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Paradoxical Effects of Amitriptyline on Borderline Patients

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A paradoxical increase in suicide threats, paranoid ideation, and demanding and assaultive behavior occurred among 15 borderline inpatients receiving amitriptyline in a double-blind study. This pattern differed significantly from that of 14 nonresponding patients receiving placebo.

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The paradoxical effects of psychotropic medications on some borderline patients have been noted in the literature, but to our knowledge, they have never been systematically characterized. Klein (1) first reported a marked increase in anger among inpatients with "emotionally unstable character disorder" after treatment with imipramine. Gardner and Cowdry (2) were forced to terminate a recent placebo-controlled trial of alprazolam with borderline patients because of a dramatic increase in aggression, self-mutilation, and suicidal behavior among the patients receiving alprazolam. In the course of our own work on the efficacy of amitriptyline and haloperidol for criteria-defined borderline inpatients, we noted a disturbing clinical worsening among some patients receiving amitriptyline. These patients appeared progressively more hostile, irritable, and behaviorally impulsive than they were at baseline. In many cases, these symptoms appeared qualitatively different from the patients' initial complaints and were progressively worse with longer duration and higher doses of medication. As our study specifically assesses changes in the affective, cognitive, and behavioral symptoms of borderline patients treated in an inpatient setting, we were able to investigate the hypothesis of a paradoxical effect of amitriptyline within our current pharmacotherapy design.

METHOD

Our study on the pharmacotherapy of borderline disorders is a double-blind, placebo-controlled comparison of amitriptyline and haloperidol in borderline patients defined by a score of 7 or more on the Diagnostic Interview for Borderline Patients (3). Patient characteristics and study design are presented in detail elsewhere (4). After informed consent, all patients are assessed after 7 days without medications (day 7) and weekly thereafter; the instruments used are the Global Assessment Scale (GAS), Symptom Checklist (SCL-90), 24-item Hamilton Rating Scale for Depression, Beck Depression Inventory, Buss-Durkee Hostility Inventory, Inpatient Multidimensional Psychiatric Scale, Schizotypal Symptom Inventory, and our Ward Scale of Impulse Action Patterns. To enter the pharmacotherapy trials, on day 7 a patient must have 1) a GAS score below 50 and 2) a Hamilton score above 17 or an Inpatient Multidimensional Psychiatric

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TABLE 1. Selected Outcome Scores of Borderline Patients Who Responded to Amitriptyline (N=13) or Had No Response to Amitriptyline (N=15) or Placebo (N=14)

Measure	Amitriptyline Responders				Amitriptyline Nonresponders			
	Score				Score			
	Day 7	Day 42	t	p	Day 7	Day 42	t	p
GAS	42.77	62.69	−7.68	≤.0005	43.30	39.17[a]	3.29	≤.005
Beck Depression Inventory	27.54	11.46	6.15	<.0005	31.93	18.07	4.35	≤.001
SCL-90								
Depression	2.14	0.92	5.31	≤.0005	2.09	1.77	1.86	<.1
Psychoticism	0.93	0.37	5.40	≤.0005	1.53	0.84	3.69	<.005
Additional items	1.60	0.80	3.74	≤.005	2.09	1.37	3.51	<.005
Buss-Durkee Hostility Inventory	49.08	40.77	1.62	n.s.	51.53	48.80	0.90	n.s.
Negativism	2.23	2.00	0.44	n.s.	3.87	2.60	2.87	≤.025
Verbal hostility	6.31	7.15	1.88	<.1	8.07	7.93	0.21	n.s.
Inpatient Multidimensional Psychiatric Scale	115.54	53.92	4.10	<.001	132.93	154.07	−1.60	n.s.
Paranoid projection	5.04	1.54	1.51	n.s.	2.87	5.63[a]	−2.43	<.05
Ward Scale of Impulse Action Patterns								
(total of six below)	7.62	1.92	2.90	<.025	8.27	16.40[a]	−3.00	≤.01
Temper tantrums	0.62	0.15	3.21	<.01	0.67	0.87[a]	−1.87	<.1
Demanding behavior	0.54	0.31	1.39	n.s.	0.33	0.73[a]	−3.06	≤.01
Suicide threats	0.23	0.08	1.48	n.s.	0.47	0.73	−1.47	n.s.
Assaultive acts	0.00	0.00	0.00	n.s.	0.00	0.33[a]	−2.65	<.025
Assaultive threats	0.31	0.00	2.31	<.05	0.27	0.53	−1.74	n.s.
Manipulative behavior	0.92	0.31	3.41	<.01	0.67	0.80	−1.47	n.s.

[a]Condition worsened.

Scale score above 66. On day 7 the patients are randomly assigned to the medications, which are titrated over 1 week to maximum daily doses of 150 mg of amitriptyline or six placebo tablets and maintained at this level for 4 additional weeks. Blood is drawn weekly for determination of the combined plasma level of amitriptyline and nortriptyline. Treatment response was defined as an increase of 6.6 points or more over the baseline GAS score (average of two raters), which was the average amount of improvement for the entire sample. To identify any behavioral effects specifically attributable to amitriptyline, we compared 15 amitriptyline nonresponders with 14 placebo nonresponders and 13 amitriptyline responders with 10 placebo responders on all weekly pharmacotherapy outcome measures. We assessed within-group change with paired t tests and between-group change with analysis of covariance, with baseline values as covariate.

RESULTS

The patients' scores on days 7 and 42 are shown in table 1. The treatment responders, to both amitriptyline and placebo, improved in global functioning, depression, and psychoticism but not in self-rated hostility. The amitriptyline responders improved in all areas of impulsive behavior on the ward scale, significantly so in temper tantrums, assaultive threats, and manipulative behavior. In contrast, the amitriptyline nonresponders became progressively worse in global functioning, paranoid ideation, and impulsive ward behavior. The increase in demanding behavior and assaultive acts was statistically significant, although worsening occurred in all six areas. By day 42 they were significantly more symptomatic than the placebo nonresponders in terms of paranoid ideation and impulsive behavior. Specifically, the amitriptyline nonresponders were more demanding, made more suicide threats, and were more physically assaultive toward others than were the placebo nonresponders. The placebo nonresponders changed little over time but had a modest yet significant increase in self-reported *verbal* hostility and negativism. Compared to the placebo nonresponders, the amitriptyline nonresponders improved more on the affectively loaded scales—the Beck scale, SCL-90 (depression, psychoticism, additional items), and Buss-Durke Hostility Inventory—suggesting that their overall treatment failure was largely attributable to the paradoxical *behavioral* effects of amitriptyline. There was no difference between amitriptyline responders and nonresponders in the final mean±SD plasma level of amitriptyline plus nortriptyline: 246.0±112.2 ng/ml for responders and 245.9±100.4 ng/ml for nonresponders.

DISCUSSION

It is uncertain whether this paradoxical response was related to the antidepressant, the diagnosis of the patient, or an interaction of the two. Paradoxical aggressiveness has been reported as an untoward effect of both amitriptyline and imipramine in the treatment of depressed patients (5). Imipramine has been shown (6) to increase outwardly directed overt hostility and anxiety in nondepressed experimental subjects. On the other hand, borderline patients are characterized by affective, cognitive, and behavioral instability and may demonstrate extreme responses to pharmacologic

Placebo Nonresponders				Drug Versus Placebo Nonresponders on Day 42		
Score						
Day 7	Day 42	t	p	F	p	More Improved
42.31	39.91	1.56	n.s.	0.16	n.s.	
33.33	31.25	0.46	n.s.	5.85	<.025	Drug
2.65	2.79	−0.66	n.s.	4.60	<.05	Drug
1.60	1.47	0.54	n.s.	7.29	<.025	Drug
1.95	2.17	−0.86	n.s.	11.57	<.005	Drug
52.62	56.38[a]	−2.46	≤.05	6.16	<.025	Drug
3.14	3.71[a]	−2.83	≤.025	10.24	<.01	Drug
8.14	9.07[a]	−3.79	≤.005	3.00	<.1	Drug
120.14	121.29	−0.11	n.s.	1.85	n.s.	
5.14	3.86	1.42	n.s.	6.27	<.025	Placebo
5.77	7.38	−1.01	n.s.	4.81	<.05	Placebo
0.42	0.67	−1.39	n.s.	0.57	n.s.	
0.33	0.33	0.00	n.s.	5.19	<.05	Placebo
0.42	0.33	0.56	n.s.	4.53	<.05	Placebo
0.08	0.00	1.00	n.s.	5.08	<.05	Placebo
0.17	0.17	0.00	n.s.	3.73	<.1	Placebo
0.58	0.67	−1.00	n.s.	0.44	n.s.	

stressors (e.g., amphetamines). The paradoxical effect described here appears to reflect a true disinhibition of impulsive behavior independent of the antidepressant effect of amitriptyline. In our opinion, these patients were not undermedicated, overmedicated, or clinically hypomanic. Clinicians should be aware of the potential for paradoxical effects in borderline patients.

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Psychotic Symptoms in Borderline Personality Disorder

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In a pilot study of 13 patients with borderline personality disorder, analysis of brief psychotic symptoms was done. Derealization and depersonalization were the most common symptoms, but drug-free hallucinations were also observed. The symptoms did not appear to be factitious.
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Borderline personality disorder is receiving widespread clinical attention, yet its phenomenology remains unclear. One critical and disputed area is the role of brief psychotic symptoms in this disorder. What is the clinical importance of transient psychotic episodes? Are they part of the main pathology or manifestations of some independent morbid phenomenon?

Kolb and Gunderson (1) claimed that "one clinical aspect of borderline patients that could appear to remain a valuable discriminating feature is the regressive potential, especially their vulnerability to transient psychotic symptoms." A similar observation was made by Tarnopolsky and Berelowitz (2), who reported that the item which discriminates best between borderline and control subjects is "brief unsystematized, psychotic episodes," but it is not included in the *DSM-III* definition of borderline personality disorder and is considered an accessory feature. A revision of the *DSM-III* definition was suggested by Gunderson (3) because the existing empirical evidence seems to support the inclusion of "brief psychotic experiences or episodic lapses in reality testing." Gunderson (personal

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