

Amitriptyline, clovoxamine and cognitive function: a placebo-controlled comparison in depressed outpatients

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Abstract. No longer prescribed only for vegetative signs of depression, tricyclic antidepressants also lessen depressive cognitive distortions. Less clear is whether they ameliorate depressed patients' other cognitive deficits in memory, information processing speed, and psychomotor performance. We tested the alternative hypothesis that amitriptyline, because of its anticholinergic and sedative properties, would exacerbate depressed patients' cognitive disturbances. Depressed outpatients received double-blind placebo ($n=15$), amitriptyline ($n=10$), or clovoxamine fumarate ($n=10$), a serotonin reuptake inhibitor relatively lacking in anticholinergic properties. Depression, memory, and psychomotor performance were assessed at baseline and after 7 and 28 days of drug treatment. Depression was alleviated after all treatments, including placebo. Only amitriptyline impaired performance on tests of memory, producing a significant decrement, relative to placebo, after 4 weeks of treatment. None of the treatments adversely affected performance on psychomotor tasks. These findings add to the evidence that antidepressant drugs with high anticholinergic activity can impair memory, despite alleviation of depression.

Key words: Antidepressants – Tricyclics – Memory – Amitriptyline – Clovoxamine – Anticholinergic

Although tricyclics lessen pessimistic, self-critical beliefs (Simons et al. 1984), it is unclear whether they ameliorate deficits in psychomotor speed and memory that also characterize depression (Newman and Sweet 1986; Abrams and Taylor 1987). Via its potent antihistaminic and anticholinergic actions, amitriptyline might induce sedation and memory impairment, exacerbating some cognitive disturbances even as the drug alleviates depression.

Amitriptyline has been shown to impair cognitive and psychomotor functioning, but most demonstrations have involved atypical clinical contexts. Tricyclics can even elicit delirium in excessive doses and/or unusually sensitive individuals (Cole et al. 1983; Pollack and Rosenbaum 1987). When given acutely to normal adults, dosages of 25–70 mg amitriptyline reliably impair short-term memory and psychomotor performance (Curran et al. 1988; Hindmarch et al. 1988; Mattila et al. 1989). When administered chronically, however, as would be done for treatment of depression, amitriptyline induces minimal or no impairment in the memory and psychomotor functions of normal humans (Seppala 1978).

Few studies have directly described amitriptyline's effects on the cognitive performance of depressed patients. The limited existing findings suggest that the drug may impair memory (Branconnier et al. 1982), including recognition (Lamping et al. 1984), while lacking an effect on psychomotor performance (Elwan et al. 1976; Lamping et al. 1984). Additional clarification is needed, however, because McNair et al. (1984) found mixed evidence that amitriptyline both facilitated and impaired memory and psychomotor performance in a sample of depressed outpatients. Moreover, other tricyclics have rarely been found to behaviorally impair depressed patients (Legg and Stiff 1976; Thompson and Trimble 1982). More typically, they leave performance unchanged (Henry et al. 1973; Glass et al. 1981) or alleviate cognitive and psychomotor dysfunctions in the course of bringing about clinical improvement (Friedman et al. 1966; Sternberg and Jarvik 1976; Glass et al. 1981). Consequently, the present study tested whether amitriptyline simultaneously impairs memory while alleviating depression.

Several new serotonin re-uptake blockers, substantially lacking in anticholinergic activity, are claimed to equal the tricyclics in antidepressant efficacy while having fewer undesired effects (Feighner 1981). Some evidence suggests that these drugs may facilitate performance, even in nonpatients (Altman et al. 1984; Linnoila et al. 1985). One such drug, clovoxamine, is, like fluvoxamine, one of a class of aminoethyl oximethers of arylkyl

ketones. Clovoxamine markedly inhibits neuronal re-uptake of serotonin, while also impeding re-uptake of norepinephrine (Claassen et al. 1978). In one prior study, clovoxamine enhanced the psychomotor performance of normal subjects (Saletu et al. 1980). In another, 1 month of treatment with clovoxamine improved recognition memory in depressed outpatients (Lamping et al. 1984). The present study aimed to replicate this finding by testing whether memory enhancement exceeded that observed in a placebo control group.

Materials and methods

Subjects

Participants were nonhospitalized individuals who responded to a newspaper advertisement requesting volunteers with symptoms of depression. Eligibility was determined by a project psychiatrist who administered a psychiatric interview and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960). All subjects met DSM-III criteria (American Psychiatric Association 1980) for major affective disorder, depressive episode, and exhibited at least five of the criteria for primary depression specified by Feigner et al. (1972). In addition, all scored at least 16 on the first 17 items of the HAM-D when withdrawn from medication prior to entering the study. Excluded from participation were women who were pregnant or of childbearing potential and not taking effective contraceptive measures, patients whose depression was secondary to another psychiatric disorder, and patients with significant organic disease or drug dependency.

Patients were randomly assigned on a double-blind basis to receive treatment with either amitriptyline (AMI) (50–350 mg/day, mean = 114 mg, SD = 44.3), clovoxamine fumarate (CLOV) (50–350 mg/day, mean = 138 mg, SD = 43.7) or placebo (PBO). Active medications and placebo were given in indistinguishable gray gelatin capsules to be taken three times per day.

Procedure

Prior to entering the protocol, patients who were receiving other treatments discontinued them as follows: electroconvulsive therapy (4 weeks), other investigational drugs (4 weeks), monoamine oxidase inhibitors (2 weeks), other antidepressants (3 days), lithium (7 days). In addition, subjects underwent a pretreatment period of up to 7 days, during which they received PBO single-blind (known to experimenters, unknown to patients), but no other medication. Baseline psychometric testing was performed during pretreatment. Depression (measured by the 21-item HAM-D), memory and psychomotor performance were assessed at baseline and on days 7 and 28 of treatment.

Assessments

Memory tests. A test of verbal recognition memory was used to measure encoding and storage in short-term memory. The subject studied 24 two- and three-syllable target words presented individually on cards for 2 s each. The instructions were to say each word aloud and remember it. On a test trial immediately following each study series, the subject inspected cards presenting 48 words, including the 24 previously presented targets and 24 new words. The task was to judge whether each stimulus was a target or a new word. Four equivalent word lists were used, with items matched on frequency of usage in the English language (Thorndike and Lorge 1944) and ability to evoke mental imagery (Paivio et al. 1968). Responses were scored for hits (number of target words correctly

identified as such) and false alarms (number of new words misidentified as targets). In prior studies, this test detected memory impairment after treatment with amitriptyline (Lamping et al. 1984) and benzotropine mesylate (McEvoy et al. 1987).

The *Benton Visual Retention Test* (Benton 1974) was used to measure memory praxis and immediate recall of visuospatial material. The subject studied cards depicting simple geometric figures. The task was to draw each card from memory after seeing it for 10 s. Three equivalent series of ten cards were used. The subjects' reproductions were scored for the total number of completely correct reproductions and the total number of errors. The correct and error indices are not identical, because as many as seven kinds of errors can be scored for each incorrect reproduction.

Psychomotor tests. The *Digit Symbol Substitution Test (DSST)* (Wechsler 1955) provided a compound measure of psychomotor speed, motor persistence, concentration, and visual-motor coordination. The subject received a key that paired each of nine digits with a different symbol. The task was to use the key to write the correct symbols in boxes that accompanied a series of randomly ordered digits. Instructions emphasized working as rapidly as possible; a time limit of 90 s was imposed. The number of correctly filled boxes, scaled to adjust for age-related differences in performance, constituted the test score.

A *tapping test* yielded a simple measure of psychomotor speed for the dominant and the nondominant hand. The subject used the index finger to tap a key as many times as possible during a 10-s trial. Three practice trials preceded the actual test; testing continued until a criterion block when scores for three consecutive trials fell within five taps of each other. A maximum number of seven trials was allowed. The mean number of taps in the criterion block constituted the test score.

Simple auditory reaction time (RT) was an additional test of psychomotor speed. The subject depressed a telegraph key with the index finger of the dominant hand and released the key as rapidly as possible in response to a tone. After 5 practice trials, 75 test trials were administered, with preparatory intervals between keypress and tone varying randomly between 1 and 4 s. Response times were measured in milliseconds, transformed to natural logarithms in order to normalize frequency distributions, averaged for each subject and reconverted to an antilog (a geometric mean) to yield the test score.

Psychometric tests were administered in the same order at all sessions: DSST, Benton Test, Recognition Memory, Reaction Time, Tapping. For tests involving equivalent forms, the sequence of forms was counterbalanced across subjects.

Data analysis

Demographic characteristics of the three treatment groups were compared by analysis of variance (ANOVA) and by Chi square tests. All remaining data were analyzed by two-factor split plot ANOVA with drug treatment as the between subjects factor and time on medication as the repeated measures factor. The Greenhouse-Geisser correction (Greenhouse and Geisser 1959; SAS Institute Inc. 1985) was used to compensate for violations of the compound symmetry assumption. Rather than make assumptions about the nature of missing data, the sample included only subjects who completed all test sessions. Significant main effects were interpreted by supplementary comparisons using the Student Newman-Keuls test. Significant interactions between drug treatment and time on medication were interpreted by Newman-Keuls analyses of changes over time within each treatment and differences between the treatments at each time.

Results

Demographic characteristics

Demographic information for the three treatment groups appears in Table 1. The clovoxamine group had a somewhat higher proportion of males than the other two groups, but there were no significant differences among the groups on any demographic characteristic.

Only one significant difference was found between individuals who discontinued treatment and those who completed all test sessions. Those who finished the study worked in higher socioeconomic status occupations than those who failed to complete testing [$F(1,59)=9.38$, $P<0.01$]. Completers also tended to have higher levels of education [$F(1,59)=2.87$, $P<0.10$]. There were no differences between completers and drop-outs on baseline psychometric test performance or on the severity of depression.

Table 1. Demographic characteristics of treatment groups

	Amitriptyline	Clovoxamine	Placebo
Gender			
Male	2	5	6
Female	8	5	9
Age (years)			
Mean	34.0	34.1	35.5
(SD)	(7.6)	(10.4)	(10.1)
Marital status			
Never married	5	4	7
Ever married	5	6	8
Education			
High school	3	1	1
Some college	6	5	9
College graduate	0	3	4
Professional school	1	1	1
Occupation			
Semiskilled	0	0	2
Skilled	4	3	1
Clerical	4	3	5
Administrative	2	2	2
Manager executive	0	2	5

Table 2. Mean (and SD) 21-item Hamilton Depression Score of treatment groups across time

	Amitriptyline (<i>n</i> = 10)		Clovoxamine (<i>n</i> = 10)		Placebo (<i>n</i> = 15)	
	M	(SD)	M	(SD)	M	(SD)
Baseline	25.2	(2.8)	24.2	(2.3)	24.8	(4.5)
Day 7	16.3	(5.9)	15.6	(6.9)	17.1	(6.3)
Day 7 minus baseline	-8.9	(6.7)	-8.6	(8.0)	-7.7	(5.2)
Day 28	8.5	(5.3)	12.3	(7.4)	13.1	(9.8)
Day 28 minus baseline	-16.7	(6.0)	-11.9	(8.7)	-11.7	(9.0)

Depression

A significant main effect of Time [$F(2,64)=55.08$, $P<0.001$] and the lack of a drug main effect or drug \times time interaction indicated that clinical improvement, assessed by the HAM-D, occurred nondifferentially over time for the three treatment groups. Newman-Keuls analyses indicated that a significant reduction in depression occurred by day 7 of the protocol for all treatments, including placebo. A further reduction took place by day 28 for all treatments except clovoxamine. Inspection of the data shown in Table 2 suggests a clinical advantage for amitriptyline after 1 month of treatment, but differences among the groups were nonsignificant.

Memory

The drug treatments differentially affected recognition memory, as shown in Table 3. A significant interaction between drug and time was detected for recognition memory hits [$F(4,64)=2.67$, $P<0.05$]. Newman-Keuls analyses indicated that AMI alone had a significant adverse effect on recognition memory. No change was evident after 1 week of treatment, but the number of correctly recognized target words decreased significantly between days 7 and 28 on drug. Neither of the other two treatments significantly affected recognition memory. Consequently, by day 28 of treatment, but not sooner, AMI-treated patients made significantly fewer hits than PBO-treated patients. CLOV-treated patients made an intermediate number of hits, failing to differ from either AMI- or PBO-treated patients. None of the treatments, nor the passage of time, significantly altered false alarms.

Performance on the Benton Test was also affected differently by the drug treatments. Significant interactions between drug and time were found for Benton correct responses [$F(4,64)=5.28$, $P<0.01$] and Benton errors [$F(4,64)=5.85$, $P<0.01$]. Again, Newman-Keuls analyses indicated that amitriptyline alone significantly impaired memory, decreasing correct responses and increasing errors between days 7 and 28 of treatment. By day 28 of treatment, but not sooner, AMI-treated patients performed significantly worse on the Benton test than either CLOV-treated or PBO-treated subjects. According to Newman-Keuls analyses, Benton errors de-

Table 3. Mean (and SD) memory test performance of treatment groups across time

	Amitriptyline (n = 10)		Clovoxamine (n = 10)		Placebo (n = 15)	
	M	(SD)	M	(SD)	M	(SD)
<i>Recognition memory hits</i>						
Baseline	21.7	(1.9)	21.2	(2.5)	21.2	(2.8)
Day 7	20.5	(2.4)	20.1	(2.6)	21.5	(2.7)
Day 7 minus baseline	-1.2	(3.3)	-1.1	(3.2)	0.3	(2.9)
Day 28	18.4	(3.9)	20.4	(2.7)	22.1	(1.6)
Day 28 minus baseline	-3.3	(4.6)	-0.8	(2.6)	0.9	(3.3)
<i>Recognition memory false alarms</i>						
Baseline	1.2	(0.8)	1.4	(2.4)	1.3	(1.4)
Day 7	1.0	(1.1)	1.5	(2.0)	1.1	(1.2)
Day 7 minus baseline	0.2	(1.1)	0.1	(2.1)	-0.2	(2.1)
Day 28	0.8	(0.9)	0.6	(1.0)	1.3	(2.0)
Day 28 minus baseline	-0.4	(1.2)	-0.8	(2.5)	0.1	(1.5)
<i>Benton correct</i>						
Baseline	7.0	(1.7)	7.0	(1.3)	6.3	(1.7)
Day 7	6.7	(1.3)	7.6	(1.3)	6.7	(1.7)
Day 7 minus baseline	-0.3	(1.4)	0.6	(1.8)	0.4	(1.2)
Day 28	4.7	(2.4)	7.4	(1.5)	7.3	(1.6)
Day 28 minus baseline	-2.3	(1.4)	0.4	(1.4)	0.9	(1.9)
<i>Benton errors</i>						
Baseline	4.6	(2.5)	3.7	(1.6)	5.5	(3.1)
Day 7	4.6	(2.3)	3.2	(2.1)	4.3	(2.2)
Day 7 minus baseline	0	(1.9)	-0.5	(2.2)	-1.3	(2.3)
Day 28	7.9	(3.9)	3.2	(2.3)	3.6	(2.3)
Day 28 minus baseline	3.3	(3.5)	-0.5	(1.4)	-1.9	(3.5)

creased significantly on placebo, such that there were fewer errors on day 28 than at baseline.

Psychomotor performance

Significant improvement occurred over time on all three psychomotor tasks: reaction time [$F(2,64)=6.53$, $P<0.01$], DSST [$F(2,64)=3.79$, $P<0.05$] and tapping [$F(2,64)=5.40$, $P<0.01$]. These data are shown in Table 4. The absence of significant drug main effects or drug \times time interactions suggests that psychomotor performance improved nondifferentially for the three treatment groups. There was no evidence to suggest an adverse effect of antidepressant treatment on psychomotor functioning.

Table 4. Mean (and SD) psychomotor test performance of treatment groups across time

	Amitriptyline (n = 10)		Clovoxamine (n = 10)		Placebo (n = 15)	
	M	(SD)	M	(SD)	M	(SD)
<i>Simple auditory RT (ms) (antilog base e log)</i>						
Baseline	212.6	(33.8)	210.1	(36.9)	219.9	(69.0)
Day 7	191.4	(25.1)	201.5	(32.9)	187.0	(33.2)
Day 7 minus baseline	-21.1	(25.7)	-8.6	(30.1)	-32.9	(62.8)
Day 28	190.1	(13.7)	192.9	(22.3)	195.4	(38.8)
Day 28 minus baseline	-22.4	(26.3)	-17.2	(23.2)	-24.4	(62.1)
<i>Tapping-dominant hand (taps/criterion block)</i>						
Baseline	45.1	(9.1)	50.1	(9.7)	49.3	(8.5)
Day 7	50.7	(5.3)	52.2	(9.9)	52.3	(9.1)
Day 7 minus baseline	5.6	(6.1)	2.1	(3.7)	3.0	(9.4)
Day 28	52.2	(10.5)	52.3	(8.6)	49.6	(9.4)
Day 28 minus baseline	7.1	(7.0)	2.2	(3.4)	0.3	(6.9)
<i>DSST (age-adjusted scaled score)</i>						
Baseline	10.5	(3.1)	11.3	(2.6)	10.8	(2.9)
Day 7	11.1	(2.5)	11.3	(2.6)	11.8	(3.5)
Day 7 minus baseline	0.6	(1.6)	0	(1.8)	1.0	(1.4)
Day 28	11.4	(2.8)	11.4	(2.8)	11.9	(3.9)
Day 28 minus baseline	0.9	(1.0)	0.1	(1.9)	1.1	(1.7)

Discussion

The findings of this study are consistent with the hypothesis that after one month of treatment with amitriptyline, depressed patients can show a deterioration of memory function, despite alleviation of depression. The decline in memory performance associated with amitriptyline apparently reflects the relatively high anticholinergic action of the drug, rather than a deficiency in its antidepressant action. Actually, remission of depression, indexed by Hamilton scores, failed to statistically differentiate among amitriptyline, clovoxamine and placebo, although marginal differences in antidepressant efficacy favored amitriptyline. Presumably, this result arises from the fact that spontaneous remission is common in depressed outpatients (Simons et al. 1984). In contrast to the comparable antidepressant response to the three treatments, adverse effects on memory were only elicited by amitriptyline. Amitriptyline decreased accuracy on both recognition memory and the Benton test. Memory difficulties appeared to be a result of chronic rather than acute amitriptyline administration. Consistent with our prior results (Lamping et al. 1984), a decline in memory function was absent after 1 week of treatment, but evident after 1 month.

The adverse behavioral effects of amitriptyline were specific to memory function, and did not seem to be attributable to generalized cognitive dysfunction. There was no evidence to indicate that performance on psychomotor tasks was adversely affected by amitriptyline. In fact amitriptyline-treated patients showed improved performance on psychomotor tasks during the course of the protocol, and were not statistically differentiable from the other treatment groups. That the psychomotor performance of AMI-treated patients tended to improve during treatment suggests that their difficulties in performing the memory tasks were not due to sedation or lowered motivation. That impairment was evident on a recognition memory task suggests that amitriptyline engendered a dysfunction in memory encoding, storage, or retrieval. Recognition memory deficits are less likely to result from extraneous factors (e.g., fluctuating attention, motivation and effort) than are deficits on more demanding tests of recall (Perlick et al. 1986).

It may be noted that our present and prior (Lamping et al. 1984) finding of amitriptyline-associated recognition memory impairment contradicts some other findings in the literature. Several investigators have reported that drugs with cholinergic activity disrupt recall but not recognition memory (Branconnier and Cole 1981; Perlick et al. 1986). It has been pointed out (Judd et al. 1987) that ceiling effects constitute a problem in many prior studies of recognition memory. Our recognition memory task differs from previous ones in being more difficult: it contains 24 target items so that subjects are unlikely to achieve a perfect score. The resultant increased discriminating power of the test may have made it possible to detect a disruption in short-term memory. It should be noted that still more items are needed for a recognition test that is fully free from ceiling effects.

The results obtained here cannot be assumed to generalize to all tricyclic antidepressants. Among the tricyclics, amitriptyline has the most pronounced anticholinergic effects, and would, therefore, be expected to have the most adverse effect on memory. On the other hand, all tricyclics have at least some peripheral and central anticholinergic activity. Even those with the least anticholinergic activity have occasionally disrupted cognitive functioning in sensitive individuals (Cole et al. 1983).

Clovoxamine, a new antidepressant, had no demonstrably unique effects on cognition or psychomotor performance. Contrary to our prior findings and our current hypothesis, clovoxamine did not enhance memory. In this study, memory improved significantly only for PBO-treated patients. However, the finding for PBO was only evident on a single index (Benton errors) for which baseline scores were inexplicably impaired; the finding may, therefore, be unreliable. The profile of behavioral effects exhibited by clovoxamine-treated subjects was similar to that shown by placebo-treated subjects. Both showed reduction of depression, and neither showed memory impairment.

Antidepressants with pronounced anticholinergic activity can impair short-term memory despite alleviation of depression. Subjective complaints of cognitive distur-

bance during antidepressant treatment may be objectively verifiable and in contrast to other clinical gains.

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