Clonidine in Acute Aversive Inner Tension and Self-Injurious Behavior in Female Patients With Borderline Personality Disorder

Alexandra Philipsen, M.D.; Harald Richter, Ph.D.; Christian Schmahl, M.D.; Julia Peters, M.D.; Nicolas Rüsch, M.D.; Martin Bohus, M.D.; and Klaus Lieb, M.D.

Background: States of strong aversive inner tension and dissociative symptoms are clinical hallmarks of borderline personality disorder and major reasons for self-injurious behavior, a severe clinical condition for which there are no established pharmacologic treatment options.

Method: The acute effect of 75 and 150 μg of clonidine administered orally in acute states of strong aversive inner tension and urge to commit self-injurious behavior was examined in 14 female patients meeting DSM-IV criteria for borderline personality disorder. Before and 30, 60, and 120 minutes after administration of clonidine, aversive inner tension and dissociative symptoms were assessed using a self-rating instrument for aversive inner tension and dissociation (Dissociation-Tension-Scale acute), and the urge to commit self-injurious behavior and suicidal ideations were assessed using self-rating Likert scales. Blood pressure and heart rate were monitored during the trial.

Results: Aversive inner tension and urge to commit self-injurious behavior before administration of clonidine were strong. After administration of clonidine in both doses, aversive inner tension, dissociative symptoms, urge to commit self-injurious behavior, and suicidal ideations significantly decreased. The strongest effects were seen between 30 and 60 minutes after drug intake and correspond to the pharmacokinetics of clonidine with maximum plasma concentrations after 1 hour. Blood pressure and aversive inner tension and dissociative symptoms were positively correlated before and after administration of clonidine.

Conclusion: Orally given clonidine may be effective for treatment of acute states of aversive inner tension, dissociative symptoms, and urge to commit self-injurious behavior in female patients with borderline personality disorder. Further placebo-controlled studies with larger populations are needed to confirm this finding.

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Received Aug. 6, 2003; accepted March 15, 2004. From the Department of Psychiatry and Psychotherapy, University of Freiburg Medical School, Freiburg, Germany (Drs. Philipsen, Richter, Peters, Rüsch, and Lieb); and the Department of Psychosomatics and Psychotherapeutical Medicine, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany (Drs. Schmahl and Bohus).

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Corresponding author and reprints: Klaus Lieb, M.D., Department of Psychiatry and Psychotherapy, University of Freiburg Medical School, Hauptstr. 5, D-79104 Freiburg, Germany (e-mail: klaus_lieb@psyallg.ukl.uni-freiburg.de).

Recurrent states of subjective aversive inner tension are a core symptom of borderline personality disorder and have been shown to be much more intensive and longer in duration in patients with borderline personality disorder than in healthy controls.[1] Such states of subjective aversive inner tension strongly correlate with dissociative symptoms such as depersonalization, derealization, tonic immobility, and altered sensory perceptions in patients with borderline personality disorder[1] and often lead to a strong urge to self-injury, since self-injurious behavior (such as cutting and burning) may effectively reduce the intensity of aversive inner tension.[2]

The locus ceruleus (LC), as the origin of noradrenergic neurons projecting to various areas of the brain, has been demonstrated to play an important role in the stress response (for review, see Bremner et al.[3]). In animals, increases in LC activity during stress are associated with an increase in regional turnover and release of norepinephrine in brain regions that are innervated by the LC, and administration of catecholamines in animals and humans results in behavioral changes seen during stress, such as increases in blood pressure, heart and respiratory rate, as well as subjective sensations of anxiety.[3,4]

There are only few data on noradrenergic functioning in patients with borderline personality disorder. Two studies demonstrated indirect evidence for increased noradrenergic activity in that the number of platelet α_2-adrenergic receptor binding sites was significantly lower in patients with borderline personality disorder than in normal controls[5] and in depressed patients with borderline personality disorder than in depressed patients without borderline personality disorder.[6] Other studies, however, did not show alterations in cerebrospinal

Table 1. Demographics and Clinical Characteristics of the 14 Female Patients With Borderline Personality Disorder

Pat. No.	Age, y	No. of DSM-IV Criteria	Comorbid Axis I Disorders	
			Current	Lifetime
1	30	8	MDD	ADHD; MDD, recurrent
2	36	5	MDD	MDD, recurrent
3	32	8	Trichotillomania	MDD, recurrent
4	30	6	–	–
5	39	7	–	MDD, recurrent; polytoxicomania
6	21	7	–	MDD, recurrent; polytoxicomania
7	22	9	MDD	ADHD
8	22	7	MDD, alcohol abuse	Anorexia nervosa
9	32	7	–	Eating disorder NOS
10	21	5	Bulimia nervosa	ADHD
11	27	5	–	MDD, recurrent
12	39	9	MDD, alcohol abuse, agoraphobia	PTSD
13	23	8	Alcohol abuse	MDD
14	28	5	MDD, OCD	ADHD
Mean	28.7	6.9		
SD	6.4	1.5		

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, MDD = major depressive disorder, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

fluid levels of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in patients with borderline personality disorder.[7–9] More data are available in patients with posttraumatic stress disorder (PTSD), a trauma-related disorder that often co-occurs with borderline personality disorder and that shares some of the clinical features with borderline personality disorder.[10] These studies showed that the α_2-adrenergic *antagonist* yohimbine, which activates noradrenergic neurons by blocking the α_2 autoreceptor, increased PTSD-related arousal and facilitated the acoustic startle response.[11] Most patients with PTSD had panic attacks and an increase in heart rate, blood pressure, and plasma MHPG after a yohimbine challenge.[11,12] Furthermore, patients reported increased dissociative symptoms such as derealization and depersonalization after administration of yohimbine. In patients with PTSD, administration of yohimbine resulted in an increase in anxiety and a decrease in brain metabolic response as shown by positron emission tomography in the prefrontal, temporal, parietal, and orbitofrontal cortices.[8]

Clonidine, an α_2-adrenergic receptor *agonist* that exerts both peripheral and central effects, suppresses release of norepinephrine through actions at the presynaptic α_2 autoreceptor. Clonidine has been reported to be helpful for symptoms of hyperarousal, hypervigilance, aggression, and behavioral irritability in combat veterans with PTSD[13] and in children with PTSD.[14,15] In addition, clonidine was effective in reducing hyperactivity and impulsivity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD),[16–19] a disorder that has recently been reported to be highly associated with a diagnosis of borderline personality disorder in adulthood.[20]

In the present study, a randomized, single-blind pilot study was conducted to investigate the effect of clonidine in states of acute aversive inner tension and dissociative symptoms leading to a strong urge to commit self-injurious behavior in patients with borderline personality disorder.

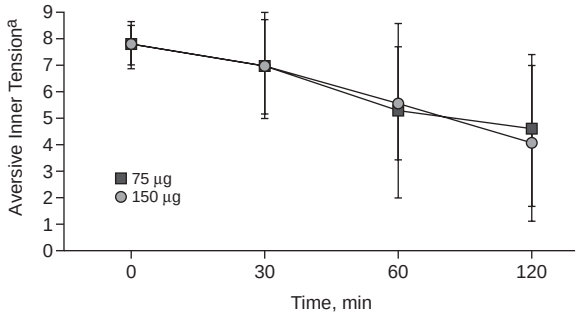
METHOD

Patients

Twenty-two female inpatients with borderline personality disorder meeting the diagnostic criteria of DSM-IV[21] entered this randomized, single-blind treatment trial. Diagnosis of borderline personality disorder was confirmed by assessment of the appropriate segment of the Structured Clinical Interview for DSM-IV (SCID-II),[22] and comorbid Axis I disorders were assessed by the SCID-I.[23] Only patients with comorbid current alcohol or substance dependency were excluded from the trial. The study protocol was approved by the local ethical board of the University of Freiburg. Written informed consent was obtained from patients prior to study participation.

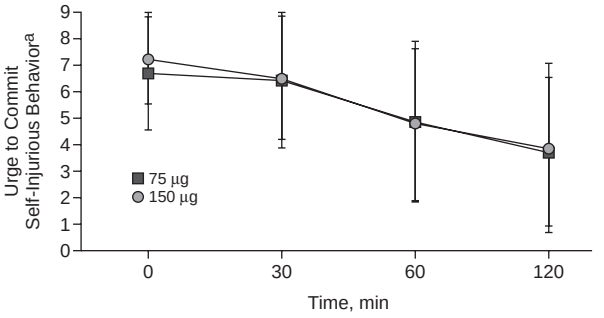
Fourteen patients finished the trial. Two patients withdrew initial study consent and 6 patients dropped out for the following reasons: 1 patient started new medication with risperidone during the trial because of persisting psychotic symptoms, 2 patients refused to fill out the questionnaires after the second dose of clonidine, and 3 patients terminated inpatient treatment before the second dose of clonidine was administered. Dropouts were not significantly different from study completers with respect to gender, age, number of DSM-IV criteria, and comorbid Axis I disorders. Demographic and clinical characteristics of the 14 study completers are given in Table 1. Thirteen patients exhibited self-injurious behavior (cutting, burning), and all patients suffered from severe aversive inner tension and dissociative symptoms before self-injurious behavior and from chronic suicidal ideations.

Figure 1. Aversive Inner Tension Before and After Administration of 75 and 150 µg of Clonidine in 14 Women With Borderline Personality Disorder



[a]Aversive inner tension was self-rated by patients using the 10-point Dissociation-Tension-Scale acute.

Figure 2. Urge to Commit Self-Injurious Behavior Before and After Administration of 75 and 150 µg of Clonidine in 14 Women With Borderline Personality Disorder



[a]Urge to commit self-injurious behavior was self-rated by patients using a 10-point Likert scale (0–9).

Psychotropic medication was held constant throughout the trial: 7 patients received antidepressants, 2 patients received neuroleptics, and 1 patient was treated with both an antidepressant and a neuroleptic. Four patients were free of psychotropic medication.

Symptom Assessment

Patients rated acute aversive inner tension using the Dissociation-Tension-Scale acute (DSS-a).[24] The DSS-a is a 22-item self-rating questionnaire integrating items of the Dissociative Experience Scale (DES)[25] (German version: Fragebogen zu dissoziativen Symptomen [FDS][26]) and items from the Somatoform Dissociation Questionnaire (SDQ-20).[27] Subjective intensity of tension and dissociation were rated on a 10-point Likert scale ranging from 0 (not at all) to 9 (most intensive). In addition, urge to commit self-injurious behavior was self-rated on a 10-point Likert scale ranging from 0 (not at all) to 9 (most intensive), and suicidal ideations were self-rated on a 6-point Likert scale ranging from 0 (not at all) to 5 (thinking is completely restricted to suicidal ideations).

Procedure

Patients were asked to contact one of the study conductors (A.P.) in case of strong aversive inner tension. Strong aversive inner tension was defined as ≥ 7 on the Likert scale (0–9). After reporting strong aversive inner tension, patients rated aversive inner tension, dissociative symptoms, urge to commit self-injurious behavior, and suicidal ideations on the respective scales. Each patient was then randomly assigned in a single-blind fashion to receive either 75 µg of clonidine for the treatment of the first acute state and 150 µg for the second acute state or vice versa. For blinding of the dose of drug, clonidine was dissolved in 20 mL of water. Systolic and diastolic blood pressure and heart rate were measured before intake of clonidine. Because patients were involved in a treatment program for patients with borderline personality disorder, which specializes in Dialectical Behavior Therapy (DBT), patients were instructed before drug intake not to use any behavioral skills or strategies. One of the study conductors (A.P.) actively questioned the use of behavior techniques during the blood pressure and heart rate measurements.

According to the pharmacokinetics of clonidine with maximal plasma levels after 1 hour,[28] self-assessments as well as blood pressure and heart rate measurements were repeated 30, 60, and 120 minutes after drug intake. Due to the relatively long elimination half-life of clonidine (10–20 hours), the second dose was given at least 4 days later. The period between the first and second drug intakes varied because of the unpredictability of acute states of tension, and ranged from 4 to 16 days (mean ± SD = 7.8 ± 3.9 days).

Statistical Analysis

Values are given as mean ± standard deviation (SD). Because of high standard deviations for raw scores of aversive inner tension, urge to commit self-injurious behavior, dissociative symptoms, and blood pressure, raw scores were transformed into logarithmic scores [aversive inner tension and urge to commit self-injurious behavior = 1 log x, dissociative symptoms = log(5 + x) – log(5), and blood pressure = log(x)] which were used for further analyses. Analysis of variance (ANOVA) was used to assess changes in rating scale scores over time during the 2 treatment conditions (75 or 150 µg of clonidine). Analysis of covariance (ANCOVA) was used to assess the effect of changes in blood pressure and heart rate on the changes in rating scores. Post hoc tests (repeated-measures ANOVA) were used to analyze differences between baseline levels and levels after administration

of clonidine. Blood pressure and heart rate were entered as covariates of interest into an analysis of variance and covariance, with psychometric data as dependent variables (aversive inner tension scale, urge to commit self-injurious behavior scale, dissociation scale, suicidal ideation scale).

RESULTS

Clonidine was well tolerated by all 22 patients who entered the trial. Severe adverse events did not occur during the trial. Baseline scores of aversive inner tension (see Figure 1) and urge to commit self-injurious behavior (see Figure 2) were high before administration of 75 and 150 μg of clonidine (tension: 7.8 ± 0.8 and 7.8 ± 0.8, respectively; urge to commit self-injurious behavior: 6.6 ± 2.1 and 7.2 ± 1.7), whereas suicidal ideations and dissociative symptoms were rated as rather moderate (suicidal ideations: 2.4 ± 1.7 and 2.8 ± 1.6, respectively; dissociative symptoms: 4.0 ± 2.1 and 3.6 ± 0.8). Since ANOVA did not reveal any main effects for dose of clonidine, data for 75 and 150 μg of clonidine were pooled.

Psychometric Data

Changes in aversive inner tension after administration of clonidine are given in Figure 1. Repeated-measures ANOVA revealed a significant main effect for time ($F = 31.8$, $df = 3,39$; $p < .001$), indicating that the severity of aversive inner tension significantly decreased over time after administration of clonidine. There was no main effect for dose ($F = 0.18$, $df = 1,13$; $p = .7$) and no time × dose interaction ($F = 0.04$, $df = 3,39$; $p = .98$). Post hoc analyses showed that the strongest decrease of aversive inner tension occurred between 30 and 60 minutes after administration of clonidine ($p < .001$).

Changes of urge to commit self-injurious behavior after administration of clonidine are shown in Figure 2. Repeated-measures ANOVA revealed a significant main effect for time ($F = 21.8$, $df = 3,39$; $p < .001$), indicating that the urge to commit self-injurious behavior was also significantly lowered over time after clonidine. Similar to the changes of aversive tension, there was no main effect for dose ($F = 0.1$, $df = 1,13$; $p = .8$) and no time × dose interaction ($F = 0.73$, $df = 3,39$; $p = .5$). None of the patients committed self-injurious behavior after clonidine. Post hoc analyses revealed a significant decrease in urge to commit self-injurious behavior between 30 and 60 minutes and between 60 and 120 minutes after clonidine ($p < .001$ and $p < .05$, respectively). In the first 30 minutes after drug application, the urge remained unchanged ($p = .3$; see Figure 2).

Similar main effects for a reduction in dissociative symptoms and suicidal ideations with time after clonidine ($F = 15.8$, $df = 3,39$; $p < .001$ and $F = 8.0$, $df = 3,39$; $p < .001$, respectively) but no dose or dose × time interaction effects were seen. Dissociative symptoms were significantly lowered after 30 minutes ($p < .01$) and between 30 and 60 minutes and between 60 and 120 minutes ($p < .05$). Suicidal ideations did not decrease in the first 30 minutes ($p = .8$) but significantly decreased after 60 and 120 minutes ($p < .01$ and $p < .01$, respectively).

Further analysis showed a significant correlation of aversive inner tension with urge to commit self-injurious behavior and with suicidal ideations (regression coefficient = 0.78, $p < .0001$ and regression coefficient = 2.43, $p < .05$, respectively).

Table 2. Changes in Blood Pressure and Heart Rate Before and After Administration of 75 or 150 μg of Clonidine Orally During Acute States of Aversive Tension in 14 Female Patients With Borderline Personality Disorder

Dose	Systolic Blood Pressure Mean ± SD	Diastolic Blood Pressure Mean ± SD	Heart Rate Mean ± SD
75 μg clonidine			
Pre	130.4 ± 22.2	82.1 ± 11.0	88.9 ± 9.7
30 min	121.4 ± 18.3	79.3 ± 14.5	86.3 ± 8.6
60 min	114.6 ± 15.6	77.5 ± 12.2	78.3 ± 11.0
120 min	115.4 ± 19.7	77.4 ± 12.7	80.7 ± 9.7
150 μg clonidine			
Pre	132.5 ± 27.6	87.1 ± 16.8	83.6 ± 13.0
30 min	120.7 ± 23.1	80.0 ± 11.8	82.6 ± 11.1
60 min	120.7 ± 15.4	77.5 ± 10.3	82.0 ± 11.4
120 min	111.1 ± 13.2	75.4 ± 11.4	80.6 ± 12.9

Blood Pressure and Heart Rate and Correlation With Psychometric Data

Changes in blood pressure and heart rate are given in Table 2. Systolic and diastolic blood pressure as well as heart rate significantly decreased after administration of clonidine (main effect for time: $F = 19.7$, $df = 3,39$; $p < .001$; $F = 6.2$, $df = 3,39$; $p < .01$; and $F = 5.9$, $df = 3,39$; $p < .01$, respectively). There was no dose effect on blood pressure, indicating that both doses similarly decreased blood pressure. With respect to heart rate, 75 μg of clonidine was more effective in lowering heart rate as compared to 150 μg (dose × time interaction $F = 3.1$, $df = 3,39$; $p < .05$). Post hoc tests showed that systolic blood pressure was significantly lowered after 30 minutes ($p < .01$) and between 60 and 120 minutes after drug intake ($p < .01$), that diastolic blood pressure significantly decreased in the first 30 minutes ($p < .05$), and that heart rate significantly decreased after 60 minutes ($p < .01$).

Covariance analyses with systolic and diastolic blood pressure as covariates revealed a significant positive correlation of aversive inner tension and diastolic blood pressure (regression coefficient = 1.4, $p < .05$) and systolic blood pressure (regression coefficient = 1.08, $p < .05$). Systolic, but not diastolic, blood pressure significantly correlated with the severity of dissociative symptoms (regression coefficient = 0.15, $p < .05$).

DISCUSSION

In this study, we showed that the oral administration of clonidine during acute states of aversive inner tension was associated with a significant decrease of acute aversive inner tension, urge to commit self-injurious behavior, suicidal ideations, and dissociative symptoms in female patients with borderline personality disorder.

This study was an open pilot study that included only a relatively small number of patients. Nevertheless, the effects were strong, and, from a clinical point of view, patients had obvious benefits from this treatment. A reduction of tension levels from around 8 to 4 or 5 on the 10-point Likert scale (0–9) indicates a meaningful clinical effect. During tension levels of 4 or 5, in contrast to tension levels of 8, patients are, for example, able to act goal-oriented and are able to follow psychotherapeutic advice.

Since the study did not include a placebo control, we cannot fully exclude that the decrease of aversive tension, dissociative symptoms, suicidal ideations, and urge to commit self-injurious behavior is simply a time effect due to the waxing and waning of acute states of aversive inner tension and dissociation. However, the strongest effects of clonidine were seen between 30 and 60 minutes after intake, which corresponds well to the pharmacokinetics of clonidine with maximum plasma concentrations reached after 1 hour.[28] Also, blood pressure and aversive inner tension and dissociative symptoms were positively correlated before and after application of clonidine. This finding may indicate that the psychological changes are due to the biological effects of clonidine (although the study design was not suited to prove causality). Although patients were instructed before drug intake not to use any behavioral skills to regulate aversive states of tension and although the use of such skills was controlled for by questioning the patients several times after drug intake, we cannot be fully sure that the patients did not use any behavioral strategies to reduce their levels of tension. Furthermore, possible placebo effects may have been increased by informing patients that they were to receive an active drug that could decrease levels of tension. Therefore, further double-blind placebo-controlled treatment trials with larger sample sizes are needed to confirm our findings.

Our study indirectly supports the hypothesis that the noradrenergic system is involved in the pathogenesis of acute states of aversive inner tension in patients with borderline personality disorder. Clonidine is an α_2-adrenergic receptor agonist, which down-regulates noradrenergic activity by lowering LC firing and norepinephrine release in target brain regions, such as the prefrontal cortex (PFC), which plays an important role in planning and organizing behavior.[29] Under stressful conditions, when norepinephrine is increased in the PFC, postsynaptic α_1 receptors become activated, causing a disturbance of PFC functioning.[30,31] This disturbance in PFC functioning can be effectively antagonized by application of α_2 agonists such as clonidine or guanfacine as shown in preclinical studies.[32,33] Since previous studies have shown alterations of the noradrenergic system[5,6] and PFC functioning[34,35] in patients with borderline personality disorder, the noradrenergic system might play a central role in the etiology of acute states of aversive tension in borderline personality disorder and the PFC might play a central role in coping with such states. Clonidine might be a useful tool to interrupt such aversive states and help patients to cope with such states in a functional way (and not by self-injurious behavior).

A previous study by our group showed a strong correlation between aversive inner tension and dissociative symptoms.[1] After clonidine application, severity of dissociative symptoms was significantly reduced as shown here. Although this finding, in conjunction with an increase in dissociative symptoms (derealization and depersonalization) in patients with PTSD after a yohimbine-challenge,[36] argues for an involvement of the noradrenergic system in the etiopathology of dissociative symptoms, other studies have provided evidence for an involvement of additional systems. In an open-label trial, we found that the opioid receptor antagonist naltrexone was effective in reducing dissociative symptoms,[37] whereas in another open trial, depersonalization was successfully reduced with serotonin reuptake inhibitors.[38] These findings might indicate that several neurobiological systems, such as the noradrenergic, serotonergic, and opioid, are involved in dissociative processes.

One important symptom of borderline personality disorder is chronic suicidal ideations. Up to 9% of patients with borderline personality disorder commit suicide in life.[2] In this study, suicidal ideations were significantly reduced after clonidine administration, indicating that this pharmacotherapeutic treatment option might help to prevent suicidal behavior during acute stress conditions. If this finding is confirmed in placebo-controlled studies of borderline patients, treatment with clonidine would be a major advance in the management of these chronically suicidal and difficult-to-manage patients.

Drug names: clonidine (Catapres, Duraclon, and others), guanfacine (Tenex and others), naltrexone (ReVia and others), risperidone (Risperdal).

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