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Polydipsia in Chronic Psychiatric Patients: Therapeutic Trials of Clonidine and Enalapril

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A six month long double-blind, placebo-controlled, crossover design pharmacological study was conducted on 14 chronically psychotic, institutionalized patients who suffered from chronic water abuse ("psychogenic polydipsia"). Effects of clonidine and enalapril administered separately and individually were assessed for possible beneficial effects on both physiological parameters such as diurnal weight gain, urine output, and serum sodium levels and on signs of delirium as measured by neurobehavioral testing. Improvement, particularly in tests reflecting fluid consumption, was found with either or both drugs in approximately 60% of test subjects, although no behavioral improvement was demonstrated. As a result of evidence for delayed and carry-over effects the authors recommend that future studies employ phases longer than one month and/or include washout periods. ***[Neuropsychopharmacology 18:272–281, 1998]*** *© 1998 American College of Neuropsychopharmalogy. Published by Elsevier Science Inc.*

KEY WORDS: *Enalapril; Clonidine; Chronic water abuse; Psychogenic polydipsia; Drug trial; Crossover design*

The present article describes a pharmacological study on patients with chronic psychoses (primarily schizophrenia) who experience chronic water abuse (psychogenic polydipsia). A recent survey in this hospital identified 61 psychiatric inpatients who suffer from this condition, approximately 40 of whom evidenced recurrent intermittent water intoxication.

The magnitude of the problem is considerable. Investigators have reported evidence of inappropriate excessive fluid consumption in 6–17% of psychiatric inpatients (DeLeon et al. 1994). Although asymptomatic in its milder and early forms, the problem may increase in severity with time, progressing to a syndrome variably including neurological abnormalities (headache, muscle cramps, blurred vision, weakness, tremors, restlessness, confusion, lethargy, delirium, seizures, coma, and death), behavioral and cognitive problems, gastrointestinal symptoms, urinary tract disease (incontinence, hydronephrosis, renal failure), congestive heart failure, and metabolic abnormalities (hypocalcemia, osteopenia).

The fact that the pathophysiology of water intoxication is complex and probably multifactorial (Vieweg et al. 1986a; Vieweg et al. 1988a; Goldman et al. 1988) makes the treatment difficult, inasmuch as particular therapeutic approaches may be beneficial in only certain patients and escape statistical recognition in small studies. Incomplete understanding of why certain patients drink fluids to excess hampers selection of potentially beneficial drugs, a problem compounded by the observation that patients with water intoxication exhibit both polydipsia and impaired water excretion as their disease progresses. Various possible etiologies have been proposed for polydipsia, including hyperactivity of hypothalamic thirst centers, secondary effects of neuroleptic medications, an increase in endogenous opiate receptor effects, and delusions having to do with fluid intake and for hyponatremia and water intoxication, including inappropriate release of the antidiuretic

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hormone, vasopressin (SIADH), and a lowering of the threshold for antidiuretic hormone (ADH) release (or resetting of the hypothalamic osmostat) (Boyd 1990; Crammer 1991; Goldman 1991; Illowsky and Kirch 1988; Patel 1994; Riggs et al. 1991).

Various therapeutic approaches based on these postulated mechanisms have been used with beneficial though limited effects claimed (Vieweg et al. 1985a; Vieweg 1994). Drugs used have included naloxone (Nishikawa et al. 1992), lithium (Khamnei 1984; Raskind and Christopher 1974), lithium plus phenytoin (Vieweg et al. 1988b), demeclocycline (Nixon et al. 1982; Goldman and Luchins 1985; Nixon et al. 1982; Khamnei 1984; Vieweg et al. 1988c), propranolol (Shevitz et al. 1980, Goldstein and Folsom 1991; Kathol et al. 1986), sodium chloride (Vieweg et al. 1985b; Goldman et al. 1994), captopril (Goldstein 1986; Sebastian and Bernardin 1990; Kathol et al. 1986; Lawson et al. 1988), and enalapril (Sebastian and Bernardin 1990). Clozapine treatment appears particularly promising (Spears et al. 1993; Munn 1993; Lee et al. 1991; Henderson and Goff 1994; Leadbetter et al. 1994; Leadbetter and Shutty 1994; Lyster et al. 1994; DeLeon et al. 1995) (see review by Vieweg et al. 1994). Some successes with behavioral approaches have been reviewed by Vieweg (1993).

METHODS

Two drugs were chosen for preliminary investigation of possible beneficial effects in chronic water abuse, both selected because they have been implicated in reducing

Table 1. Demographic Data on Study Patients

Pt. No.	Group Number	Diagnosis (DSM IV)	Age (yrs)	Duration of Psychiatric Hospitalization (years)	Estimated Duration of Water Abuse (years)	Current Medications
1	3	chronic schizophrenia	44	12	?	haloperidol lithium lorazapam
2	3	chronic schizophrenia	67	39	32	carbamazepine fluphenazine nortriptyline
3	3	chronic schizophrenia	65	15	8	carbamazepine risperdol lorazapam
4	3	chronic schizophrenia	50	11	?	haloperidol lithium
5	1	chronic schizophrenia	61	21	15	lithium risperdol valproate lorazapam
6	1	chronic schizophrenia	56	8	5	carbamazepine risperdol trazadone lorazapam
7	1	chronic schizophrenia	43	18	2	risperdol
8	1	chronic schizophrenia	38	12	5	benztropine risperdol lorazapam
9	2	chronic schizophrenia	46	14	8	risperdol trazadone
10	2	chronic schizophrenia affective psychosis	49	20	?	carbamazepine chlorpromazine lithium
11	2	chronic schizophrenia	31	8	?	fluphenazine lithium trazadone valproate
12	2	post-traumatic psychosis	44	14	1	carbamazepine fluphenazine
13	2	undifferentiated psychosis	50	29	2	chlorpromazine valproate lorazapam
14	2	schizophrenia	46	10	4	risperdol

Table 2. Scheme of Drug Administration

	Phases					
Patient Group	**1**	**2**	**3**	**4**	**5**	**6**
1	Placebo[a]	Placebo	Clonidine	Placebo	Enalapril	Placebo
2	Placebo[a]	Placebo	Enalapril	Placebo	Clonidine	Placebo
3	Placebo[a]	Placebo	Placebo	Clonidine	Placebo	Enalapril

[a]Water restriction was used during phase 1 but not thereafter. Experimental design used. All phases were 4 weeks in duration with the exception of phase 2, which was 5 weeks in duration.

water intake: clonidine, an α-adrenergic blocking agent, and enalapril, an angiotensin-converting enzyme inhibitor (Sebastian and Bernardin 1990; Crammer 1991; Verghese et al. 1993). Both agents have been widely used for treatment of hypertension. The inpatient psychiatric population of the hospital was surveyed, using a questionnaire administered to head nurses to detect patients in whom water abuse had been observed. A total of 61 patients was identified in a population of 244. These patients were then visited by two of the authors, their nursing attendants interviewed and their clinical records reviewed to assess the nature and severity of the problem. Patients with specific etiologies for polydipsia were excluded as were those considered too frail to tolerate the drug regimen proposed. Although we appreciated the role that carbamazepine can play in impairing water excretion, it was noted that in three of the five patients receiving the drug, their problem with water abuse antedated its use. Similarly, the five patients being treated with lithium, which may cause a secondary polydipsia, had exhibited water abuse during prolonged periods over the years in which lithium was not given.

Written authorization and consent from 17 male patients and their next of kin were obtained. One patient dropped out of the investigation because of the multiple venipunctures involved. The remaining 16 patients were randomly assigned to three groups (group 1, $n = 5$; group 2, $n = 5$, and group 3, $n = 6$). Two patients (one from group 1 and one from group 3) were dropped from the study because they failed to exhibit sufficient evidence of a current problem with excessive water intake during the two initial baseline phases. All 14 of these patients had histories of at least occasional water intoxication in addition to polydipsia. Severity ratings of these patients' water intoxication based upon interviews with staff who were familiar with them placed two in the mild range, seven in the moderate range, and five in the moderate to severe range. Table 1 presents pertinent demographic data on the 14 patients who completed the study. A double-blind, placebo-controlled, crossover design was used as shown in Table 2. Clonidine was administered in a dose of 0.2 mg PO BID and enalapril 10 mg PO BID in single capsules prepared to appear identical to the placebo, which was also administered PO BID. The study

Table 3. Range of Abnormality in Study Patients without Water Restriction but before Experimental Drug Treatment

	Selected Baseline (Phase 2) Assessment Data								
	CUO			PDWG			SNa		
Pt. No.	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**
1	3.3	16.4	12.5	−1.3	6.1	1.4	125	141	136
2	3.9	12.2	6.1	−3.0	5.1	2.0	126	138	133
3	4.3	10.4	6.5	−2.9	10.4	4.5	128	139	132
4	1.0	6.8	2.0	−0.7	3.8	1.3	137	140	138
5	1.8	12.5	6.5	−0.3	9.3	2.9	129	141	138
6	1.3	5.8	3.7	−2.5	5.1	0.6	122	132	127
7	2.9	18.7	13.7	−0.9	2.1	0.4	139	141	141
8	0.7	5.2	2.3	−1.9	7.0	3.4	128	138	134
9	2.0	11.1	5.8	−1.1	2.9	1.0	133	138	135
10	1.2	4.74	2.5	0.3	3.7	1.8	138	142	140
11	1.4	7.6	4.4	−1.1	2.8	1.0	139	142	141
12	0.8	1.7	1.1	0	3.9	2.0	127	137	132
13	1.4	6.14	2.9	−1.8	2.9	1.8	136	139	138
14	1.9	10.8	5.4	−2.3	7.2	3.1	124	138	131

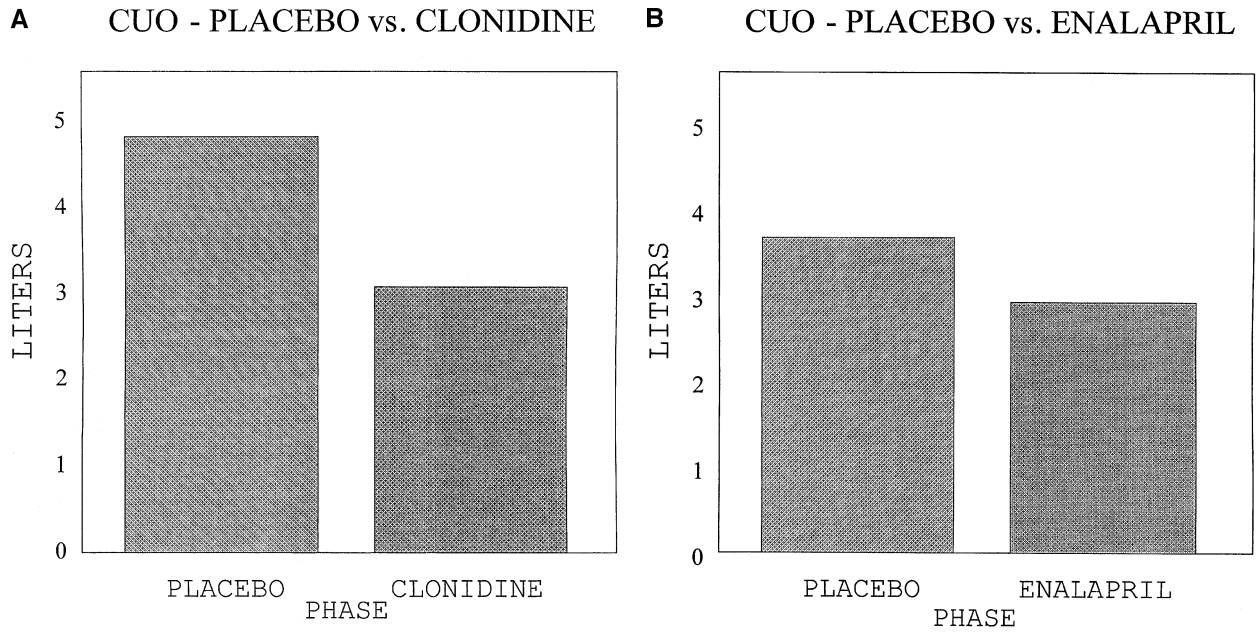


Figure 1. Calculated 24-h urine output in 14 patients treated with placebo, clonidine, and enalapril.

patients were all cohorted in one area of a single hospital floor.

Initial patient assessment included a detailed medical and psychiatric history, repeat physical examination, cognitive testing, electrocardiogram (EKG) and laboratory evaluation, including complete blood count (CBC), serum electrolytes, glucose, liver function tests, T4, and urinalysis. Current medications (see Table 1) were maintained unchanged throughout the 6 months of the study. Any fluid restriction being imposed on the study patients was terminated after 1 month except for emergency situations. Assessment measures included: twice daily determinations of body weight (6:00 A.M. and 7:00 P.M.), vital signs TID for week 1 of each experimental phase and QD thereafter, determination of serum sodium, creatinine and osmolality plus urine osmolality and creatinine twice a week (3:00 P.M. Tuesday and Friday) and weekly CBC. Behavioral and cognitive functioning were assessed using the Nursing Observation Scale for Inpatient Evaluation (NOSIE) (administered by the same nurses on

Table 4. Changes in Dependent Variables in Individual Subjects with Drug Treatment

Positive Response to:	Pt. No.	Clonidine							Enalapril						
		CUO	UOSM	SNa	DWGP	NOSIE	BPRS	BCOG	CUO	UOSM	SNa	DWGP	NOSIE	BPRS	BCOG
Clonidine and enalapril	2	42%	29%	0.8	−14%	−6%	−16%	−5%	41%	47%	−1.1	40%	3%	19%	−30%
	3	55%	125%	1.9	122%	24%	4%	−20%	45%	51%	−3.3	50%	−13%	5%	75%
	7	75%	261%	−0.4	−80%	−9%	3%	−19%	63%	24%	−0.9	15%	−4%	14%	−8%
Clonidine only	1	45%	52%	0.2	−54%	24%	14%	1%	1%	−40%	−3.5	−1%	28%	−2%	4%
	8	49%	15%	2.5	36%	−14%	−8%	−22%	−56%	4%	−1.2	−45%	−4%	−6%	−31%
	10	39%	76%	−0.4	30%	−3%	−7%	−4%	−17%	−34%	−2.3	−18%	−4%	5%	−4%
	13	46%	31%	0.3	−54%	1%	−22%	−17%	14%	−21%	−1.0	19%	−12%	25%	−17%
Enalapril only	6	2%	−31%	−0.6	73%	−26%	3%	11%	22%	51%	−0.7	−51%	−3%	12%	−11%
	9	9%	32%	0.8	−34%	17%	−2%	50%	57%	57%	0.5	−16%	14%	−25%	50%
Neither drug	4	−24%	−11%	0.0	−36%	−6%	−20%	−17%	0%	13%	−1.1	5%	3%	7%	−2%
	5	16%	−4%	0.4	59%	8%	13%	125%	18%	9%	0.4	28%	−4%	1%	−42%
	11	−13%	11%	−0.9	−11%	0%	−6%	8%	20%	−25%	−0.1	−12%	−8%	11%	8%
	12	−96%	26%	−3.1	−38%	6%	4%	−6%	−76%	−42%	−2.5	50%	−2%	3%	−6%
	14	−10%	26%	4.7	12%	19%	6%	−38%	34%	−3%	−1.4	69%	−25%	15%	−38%

All cells show percent improvement during drug phase compared with previous placebo phase except serum sodium, where improvement is expressed as positive change in absolute value.

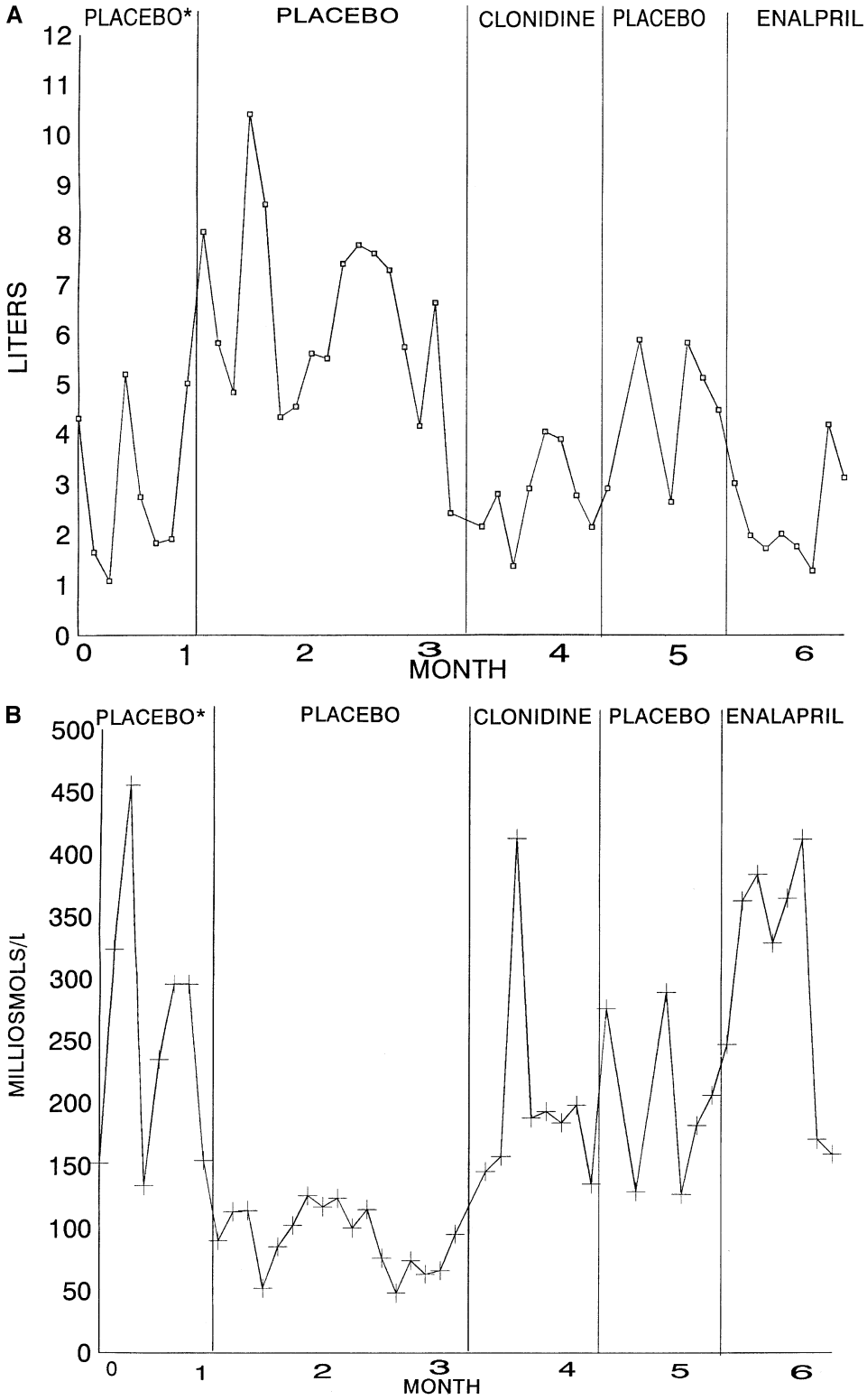
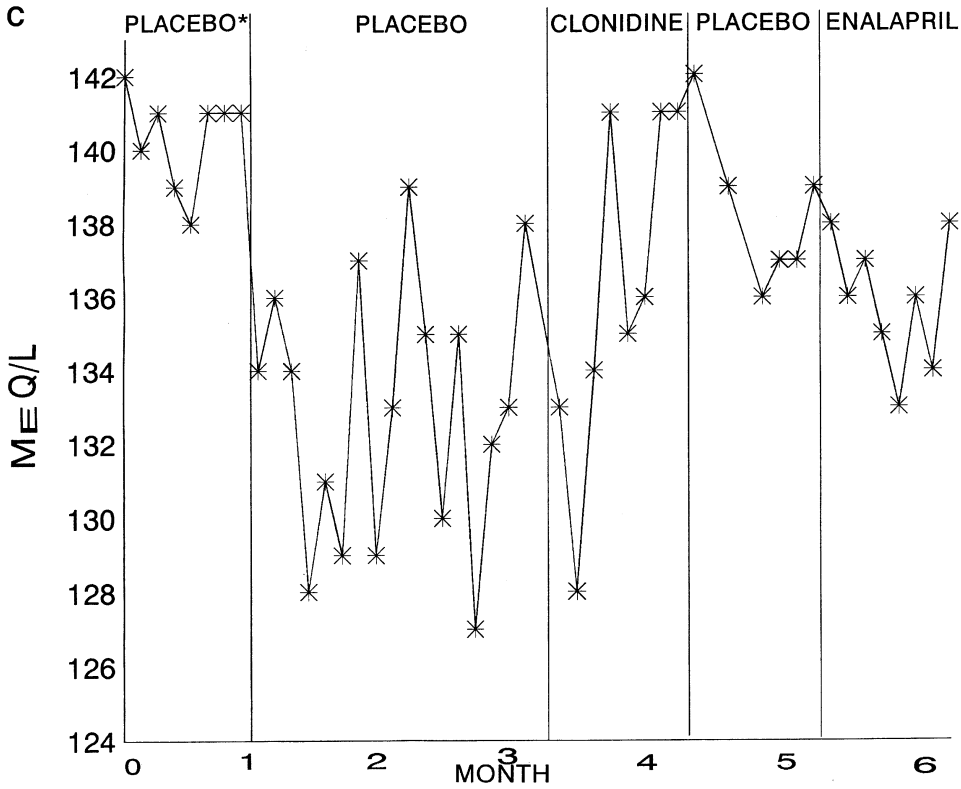


Figure 2. Selected results on one of the study patients (patient #3): (**A**) Calculated urine output (L/24 h); (**B**) 3:00 P.M. urine osmolality (mOsM/L); (**C**) Serum sodium (mEq/L); (**D**) 8:00 A.M. to 3:00 P.M. weight gain (lb). *Placebo plus water restriction. Free access to fluids was permitted throughout subsequent phases.

the same patients once per week), the Brief Psychiatric Rating Scale (BPRS) (administered once weekly by one of the psychiatrist authors, and a clinical nurse specialist) and brief psychological testing, comprising elements of the Mini-Mental state examination, Benton Temporal Orientation, and the Digit Span subscale (multiple forms) of the WAIS-R, administered weekly by one of the psychologist authors, and a psychology assistant.

Because of the patients' inability to cooperate, traditional intake and output records could not be main-



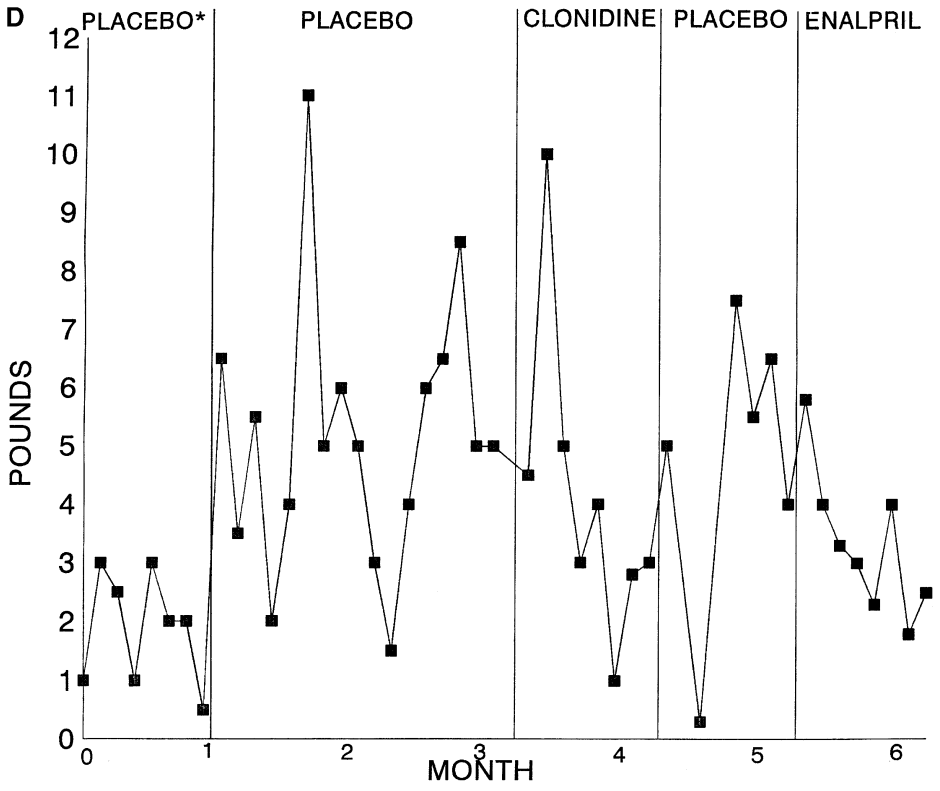


Figure 2. Continued.

tained, and surrogate measures were used as described by previous authors (Vieweg et al. 1992). Thus, diurnal weight gain provided a crude minimum estimate of fluid consumption or more specifically fluid retention in excess of excretion (Vieweg et al. 1988a, b, c, 1989a, b, c, 1990). Calculated urine output (CUO) was based upon the work of Vieweg et al. (1986b, 1988a, 1992), using expected 24-h creatinine production and urine creatinine levels to calculate predicted excretion. Table 3 shows selected baseline (phase 2) assessment data.

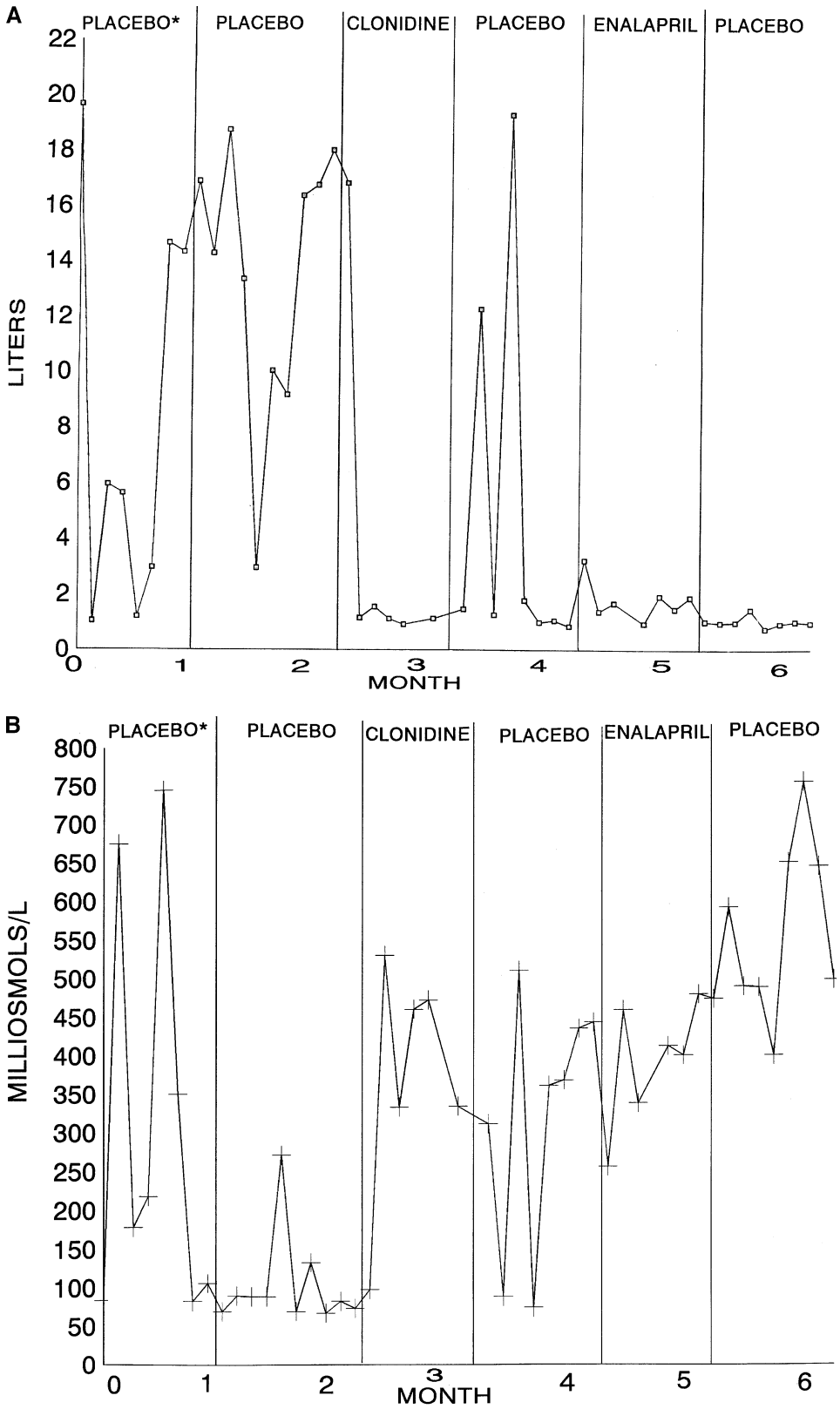


Figure 3. Selected results on one of the study patients (*#7): (**A**) Calculated urine output (L/24 h); (**B**) 3:00 P.M. urine osmolality (mOsM/L). *Placebo plus water restriction. Free access to fluids was permitted throughout subsequent phases.

RESULTS

The outcome measures used to assess possible drug effects can be conveniently grouped as biological changes, including calculated urine output (CUO), urine osmolality (UOSM), serum sodium (SNa), and percentage diurnal weight gain (PDWG), plus secondary psychiatric or neurobehavioral changes as measured by the NOSIE,

BPRS, and brief cognitive testing (BCOG). The results of group-statistical analyses conducted are reported first, followed by a detailed examination of individual subject's responses to the two experimental medications.

One tailed *t*-tests for correlated measures, comparing subjects' mean scores during phase 1, the first baseline phase, to phase 2, the second baseline phase, resulted in significant *p* values showing adverse effects of subjects' free access to water after a month of water restriction on all four biological variables, including CUO ($p < .001$), UOSM ($p < .001$), SNa ($p < .05$), and PDWG ($p < .05$). Similar comparisons on the three behavioral measures failed to yield significant results.

One tailed *t*-tests for correlated measures found CUO to be significantly lower ($p < .05$) and UOSM to be significantly higher ($p < .01$) during the clonidine phase than the preceding placebo phase. *T*-tests comparing the enalapril treatment phase with the preceding baseline phase yielded a significant difference in the same (predicted) direction for CUO ($p < .01$) only. Comparisons on all other dependent variables failed to yield significant results. These tests used an *n* of 14 (collapsing across groups), because the counterbalanced design of the study controlled for order effects. Mean CUOs for drug versus placebo phases are depicted graphically in Figure 1.

Based upon the magnitude of the percentage of change in the predicted direction on the two measures most directly affected by excessive drinking, CUO and UOSM, the authors classified subjects as being "responders" or "nonresponders" to the two experimental drugs. The criteria for judging a subject to be a "responder" was that he showed a mean decrease on CUO and increase on UOSM of 30% or more. These data are summarized in Table 4, where it will be seen that, of the 14 patients who participated in the study, three responded well biologically to both drug treatments (improvement in CUO and UOSM), four responded favorably to clonidine only, two responded favorably to enalapril only, and five showed no clear evidence of benefit from either drug.

Figure 2 depicts data from a patient (#3 in Tables 1 and 3) who responded favorably to both drug treatments across all four biochemical measures (CUO, UOSM, SNa, and PDWG). With the exception of SNa values during the enalapril phase, all the other data show evidence of favorable changes during experimental drug phases and reversals during the placebo phase after the initial drug phase (ABAC). The U-shape of the curve connecting SNa values during the enalapril phase would be consistent with a delayed effect of enalapril. Behavioral measures showed no consistent pattern of change following introduction of drugs for this subject.

Figure 3 depicts data from another patient (#7 in Tables 1 and 3), who showed a reversal of his CUO and UOSM values in the predicted direction after the introduction of both clonidine and enalapril, providing strong evidence of an effect of the experimental medications on his fluid intake. Unlike the previous subject, however, patient #7 did not show any favorable change in SNa or PDWG nor on any of the behavioral measures. A possible explanation for the difference between this subject's data and the previously discussed subject is discussed below.

Both subjects #3 and #7 above showed some evidence of delayed and prolonged effects of the experimental treatments. Similar evidence of delayed effects (ranging from 3 to 14 days) and prolonged effects (ranging from 1 to 4 weeks) was seen in over half of the patients who responded to drug treatment.

DISCUSSION

The results of this study suggest that drugs known to affect body water balance may diminish excess water intake in some patients with histories of water abuse. Indirect measures of fluid intake (CUO and UOSM) were beneficially affected by both clonidine and enalapril in some subjects. In fact, 60% of our study group clearly improved (using the criteria of a mean change of 30% or greater in the predicted directions for both CUO and UOSM), and a few subjects showed associated changes in serum sodium and percentage diurnal weight gain, while on even a brief trial of clonidine or enalapril. These numbers might be greater if trials were prolonged. Individual data presented on two subjects, demonstrated a direct effect of clonidine and enalapril on both CUO and UOSM in the predicted direction during both treatment and placebo phases. Individual data also illustrated a time lag after initial response to drug treatment as well as effects enduring as long as a month after drug treatment. As a result of evidence for carryover effects of both fluid restriction and the study drugs on fluid intake, it is recommended that future studies use longer washout periods after drug and water restriction phases. Similarly, due to delayed effects, it may be useful to use longer drug phases also.

Finally, the data showed inconsistent changes in SNa and PDWG. Subject #3, for example, showed changes in these measures during the experimental phases, whereas subject #7 did not. Likewise, there was no consistent improvement in behavior or cognition in study patients during treatment phases. These findings may be explained by the fact that many subjects, in spite of their history of polydipsia, still had adequate renal function and therefore might not be expected to show changes in SNa or PDWG with excess fluid intake. Changes in those measures would occur only in patients who retain the excess water. It is postulated that many of the subjects still had good kidney function and did not retain fluid volume abnormally. The failure to achieve greater therapeutic effects could also be a consequence of the

relatively brief duration of the treatment phases. In most of our patients, water abuse was of prolonged duration (see Table 1) with changes unlikely to be reversed within the space of a single month of treatment. Although further studies will be required to replicate our findings, the initial data suggest that results comparable to water restriction may be obtainable through medication. We urge that future studies in this area use appropriate placebo controls and crossover designs with statistical analysis to allow more sophisticated evaluation of potentially beneficial drugs than has been possible with previously published work.

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