

Naltrexone in the Treatment of Dissociative Symptoms in Patients With Borderline Personality Disorder: An Open-Label Trial

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Background: Dissociative phenomena, including flashbacks, are common in patients with borderline personality disorder and posttraumatic stress disorder (PTSD). Although dissociative symptoms can be severe and may interfere with psychotherapy, there is no established pharmacotherapy for these symptoms. Evidence suggests that alterations of the endogenous opiate system contribute to dissociative symptoms in patients with borderline personality disorder and PTSD.

Method: We treated 2 groups of female borderline personality disorder patients (N = 13, with an overlap of 5 patients between the 2 groups; all met the diagnostic criteria of DSM-IV and the revised Diagnostic Interview for Borderline Patients) who experienced prominent dissociative phenomena including flashbacks with the nonselective opiate receptor antagonist naltrexone, 25 to 100 mg q.i.d., for at least 2 weeks. A self-rated questionnaire measuring dissociation, analgesia, tonic immobility, and tension (DAISS) was applied to 9 patients, who completed it for 7 consecutive days before and during treatment with naltrexone. In addition, 9 patients (with an overlap of 5 patients from the other group) completed a flashback protocol.

Results: DAISS scores reflected a highly significant reduction of the duration and the intensity of dissociative phenomena and tonic immobility as well as a marked reduction in analgesia during treatment with naltrexone. Six of 9 patients reported a decrease in the mean number of flashbacks per day.

Conclusion: These observations support the hypothesis that an increased activity of the opioid system contributes to dissociative symptoms, including flashbacks, in borderline personality disorder and suggest that these symptoms may respond to treatment with opiate antagonists. In view of these results, a placebo-controlled, double-blind study to assess the potential benefit of naltrexone in a more rigorous way appears justified.

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The prevalence of borderline personality disorder is estimated to be 1% to 2% within the general population¹ and 19% among psychiatric inpatients.² Patients with borderline personality disorder therefore represent an important but difficult-to-treat group of psychiatric patients. There are several hypotheses as to the etiology of borderline personality disorder (for review, see reference 3). According to biosocial theory (for review, see reference 4), an affective dysregulation is central to this disorder. Aside from self-mutilating and recurrent suicidal behavior, dissociative symptoms⁵ are common. This has been acknowledged by the recent addition of item 9 (“transient, stress-related paranoid ideation or severe dissociative symptoms”) to the diagnostic criteria for borderline personality disorder in DSM-IV.⁶ Dissociative phenomena include derealization, depersonalization, analgesia, and altered perceptions in several sensory modalities.⁷ In an open field study, patients with borderline personality disorder were found to experience significantly more severe dissociative phenomena than controls (C.E.S. and M.J.B., unpublished data). In addition, this study disclosed a high correlation between dissociation, analgesia, and tonic immobility⁸ and the level of tension. These observations are in agreement with findings of Russ et al.⁹ of a significant reduction in pain perception in self-injurious patients with borderline personality disorder. In addition, patients with borderline personality disorder often report flashbacks, the vivid, visual, emotionally draining recall of traumatic episodes. Aside from occurrence in borderline personality disorder, dissociative phenomena occur frequently in patients with posttraumatic stress disorder (PTSD).^{10,11} Beyond the threatening emotional experience, clinical evidence suggests that dissociative phenomena in borderline personality disorder patients may disturb habituation processes in therapies based on exposure techniques.

The serotonergic system and the opioid system are implicated in pain perception. Stress-induced analgesia is thought to involve the endogenous opiate system.¹² In patients with PTSD, stress-induced analgesia can be blocked by the opiate antagonist naloxone.^{13,14} In addition, there are several case reports on the reduction of self-mutilating behavior in mentally retarded patients by naloxone or naltrexone (for review, see reference 15) as well as reports on the reduction of repetitive self-injurious behavior by naltrexone in patients with borderline personality disorder.¹⁶ Furthermore, flashbacks in patients with PTSD were found to be reduced by naltrexone.¹⁷ These observations prompted us to study the effects of naltrexone in patients with borderline personality disorder and prominent dissociative phenomena including flashbacks in more detail in an open-label trial.

METHOD

Two groups of patients with borderline personality disorder meeting the diagnostic criteria of DSM-IV⁶ and the revised Diagnostic Interview for Borderline Patients (DIB-R)¹⁸ entered this open-label trial. Each group consisted of 9 female patients, ranging in age from 17 to 47 years. Patients with schizophrenia, lifetime bipolar disorder, or drug or alcohol dependency were excluded. All patients displayed prominent dissociative symptoms and/or flashbacks as measured by the newly developed Dissociation, Analgesia, Immobility, and Tension Scale (in German, Dissoziations-, Analgesie-, Immobilitäts- und Spannungsskala [DAISS], C.E.S., M.J.B., H. Richter, Ph.D., et al., unpublished scale). Five patients did not receive concomitant medication; the others received antidepressive medication, which was held constant throughout the trial. All patients were consecutively admitted to the psychiatric ward of the University of Freiburg Germany, which specializes in dialectical behavioral therapy for borderline personality disorder.¹⁹ Before entering this trial, each patient had been hospitalized for at least 2 weeks.

Dissociative symptoms were assessed using the DAISS. The DAISS is a self-rating questionnaire integrating elements of the Dissociative Experience Scale (DES)²⁰ with items from the Fragebogen zu dissoziativen Symptomen (FDS),²¹ the German adaptation of the DES, and items from the Somatoform Dissociation Questionnaire (SDQ-20).²² The 22 items of the DAISS are divided into 5 subscales termed dissociation, analgesia, tonic immobility, tension, and global. The dissociation subscale consists of 13 items (e.g., "I had the impression that other people or other things or the world around me was not real"), the analgesia subscale has 3 items (e.g., "I could not feel my body or a part thereof"), and the tonic immobility subscale consists of 3 items (e.g., "I felt paralyzed, frozen"). Tension was assessed by 1 item: "I felt inner ten-

sion." Two items ("I had the impression of being unable to experience emotions" and "I had the impression that my breathing pattern changed") were combined into the global subscale; results of this subscale will not be discussed here.

Homogeneity of the DAISS was demonstrated and a reliability analysis resulted in a Cronbach α between 0.88 and 0.94 (C.E.S., M.J.B., H. Richter, Ph.D., et al., unpublished data). A reliability analysis of the subscales resulted in a Cronbach α between 0.55 and 0.90.

The highest intensity of dissociative phenomena during the last 24 hours was rated on a scale from 0 to 9. The duration of dissociative phenomena was expressed as percentage of the time spent awake during the last 24 hours. The number of flashbacks were reported by the patients on a flashback protocol that was completed every day at 10 p.m.

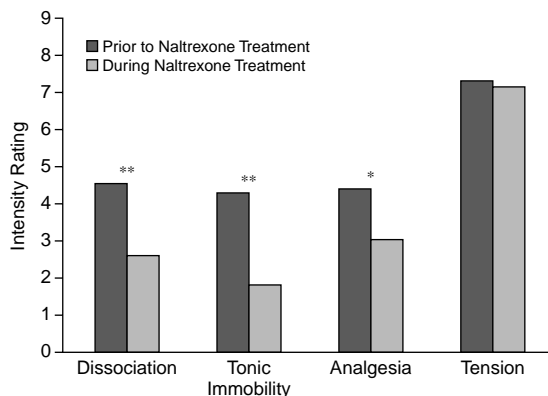
Following informed consent, 1 set of 9 patients completed the DAISS and another set of 9 patients (with an overlap of 5 patients) completed flashback protocols for 7 consecutive days. Treatment with naltrexone was started at a dose of 25 mg q.i.d. If patients reported no effect within 3 days, the dose was increased to 50 mg. Patients were maintained on the regimen of 25 mg q.i.d. or 50 mg q.i.d. for at least 2 weeks. The dose of naltrexone was further increased to a maximum of 100 mg in the course of 3 weeks in an attempt to maximize the clinical improvement. Overall, 2 patients were treated with 25 mg, 6 patients with 50 mg, 3 patients with 75 mg, and 2 patients with 100 mg q.i.d. To assess the effect of naltrexone, the mean DAISS scores and the mean number of flashbacks per day during the second week of treatment with the final dose of naltrexone were compared with DAISS scores and number of flashbacks, respectively, during the week prior to treatment. Statistically significant differences were assessed using a 2-tailed *t* test for paired samples.

RESULTS

During treatment with naltrexone, all patients reported a marked reduction in the intensity and duration of dissociative phenomena, tonic immobility, and analgesia as measured by the DAISS as well as a reduction of the mean number of flashbacks per day. Patients never reported changes in symptoms following a single dose of naltrexone. As a rule, 3 days of treatment were required before any effects were reported.

In the group of 9 patients assessed with the DAISS, we observed a highly significant ($p = .001$) reduction in the mean \pm SD intensity rating on the dissociation subscale, from 4.5 ± 1.6 to 2.6 ± 1.0 (Figure 1). A reduction in the intensity ratings was observed in every patient studied as shown in Figure 2 (upper panel). In addition, the percentage of time during which the group of patients reported dissociative symptoms decreased highly significantly ($p = .003$) from $29\% \pm 14\%$ to $13\% \pm 7\%$.

Figure 1. Mean Intensity Ratings in a Group of 9 Patients for All Subscales of the DAISS Prior to and During Treatment With Naltrexone^a



^aAbbreviation: DAISS = Dissociation, Analgesia, Immobility, and Tension Scale.

** $p < .01$. * $p < .1$.

A similar highly significant reduction ($p = .002$) in the mean intensity rating was apparent on the tonic immobility subscale (4.3 ± 2.2 to 1.8 ± 1.3 ; see Figure 1). As with the dissociation subscale, this effect was reported by every patient (Figure 2, middle panel). The time reported immobile on the DAISS decreased as well, from $26\% \pm 19\%$ to $9\% \pm 8\%$ ($p = .006$).

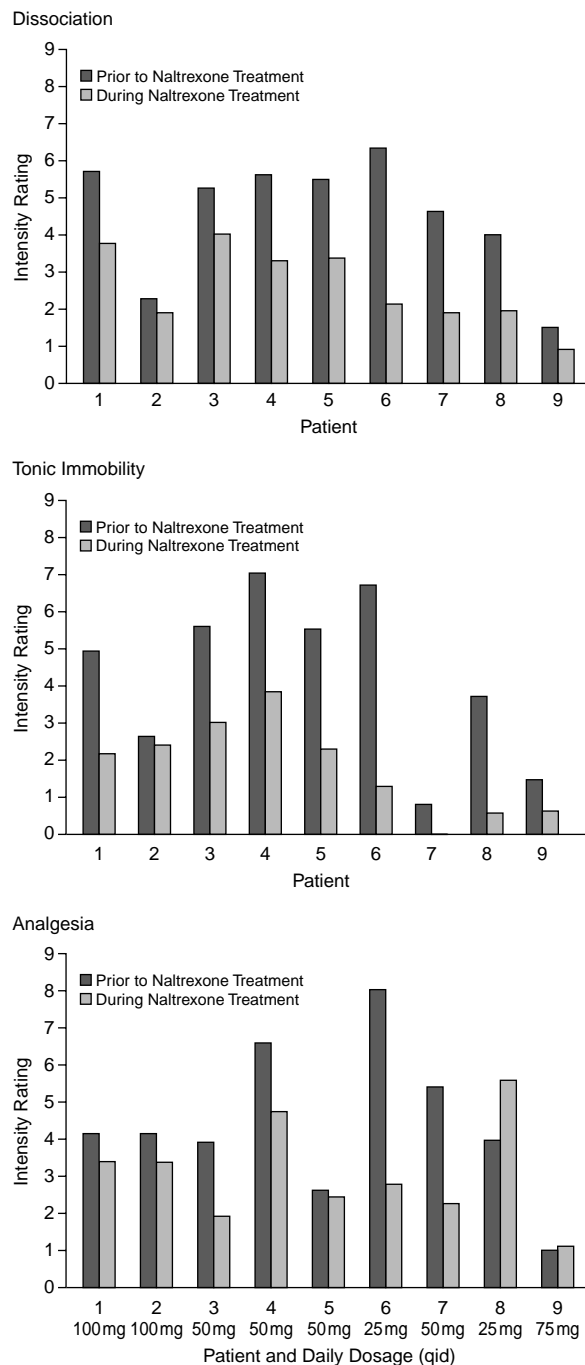
Intensity rating on the analgesia subscale was found to be lower with naltrexone treatment (4.4 ± 2.1 vs. 3.0 ± 1.4 , $p = .078$; see Figure 1). However, 2 of 9 patients reported higher intensity ratings in the analgesia subscale (patients 8 and 9 in Figure 2, lower panel). The time during which analgesia was reported decreased from $44\% \pm 21\%$ to $30\% \pm 14\%$ ($p = .101$, not significant).

Inner tension as reflected by the tension subscale of the DAISS was not influenced by the treatment with naltrexone both in mean intensity (7.3 ± 1.3 vs. 7.2 ± 1.3 ; see Figure 1) and in duration ($58\% \pm 14\%$ vs. $58\% \pm 19\%$).

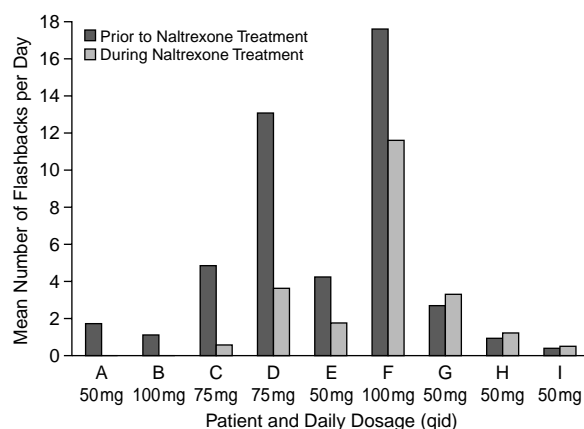
A correlation between the final dose of naltrexone and the change in intensity ratings was calculated. In addition, the correlation between intensity ratings prior to treatment and final dose of naltrexone was determined. There was a negative correlation between the change in intensity reported and final dose (dissociation subscale, -0.6 ; tonic immobility subscale, -0.4 ; analgesia subscale, -0.4) and a negative correlation between intensity ratings at baseline and final dose (dissociation subscale, -0.2 ; tonic immobility subscale, -0.1 ; analgesia subscale, -0.3), suggesting that patients with more severe symptoms tended to benefit already from small dosages of naltrexone.

In the group of 9 patients who completed flashback protocols, we observed a significant reduction in the mean \pm SD number of flashbacks per day from 6.3 ± 6.3 to 2.5 ± 3.7 ($p = .038$). Six patients reported a marked re-

Figure 2. Intensity Ratings of the Dissociation (upper panel), Tonic Immobility (middle panel), and Analgesia (lower panel) DAISS Subscales for Each Patient (1–9) Prior to and During Treatment With Naltrexone



duction in the number of flashbacks (patients A through F in Figure 3); 3 patients reported essentially no change during treatment with naltrexone (patients G through I in Figure 3). These results are in agreement with ratings of item 4 of the DAISS ("I recalled an event so vividly, as if I

Figure 3. Mean Number of Flashbacks per Day for 9 Patients (A–I) Prior to and During Treatment With Naltrexone

would live it again”): intensity ratings and the mean time during which patients experienced flashbacks decreased from 4.5 ± 2.7 to 3.5 ± 2.8 ; $p = .171$) and from $24\% \pm 27\%$ to $17\% \pm 20\%$ ($p = .132$), respectively.

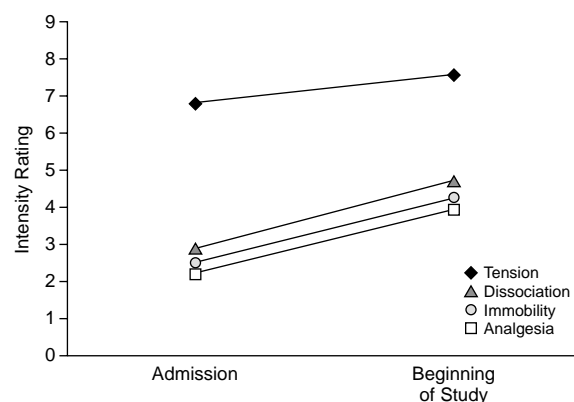
There was a positive correlation between the change in the mean number of flashbacks per day and final dose of naltrexone ($r = 0.5$) and a positive correlation between the mean number of flashbacks at baseline and final dose ($r = 0.6$), suggesting that patients with frequent flashbacks require higher dosages of naltrexone.

To rule out the effect of hospitalization on dissociative behavior, we compared DAISS data of 5 patients obtained during the first week following admission with DAISS data obtained 1 week before the beginning of the study (mean time interval = 39 days). We found no significant differences, but did see a tendency to increased scores at the beginning of the naltrexone trial compared with admission (Figure 4).

DISCUSSION

All 9 patients studied who had borderline personality disorder reported a marked reduction of dissociative symptoms, analgesia, and tonic immobility during open-label treatment with the nonselective opioid receptor antagonist naltrexone. In addition, 6 of 9 patients with borderline personality disorder displayed a marked reduction in the number of flashbacks they experienced while on naltrexone treatment. The level of tension reported by the patients was not influenced. These observations suggest that dissociative phenomena in borderline personality disorder are mediated by an activation of the endogenous opioid system and indicate that dissociative phenomena in borderline personality disorder are responsive to pharmacotherapy.

For our study, we used a recently developed self-rating questionnaire (the DAISS) that integrates elements of the

Figure 4. Mean Intensity Ratings in Subscales of DAISS at Admission to Hospital and at the Time of Starting Treatment With Naltrexone (N = 5; mean time interval = 39 days)^a

^aOnly 5 patients completed the DAISS at admission to the hospital.

DES¹⁹ with items from the FDS²⁰ and items from the SDQ-20.²¹ So far, the validity of the DAISS has not been demonstrated in a formal study; however, the reduction of dissociative symptoms reported in the self-assessment rating scale was in accord with the impression of trained observers caring for patients in an inpatient setting. The observations reported in the present study agree well with the observations of Bills and Kreisler¹⁷ of a reduction of flashbacks in PTSD patients.

This study was conducted as an open-label trial, a design sensitive to bias. Given the observation that admission to hospital has a profound effect on reducing borderline stress and symptoms, there is concern that the reduction in dissociative symptoms observed during treatment with naltrexone may reflect the effect of inpatient hospitalization rather than a pharmacologic effect of the opioid receptor antagonist. Indeed, dissociative symptoms as measured by the DAISS were less intense during the first week of inpatient hospitalization compared with the time of starting naltrexone (3–4 weeks later). Since all patients studied were hospitalized as inpatients for 3 to 4 weeks before treatment with naltrexone and DAISS scores tended to increase during this time, the reduction of dissociative symptoms during treatment with naltrexone cannot easily be explained as a side effect of inpatient hospitalization.

In addition, 8 patients were taking concomitant antidepressant treatment during the study period, raising the possibility of important effects on overall symptom severity, including dissociative symptoms, by these compounds. These 8 patients had been taking antidepressant medication for a period of at least 4 weeks. There was no dose adjustment in any patient during inpatient treatment. However, in patients not treated with antidepressants, we observed effects of naltrexone similar to those in patients

with concomitant antidepressant treatment, suggesting effects independent of thymoleptics.

The mechanisms by which naltrexone reduces dissociative symptoms in patients with borderline personality disorder are unknown at present. Naltrexone is a nonselective antagonist at opioid receptors.²³ It is well documented that naltrexone in humans with no history of drug abuse does not alter behavior, perception, mood, or cognition,²⁴ at least not in the dose range used in the present study. These observations suggest that the endogenous tone on opioid receptors under physiologic conditions is low. The effects of the application of naltrexone reported in the present study suggest that the opioid system is stimulated in borderline personality disorder. Stress is thought to activate the endogenous opiate system and may lead to stress-induced analgesia.¹² The observation that treatment with naltrexone reduced scores on the analgesia subscale in our study supports an opioid-dependent mechanism for analgesia in patients with borderline personality disorder and agrees with a similar sensitivity of stress-induced analgesia to naloxone in patients with PTSD.^{13,14} Similarly, the striking effects of naltrexone reflected in the dissociation and tonic immobility subscales suggest that activation of the endogenous opiate system may impair perception of the environment and of self in borderline personality disorder patients. Indeed, there is evidence for increased levels of endogenous opioid peptides in these patients: Coid et al.²⁵ reported increased plasma met-enkephalin levels in patients with borderline personality disorder. Pickar et al.,²⁶ however, reported low levels of opioid activity in cerebrospinal fluid using a radioreceptor assay that detects total opioid binding activity. Similar results have been reported in patients with PTSD.^{27,28} To our knowledge, there are no reports on dynorphin levels in borderline personality disorder or PTSD and no published studies attempting to correlate dissociative symptoms with endogenous opioid levels. A correlation like this might be critical since alterations in endogenous opioid levels may be a state rather than a trait marker.

Three classes of endogenous opioids (β -endorphins, enkephalins, and dynorphins) activate 3 types of opioid receptors: μ -, δ -, and κ -opioid receptors.²³ Interestingly, the application of κ -opioid receptor agonists like ketocyclazocine or MR-2033 in humans results in symptoms reminiscent of dissociative states.^{29,30} For instance, volunteers exposed to these compounds reported detachment, depersonalization, derealization, and disturbances of tactile and visual perception in a dose-dependent fashion. We would therefore like to suggest a stress-induced activation of the endogenous opiate system in borderline personality disorder resulting in an increased activity of κ -opioid receptors, e.g., by an increased release of dynorphins, the endogenous agonist at κ -opioid receptors. This hypothesis would predict increased levels of dynorphins in pa-

tients with borderline personality disorder during dissociative symptoms. Clearly, this hypothesis requires further testing, but may provide a framework to improve our understanding of dissociative symptoms.

There are several caveats to keep in mind in interpreting our observations. This study relied on self-reported phenomena; we did not attempt to confirm and validate the self-reports of our patients by psychophysical measurements (e.g., the determination of pain thresholds). Interestingly, 2 patients in our study did not report reduced scores on the analgesia subscale during treatment with naltrexone, raising the possibility that opioid-independent mechanisms may influence scores on that subscale. The contribution of opioid-independent mechanisms is further supported by the observation that there is a marked reduction but no complete disappearance of dissociative symptoms during treatment with naltrexone.

Importantly, the level of tension reported by patients was not influenced by treatment with naltrexone. Therefore, the effects of naltrexone can not be easily explained by a general sedative effect (like the one associated with neuroleptic compounds of low potency). One of the clinical consequences of this result is that patients experience more difficulties coping with intense sensations at the beginning of treatment with naltrexone. Since this is the case, we want to emphasize that treatment with naltrexone should not be started outside a treatment program involving psychotherapy. Unless patients are assisted in coping with their altered perception, an increased incidence of suicide in this patient population may occur. On the other hand, experienced cognitive-behavioral therapists agreed that responsiveness to psychotherapy improved during treatment with naltrexone. Presumably, the reduction of dissociative symptoms during treatment resulted in an improved emotional awareness. The ability of patients to orientate themselves to the present was enhanced, and their ability to learn new behavioral patterns improved. In addition, we observed rebound phenomena in patients who abruptly discontinued naltrexone. Therefore, we suggest that naltrexone should be tapered down slowly.

One of the major goals in the treatment of borderline personality disorder is to prevent suicide and to reduce self-injurious behavior. Roth et al.³¹ reported in an open-label trial that repetitive self-injurious behavior accompanied by analgesia and dysphoria may be ameliorated by naltrexone. They suggested that naltrexone may work by removing a reward (supranormal levels of endorphins). Alternatively, we propose that the simultaneous presence of dysphoria, dissociative symptoms, and analgesia reflects an activation of κ -opioid receptors; naltrexone, by blocking κ -opioid receptors, suppresses a trigger for self-injurious behavior, thus reducing the need for this maladaptive antidissociative behavior.

In this open-label trial, we used variable doses of naltrexone. We observed a positive correlation between the

reduction in the frequency of flashbacks and the dosage of naltrexone. This observation suggests a dose-dependent effect of naltrexone. In contrast, the reduction in the severity of dissociative symptoms, tonic immobility, and analgesia was negatively correlated with the dosage of naltrexone. In combination with the observation that there was a similar negative correlation with the severity of symptoms prior to treatment, we suggest that more severely affected patients are more sensitive to even low dosages of naltrexone. No subscale stood out as being strikingly more sensitive. The small number of patients and the limited range of doses tested did not allow us to define with confidence optimal doses to achieve effects in each subscale.

To further assess the effects of naltrexone on dissociative symptoms in borderline personality disorder, we are currently conducting a double-blind placebo-controlled trial.

Drug names: naloxone (Narcan and others), naltrexone (ReVia).

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