An Open Trial of Naltrexone in the Treatment of Depersonalization Disorder

Daphne Simeon, MD and Margaret Knutelska, PhD

Abstract: Depersonalization disorder (DPD) remains one of the few disorders in modern psychiatry for which no treatments are established that are even partially effective, whether pharmacological or psychotherapeutic. Depersonalization disorder is a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* dissociative disorder characterized by a pervasive subjective sense of unreality and detachment with intact reality testing. Two recent controlled medication trials, one with lamotrigine and one with fluoxetine, failed to show efficacy. There is some evidence for dysregulation of endogenous opioid systems in depersonalization, and a few studies have suggested that opioid antagonists may have efficacy in the treatment of dissociation and depersonalization symptoms. In this prospective open treatment trial, 14 subjects were recruited and treated with naltrexone for 6 weeks to a maximum dose of 100 mg/d (first 7 subjects) or 10 weeks to a maximum dose of 250 mg/d (next 7 subjects). Mean naltrexone dose was 120 mg/d. There was an average 30% reduction of symptoms with treatment, as measured by 3 validated dissociation scales. Three patients were very much improved, and 1 patient was much improved with naltrexone treatment. These findings are potentially promising in a highly treatment-refractory disorder for which no treatment guidelines exist and warrant a randomized controlled trial.

(*J Clin Psychopharmacol* 2005;25:267–270)

Depersonalization disorder (DPD) remains one of the few psychiatric disorders for which no treatment guidelines exist. DPD is classified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* as a dissociative disorder, characterized by a pervasive subjective sense of unreality and detachment. The self does not ''feel real,'' although in contrast to psychosis, reality testing remains intact. The disorder has an approximately 1:1 sex ratio with early onset around age 16 years.[1–3] Previously considered rare, it is now believed to affect approximately 2% of the population,[4] and its course is usually chronic with continuous symptoms.[1–3] The disorder has been associated with childhood emotional trauma,[5] as well as with severe life stress.[2,3] It is also often triggered by severe episodes of depression or panic, yet continues on after the former have abated.[2] To date, there is no known efficacious treatment of the disorder, pharmacological or psychotherapeutic. Two recent controlled medication trials, one with lamotrigine[6] and one with fluoxetine,[7] failed to show efficacy. Thus, DPD remains one of the few truly treatment-refractory illnesses in modern psychiatry.

There are few neurochemical and neurohormonal studies of chronic depersonalization, and they have suggested possible dysregulation of several systems including the hypothalamic-pituitary-adrenal axis, noradrenergic, serotonergic, glutamatergic, and endogenous opioids (see Ref. 8 for a review). The endogenous opioid system is well known to mediate stress-induced analgesia.[9] For example, in posttraumatic stress disorder, the analgesic response to combat stimuli can be blocked by pretreatment with the opioid antagonist naloxone.[10] The κ opioid system is also implicated in dissociation: the κ opioid agonist enadoline has been shown to induce a potent ''clean'' depersonalization-like syndrome in healthy subjects compared to placebo, with perceptual disturbances and a sense of detachment.[11] Along these lines, opiate antagonists have been reported to reduce symptoms of dissociation and depersonalization in a few preliminary studies. In one study of subjects with borderline personality disorder, decrease in dissociation was reported using high-dose naltrexone.[12] Similarly, the opioid antagonist nalmefene was reported to decrease emotional numbing in veterans with posttraumatic stress disorder.[13] Specifically in DPD, one study reported a marked decline in chronic depersonalization in subjects treated intravenously with naloxone, although the duration of the response was not clearly explicated.[14] Of note, naloxone, naltrexone, and nalmefene are all nonspecific opioid antagonists, whereas selective κ opioid antagonists have not yet been developed for human use.

To further test the possible efficacy of opioid antagonists in the treatment of DPD, we conducted an open prospective trial of naltrexone in *Diagnostic and Statistical*

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.
Received June 4, 2004; accepted after revision December 28, 2004.
Address correspondence and reprint requests to Daphne Simeon, MD, Department of Psychiatry, Box 1230, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029. E-mail: daphne.simeon@mssm.edu.

ISSN: 0271-0749/05/2503-0267
DOI: 10.1097/01.jcp.0000162803.61700.4f

TABLE 1. Characteristics and Treatment Response of the 14 Naltrexone Trial Participants

Case	Age	Sex	Current Axis I Disorders	Concurrent Medications	Naltrexone Dose (mg/d)	No. Weeks Completed	CGI Score at Termination
1	41	M	GAD, DYS	Fluoxetine	100	6	4
2	25	M	SOM		50	4	5
3	27	M	SP	Fluoxetine	100	6	3
4	25	M	MD, SP	Citalopram, clonazepam	100	6	4
5	31	M		Clonazepam	100	6	4
6	27	M		Alprazolam	100	6	3
7	35	M		Fluoxetine	100	6	1
8	19	F	MD, OCD	Bupropion	250	10	2
9	26	M		Citalopram	150	6	3
10	51	M			25	0	
11	23	F	PD, GAD, SP		50	2	3
12	37	M	GAD	Clonazepam	150	8	1
13	29	M		Amitriptyline, sertraline, clonazepam	250	10	4
14	37	M			150	10	1

Cases 1 to 7 received a maximum 100 mg/d dose for 6 weeks; cases 8 to 14 received a maximum 250 mg/d dose for 10 weeks. Case 10 did not return after week 0 and does not have a CGI score. GAD indicates generalized anxiety disorder; DYS, dysthymia; SOM, somatoform disorder; MD, major depression; PD, panic disorder; SP, social phobia; OCD, obsessive-compulsive disorder.

Manual of Mental Disorders, Fourth Edition DPD. We hypothesized that naltrexone treatment would result in a significant decrease of depersonalization symptoms with treatment.

MATERIALS AND METHODS

The trial was approved by the institution's review board, and all participants gave written informed consent before participation. Subjects were allowed to be on concurrent medications only if they had been on the same regimen and dosage for at least 2 months, and their regimens were kept constant for the duration of the study; most subjects had been on stable regimens for much longer. Concomitant psychotherapy was allowed only if it was initiated at least 2 months prior and was not symptom-focused such as cognitive behavioral therapy.

Subjects were diagnosed with DPD by both clinical interview and by the Structured Clinical Interview for Dissociative Disorders.[15] Subjects with lifetime diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, or organic mental disorder were excluded from the study, as were individuals with current substance use disorder. Axis I disorders were assessed by the Structured Clinical Interview for Axis I disorders.[16] Individuals with acute or unstable medical illnesses, as well as any history of seizure disorder or head trauma, were excluded. All subjects had a normal baseline routine laboratory evaluation with negative urine toxicology screenings.

The initial 7 subjects were treated for 6 weeks at a maximum daily dose of 100 mg. The trial was subsequently extended in duration and dosing, so that the next 7 subjects were treated for 10 weeks at a maximum daily dose of 250 mg. The rationale for the use of high-dose naltrexone, as well as the increase in naltrexone dosing halfway through the trial, is that naltrexone is a nonspecific opioid antagonist which blocks μ receptors at low doses but requires higher doses to block other opioid receptors such as the κ receptors.

Four measures of change were used: 2 clinician-rated (Clinical Global Improvement [CGI] and Clinician-Administered Dissociative States Scale) and 2 self-report (Cambridge Depersonalization Scale and Dissociative Experiences Scale). The CGI[17] is a standard clinician-rated 7-point scale which was specifically applied to rate change in depersonalization. The Clinician-Administered Dissociative States Scale[18] is a 27-item clinician-rated scale of dissociative

TABLE 2. Baseline and End Point Dissociation Measured by 3 Scales in 13 Depersonalization Disorder Subjects Prospectively Treated With Naltrexone*

Measure	Baseline	End Point	% Decrease	Paired t (df = 12)	P
CADSS	14.8 ± 10.5	8.9 ± 6.5	39.6	2.65	0.021
CDS	86.3 ± 44.1	65.2 ± 43.2	24.5	2.58	0.024
DES-DPS	43.5 ± 24.3	32.2 ± 24.0	26.2	2.51	0.027

CADSS indicates clinician-administered dissociative states scale; CDS, cambridge depersonalization scale; DES, dissociative experiences scale.
*One of the 14 subjects dropped out after week 0 and is not included.

symptoms, scored on a 5-point scale ranging from ''not at all'' to ''extremely.'' It has good interrater reliability, high internal consistency, and good validity. The Cambridge Depersonalization Scale, specifically designed to measure depersonalization/derealization symptoms, consists of 29 self-report items, each rated for both frequency and duration.[19] The scale has good internal consistency, convergent validity, and discriminant validity. The Dissociative Experiences Scale[20] is a 28-item self-report questionnaire of dissociative experiences, shown to have good test-retest reliability, high internal consistency, and strong convergent, discriminant, and criterion validity. The depersonalization factor subscore of the Dissociative Experiences Scale was used in this study.[21]

RESULTS

Fourteen adult subjects were enrolled with a mean age of 30.9 ± 8.5 years, 12 men and 2 women. Table 1 presents the characteristics and overall treatment response of the 14 participants. With respect to concomitant psychotropic medication treatment, 4 subjects were taking selective serotonin reuptake inhibitors, 3 benzodiazepines, 1 bupropion, 2 combinations of antidepressants and benzodiazepines, and 4 were medication-free. Five subjects did not complete the entire trial duration, one of whom (case 10) did not return after the baseline visit and was therefore excluded from statistical analyses. Of the 5 noncompleters, 2 subjects discontinued secondary to naltrexone-related side effects, 1 subject was withdrawn from the trial because of increasing depression to commence antidepressant therapy, and 2 subjects were lost to follow-up.

Mean final naltrexone daily dose across all subjects was 120.0 ± 66.6 (range 25–250) mg/d. According to CGI score at termination, 3 subjects were rated as 1 (very much improved), 1 subject as 2 (much improved), 4 subjects as 3 (slightly improved), 4 subjects as 4 (unchanged), and 1 subject as 5 (slightly worse). There was no significant correlation between naltrexone dose and CGI score at termination ($r = -0.27$, $df = 12$, $P = 0.37$). Scores on the dimensional scales were compared between baseline and termination by paired-sample t tests (Table 2). It can be seen that all 3 scale scores declined significantly with treatment. Average symptom improvement for all subjects across the 3 scales was approximately 30%.

Adverse effects reported by the 14 trial participants were, in order of decreasing frequency, as follows: sedation/fatigue (N = 7), nausea (N = 5), depression (N = 3), diarrhea (N = 1), insomnia (N = 1), activation (N = 1), tingling (N = 1), feeling hot (N = 1), and nightmares (N = 1). Two subjects reported no adverse effects.

DISCUSSION

Our preliminary findings appear promising, especially given the absence of any medications known to have efficacy for primary depersonalization and the well-known negligible ''placebo'' response of this disorder. Indeed, of the 12 participants who completed at least 4 weeks of naltrexone treatment, 4 (33%) showed marked improvement with a 50% to 90% reduction in symptoms. All 3 very much improved subjects, exhibiting at least 70% symptomatic improvement, opted to continue naltrexone after terminating the trial; they were not subsequently followed up. The findings are in accordance with the other few existent studies suggesting that opioid antagonists may be useful in the treatment of dissociation.[12–14] Strengths of the study include its prospective design; the use of standardized validated scales, both clinician and self-rated; and the well-controlled use of concomitant treatments. Limitations include the small sample size, the modified trial duration and dosing halfway, and the absence of blinded controlled design. Still, the results indicate that a larger randomized controlled trial of opioid antagonists in the treatment of DPD is warranted.

ACKNOWLEDGMENT

Partly supported by NIH grant 5MO1 RR00071 to the Mount Sinai General Clinical Research Center.

REFERENCES

1. Simeon D, Gross S, Guralnik O, et al. Feeling unreal: 30 cases of *DSM-III* depersonalization disorder. *Am J Psychiatry*. 1997;154:1107–1113.
2. Simeon D, Knutelska M, Nelson D, et al. Feeling unreal: a depersonalization disorder update of 117 cases. *J Clin Psychiatry*. 2003;64:990–997.
3. Baker D, Hunter E, Lawrence E, et al. Depersonalisation disorder: clinical features of 204 cases. *Br J Psychiatry*. 2003;182:428–433.
4. Ross CA. Epidemiology of multiple personality disorder and dissociation. *Psychiatr Clin North Am*. 1991;14:503–517.
5. Simeon D, Guralnik O, Schmeidler J, et al. The role of childhood interpersonal trauma in depersonalization disorder. *Am J Psychiatry*. 2001;158:1027–1033.
6. Sierra M, Phillips ML, Krystal J, et al. A placebo-controlled, crossover trial of lamotrigine in depersonalization disorder. *J Psychopharmacol*. 2003;17:103–105.
7. Simeon D, Guralnik O, Schmeidler J, et al. Fluoxetine therapy in depersonalization disorder: randomised controlled trial. *Br J Psychiatry*. 2004;185:31–36.
8. Simeon D. Depersonalization disorder: a contemporary overview. *CNS Drugs*. 2004;18:343–354.
9. Madden J, Akil H, Patrick RL, et al. Stress-induced parallel changes in central opioid levels and pain responsiveness in the rat. *Nature*. 1977;265:358–360.
10. Pitman RK, Van der Kolk BA, Orr SP, et al. Naloxone-reversible analgesic response to combat-related stimuli in posttraumatic stress disorder: a pilot study. *Arch Gen Psychiatry*. 1990;47:541–544.
11. Walsh SL, Strain EC, Abreu ME, et al. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. *Psychopharmacology (Berlin)*. 2001;157:151–162.
12. Bohus MJ, Landwehrmeyer B, Stiglmayr CE, et al. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: an open-label trial. *J Clin Psychiatry*. 1999;60:598–603.
13. Glover H. A preliminary trial of nalmefene for the treatment of emotional numbing in combat veterans with post-traumatic stress disorder. *Isr J Psychiatr Relat Sci*. 1993;30:255–263.
14. Nuller YL, Morozova MG, Kushnir ON, et al. Effect of naloxone therapy on depersonalization: a pilot study. *J Psychopharmacol*. 2001;15:93–95.

15. Steinberg M. *Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D), revised*. Washington, DC: American Psychiatric Press, Inc; 1994.
16. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Version (SCID-P), Version 2*. New York: New York State Psychiatric Institute Biometrics Research; 1995.
17. Guy W. *Assessment Manual for Psychopharmacology*. Washington, DC: US Department of HEW Publications; 1976.
18. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress*. 1998;11:125–136.
19. Sierra M, Berrios GE. The Cambridge Depersonalisation Scale: a new instrument for the measure of depersonalization. *Psychiatry Res*. 2000; 93:153–164.
20. Bernstein-Carlson E, Putnam FW. An update on the Dissociative Experiences Scale. *Dissociation*. 1993;6:16–27.
21. Simeon D, Guralnik O, Gross S, et al. The detection and measurement of depersonalization disorder. *J Nerv Ment Dis*. 1998;186: 536–542.