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Efficacy of naltrexone in borderline personality disorder, a retrospective analysis in inpatients

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Abstract

Objective: The endogenous opioid system is assumed to be involved in the pathophysiology of borderline personality disorder (BPD), and opioid antagonists may improve core features of BPD. The aim of this retrospective chart analysis was to evaluate the relative contribution of the opioid antagonist naltrexone and other psychotropic drugs in the improvement of overall symptomatology in BPD.

Methods: One hundred sixty-one inpatients with BPD treated between January 2010 and October 2013 were classified as either treatment responders or non-responders. Treatment responders were defined as subjects with significant improvements in four or more symptoms from a defined symptom list. The relative contribution of all psychotropic drugs to improvement of BPD symptomatology was assessed by means of a stepwise logistic regression.

Results: None of the drugs applied contributed significantly to improvement, with the exception of naltrexone (odds ratio [OR] 43.2, $p \leq 0.0001$). Patients treated with naltrexone ($N = 55$, 34%) recovered significantly more often. Higher doses of naltrexone were more effective (OR 791.8, $p \leq 0.0001$) than lower doses (OR 26.6, $p \leq 0.0001$); however, even low-dose treatment was better than any other pharmacological treatment.

Conclusions: Naltrexone was associated with improvement in BPD in a dose-dependent manner. The present study provides additional evidence that dysregulation of the endogenous opioid system is implicated in the pathophysiology of BPD symptoms.

KEYWORDS

borderline personality disorder, naltrexone, neuropeptide, opioid receptor, psychopharmacology

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1 | INTRODUCTION

Borderline personality disorder (BPD) is a severe psychiatric disorder affecting about 1%–2% of the adult population. Approximately 6% of individuals presenting in primary care settings and up to 10% of psychiatric outpatients were reported to suffer from BPD (Dubovsky & Kiefer, 2014; Widiger & Weissman, 1991). Currently available international guidelines favor psychotherapy as first-line treatment over drug therapy, which is rather considered as adjunctive option at best (National Collaborating Centre for Mental Health, 2009; National Health and Medical Research Council, 2013; The National Institute for Health and Care Excellence, 2018). In clinical practice, the use of psychotropic medications is a common approach with only limited effects in distinct symptoms in BPD, and polypharmacy is still highly prevalent despite the lack of evidence (Stoffers & Lieb, 2015; Zanarini et al., 2015). There is a pressing need for suitable neurobiological models of BPD delivering biological targets which can be utilized for further investigation of innovative and preventative treatments. The growing body of neuropsychobiological data accumulated in findings of pharmacology, brain imaging, and candidate gene/association studies in the last years contributed to several comprehensive dimensional models of BPD (Dell'Osso et al., 2010). The disorder is most likely the result of the interaction of environmental–genetic factors (Martín-Blanco et al., 2016), early developmental (Schwarze et al., 2013) and biological processes, and thus might not be completely explained by a single model due to overlapping pathophysiologies in BPD. BPD is characterized by three symptom dimensions (Sanislow et al., 2002): (1) affective dysregulations, (2) impulsivity or behavioral dyscontrol, and (3) interpersonal hypersensitivity. Each of the aforementioned core features gave rise to several models, but only impairments of interpersonal functioning can differentiate BPD from other personality disorders (Gunderson & Lyons-Ruth, 2008) and mainly contribute to affective and behavioral dysregulation (Koenigsberg et al., 2001). Neuropeptides, such as opioids and oxytocin, were recently proposed to regulate affiliative and interpersonal behaviors (Herpertz & Bertsch, 2015; Stanley & Siever, 2010). Particularly, a pathogenetic role of the endogenous opioid system (EOS) and dopaminergic reward system in BPD has been suggested (Bandelow et al., 2010; Moghaddas et al., 2017). Endogenous endorphins usually exert stress-induced analgesic and mood elevating effects via μ -opioid receptors. μ -opioid receptors were highly expressed in the basolateral amygdala, nucleus accumbens, hypothalamus, thalamus, ventral tegmental area and caudate putamen. Therefore, the EOS is closely linked to the dopaminergic reward system (Roth-Deri et al., 2008). Evidence from experimental, genetic, and preclinical studies strongly indicate that the EOS mediates social bonding, attachment, coping with interpersonal stress (Kalin et al., 1995; Panksepp et al., 1978), affective experiences, and responses (Zubieta et al., 2003). Accordingly, a dysregulation of EOS might be responsible for several core symptoms associated with BPD. The biological underpinning is most likely a reduced basal opioid activity resulting in a compensating upregulation of μ -opioid receptor (Prossin et al., 2010) causing chronic dysphoria, lack of a sense of well-being (Stanley & Siever, 2010), and anhedonia due to a lower basal

hedonic opioid activity (Narayanan et al., 2004). Furthermore, a relative overactivation of κ opioid receptors leading to a shift toward a decreased μ/κ -activity ratio is most likely involved in dysphoria (Anderson, 2020; Bruchas et al., 2010; Karkhanis et al., 2017). Non-suicidal self-injury was shown to be associated with lower cerebrospinal fluid levels of β -endorphin and met-enkephalin compared to those without self-injury (Stanley et al., 2010) and with differential nociceptive deficits in BPD (Schmahl et al., 2004). Thus, non-suicidal self-injuries and other BPD-related self-harming behaviors, such as eating disorder and drug addiction, might be considered as the patients' attempts to compensate for the lack of stimulation of the EOS and reward system. Indeed, self-injury was effectively treated with the opioid antagonist naltrexone (Symons et al., 2004). Opioid antagonists like naltrexone appear to unfold its effects biphasically: as an acute effect, naltrexone blocks rewarding effects of problematic self-destructive symptoms, such as self-harm, substance abuse, or eating disorders, while chronic administration of the drug may restore the neurotransmission via μ -opioid receptors. Treatment with opioid antagonists had been previously shown effective in further BPD-associated symptoms and comorbidities, such as substance-related disorders (Adi et al., 2007; Anton et al., 2004; Drobos et al., 2004; Jayaram-Lindström et al., 2008; Martín-Blanco et al., 2017; Streeton & Whelan, 2001), anorexia/bulimia nervosa (Marrazzi et al., 1995), and dissociations (Bohus et al., 1999). Most of these studies were not controlled, adequately powered, or did not investigate BPD global symptomatology. Interestingly, Martín-Blanco recently evaluated nalmefene in BPD patients with comorbid alcohol disorder and reported a significant reduction in both alcohol consumption and symptoms in a BPD self-rating instrument (Martín-Blanco et al., 2017).

A previous evaluation of prescribing patterns in our psychiatric hospital from 2008 to 2012 revealed that over 90% of all BPD inpatients received at least one psychotropic medication at the time of discharge. In our cohort, second-generation antipsychotics were preferred rather than tricyclic antidepressants and low-potency antipsychotics. Because it was an “insiders' tip” in the hospital that naltrexone may be useful, about one-third of all BPD inpatients were treated with naltrexone during the treatment period between 2008 and 2012 (Timäus et al., 2019). Differential effects of the applied drug treatments were not assessed in this preliminary study. We hypothesized that naltrexone was effective and well tolerated given the high prescription rate of naltrexone. We performed the present consecutive study in order to assess the treatment effects of naltrexone in BPD patients in a retrospective way. Furthermore, we analyzed the relative contribution of naltrexone to the improvement of overall symptomatology in BPD among all prescribed psychopharmacological medications.

2 | METHODS

Patients were identified using the electronic database of the Department of Psychiatry and Psychotherapy of the University Medical Center Goettingen, Germany. Charts of 193 adult (minimum

age of 18 years) patients with a main diagnosis of BPD treated between January 2010 and October 2013 were analyzed. Diagnoses (F60.31) were based on the ICD-10 (World Health Organization, 1992). Thirty-two patients were excluded, as they were exclusively treated in an outpatient setting and/or because the individual data were not completely available. One hundred sixty-one BPD inpatients were finally included in this study. Data were collected from patient charts, processed on protocol sheets, and digitally stored. Recorded patient characteristics included sociodemographic parameters, previous inpatient or outpatient treatment periods, frequency of admissions during the current year, comorbidities, recorded diagnostic criteria for BPD, history of suicide attempts, and first-degree relatives with psychiatric disorders. All prescribed psychotropic medications and their daily dosages during the inpatient stay were recorded and assigned to the corresponding substance classes (antidepressant, low-potency and high-potency antipsychotics, mood stabilizers, sedatives/hypnotics, psychostimulants, maintenance drugs, medications for substance withdrawal treatment, and the opioid antagonist naltrexone). BPD symptoms were analyzed in order to monitor clinical improvement during the inpatient stay. Therefore, five clinical symptoms (mood/drive disturbances, suicidal thoughts or tendencies, impulsivity, insufficient therapy adherence, and self-harming behavior) were identified at time of admission and at time of discharge. Subjects with significant improvements in four or more symptoms of the symptom list were classified as treatment responders.

2.1 | Statistical analysis

Statistical analysis was performed with STATA/IC 12.1. For bivariate analyses of nominal-scaled data, Fisher's exact test was applied. Stepwise logistic regression analysis was performed in order to estimate the contribution of drug classes, including naltrexone, and of all sociodemographic and biological variables to the clinical endpoint. Outliers and influential observations were detected by using Pregibons DBeta-test and Pearson's residuals test. Statistical significance level, Pseudo- R^2 , and log likelihood were given for each computed model. Results were statistically significant if $p \leq 0.05$.

3 | RESULTS

3.1 | Description of the study cohort

Between January 2010 and October 2013, 136 of all included inpatients with the main diagnosis BPD were female (84.5%) and 25 (15.5%) were male, respectively. The mean age was 31.8 years (± 11.7 ; range 18–67 years). 45.3% of all subjects were 30 years old or younger. The mean duration of the hospital stay was 29 days (± 33.9). Seventeen patients were admitted for the first time. At least one preceding inpatient treatment was found in the charts of 144 patients (89.4% of the study cohort).

3.1.1 | Suicide attempts

One hundred and three subjects (64%) reported at least one suicide attempt. Two or more suicide attempts were documented in the charts of 39 patients corresponding to 24% of all subjects. Fifty-eight (36%) reported no previous suicide attempt.

3.1.2 | Comorbidities

Table 1 provides data on psychiatric comorbidities of the present study cohort and the frequency of BPD inpatients having at least one first-degree relative suffering from psychiatric disorders. A total of 134 (83%) BPD patients showed one or more additional psychiatric disorders. Substance use disorders were common among BPD inpatients. About 27% of them had alcohol abuse and 15% additional multiple substance use disorder, respectively. Almost 45% of all BPD patients had a history of major depression. 18% of the patients suffered from comorbid posttraumatic stress disorder. We found 42 (26%) BPD patients having first-degree relatives with one or more psychiatric disorders. First-degree relatives of BPD patients suffered mainly from major depression and alcohol-related disorders. 16.7% were found to have a somatic illness. Five of the BPD inpatients showed frequent intravenous drug use, and all of these five were tested positive for a hepatitis C virus infection. 5.3% had an autoimmune disease and 13% suffered from neurological disorders (including 4.9% with epilepsy).

3.2 | Psychotropic drug treatment

As shown in Table 2, almost 90% of all inpatients received at least one psychotropic medication and 72% had two or more different medications, respectively.

3.2.1 | Classes of psychotropic drugs

One hundred and ten (68%) of the BPD patients received antidepressants. High-potency antipsychotics were prescribed to 76 (47%) BPD patients and low-potency antipsychotics to 19 (12%) patients during the inpatient treatment period. Twenty-two (14%) of the subjects were treated with mood stabilizers and 26 (16%) with benzodiazepines, respectively (Table 3). Four patients received buprenorphine and one patient L-methadone as opioid maintenance treatment. Disulfiram was given in one case. Three patients were treated with an extended-release formulation of the antiparkinsonian drug biperiden. A total of 55 (34.2%) BPD inpatients were treated with naltrexone. Naltrexone was applied and titrated according to the official summary of product characteristics. The mean duration of naltrexone treatment was 31.4 days. Patients were titrated to their effective daily dose ranging from 50 to 150 mg. A total of 40 BPD

TABLE 1 Frequency of comorbidities

Psychiatric comorbidities	A		B	
	(N)	(%)	(N ^R)	(% ^R)
Substance use disorders (F10–F19)				
Alcohol	44	27.3	13	8.1
Opioids	9	5.6	0	0
Cannabinoids	18	11.2	0	0
Sedatives und hypnotics	28	17.4	0	0
Hallucinogens	1	0.6	0	0
Multiple substance use disorder	24	14.9	2	1.2
Affective disorders (F30–F39)				
Bipolar affective disorder	4	2.5	0	0
Major depression	72	44.7	27	17
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40–F48)				
Acute stress reaction	21	13.0	0	0
Posttraumatic stress disorder	29	18	0	0
Panic disorder	3	1.9	1	0.6
Obsessive–compulsive disorder	0	0	1	0.6
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20–F29)				
Paranoid schizophrenia	0	0	4	2.5
Schizoaffective disorder	0	0	1	0.6
Behavioral syndromes associated with physiological disturbances and physical factors (F50–F59)				
Anorexia nervosa	7	4.3	2	1.2
Bulimia nervosa	5	3.1	0	0
Disorders of adult personality and behavior (F60–F69)				
BPD	n.a.	n.a.	5	3.1

Note: Frequency of BPD patients with comorbidities (A: N, number of BPD patients; %, proportion of all included BPD patients) and BPD patients with first-degree relatives suffering from psychiatric disorders (B: N^R, number of BPD patients; %^R, proportion of all included BPD patients).

Abbreviations: BPD, borderline personality disorder; n.a., not applicable.

TABLE 2 Frequency of psychotropic medication

Frequency of psychotropic medication	N	%
0	17	10.5
≥1	144	89.4
≥2	116	72.1
≥3	70	43.5
≥4	32	19.9
≥5	8	5.0

Note: N = number of BPD inpatients, % = proportion of all included BPD inpatients.

inpatients (24.8% of the study population) received 50 mg naltrexone per day (Table 4). One inpatient received 25 mg naltrexone per day. The mean daily dosage was 63.2 mg.

3.3 | Interrelation between treatment response and naltrexone

3.3.1 | Results of bivariate analyses

The frequency of treatment responders was significantly higher among BPD patients treated with naltrexone compared to BPD patients not being treated with naltrexone (Fisher's exact test: $p \leq 0.0001$, OR 11.4) (Table 5). A high daily dosage of naltrexone (>50–150 mg per day) was associated with higher rates of response compared to BPD patients without naltrexone (Fisher's exact test: $p \leq 0.0001$, OR 32.9). Even subjects with low dosages of naltrexone (25–50 mg per day) showed more improvement compared to subjects with no naltrexone at all (Fisher's exact test: $p \leq 0.0001$, OR 9.0).

TABLE 3 Frequency of classes of psychotropic drugs

Classes of psychotropic drugs	N	%
Benzodiazepines	26	16.2
Antidepressants	110	68.3
Low-potency antipsychotics	19	11.8
High-potency antipsychotics	76	47.2
Mood stabilizers	22	13.7

Note: N = number of BPD inpatients, % = proportion of all included BPD inpatients.

TABLE 4 Frequency of naltrexone among BPD inpatients

Naltrexone	N	%
25 mg per day	1	0.6
50 mg per day	40	24.8
100 mg per day	13	8.1
150 mg per day	1	0.6
Total	55	34.2

Note: N = number of BPD inpatients, % = proportion of all included BPD inpatients.

Abbreviation: BPD, borderline personality disorder.

TABLE 5 Frequency of treatment responders/non-responders among BPD patients with/without naltrexone treatment

	Non-responders		Responders	
	(N)	(%)	(N)	(%)
Without naltrexone	76	71.7	30	28.3
Naltrexone (total)	10	18.2	45	81.8
Naltrexone (low dose) ^a	9	22.0	32	78.1
Naltrexone (high dose) ^b	1	7.1	13	92.9

Note: N = number of BPD inpatients, % = proportion of BPD inpatients.

Abbreviation: BPD, borderline personality disorder.

^a25–50 mg naltrexone per day.

^b>50–150 mg naltrexone per day.

3.3.2 | Results of multiple stepwise logistic regression analyses

In order to investigate the contribution of naltrexone to the improvement of BPD inpatients, a stepwise logistic regression analysis was performed. Each model shared a common set of predictors comprising five different psychotropic drug classes, patient demographic data and medical history data, most frequent psychiatric comorbidities, and first-degree relatives with alcohol disorder or major depression (Table 6). Three different models were consecutively calculated for high-dose (>50–150 mg per day) naltrexone, low-dose (≤50 mg per day) naltrexone, and any given daily dosage of naltrexone. Naltrexone was significantly associated with a higher

chance for improvement of symptoms during the current treatment period. This was true if naltrexone was prescribed at any daily dosage (odds ratio [OR] 43.2; 95% CI [11.24, 166.22]). The OR was even higher for high-dose naltrexone (OR 791.8; CI [35.48, 17,667.42]). Low-dose naltrexone was significantly associated with improvement of symptoms; however, the effect was less pronounced compared to the model including high-dose naltrexone (OR 26.6; CI [6.65, 106.23]). None of the other substance classes (antipsychotics, antidepressants, mood stabilizers, and benzodiazepines) showed a significant contribution to the overall improvement of BPD patients. Only low-potency antipsychotics showed some positive effects without reaching the significance level. Female gender and an additional substance use disorder were associated with a lower chance for improvement during the treatment period. Having first-degree relatives with major depression (F33) was associated with a higher probability of better clinical outcome. All logistic regression analyses were statistically significant at $p < 0.0001$.

4 | DISCUSSION

In this study, we found a high utilization of psychotropic drug treatment among BPD inpatients. It was difficult to disentangle the contribution of every single drug to overall symptom improvement. However, the method of logistic regression is able to overcome this difficulty. According to the results of the stepwise logistic regression analysis, naltrexone was the only medication which significantly contributed to improvement of symptoms during the treatment period. Moreover, high-dose naltrexone appears to be superior to low-dose naltrexone. However, even low-dose naltrexone was significantly associated with a better outcome in terms of improvement of symptoms. For low-potency antipsychotics, positive effects on outcome were observed, but this result was not significant. None of the other psychotropic drug classes was significantly associated with better outcome.

Our findings support a pathogenetic role of the endogenous opioid system (EOS) and the reward system in BPD. Furthermore, dysregulation of the EOS may be counteracted by opioid antagonists. In this regard, nalmefene was shown to reduce global symptomatology in BPD patients (Martín-Blanco et al., 2017). The results of this study and previous clinical studies underline the potential role of opioid antagonists in the clinical management of BPD-associated symptoms, such as self-harming behaviors (McGee, 1997; Roth et al., 1996; Sonne et al., 1996), dissociation (Bohus et al., 1999), substance-related disorders, including heroin (Adi et al., 2007), amphetamine (Jayaram-Lindström et al., 2008), and alcohol addiction (Anton et al., 2004; Drobos et al., 2004; Martín-Blanco et al., 2017; Streeton & Whelan, 2001), and eating disorders (Marrazzi et al., 1995). Well-designed randomized controlled clinical studies focusing on the efficacy of opioid antagonists in BPD are missing and previous studies were limited so far. The presence of major depression among first-degree relatives of BPD patients was significantly associated with improvement of global BPD symptoms whereas

TABLE 6 Results of multiple logistic regression analyses

	Model 1			Model 2			Model 3		
	OR	SE	P-value	OR	SE	P-value	OR	SE	P-value
Gender	0.1193153	0.0907019	0.005	0.0238211	0.02799	0.001	0.1206399	0.0916234	0.005
Age in days	0.9999097	0.0000723	0.212	0.9999371	0.0000936	0.502	0.9999206	0.0000732	0.278
Substance-related disorders	0.1694931	0.133793	0.025	0.0405641	0.0536559	0.015	0.1606051	0.130129	0.024
Number of admissions of the current year	1			1			1		
History of inpatient treatments	2.898092	2.188134	0.159	20.6227	27.29951	0.022	2.951361	2.246777	0.155
Outpatient services	0.9579002	0.4729759	0.931	1.097678	0.7055296	0.885	0.8438697	0.4420394	0.746
Comorbidities									
F10	1.191518	0.7904888	0.792	0.4213479	0.4261772	0.393	0.9881981	0.6058279	0.985
F12	0.5726003	0.521427	0.540	1.73248	2.744063	0.729	0.1624479	0.8348154	0.345
F13	1.209537	0.826777	0.781	1.48555	1.545185	0.704	1.164968	0.833085	0.831
F19	0.5180122	0.3898722	0.382	0.0898323	0.1166383	0.063	1.823768	1.335417	0.412
F32	2.193492	1.766436	0.329	2.497041	2.551488	0.370	0.5547877	0.4268738	0.444
F33	1.599487	0.9218292	0.415	1.664094	1.444725	0.557	0.54069	0.514944	0.519
F43	1.890255	0.9389513	0.200	3.279541	2.246474	0.083	1.731315	1.407463	0.500
First-degree relatives									
F10	1.135974	1.049053	0.890	1.30221	1.64039	0.834	0.9507518	0.9931781	0.961
F33	4.942165	3.474841	0.023	14.83646	14.21647	0.005	5.424864	3.896514	0.019
Substance classes									
Benzodiazepines	0.8711577	0.5659299	0.832	0.4136393	0.3920236	0.352	0.7757658	0.5335838	0.712
Mood stabilizers	0.8024496	0.5339327	0.741	0.7379399	0.6824554	0.742	0.8590073	0.5650338	0.817
Low-potency antipsychotics	2.434541	1.614818	0.180	3.767545	3.189384	0.117	1.906832	1.352718	0.363
High-potency antipsychotics	0.9363846	0.446576	0.890	0.7200761	0.4567922	0.605	0.7941717	0.3856869	0.635
Antidepressants	0.5804676	0.3332887	0.343	0.3548752	0.2862255	0.199	0.7752681	0.4633113	0.670
Naltrexone									
Naltrexone (any daily dosage)	43.22735	29.70433	<0.0001						
Naltrexone (>50 to 150 mg per day)				791.7602	1254.405	<0.0001			
Naltrexone (≤50 mg per day)							26.56852	18.78615	<0.0001
Log likelihood	−69.534483			−41.949949			−65.063779		
LR X ²	79.33			70.62			66.12		
Prob > X ²	<0.0001			<0.0001			<0.0001		
Pseudo R ²	0.3632			0.4570			0.3369		

Note: Multiple logistic regression analyses were performed in order to identify possible predictors of clinical improvement in BPD. Odds ratios (OR) and standard errors (SE) of each independent variable were given in Model 1 (any daily dosage of naltrexone), Model 2 (high-dose naltrexone) and Model 3 (low-dose naltrexone). Numbers in bold indicate statistically significant results ($p \leq 0.05$). Italic numbers was used to highlight p-values.

female gender and substance-related disorders were possible predictors for worse outcome. As biomarkers and reliable predictors are urgently needed for optimizing treatment strategies for BPD patients, these findings are recommended for further clinical investigation. So far, clinical studies focusing on psychotherapy alone (Barnicot et al., 2012; Kröger et al., 2013; Yen et al., 2009) or combined treatment with fluoxetine (Bellino et al., 2015) revealed a host of interesting factors possibly predicting beneficial treatment outcome in BPD, such as a stronger BPD psychopathology, a higher degree of core symptoms, a robust patient-rated therapeutic alliance, and a higher educational level.

5 | LIMITATIONS OF THE STUDY

The retrospective study design, the relatively small sample size and the lack of matched controls are important limitations of this study. Furthermore, only inpatients were analyzed and BPD patients in outpatient services were not included. However, it is estimated that 80% of individuals affected with BPD receive inpatient treatment once in their life, thus it can be assumed that our sample was representative. Due to incomplete data in the patient database, this approach could not address the impact of any psychological treatments during the inpatient stay. Furthermore, this study did not consider previous outpatient or inpatient psychological treatments. It has to be considered that we used a non-validated scoring instrument comprising five BPD-related symptoms, as the assessment was performed retrospectively. Outcome measurements of future prospective studies should be operationalized by means of standardized diagnostic instruments, such as the Zanarini rating scale for BPD, or BSL. Furthermore, the study is limited by the absence of information on side effects of naltrexone. Thus, we recommend a thorough ascertainment of adverse events to control for this selection-bias in future prospective investigations.

6 | CONCLUSIONS

The present study indicates that naltrexone might significantly reduce BPD-related symptoms, and its effects in BPD might be superior to all available psychoactive drugs. Our findings also suggest a dose-dependent effect of naltrexone, as higher doses (>50 to 150 mg per day) were associated with stronger improvement. Our findings need to be explored by means of consecutive large-scale, well-designed, double-blinded controlled clinical studies evaluating the treatment efficacy of naltrexone or related opioid antagonists in BPD. Our findings align with previous evidence and highlight the essential role of the EOS in the pathophysiology of BPD.

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CONFLICTS OF INTEREST

In the past 36 months, Dr. Bandelow has been on the speakers' board for Janssen, Pfizer, Roche, Schwabe, and on the advisory board for Lundbeck and Pfizer. In the past 36 months, Dr. Wedekind has been on the speakers' board for Pfizer, Mundipharma and Schwabe. Miriam Meiser, Jens Wiltfang, and Charles Timäus declare that they have no conflict of interest.

ETHICS APPROVAL

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of the University Medical Center Goettingen.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Miriam Meiser and Charles Timäus. The first draft of the manuscript was written by Charles Timäus, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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