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# Cognitive and Behavioral Effects of Cholinergic, Dopaminergic, and Serotonergic Blockade in Humans

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*The purpose of this study was to investigate the cognitive and behavioral effects of anticholinergic, antidopaminergic, and antiserotonergic agents given alone and in combination to normal volunteers. Twelve young male volunteers took part in this double-blind, randomized, placebo-controlled, crossover study of six drug conditions, each administered on separate days [haloperidol (2 mg PO) ± scopolamine (0.5 mg IV), metergoline (4 mg PO) ± scopolamine (0.5 mg IV), placebo, and scopolamine alone (0.5 mg IV)]. Scopolamine-induced sedation ($p < .01$), slowed information processing ($p < .01$) and impaired new learning and memory ($p < .01$), but did not affect attention or retrieval from semantic memory. Given alone, haloperidol selectively impaired the ability to rapidly switch cognitive sets ($p < .05$), and metergoline decreased pupil size ($p < .01$) but did not induce cognitive deficits. In combination with scopolamine, neither haloperidol nor metergoline produced a worsening of the subjects' cognitive performance above and beyond that seen with scopolamine alone. On the contrary, a trend ($p < .10$) for haloperidol to reverse some of the scopolamine-induced exacerbation of verbal short-term forgetting was observed. The data indicate that scopolamine and haloperidol can independently and selectively affect cognition and that at the doses tested in this study no synergistic exacerbation of cognitive functioning was found when cholinergic blockage was coupled with dopaminergic or serotonergic blockade.* **© 1997 American College of Neuropsychopharmacology [Neuropsychopharmacology 16: 15–24, 1997]**

KEY WORDS: *Scopolamine; Haloperidol; Metergoline; Cognition*

The anticholinergic agent scopolamine has been used as a research tool to model some of the cognitive deficits typical of dementia of the Alzheimer type (DAT) in both young and older normal subjects (Drachman and Leavitt 1974; Sunderland et al. 1986, 1987; Flicker et al. 1990). However, this pharmacological model of DAT is incomplete. Scopolamine does not reproduce the full profile of cognitive loss seen in DAT (Molchan et al. 1992). It disrupts learning (anterograde memory) in normal subjects, but it does not consistently affect semantic memory (Beatty et al. 1986; Dunne 1990), which is characteristically impaired in DAT (Martin and Fedio 1983; Weingartner et al. 1983). This discrepancy is not surprising, as it has long been recognized that multiple neurotransmitter systems are affected in DAT (Gottfries and Ross 1973; Curcio and Kemper 1984; Morgan et al. 1987; Palmer et al 1987). In addition to acetylcholine, both serotonin and dopamine are likely to be involved in cognitive processes. Serotonergic projections provide input to the hippocampus and appear to be involved in

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A previous version of this report was presented at the 30th annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1991.

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Received October 17, 1995; revised May 8, 1996; accepted May 22, 1996.



Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/97/$17.00
PII S0893-133X(96)00134-8

the higher functions of the neocortex (Vanderwolf and Baker 1986), and postmortem investigations in DAT patients found deficits in both the presynaptic and postsynaptic serotonergic system (Bowen et al. 1983). Specific cognitive functions have been related to dopamine, which seems to play an essential role in the ability to shift sets, as shown by the haloperidol-induced impairment of this cognitive function in man (Berger et al. 1989).

In this study we have combined cholinergic with dopaminergic or serotonergic blockade in an effort to understand better the interaction of these neurotransmitter systems on cognitive performance in young controls and, possibly, to develop a more complete human pharmacological model of DAT. We have chosen serotonergic (metergoline) and dopaminergic (haloperidol) antagonists because of the known deficits of these systems in DAT patients and because of the animal evidence indicating that combined pharmacological blockade leads to a more global amnesia (Vanderwolf 1987). Because of the known multineurotransmitter deficit associated with DAT, it was predicted that the combined administration of anticholinergic (scopolamine) and antidopaminergic (haloperidol) agents would cause more profound impairments than either drug in isolation. More specifically, we hypothesized that dopamine blockade would impair performance on tests that required alternation of response set (Berger et al. 1989; Bubser and Schmidt 1990). It was also expected that adding a nonselective serotonergic antagonist such as metergoline to scopolamine would result in a more global cognitive impairment, although the available animal and human data on the effects of this interaction are not fully consistent (Altman and Normile 1986; Flood and Cherkin 1987; Vanderwolf 1987; Martin et al. 1989; Petkov et al. 1991). Therefore, this study was considered an exploratory trial of combination pharmacological challenges in humans.

## METHODS

### Design

This was a double-blind, placebo-controlled, crossover study. Six drug or placebo conditions were administered to each subject, with a washout period of at least 72 hours between administrations. The design consisted of two modified Latin squares balanced for possible carryover effects.

### Subjects

Twelve male normal subjects were enrolled in the study. Their age ranged from 20 to 33 years (mean ± SD, 25 ± 4 years), and their weight ranged between 60 and 104 kg (mean ± SD, 76.7 ± 4 kg). On careful screening, they reported no history of cognitive, psychiatric, or significant medical problems. Their native language was English, and their level of education was 12 to 20 years (16 ± 2 years). Physical examination, EKG, blood cytology and chemistry, and urine analysis with toxicology were normal. None of the subjects were smokers, abused drugs or coffee, or had received pharmacological agents for at least 1 month prior to the study. When receiving the study medication, they had abstained from coffee for at least 12 hours. Subjects gave informed consent and were paid for their participation in this study.

### Drugs

The following drug conditions were randomly administered to each subject:

| First Time Point | Second Time Point |
|---|---|
| 1. Placebo PO | + Scopolamine 0.5 mg IV |
| 2. Haloperidol 2 mg PO | + Placebo IV |
| 3. Haloperidol 2 mg PO | + Scopolamine 0.5 mg IV |
| 4. Metergoline 4 mg PO | + Placebo IV |
| 5. Metergoline 4 mg PO | + Scopolamine 0.5 mg IV |
| 6. Placebo PO | + Placebo IV |

Following overnight rest and fast, an intravenous catheter was inserted, usually in the nondominant arm. After a rest period of 30 minutes, the first test session with the Repeat Battery (see later) was administered. The oral drug or placebo was then given with about 100 ml of tap water. Half an hour later, a light snack was served. The intravenous scopolamine or placebo (saline) was administered 60 minutes after the oral dose (Figure 1).

The dose of scopolamine was selected based on previous challenge studies that had shown that 0.5 mg IV produced significant cognitive changes in humans that peak about 90 minutes after administration (Sunderland et al. 1987; Molchan et al. 1992) without causing confusion or delirium (Ketchum et al. 1973). The intravenous route was chosen because it results in more consistent absorption and effects than other routes. Among the available antidopaminergic agents, haloperidol was chosen because of its low anticholinergic activity. Haloperidol has a plasma half-life that varies from 13 to about 40 hours, but its cognitive effects after a single dose parallel the prolactin curve, with a peak at about 3 to 4 hours (Magliozzi et al. 1989). The dose of haloperidol (2 mg) was selected as a relatively low but active dose unlikely to cause acute dystonic reactions in young subjects. The serotonergic system was blocked with metergoline, a nonspecific blocker of serotonin receptors (Beretta et al. 1965). Metergoline has a plasma elimination half-life of about 50 minutes and its major metabolite, 1-demethyl–metergoline, of about 100 minutes (Martini et al. 1983). A 4-mg dose was given as an effective dose, which is clinically used in Europe to block prolactin and lactation. Both haloperidol and metergoline were administered orally, given their good oral absorption and the fact that intravenous administration would have

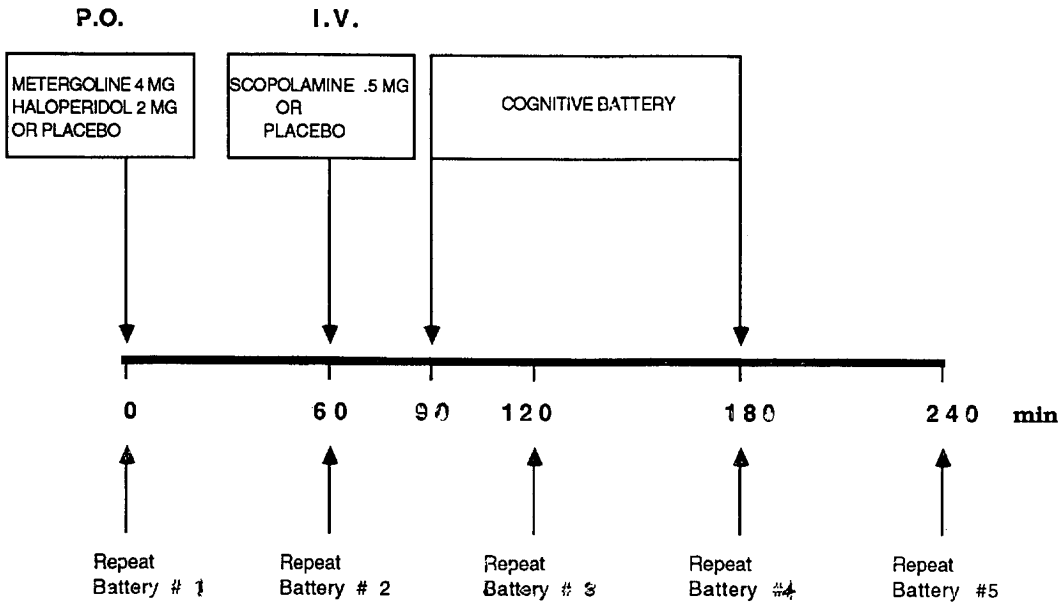


**Figure 1.** Experimental design for double-blind crossover challenge trial with a total of 6 test days (5 drug days and 1 placebo day). Each test day followed the schedule of this paradigm, and test days were separated by at least 72 hours.

been impractical. The 72-hour washout between doses was considered adequate given the half-life of the drugs employed and the single-dose administrations, even though, theoretically, the possibility of long-term drug interactions cannot be completely excluded.

### Assessments

***Repeat Battery.*** The following behavioral and medical measures were obtained immediately before, and 1, 2, 3, and 4 hours after oral administration.

***Behavioral.*** SIMPLE REACTION TIME (RT). Subjects responded as quickly as possible to the onset of a red square presented in the center of an IBM computer screen. Responses were performed by pressing a red key with the index finger of the right hand. The square was presented at a variable interval (500, 1,000, or 1,500 msc) after the subjects' response to prevent anticipatory responses. Subjects completed 6 practice and 15 experimental trials at each time point. Performance was measured in milliseconds, and the median was recorded. This test was also included in the Cognitive Battery (see below).

RATING SCALES. At each time point, the subjects rated sedation and mood changes using visual analog scales, (Bond and Lader 1974). In addition, based on an interview with the subject, a trained examiner (BV) completed the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) and a somatic symptoms checklist (Van Kammen and Murphy 1975).

***Physiological and Biochemical Assessments.*** Blood pressure, pulse, temperature, and pupil size were measured before drug administration and 1, 2, 3, and 4 hours afterward. Pupil size was measured by the examiner with a ruler and, in five subjects, also with a close-up camera to ensure the reliability and validity of the manual measurement (Pearson $r = 0.84$). Blood for plasma prolactin levels was obtained before and 1, 2, and 3 hours after drug administration. Plasma was immediately frozen at −70°C. Plasma prolactin was measured with a radioimmunoassay by Hazleton Washington Laboratories (Vienna, VA). The method had an interassay coefficient of 11% and a sensitivity limit of 2.6 ng/ml.

***Cognitive Battery.*** Thirty minutes after the IV administration (i.e., 90 minutes after oral administration), the tests to be described were administered. Seven different versions of each task were created. Test versions were equated for word frequency (word list learning), perceptual identification thresholds (for fragmented pictures), and number of words retrieved (for fluency tasks) based on published normative data. The different versions, whose equivalence has been established in previous studies, were randomly grouped to create seven unique test packets. Each subject participated in a practice session followed by the six drug conditions. The assignment of test packet was counterbalanced across drug administration days to guard against the possible risk of confounding test form differences with drug effects. The tests were administered in a fixed order at all sessions.

SIMPLE AND COMPLEX VISUAL REACTION TIME. Simple Reaction Time is a test of attention, and complex reaction time assesses information processing. Subjects underwent a simple reaction test as described in the Re-

peat Battery. This condition was followed by a second-choice condition in which either a red or blue circle was presented and the subjects responded by pressing the appropriate key and then a third-choice RT condition in which either a red, blue, or green circle was presented. For the choice conditions, the target circles appeared with equal probability and in random order. Subjects completed 6 practice and 15 experimental trials for the simple RT conditions, 9 practice and 30 experimental trials for the second-choice, and 12 practice and 45 experimental trials for the third-choice. Median RTs were computed for each condition. At the end of this session, the simple RT was repeated to assess fatigue effects.

VISUAL SEARCH. (test of attention). Subjects were presented with an 8″ × 11″ sheet of white paper containing a pseudorandomly arranged array of 128 single-digit numbers. There were 16 occurrences (four per quadrant) of each of eight different numbers. Subjects were given a pair of digits (e.g., 2 and 5) and required to draw a line through every occurrence of both numbers as quickly as possible. Time to perform the task was manually recorded in seconds by the observer.

DIGIT AND BLOCK SPAN. (working memory). Digit span forward (Wechsler 1955) and block span forward (Corsi blocks; Lezak 1983) were determined by standard procedure.

WORD LIST LEARNING. (episodic memory). Subjects were read a list of 12 words for free recall. Five recall trials were administered. Recall and recognition (12 targets, 12 distracter items) were also evaluated after a 30-minute delay.

FRAGMENTED PICTURES TEST. (Perceptual Learning; modified from Snodgrass and Corwin 1988). The subjects viewed fragmented versions of line-drawn objects presented on cards. For each object there were eight levels of fragmentation from the most fragmented (level 1) to completed drawing (level 8). Each card was presented for 10 s. The material was presented in ascending order starting from level 1 and continued until the subject named the depicted object. Perceptual threshold (presentation time in seconds) was established for each of seven objects during initial learning.

AUDITORY, VERBAL BROWN-PETERSON TASK. (modified from Peterson and Peterson 1959). This is a test of short-term memory during distracting interference. Subjects were read a list of three consonants that they repeated immediately (0 delay) or after filled delays of 5, 10, or 20 s. During the delay the subjects counted backward from a randomly chose, three-digit number. There were four practice trials followed by 20 experimental trials, with five presentations at each delay. Delay intervals were randomized across trials. The subject's score was the number of letters recalled in the correct sequence at each delay interval.

VISUAL, NONVERBAL BROWN-PETERSON TASK. (modified from Sullivan et al. 1986 and Kopelman and Corn 1988). This also is a test of short-term memory, during distracting interference. The same general procedure as used for the verbal task was followed except that a three-block spatial sequence was substituted for the consonant trigram. The experimenter tapped the sequence on the Corsi blocks. During the interference/distraction interval the block board was covered by a sheet of paper on which were printed eight small circles arranged in a circular pattern. The experimenter touched the small circles in a random order. Immediately after a circle was touched, the subject touched the same circle and continued mimicking the experimenter's actions until the distracter interval ended. The subject's score was the number of blocks recalled (tapped) in the correct sequence at each delay interval.

VERBAL FLUENCY TASKS. Subjects were given 60 s to generate as many words as possible. Five trials were administered. The retrieval cue was a letter for two of the trials (*Letter Fluency*; Benton and Hamsher 1983) and a semantic category for two trials (*Semantic Fluency*; Newcombe 1969). The fifth trial required subjects to produce an alternating list of words (*Switching Fluency*; Martin et al. 1993). Subjects were given a pair of letters (e.g., S and B) and told to generate a word that began with the first letter (S), followed by a word that began with the second letter of the pair (B), and to keep alternating in this fashion for the 60-s retrieval period. This condition was included to provide a measure of the ability to continuously switch set under time pressure.

### Statistics

Repeated-measures analysis of variance (ANOVA) was used to test the following study hypothesis: (1) whether there was a scopolamine effect on the measured variables; (2) whether haloperidol or metergoline given in isolation produced any effects; and (3) whether the addition of haloperidol or metergoline changed the scopolamine effect.

The data were analyzed using a modified Latin square design (Fleiss 1986), with repeated-measures ANOVA, accompanied by a priori contrasts. With this ANOVA, the scopolamine effect was first tested by comparing the scopolamine conditions (scopolamine + placebo, scopolamine + haloperidol, and scopolamine + metergoline) with the conditions without scopolamine (placebo, haloperidol, and metergoline). Second, the possible presence of differences among the effects of haloperidol, metergoline, and placebo was tested by contrasting the two haloperidol conditions (haloperidol and haloperidol + scopolamine) and the two metergoline conditions (metergoline and metergoline + scopolamine) with the other conditions (placebo and placebo + scopolamine). Then the interaction effect tested differences between individual treatments (haloperidol versus haloperidol + scopolamine versus metergoline ver-

sus metergoline + scopolamine versus placebo versus placebo + scopolamine). Significant interactions were further amplified using repeated-measures ANOVA accompanied by a priori contrasts that compared the individual drug effects. Where there were significant interactions of treatment effects over time, individual contrasts of treatments were made at each time point. When specific two-factor comparisons were made, paired *t*-tests were used.

When the sphericity (homogeneity of covariance) assumption was not met, the Huynh-Feldt correction was applied. The *p* values presented are two-tailed. Nonparametric tests were used when appropriate, as indicated in the text. The possible presence of an order effect (i.e., an effect attributable to the order in which the different compounds were administered) was tested and excluded with a two-way ANOVA in a procedure similar to that reported by Littell et al. (1991).

Throughout the text, *scopolamine effect* indicates the result of the comparison between the drug conditions with scopolamine (scopolamine + placebo, scopolamine + haloperidol, scopolamine + metergoline) and those without scopolamine (placebo, haloperidol, metergoline). *Other drugs effect* indicates the global significance of the haloperidol and metergoline effects. *Metergoline or haloperidol effect* indicates the significance of the a priori contrast between each of these drugs and placebo. *Interaction effect* indicates the global significance of the effect of combining haloperidol and metergoline with scopolamine. A specific effect of haloperidol on the subjects' ability to switch was predicted and its presence was therefore tested outside the constraints of the described ANOVA.

## RESULTS

### Behavioral Effects

Scopolamine-induced psychomotor slowness on the BPRS (scopolamine effect × time, $F(2.5, 27.5) = 19.7$, $p < .001$). In parallel, the subjects also rated themselves as sedated after receiving scopolamine on the visual analog scales (factor 1, or "alertness"; Bond and Lader 1974) (scopolamine effect × time, $F(2.7,29.5) = 30.4$, $p < .001$). Sedative effects, both observed and self-reported, were most evident 1 hour after the scopolamine injection, and they were still evident 3 hours after the injection (Figure 2). Haloperidol and metergoline did not affect motor activity or alertness, nor did they interfere with scopolamine-induced sedation.

### Overall Effects on Cognitive Performance

Scopolamine alone impaired ($p < .01$) the speed of information processing (second- and third-choice RT), without impairing simple RT on initial testing (Table 1). It is of note that simple RT was impaired on testing at the end of the session. Episodic memory (word list learning), perceptual learning (fragmented pictures test), and short-term memory (Brown-Peterson verbal and nonverbal tasks) were all impaired during the scopolamine conditions (Table 2). However, attention (digit and block spans, visual search) and retrieval from lexical and semantic memory (verbal fluency tasks) were spared in these young controls. As expected, haloperidol selectively affected the ability to switch cognitive sets ($p < .05$). When these compounds were combined, no significant interactions emerged, except for a trend for haloperidol to reverse the scopolamine effects on short-term memory in the Brown-Peterson ($p < .10$).

***Simple Reaction Time (attention).*** Scopolamine, haloperidol, or metergoline did not affect simple visual RT when measured at 0, 60, 120, 180, and 240 s, as part of the Repeat Battery. However, a significant scopolamine effect [$F(1,11) = 16.6$, $p < .01$] was noted on the second, but not the first measurement of simple RT administered as part of the Cognitive Battery, thus suggesting a possible interaction between scopolamine and fatigue (Table 1).

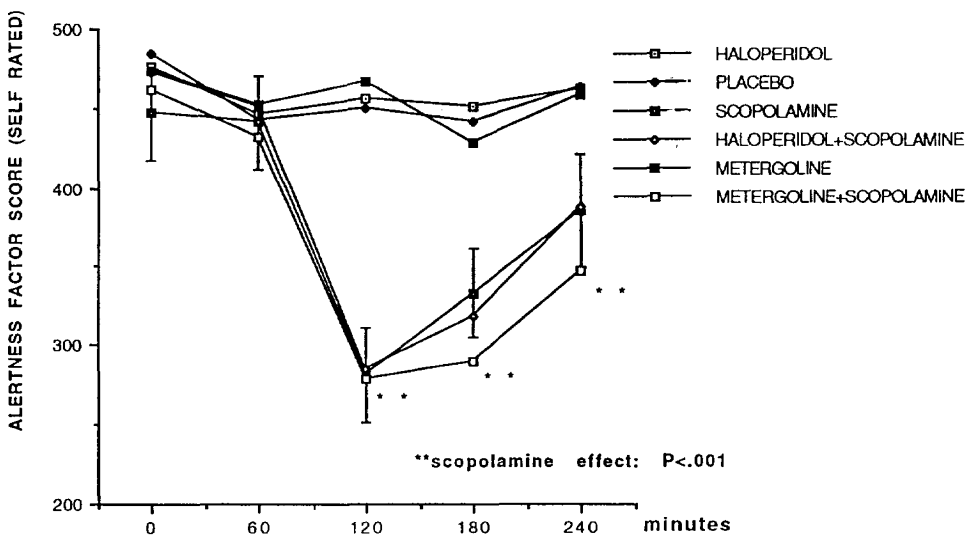


**Figure 2.** Alertness factor score from visual analog scales (mean; SE is shown only for one condition for graphical simplicity).

**Table 1.** Reaction Times in 12 Young Controls across the Six Drug Conditions

| | | | | | | | Scopolamine Effect | | Other Drugs Effect | | Interaction Effect | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test | P | H | M | S | H + S | M + S | $F(1,11)$ | $p$ | $F(2,22)$ | $p$ | $F(2,22)$ | $p$ |
| Simple | 274 ± 101 | 278 ± 102 | 239 ± 36 | 266 ± 56 | 286 ± 106 | 253 ± 36 | 0.3 | NS | 1.9 | NS | 0.5 | NS |
| Second choice | 423 ± 126 | 426 ± 132 | 405 ± 96 | 459 ± 123 | 446 ± 124 | 440 ± 78 | 10.5 | <.01 | 0.5 | NS | 0.5 | NS |
| Third choice | 518 ± 126 | 500 ± 119 | 515 ± 101 | 550 ± 112 | 539 ± 115 | 544 ± 82 | 16.3 | <.01 | 0.4 | NS | 0.1 | NS |
| Simple repeated | 288 ± 107 | 278 ± 95 | 243 ± 40 | 297 ± 73 | 312 ± 146 | 282 ± 54 | 16.6 | <.01 | 1.4 | NS | 0.6 | NS |

P, Placebo; H, haloperidol; M, metergoline; S, scopolamine. Values are mseconds, means ± SD. Reaction times were all obtained 30 minutes after IV administration.

***Complex Reaction Time (information processing).*** Scopolamine increased RT under both second-choice [scopolamine effect, $F(1,11) = 9.5$, $p < .05$] and third-choice conditions [$F(1,11) = 22.8$, $p < .01$]. In contrast, metergoline and haloperidol did not affect performance on this test when given alone, nor did these drugs interact with scopolamine when given in combination (Table 1).

***Word List Learning (episodic memory).*** Scopolamine impaired immediate free recall [total number of words recalled in the five trials: scopolamine effect, $F(1,11) = 13.0$, $p < .01$; Table 2] and delayed recall [$F(1,11) = 22.8$, $p < .01$]. No drug-induced intrusion effects were seen. Delayed recognition was not impaired. Haloperidol and metergoline alone showed no significant effects and did not interact with scopolamine.

***Switching Fluency (response set alternation).*** Although there was no overall drug effect [$F(1,11) = 0.1$, NS], the a priori formulated hypothesis that haloperidol would selectively impair performance on this test was confirmed (haloperidol vs. placebo, paired $t$-test, t = 2.42, df = 11, $p < .05$), as shown in Figure 3. Scopolamine had no effect on this task.

***Fragmented Pictures Test (perceptual learning).*** Scopolamine impaired performance on this test, as indicated by increased identification thresholds for previously presented fragmented pictures [scopolamine effect, $F(1,11) = 14.8$, $p < .01$], but perception of newly presented pictures was unaffected. Metergoline and haloperidol had no significant effects on this test, either alone or when combined with scopolamine (Table 2).

***Verbal and Nonverbal Brown-Peterson Tests.*** Scopolamine produced increased short-term forgetting, at the 5-, 10-, and 20–s delays (scopolamine effect, $p < .01$, at each delay for both the verbal and nonverbal tasks; see Table 2 for 0- and 20-s delay data). Haloperidol and metergoline given in isolation had no effects. There was a significant interaction effect among drugs on the verbal test, which was most pronounced after a 20-s delay [$F(2,22) = 4.1$, $p < .05$]. This interaction was due to a trend for haloperidol to reverse the scopolamine effect [scopolamine vs. haloperidol + scopolamine; $F(1,11) = 3.4$, $p < .10$].

***Attention and Retrieval from Lexical and Semantic Memory.*** No main drug effects or drug interactions were detected on the visual search, digit span, block span, or letter and semantic category fluency tasks.

## Physiological, Behavioral, and Biochemical Effects

Scopolamine administration was associated with the expected somatic and physiological effects. For instance, it caused a blurred vision [scopolamine effect × time, $F(2.4, 26.4) = 9.2$, $p < .001$], dry mouth [$F(1.8, 19.5) = 28.9$, $p < .001$], and weakness [$F(4,44) = 11.52$, $p < .001$]. It decreased heart rate [scopolamine effect × time, $F(2.6, 28.3) = 6.3$, $p < .01$], decreased diastolic blood pressure [scopolamine effect × time, $F(4,44) = 3.2$, $p < .05$], and increased pupil size (scopolamine effect × time, $F(2,22.6) = 24.4$, $p < .01$; Table 3]. Given alone, metergoline decreased pupil size [other drug effect × time, $F(6,66) = 2.0$, $p = .08$; metergoline effect, $F(1,11) < 11.6$, $p < .01$] and also reversed, in part, the mydriasis

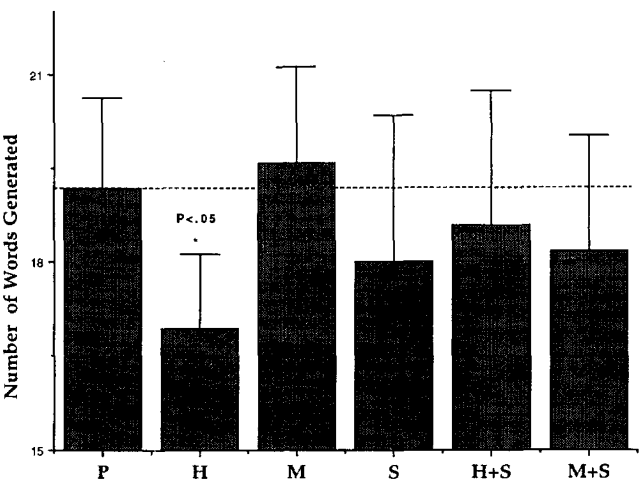


**Figure 3.** Verbal switching fluency score: Number of words produced in 60s (mean and SE). *Dashed line,* mean performance on placebo. Haloperidol versus placebo, paired $t$ = 2.42, df = 11, $p < .05$. P, placebo; H, haloperidol; M, metergoline; S, scopolamine; H + S, haloperidol + scopolamine; M + S, metergoline + scopolamine.

**Table 2.** Episodic, Perceptual, and Short-Term Memory Performance in 12 Young Controls: Cognitive Scores (mean ± SD) Across Drug Conditions

| | | | | | | | Scopolamine Effect | | Other Drugs Effect | | Interaction Effect | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test | P | H | M | S | H + S | M + S | *F*(1,11) | *p* | *F*(2,22) | *p* | *F*(2,22) | *p* |
| World list (0–60 words)[a] | 49 ± 7 | 47 ± 6 | 49 ± 9 | 42 ± 11 | 44 ± 11 | 40 ± 11 | 13.1 | <.01 | 0.1 | NS | 1.4 | NS |
| Fragmented pictures (s)[b] | 14 ± 9 | 15 ± 6 | 16 ± 10 | 25 ± 8 | 25 ± 10 | 25 ± 13 | 14.8 | <.01 | 0.1 | NS | 0.3 | NS |
| Brown-Peterson (0–15 items)[c] | | | | | | | | | | | | |
| Verbal | | | | | | | | | | | | |
| No delay | 15 ± 0 | 15 ± 1 | 15 ± 1 | 15 ± 0 | 15 ± 1 | 15 ± 1 | | | | | | |
| 20 s delay | 10 ± 4 | 9 ± 4 | 9 ± 5 | 5 ± 7 | 8 ± 4[d] | 5 ± 3 | 19.4 | <.01 | 0.7 | NS | 4.1 | <.05 |
| Spatial | | | | | | | | | | | | |
| No delay | 15 ± 0 | 15 ± 0 | 15 ± 0 | 15 ± 1 | 15 ± 0 | 14 ± 2 | | | | | | |
| 20 s delay | 9 ± 4 | 10 ± 4 | 10 ± 4 | 6 ± 4 | 6 ± 4 | 6 ± 4 | 16.2 | <.01 | 0.6 | NS | 0.1 | NS |

P, Placebo; H, haloperidol; M, metergoline; S, scopolamine.
[a]Number of correct words recalled in five trials.
[b]Time required for recognition of previously seen items.
[c]Number of correct responses.
[d]Haloperidol + scopolamine versus scopolamine, $F(1,11) = 3.4$, $p < .10$.

induced by scopolamine [interaction effect, $F(6.4, 70.3) = 2.6$, $p < .05$; scopolamine vs. scopolamine + metergoline effect at 120 min, $t = 4.5$, df = 11, $p < .001$]. There was a trend for metergoline to decrease temperature [other drugs effect × time, $F(4.4, 48.4) = 2.3$, $p = .06$; metergoline effect, $F(1,11) = 4.2$, $p = .06$]. No changes in blood pressure or somatic side effects were detected. Haloperidol did not induce any detectable changes in the physiological variables or somatic side effects. Table 3 summarizes the relevant physiological data.

Plasma prolactin was increased by haloperidol [drugs effect × time, $F(4, 45) = 3.8$, $p < .01$]. At 180 minutes, prolactin level was 11.4 ± 6.3 ng/ml (mean ± SD) after haloperidol and 6.1 ± 6.0 after placebo [$F(1,11) = 8.4$, $p < .05$]. Metergoline decreased prolactin (binomial test, $p < .05$). In the case of metergoline, a nonparametric test, the binomial test, was used because in many plasma samples collected after metergoline the prolactin level was below the detection limit of the assay (2.6 ng/ml).

## DISCUSSION

The effects of combining cholinergic with dopaminergic or serotonergic blockade had not been previously studied in humans, in spite of its common occurrence in clinical practice (e.g., neuroleptics and anticholinergics). The effect of anticholinergic agents on cognitive processes is not a simple one. There is general agreement that scopolamine disrupts new learning (Warburton and Wesnes 1985; Beatty et al. 1986; Sunderland et

**Table 3.** Physiologic Responses of the Young Normal Control Across Different Drug Conditions (mean ± SD)

| Vital Signs | Time (min) | P | H | M | S | H + S | M + S | *F*(4,44) | *p* | *F*(8,88) | *p* | *F*(8,88) | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pulse (bpm) | 0 | 60 ± 10 | 61 ± 11 | 62 ± 9 | 59 ± 12 | 58 ± 10 | 60 ± 11 | | | | | | |
| | 180 | 56 ± 7 | 57 ± 7 | 58 ± 7 | 49 ± 6 | 49 ± 7 | 48 ± 5 | 6.3 | <.01 | 0.3 | NS | 1.0 | NS |
| Diastolic BP | 0 | 65 ± 6 | 65 ± 6 | 66 ± 8 | 63 ± 6 | 62 ± 5 | 67 ± 8 | | | | | | |
| (mm Hg) | 180 | 65 ± 6 | 63 ± 7 | 65 ± 7 | 58 ± 7 | 59 ± 8 | 60 ± 8 | 3.2 | <.05 | 0.9 | NS | 0.5 | NS |
| Temperature | 0 | 36.4 ± 0.3 | 36.4 ± 0.3 | 36.3 ± 0.3 | 36.4 ± 0.4 | 36.5 ± 0.4 | 36.6 ± 0.5 | | | | | | |
| (°C) | 180 | 36.5 ± 0.4 | 36.3 ± 0.3 | 36.1 ± 0.3[a] | 36.3 ± 0.4 | 36.3 ± 0.4 | 36.0 ± 0.6 | 1.1 | NS | 2.3 | <.10 | 1.0 | NS[a] |
| Pupil size | 0 | 4.1 ± 0.5 | 4.4 ± 0.6 | 4.2 ± 0.5 | 4.4 ± 0.7 | 4.1 ± 0.6 | 4.1 ± 0.6 | | | | | | |
| (mm) | 180 | 4.4 ± 0.7 | 4.1 ± 0.5 | 3.7 ± 0.3[b] | 5.0 ± 0.8 | 5.0 ± 0.8 | 4.7 ± 0.7[b] | 24.4 | <.01 | 2.0 | <.10 | 2.6 | <.05[b] |

P, Placebo; H, haloperidol; M, metergoline; S, scopolamine. Only times 0′ and 180′ were tabulated for simplicity. Degrees of freedom are shown before the Huynh-Feldt correction.
[a]Metergoline effect, $F(1,11) = 4.2$, $p < .10$.
[b]Metergoline effect, $F(1,11) = 11.6$, $p < .01$.

al. 1986), but there is controversy over the effects on semantic memory. Some groups have shown no scopolamine effects (Kopelman and Corn 1988; Dunne 1990; Flicker et al. 1990) or even an improvement (Dunne et al. 1993), but other groups have reported significant impairments (Drachman and Leavitt 1974; Caine et al. 1981; Molchan et al. 1992). Some of these discrepancies may be attributed to dose, route of administration, and age differences across studies, as the scopolamine effect appears to be age-related (Flicker et al. 1992; Molchan et al. 1992).

In the present study, scopolamine was associated with deficits in learning verbal (word list learning) and nonverbal material (fragmented pictures), whether measured explicitly by free recall or implicitly by a change in the perceptual identification threshold for previously seen pictures. Scopolamine also produced slowed processing (complex RT) and increased the rate of forgetting from short-term memory (Brown-Peterson tasks). However, simple response speed (simple RT), sustained attention (visual search), immediate recall (digit and block spans), and retrieval from lexical and semantic memory (fluency tasks) were unaffected. These findings are generally consistent with most previously reports on the effects of scopolamine when given alone to young subjects (Beatty et al. 1986; Kopelman and Corn 1988). The pattern of results suggests that this anticholinergic agent may selectively interfere with processes necessary for the efficient acquisition of new information but that it has little effect on the organization or retrieval of previously acquired knowledge. It should be noted, however, that this study, as well as all others reported in the literature, have used verbal fluency tasks to assess the status of semantic memory. Other types of measures (e.g., object naming and knowledge probes) are clearly needed to evaluate fairly the effects of scopolamine, as well as other agents, on previously acquired knowledge and skills.

The cognitive effects of selective antidopaminergic agents, such as haloperidol, have been studied both in patients and in normal subjects (as reviewed by King 1990), with results that are not entirely consistent. In schizophrenic patients, findings of impaired, unchanged, or improved performance have all been reported during neuroleptic administration, perhaps reflecting the contrasting cognitive effects of some anticholinergic neuroleptics with their clinical benefits (King 1990; Goldberg et al. 1993). In normals, haloperidol caused a dose-related impairment on the digit symbol substitution test (Magliozzi et al. 1989), but did not affect recall and learning (Mungas et al. 1990). Haloperidol had been shown to impair selectively the ability to alternate or to switch cognitive sets both in animals (Bubser and Schmidt 1990) and humans (Berger et al. 1989), a finding associated with lesions of the dopaminergic terminals of the prefrontal cortex in the rat (Bubser and Schmidt 1990). Consistent with these reports, we found that haloperidol selectively impaired the subjects' ability to switch sets in a verbal fluency test. One can wonder whether a higher dose than the one employed in this study would affect other aspects of cognition, including RT (Nordstrom et al. 1992). Nevertheless, this dose did result in significant dopaminergic blockade at the pituitary level, as indicated by the surge of plasma prolactin. As the cognitive battery was given between 90 and 180 minutes after the dose of haloperidol, it cannot be excluded that other cognitive deficits could have emerged either prior to 90 minutes or after 180 minutes.

Metergoline is a relatively nonspecific blocker of serotonergic 5-$HT_{1,2}$ receptors (Beretta et al. 1965). It has especially high affinity for 5-$HT_{2C}$, 5-$HT_{2A}$, and 5-$HT_{1D}$ receptor (Hoyer 1989). Its effects on cognition in humans had not been previously explored. As noted, the literature on the cognitive effects of serotonergic agents is somewhat contradictory. There have been reports of improved memory performance in animals given serotonergic antagonists (Altman and Normile 1986) and humans given serotonin reuptake inhibitors (Martin et al. 1989). m-CPP, a mixed 5-HT agonist-antagonist, was found to potentiate some of the cognitive, behavioral, and physiological effects of scopolamine (Little et al. 1995). In our current study, metergoline caused a significant decrease in plasma prolactin and pupil size, which indicates that a significant serotonergic blockade was achieved at the dose administered (4 mg). Furthermore, the metergoline-induced miosis is consistent with a blockade of 5-$HT_2$ receptors (Millson et al. 1992). Nonetheless, the cognitive battery was not affected by this dose of metergoline.

Similarly, the combination of scopolamine with haloperidol or metergoline did not result in more profound deficits. On the contrary, there was a trend for haloperidol to reverse the scopolamine-induced exacerbation of short-term forgetting on the Brown-Peterson test. This is in agreement with recent reports on a partial reversal by haloperidol of the scopolamine-induced impairment of the rat performance on the radial-arm maze (McGurk et al. 1988, 1989). The reversal seems to be limited to the antimuscarinic activity of scopolamine, as shown by the fact that haloperidol worsened the deficit caused by the antinicotinic compound mecamylamine in a radial-arm maze task with rodents (McGurk et al. 1989). These data suggest that a balance between dopamine and acetylcholine may be needed for normal cognitive performance, as it is for extrapyramidal functioning. However, it cannot be excluded that the effect of haloperidol on the scopolamine-induced deficit is due to the blocking of alpha-2-adrenergic receptors by haloperidol. In fact, haloperidol was found to improve retrieval from memory when given alone to rats. This effect was blocked by clonidine pretreatment (Chugh et al. 1991).

In conclusion, we found that both scopolamine and haloperidol affected cognition when administered separately. However, the combination of scopolamine with a fixed-dose nonspecific antiserotonergic agent (metergoline) or an antidopaminergic agent (haloperidol) did not result in more profound cognitive deficits than when scopolamine was given alone. This failure to mimic more closely the cognitive deficits of Alzheimer's disease confirms the predominant importance of the cholinergic system in this disease, but leaves open the possibility that further testing with more selective agents using a variety of doses may clarify the pharmacological profile of cognitive impairment.

## ACKNOWLEDGMENTS

We are indebted to Bruce Pappas, Ph.D., for his contribution to the planning of the study, to Theresa Witte and Kathleen Dietrich, RNs, for their help with data collection, and to Karen Putnam, B.S., for her assistance with data handling. The authors would especially like to thank Wilma Davis for her help in preparing this manuscript.

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