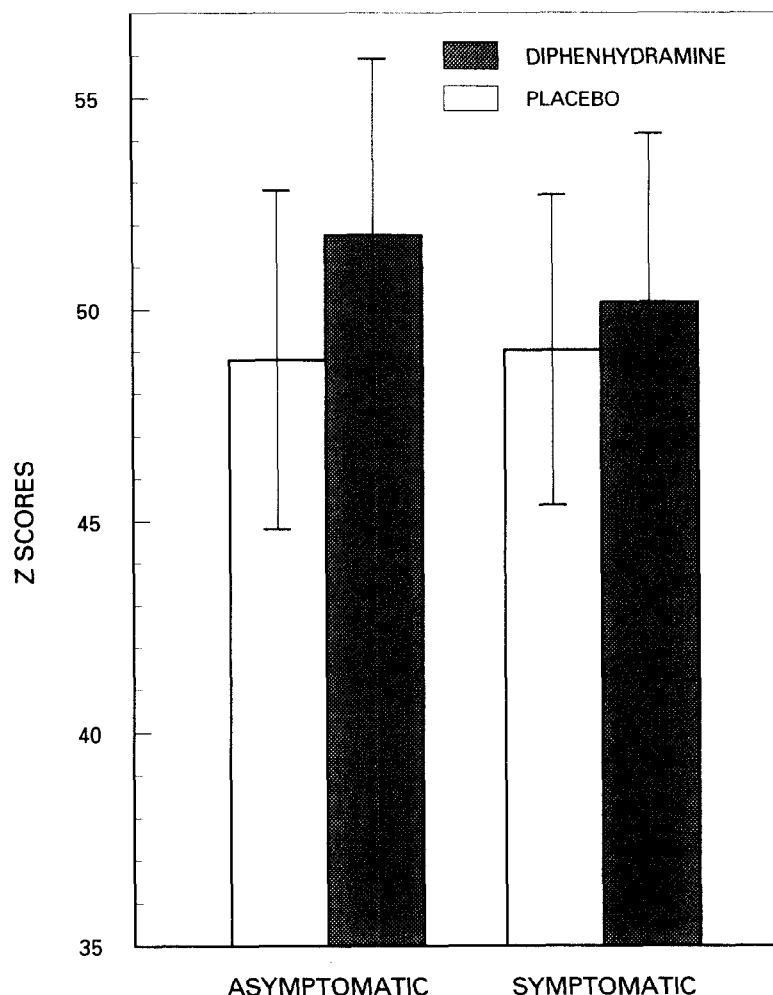


FIG. 3. Divided Attention Z score measure of total performance.

Treatment-symptom interactions

Test scores obtained in placebo sessions tended to be poorer when subjects were experiencing symptoms than when they were free of symptoms. With the active treatment, the trend reversed, and scores were often better for subjects with symptoms than for those who were free of symptoms (Table II).

Note the asymptomatic-symptomatic comparisons for divided attention (Figs. 1, 2, and 3). During diphenhydramine sessions, tracking error scores were smaller, response times were faster, and response errors were less numerous if subjects were experiencing symptoms. When they had symptoms, subjects' visual search performance with diphenhydramine was as good or better than with placebo. As measured by Z scores, diphen-

hydramine had the most impairing effect on divided attention performance when it was given to subjects who were free of symptoms.

Symptom and treatment effects on mood states

As expected, subjects' moods were more positive when they were both symptom-free and drug-free. Five of six Profile of Mood States scales were less positive when subjects received diphenhydramine. However, when the two diphenhydramine sessions were compared, subjects' moods were more positive when they were experiencing symptoms. This finding, which parallels findings for performance measures, suggests that symptom relief may have offset the negative impact of the drug on moods.

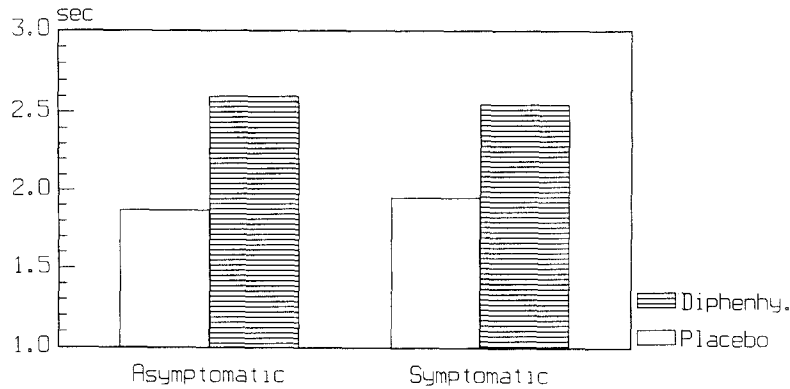


FIG. 4. Vigilance Performance. RT to signal (with allowance for missed signals) in 24 patients with chronic allergic rhinitis.

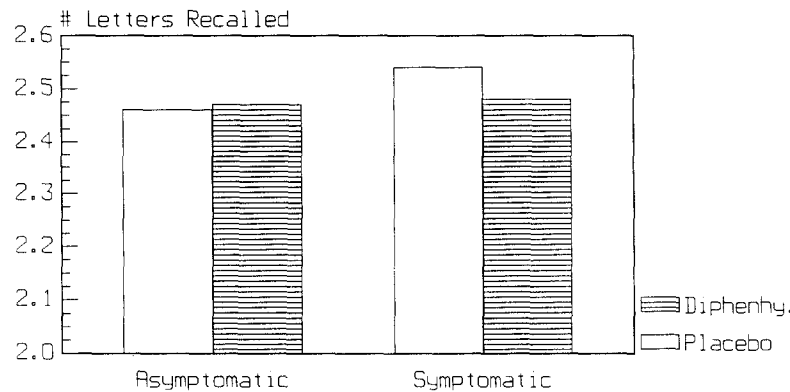


FIG. 5. Visual Backward Masking Performance (mean, all inter-stimulus interval) in 24 patients with chronic allergic rhinitis.

TABLE III. Analyses of variance, performance measures, and significant F ratios for treatment effects

Test/measure	F	p Value
Divided-Attention test		
Tracking error	6.83	0.017*
Z scores (Tracking + RT ÷ 2)	4.72	0.042*
Stimulus-Response conflict		
Condition: same meaning	9.09	0.007†
Condition: all (same meaning)	4.93	0.040*
Vigilance		
RT without MART	26.01	0.0001‡
RT with MART	25.19	0.0001‡
Correct responses	18.95	0.0003‡

**p* < 0.05.

†*p* < 0.01.

‡*p* < 0.001.

TABLE IV. Paired *t* tests: Mean score difference for placebo versus diphenhydramine

Test/measure	<i>t</i> Value		Change scores	
	AC	SC	AC	SC
Divided attention				
Tracking error	−2.68	−1.82	−2.73	−1.64
Z scores	−2.28	−1.10	−2.89	−1.13
SRC				
Same meaning	−2.45	−2.12	−0.041	−0.035
All (same meaanaing)	−2.98	0.14	−0.114	−0.024
Vigilance				
RT without MART	−2.89	−3.56	−0.11	−0.17
RT with MART	−4.16	−3.72	−0.73	−0.60
Correct responses	3.86	3.12	−7.00	−5.00

N = 24, *df* = 23.

t = 1.714, *p* < 0.05.

t = 2.500, *p* < 0.01.

t = 2.807, *p* < 0.005.

AC, Asymptomatic condition; SC, symptomatic condition; SRC, Stimulus Response Conflict.

The Agreeable-Hostile scale of the Profile of Mood States, which was not affected by treatment, was affected by symptom order. Subjects who were free of symptoms at their first treatment session felt significantly more agreeable throughout the study.

DISCUSSION

This study examined the effects of diphenhydramine on patients' performance of several behavioral tests. The central issue was whether the drug, which has been shown to impair some kinds of skills in healthy adults, also impairs the performance of patients with symptoms.

Symptoms of chronic allergic rhinitis, as experienced by the patients in this experiment, did not significantly impair performance. However, the performance of subjects with untreated, moderate symptoms tended to be poorer when they were experiencing symptoms than when they were free of symptoms. It is possible that more severe symptoms would be associated with statistically significant changes.

The largest observed changes from baseline performance occurred when subjects who were free of symptoms received diphenhydramine. This relationship between symptom condition and treatment effect is of considerable interest. If a drug is most impairing in the absence of symptoms, experiments with healthy subjects may over-

TABLE V. Subjects' symptom severity scores

Subject No.	Symptom checklist scores	
	Asymptomatic	Symptomatic
001	0	11
002	2	14
003	1	10
004	0	7
005	2	8
006	1	8
008	3	9
009	0	6
010	1	8
011	0	9
012	3	8
013	0	4
014	0	7
015	0	8
016	2	9
017	1	4
018	2	12
019	0	6
020	1	5
021	2	6
022	1	12
023	2	7
024	0	8
Mean	1.000	8.0
SD	1.022	2.502

estimate the impairment that will occur when it is used by patients experiencing symptoms.

Studies of a drug's effects on performance with healthy, normal volunteers provide important information about drug effects per se. To fully examine potential effects, however, the drug's effects should also be studied with subjects from a patient population.

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