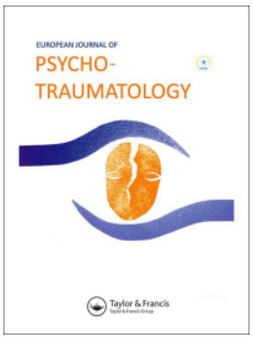

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REVIEW ARTICLE

Treatment of dissociative symptoms with opioid antagonists: a systematic review

Irene Escamilla [a,b], Nerea Juan [a,b], Celeste Peñalva [a,b], Marta Sánchez-Llorens [c], Jorge Renau [a,b], Ana Benito [a,d] and Gonzalo Haro [a,e]

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ABSTRACT

Background: The clinical guidelines for the treatment of dissociation focus primarily on psychotherapy. However, different psychoactive drugs are used in clinical practice. The use of opioid antagonists has been proposed as a therapeutic option based on the theory that dissociation might be a phenomenon mediated by dysregulation of the endogenous opioid system.

Objective: To review and meta-analyse the available evidence on the efficacy of the opioid antagonists naltrexone, naloxone, and nalmefene as treatments for dissociative symptoms and disorders.

Method: The PRISMA guidelines were followed, and this review was registered in Prospero with reference number CRD42021280976. The search was performed in the PubMed, Scopus, Web of Science, EMBASE, PsycINFO, and PubPsych databases.

Results: 1,798 citations were obtained. After removing duplicates and applying inclusion and exclusion criteria, we included 5 comparative studies with 9 dissociation measures that had included a total of 154 participants, of whom 134 had been treated with an opioid antagonist. The results of the meta-analysis showed a treatment effect for dissociation when using opioid antagonists [pooled $d = 1.46$ (95% CI: 0.62–2.31)]. However, the studies we included were very heterogeneous [$Q = 66.89$ ($p < .001$)] and there may have been publication bias.

Conclusions: Although more research is needed and the results must be interpreted with caution because of the limited amount of data and heterogeneity in the studies and their methodological qualities, opioid antagonists (particularly naltrexone) are promising candidates for the treatment of dissociative symptoms and showed a moderate – large effect size in reducing these symptoms.

Tratamiento de síntomas disociativos con antagonistas opiáceos: una revisión sistemática

Introducción: Las guías clínicas para el tratamiento de la disociación se centran principalmente en la psicoterapia. Sin embargo, diferentes sustancias psicoactivas se usan en la práctica clínica. El uso de antagonistas opioides se ha propuesto como una opción terapéutica basada en la teoría de que la disociación podría ser un fenómeno mediado por la desregulación del sistema opioide endógeno.

Objetivo: Revisar y meta-analizar la evidencia disponible sobre la eficacia de los antagonistas opiáceos naltrexona, naloxona y nalmefeno como tratamientos para los síntomas y trastornos disociativos.

Método: Se siguió la guía PRISMA y la revisión se registró en Prospero con número de referencia CRD42021280976. La búsqueda se realizó en las bases PubMed, Scopus, Web of Science, EMBASE, PsycINFO y PubPsych.

Resultados: Se encontraron 1.798 citaciones. Tras eliminar duplicados y aplicar los criterios de inclusión y exclusión, se incluyeron 5 estudios comparativos con 9 medidas de disociación que incluían un total de 154 participantes, de los cuales 134 habían sido tratados con un antagonista opiáceo. Los resultados del meta-análisis mostraron un efecto del tratamiento para la disociación al usar antagonistas opiáceos [d combinada = 1,46 (95%IC: 0,62–2,31)]. Sin embargo, los estudios incluidos eran muy heterogéneos [$Q = 66,89$ ($p < 0,001$)] y podría haber sesgo de publicación.

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KEYWORDS
Dissociation; naloxone; naltrexone; opioid antagonists; meta-analysis

PALABRAS CLAVE
Disociación; naloxona; naltrexona; antagonistas opiáceos; metanálisis

关键词
解离；纳洛酮；纳曲酮；阿片类拮抗剂；元分析

HIGHLIGHTS

- The results of the meta-analysis showed a treatment effect for dissociation when using opioid antagonists [pooled $d = 1.46$ (95% CI: 0.62–2.31)].
- The results must be interpreted with caution because of the limited amount of data and heterogeneity in the studies and their methodological qualities.
- Opioid antagonists (particularly naltrexone) are promising candidates for the treatment of dissociative symptoms and showed a moderate – large effect size in reducing these symptoms.

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Conclusiones: Aunque es necesaria más investigación, así como los resultados deben ser interpretados con cautela debido al limitado número de datos y la heterogeneidad de los estudios y sus calidades metodológicas, los antagonistas opiáceos (particularmente la naltrexona) son candidatos prometedores para el tratamiento de los síntomas disociativos, mostrando un tamaño del efecto moderado-grande en la reducción de estos síntomas.

阿片类拮抗剂治疗解离症状：系统综述

背景：解离治疗的临床指南主要侧重于心理治疗。然而，临床实践中使用不同的精神活性药物。基于解离可能是内源性阿片系统失调中介现象的理论，使用阿片拮抗剂已被提议作为一种治疗选择。
目的：回顾和元分析关于阿片类拮抗剂纳曲酮、纳洛酮和纳美芬治疗解离症状和疾病疗效的现有证据。
方法：遵循 PRISMA 指南，该综述在 Prospero 注册，参考号 CRD42021280976。检索是在 PubMed、Scopus、Web of Science、EMBASE、PsycINFO 和 PubPsych 数据库中进行的。
结果：获得 1,798 次引用。在删除重复项并应用纳入和排除标准后，我们纳入了 5 项比较研究，涉及 9 项解离措施，总共包括 154 名参与者，其中 134 人接受过阿片类拮抗剂治疗。元分析的结果显示，使用阿片类拮抗剂对解离有治疗作用[汇总 $d = 1.46$ (95% CI: 0.62–2.31)]。然而，我们纳入的研究非常异质 [$Q = 66.89$ ($p < .001$)]，并且可能存在发表偏倚。
结论：虽然需要更多的研究，并且由于研究中的数据量和异质性及其方法学质量有限，必须谨慎解释结果，但阿片类拮抗剂（特别是纳曲酮）是治疗解离症状的有前途的候选药物，并显示出中等至较大的减轻这些症状的效果。

1. Introduction

Dissociation is a complex psychopathological phenomenon, defined by an interruption to and/or discontinuity in the normal integration of consciousness, memory, self, and subjective identity, emotion, perception, body identity, motor control, and behaviour (American Psychiatric Association [APA], 2014). Dissociative phenomena cover a range of conditions that include relatively common disturbances that any individual can experience (such as getting on a train and not remembering what happened during the journey), to severe states such as not being able to recognise oneself in the mirror (Lanius et al., 2014; Mosquera, 2013; Perry & Szalavitz, 2017). In its more complex forms, dissociation can be understood as a defence mechanism with which an individual tries to deal with situations such a trauma that generate high levels of stress, especially if it had occurred in the early stages of development (Lyssenko et al., 2018). Various studies explain how sometimes children's only response to being attacked or hurt is dissociation, a phenomenon that can help them survive the immediate trauma. However, if this defence persists when faced with any stress, it could lead to the appearance of dissociative disorders (Perry & Szalavitz, 2017). The defence cascade model provides a description of neurobiological responses to threat. This model describes differential responses to threat depending on perceived imminence and chances of escaping. On one side, this model describes active defensive responses (e.g. fight or flight), which are driven by subcortical brain structures, modulated by endocannabinoid system, and inhibited by opioid peptides. On the other side, when threat is deemed inescapable, the model describes passive defensive response (dissociative symptoms), which are associated with an increased prefrontal cortex and modulated by the opioid system (Lanius, 2014; Lanius et al., 2018). The dissociative disorders included in the DSM-5 are dissociative amnesia, dissociative identity disorder (DID), and depersonalisation/derealisation disorder. In addition, there is a fourth group that acts as a miscellaneous group and includes mixed dissociative disorders, secondary dissociative disorders, and acute dissociative reactions (APA, 2014). In addition to constituting a complete clinical entity, dissociation may also form part of other entities as a symptom of post-traumatic stress disorder (PTSD), borderline personality disorder (BPD), and conversion disorder (Lyssenko et al., 2018). The prevalence of dissociative disorders is 5–10% in the general population, while in the population of psychiatric patients it is 10–41% (García et al., 2006; Maldonado et al., 2002; Romero-López, 2016). However, it is considered that, in practice, these disorders are underdiagnosed or misdiagnosed (Gentile et al., 2013), which would explain the scarcity of rigorous research on their treatment (International Society for the Study of Trauma and Dissociation [ISSTD], 2011).

The few clinical guidelines that exist (Agarwal et al., 2019; ISSTD, 2011) focus mainly on psychotherapeutic treatment. They also consider medication not to be a primary treatment for dissociative symptoms (ISSTD, 2011) and so no guides on their pharmacological treatment currently exist. However, in a naturalistic study on the outpatient treatment of dissociative disorders, 80% of patients received adjuvant medication (Brand et al., 2009). In fact, different psychoactive drugs have been used, but there is still insufficient evidence in favour of any medication to treat dissociative symptoms (Sutar & Sahu, 2019). In their systematic review, Sutar and Sahu (2019) concluded that

pharmacotherapy is favourable compared to placebo, specifying that the only drugs with modest evidence for the control of comorbid dissociative symptoms in PTSD and BPD were paroxetine and naloxone. However, these results should be interpreted with caution because of the scarcity and high heterogeneity of the clinical trials included in their work.

Improvement in dissociation has been shown using naloxone (Nuller et al., 2001). The rationale for its use is based on the defence cascade model, where passive defensive response (dissociative symptoms) is a phenomenon mediated by deregulation of the endogenous opioid system (EOS) (Bandelow et al., 2010), which is why opioid antagonists such as naloxone, as well as naltrexone and nalmefene, could be considered therapeutic options. On the one hand, MOR (a μ opioid receptor) antagonism would reduce analgesia associated with stress and, on the other hand, KOR (a κ opioid receptor) antagonism would attenuate dysphoric states, producing an antidepressant effect (García, 2020). Several studies support the efficacy of dissociation treatment with naltrexone (Bohus et al., 1999; Lubin et al., 2002; Simeon & Knutelska, 2005). In the same line, there are promising results with nalmefene (Enning & Schmahl, 2022; Glover, 1993). Although less research has been performed with this drug, there is some suggestion that nalmefene may be more easily tolerated than naltrexone at higher doses (Enning & Schmahl, 2022; Glover, 1993).

The objective of this systematic review was to compile the available evidence on the efficacy of the opioid antagonists naltrexone, naloxone, and nalmefene as treatments for dissociative symptoms and disorders, synthesising these results through a meta-analysis. The PICO (Participant, Intervention, Comparator, Outcome) question was: do opioid antagonists reduce the presence of dissociative symptoms? The PICO components were as follows: Participants (P): individuals with dissociative disorders or symptoms; Intervention (I): treatment with opioid antagonists; Comparator (C): placebo; and Outcome (O): improvements in the presentation of dissociative symptoms (assessed with validated scales). Our hypotheses were that, compared to the placebo, dissociative symptoms are reduced by (1) naltrexone; (2) naloxone; (3) nalmefene; and (4) opioid antagonists.

2. Experimental procedures

2.1. Protocols and records

In preparing this study, we followed the PRISMA guidelines for reporting in systematic reviews and meta-analyses (Moher et al., 2010). The protocol was registered in the Prospero Centre for Reviews and Dissemination on 22 October 2021 (CRD42021280976): *Treatment of dissociation with opioid antagonists: meta-analysis*, which is available online: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID = 280976 (accessed on 19 October 2022).

2.2. Search strategy

We searched for relevant studies in the PubMed, Scopus, Web of Science, EMBASE, PsycINFO, and PubPsych databases. We also reviewed the bibliographies of the included articles, reviews, and meta-analyses. The search start year was not limited, and the search terms were: '(Dissociative Disorder OR Dissociation OR Dissociative OR Dissociative Reaction OR Dissociative Hysteria OR Dissociative Fugue OR Dissociative Trance OR Dissociative Possession OR Dissociative Identity Disorder OR Multiple Personality Disorder OR Multiple Identity Disorder OR Dual Personality OR Depersonalization OR Derealization OR Dissociative Amnesia) AND (Naloxone OR Naltrexone OR Nalmefene)'.

2.3. Inclusion and exclusion criteria

The inclusion criteria were: (1) original quantitative comparison studies regardless of their design; (2) the drugs of interest were treatment with naltrexone or naloxone or nalmefene; (3) the comparison group received a placebo treatment; (4) outcomes: scores on dissociative symptoms or disorders assessed with validated scales. Studies were included irrespective of their publication language, publication data, patient nationality, sex, race, age, or population origin. The exclusion criteria were: (1) studies that did not include a comparison group or the comparison was narrative/qualitative; (2) in which the comparison was to other drugs or to psychotherapy; (3) that did not distinguish between dissociative and other symptoms (e.g.: psychotic symptoms); (4) dissociative symptoms were assessed by clinical judgment or patient self-assessment without using a validated instrument.

As shown by our results, only three studies that met the inclusion criteria were included in the first selection (and in these, the necessary data could not be obtained in 2 cases). Thus, inclusion criterion 3 and exclusion criterion 2 were eliminated and a second selection was performed which allowed the inclusion of comparators other than a placebo as well as studies with a pre–post within-subject design.

2.4. Data extraction

The articles assessed for eligibility were divided into two equal parts; two authors independently extracted the information from each half (a total of four researchers) using a standardised form and resolving any disagreements by discussing the matter with the other two authors until a consensus was reached. The variables extracted from the included studies were: first

author's name, year, country, publication language, study design (including sample selection), overall sample size, age of the sample, patient race/ethnicity, sex, study quality, diagnosis, assessment instrument, treatment, comparator, follow-up time, treatment group sample size, comparison group sample size and scores for dissociative symptoms or disorders (mean and standard error). When data for the meta-analysis was not directly presented, it was calculated using the data provided or was requested from the authors.

2.5. Summary measures

We used sample sizes, means, and standard errors to calculate the standardised mean difference (Cohen's d) between the treatment group and comparison group as well as its 95% confidence interval (95% CI) to calculate the effect of opioid antagonists on dissociative symptoms. We employed a random-effects model, weighting the studies by the inverse of the variance, and performed all the statistical analyses using Epidat 3.1 software (Xunta de Galicia, A Coruña, Spain; Pan American Health Organization, Washington, DC, USA). Because this programme was designed in Spain, the decimals in its outputs are expressed with commas. Therefore, when they appear later in the text, in Figures 2–5, commas should be interpreted as decimal points.

2.6. Quality assessment

The quality of the randomised studies was assessed using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Sterne et al., 2019). The quality of the case–control and cross-sectional studies was assessed with the Newcastle–Ottawa Scale (NOS; Wells et al., 2019).

2.7. Heterogeneity and publication bias

Heterogeneity was evaluated using DerSimonian – Laird Q tests with Galbraith graphics. Possible publication bias was examined by employing Egger and Begg tests with funnel plots.

2.8. Sensitivity and subgroup analysis

We performed a sensitivity analysis by repeating the meta-analysis the same number of times as the selected datasets, each time omitting one dataset and combining all the remaining ones and then plotting the influence graphs. We decided whether we needed to analyse subgroups of studies by performing heterogeneity and sensitivity analyses. Specifically, the meta-analyses were repeated, eliminating the articles that contributed the most to heterogeneity according to the Galbraith graphs produced.

3. Results

3.1. Included studies

The initial search collected 1,798 citations, of which 5 articles containing 9 dissociation measures from comparisons were included in the meta-analysis. Figure 1 illustrates the article selection process. The studies included a total of 154 participants, of whom 134 had been treated with an opioid antagonist.

Of the 5 articles included, 1 had used naloxone and 4 naltrexone; 2 had evaluated dissociative symptoms as part of borderline personality disorder, 1 in opioid use disorder, and 1 in post-traumatic stress disorder; another study had evaluated depersonalisation disorder. Table 1 shows the characteristics of the studies included, while Table 2 shows the data from the 9 comparisons included in the meta-analysis. All the included articles were in English and only 1 (Gainer et al., 2021) specified the race of the participants (white and non-white).

3.2. The effect of treatment with opioid antagonists

As shown in the forest plot presented in Figure 2, the pooled d was 1.46 (95% CI: 0.62–2.31).

3.3. Analysis of heterogeneity and sensitivity

The Q index was 66.89 ($p < .001$). Both the Q index and the Galbraith plot (Figure 3) indicated the presence of heterogeneity. The data contributing the most to the heterogeneity were PhilipsenDSS, SimeonCDS, and Lubin. SimeonCADSS and Bohus also contributed to the heterogeneity, although to a lesser extent.

As shown in the influence graph (Figure 4), the sensitivity analysis indicated that eliminating each of these studies did not substantially modify the result or the precision. If the three data sets that most contributed to heterogeneity were eliminated, the pooled d for the analysis of the resulting subgroup was 1.76 (95% CI: 0.55–2.97) while the heterogeneity remained $Q = 61.34$ ($p < .001$).

3.4. Publication bias

The result of the Berg test was $Z = 0.72$ ($p = .465$) and that of the Egger test was $t = 1.09$ ($p = .311$), indicating that there was no publication bias, although the funnel plot (Figure 5) did indicate the presence of bias.

4. Discussion

This present review aimed to collect evidence regarding the efficacy of the use of opioid antagonists

Figure 1. Flowchart of the systematic review process used to select articles for inclusion in this meta-analysis.

(naloxone, naltrexone, and nalmefene) in the treatment of dissociative symptoms and disorders. The most striking result was the paucity of research in this regard. Our initial search with strict methodological criteria found only studies (Nuller et al., 2001; Philipsen et al., 2004; Schmahl et al., 2012), of which the data required for a quantitative synthesis could not be obtained in 2 cases. This reflects how little quality research there is available on the subject. In a second search in which we applied more lax methodological criteria, we obtained data from only 4 more articles (Bohus et al., 1999; Gainer et al., 2021; Lubin et al., 2002; Simeon & Knutelska, 2005). This reflects the scarcity of any kind of research in this regard. In total, only 5 articles could be included in this quantitative synthesis, from which 9 quantitative dissociation measures were obtained. Furthermore, only one study was a randomised controlled trial, and

Table 1. Characteristics of included studies.

AUTHOR	YEAR	COUNTRY	DESIGN	SAMPLE	AGE	SEX	QUALITY	DIAGNOSIS
Philipsen	2004	Germany	Double-blind, randomised, crossover	9	Mean = 34.9 SD = 6.7	Women: 100%	RoB2.2: L, SC, L, L, L, L	Dissociative symptoms in BPD
Bohus	1999	Germany	Open label pre-post trial without a control group	9	17–47	Women: 100%	NOS 6	Dissociative symptoms in BPD
Gainer	2021	USA	Cross-sectional	116	Over 18	Women: 51.7% Men: 48.3%	NOS 7	Dissociative symptoms in opioid use disorder
Lubin	2002	Israel	Prospective, open label, pre-post trial without a control group	7	Mean = 36.1 SD = 10.7	Women: 25% Men: 75%	NOS 6	Dissociative symptoms in PTSD
Simeon	2005	USA	Prospective, open trial pre-post trial without a control group	13	Mean = 30.9 SD = 8.5	Women: 14.3% Men: 85.7%	NOS 6	Depersonalisation disorder

Note: RoB2.2, Revised Cochrane risk-of-bias tool for randomised trials; L, low risk of bias; SC, some concerns about risk of bias; NOS, Newcastle – Ottawa Scale; BPD, borderline personality disorder; PTSD, post-traumatic stress disorder.

this study had a sample size of 9. In fact, the findings are heavily weighted by one cross-sectional study, which had 116 participants, while the rest were open label studies with very small sample sizes. However, despite the scarcity of research, the results indicated a moderate-large effect size, which would indicate that the results obtained with the use of these drugs were strongly positive, providing positive expectations for future therapeutic options.

As we previously described in introduction, dissociative phenomena cover a range of conditions that must include variability between individuals in the degree and type of symptoms. That is, dissociation is understood as a transdiagnostic phenomenon, where variables such as culture (Şar, 2022), age and gender (Putnam et al., 1996) can influence different clinical expressions. It is normal for culture to influence how 'individuals display and communicate their symptoms, how such symptoms are interpreted, and what type of care is sought' (Dorahy et al., 2014). For instance, there are a higher prevalence of possession-form DID in non-Western cultures due to their way of understanding the person as a unit (Dorahy et al., 2014). In relation to age, it has been shown that childhood trauma is a very significant risk factor for development of dissociative disorders (Farina et al., 2019). Regarding gender, there is a dominance of dissociative disorders in women, but empirical studies have indicated that dissociative symptoms do not differ between genders. Women dominance may be explained because men with dissociative disorders usually do not enter health system (Spitzer & Freyberger, 2008). These are some reasons that explain importance of why race, age, and gender/sex need to be considered in studies of dissociative symptoms. However, in the present review, only the article by Gainer et al. (2021) considers gender variable, without finding a significant influence of said variable. Furthermore, none of the included articles consider other variables in the explanation of their results. These facts must be kept in mind when interpreting findings of this review. Similarly, it should be noted that, except for Simeon and Knutelska (2005) research, the rest of the articles do not pay attention to the differences between dissociative disorders such as dissociative amnesia or depersonalisation. These are

Table 2. Data characteristics of the included comparisons.

AUTHOR	YEAR	INSTRUMENT	TREATMENT	COMPARATOR	FOLLOW UP	*d* (95% IC)
Philipsen DDS	2004	Dissociation-Tension Scale (DSS; Stiglmayr et al., 2001)	Naloxone ($n = 9$)	Saline placebo ($n = 9$)	15 min	2.58 (1.95, 3.22)
Philipsen CADSS	2004	Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., 1998)	Naloxone ($n = 9$)	Saline placebo ($n = 9$)	15 min	0.46 (−0.47, 1.40)
Bohus	1999	Dissociation, Analgesia, Immobility, and Tension Scale (DAISS; C.E.S., M.J.B., H. Richter, Ph.D., et al., unpublished data), dissociation intensity sub-scale	Naltrexone ($n = 9$)	None: intra ($n = 9$)	2 weeks	0.15 (−0.76, 1.08)
Gainer Buprenorphine	2021	Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986)	Naltrexone ($n = 64$)	Buprenorphine ($n = 20$)	None	1.74 (0.84, 2.64)
Gainer Methadone	2021	Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986)	Naltrexone ($n = 32$)	Methadone ($n = 20$)	None	1.68 (0.79, 2.58)
Lubin	2002	Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986)	Naltrexone ($n = 7$)	None: intra ($n = 7$)	2 weeks	4.30 (2.62, 5.98)
Simeon CADSS	2005	Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., 1998)	Naltrexone ($n = 13$)	None: intra ($n = 13$)	7–10 weeks	2.43 (1.42, 3.45)
Simeon CDS	2005	Cambridge Depersonalisation Scale (CDS; Sierra & Berrios, 2000)	Naltrexone ($n = 13$)	None: intra ($n = 13$)	7–10 weeks	−0.03 (−0.59, 0.52)
Simeon DES-DPS	2005	Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986) Depersonalisation factor sub-score	Naltrexone ($n = 13$)	None: intra ($n = 13$)	7–10 weeks	0.57 (−0.49, 1.64)

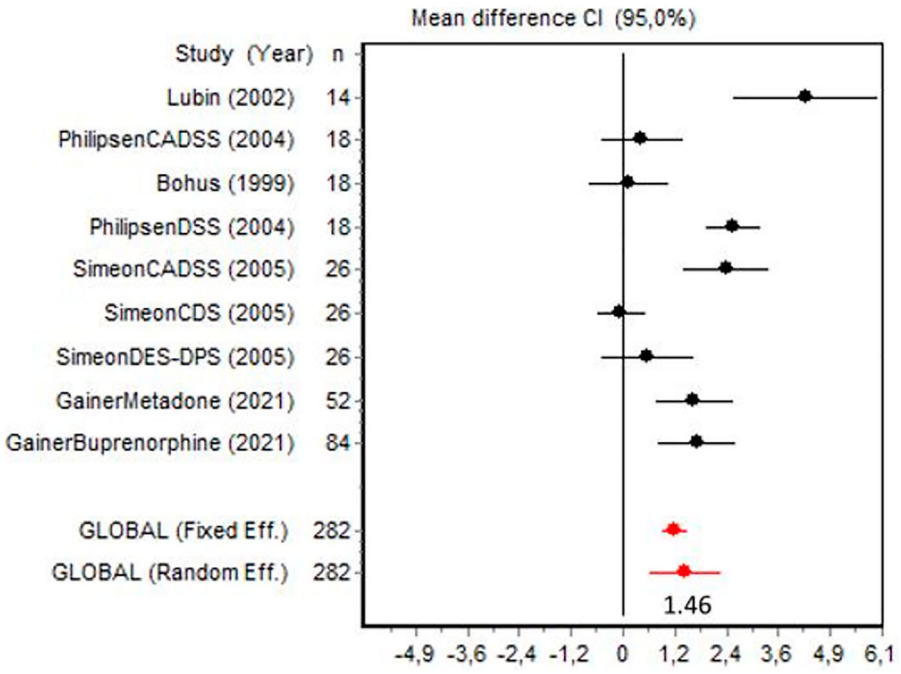

Figure 2. Forest plot. Abbreviations: CADSS, Clinician-Administered Dissociative States Scale; DSS, Dissociation-Tension Scale; CDS, Cambridge Depersonalisation Scale; DES-DPS, Dissociative Experiences Scale-Depersonalisation factor sub-score.

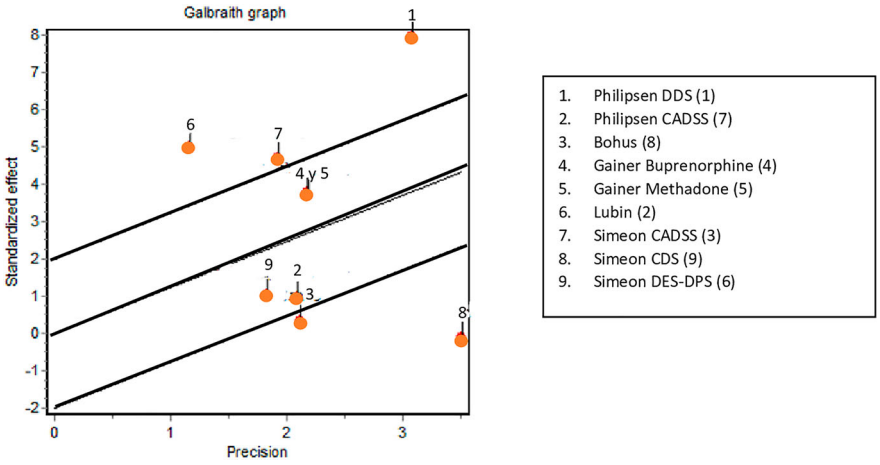

Figure 3. Galbraith graph.

disorders with differential characteristics (APA, 2014). The literature suggests that different endogenous opioids are involved in differential characteristics. For example, beta-endorphin in amnesia and dynorphin in depersonalisation and derealization. Therefore, it would be expected that the response to treatment would also have differences. Not considering these differences limits the scope of included studies (Lanius, 2014).

Most of the articles included in this meta-analysis had analysed naltrexone, a nonspecific competitive opioid antagonist of the MOR, DOR, and KOR receptors (García, 2020). Two open trials conducted in patients with BPD and depersonalisation disorder presented favourable results regarding the use of naltrexone in dissociative symptoms (Bohus et al., 1999; Simeon & Knutelska, 2005). Furthermore, an open trial, conducted by Lubin et al. (2002), showed an improvement in dissociative symptoms in PTSD patients treated with naltrexone. They also found a small statistically but not clinically significant improvement in intrusion and hyperarousal symptoms. This improvement could be explained through opioid antagonism, since it exerts an inhibitory effect on the hyperactive endogenous opioid system and allows the recovery of aminergic neurotransmission, achieving an effect like that of antidepressants (Johnson & Ait-Daoud, 1999). However, because of side effects presented during the investigation, naltrexone was not recommended in patients with PTSD.

Regarding the side effects of naltrexone, some appear immediately after starting the drug and disappear within a few days, such as headache, tiredness,

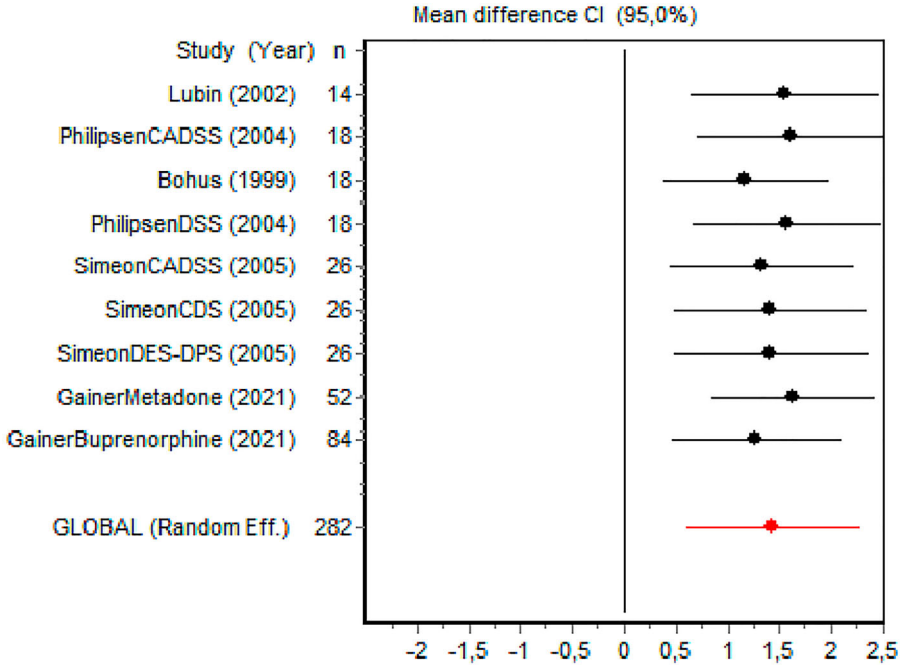

Figure 4. Influence graph. Abbreviations: CADSS, Clinical Administered Dissociative States Scale; DSS, Dissociation-Tension Scale; CDS, Cambridge Depersonalisation Scale; DES-DPS, Dissociative Experiences Scale-Depersonalisation factor sub-score.

drowsiness/dizziness, restlessness, and a feeling of fullness. On the other hand, others appear after a few days and persist, such as high blood pressure, increased traumatic memories, and urinary retention. Finally, other adverse effects appear after weeks or months but subside after dose reduction or discontinuation, such as muscle or joint pain. It was hypothesised that the adverse effects could be explained by the high doses of naltrexone initially used. For example, Johnson and Ait-Daoud (1999) used oral naltrexone doses of 100 mg, while in the papers included in this study, doses range from 50 to 250 mg. There is some suggestion that lower doses of naltrexone may be much lower in side effects while still providing therapeutic effects (Oncken et al., 2001; Pape, 2020; Pape & Wöller, 2015). In this sense, naltrexone may be a helpful element in the treatment of patients with complex posttraumatic stress disorder (Pape & Wöller, 2015). However, the decrease of dissociation may lead patients to a not yet resolvable challenge, in as much as dissociation had previously been a necessary mechanism of self-protection (Pape & Wöller, 2015). This means that patients on treatment would not present passive defensive responses but instead would exhibit an increase in active defensive response (e.g. fight or flight), with a raised sense of threat, and this clinic requires a treatment that is also under development (Lanius, 2014; Lanius et al., 2018). A naturalistic, exploratory, non-randomised study without a control group with the objective of analysing dissociative symptoms in patients undergoing treatment for opioid use disorder was also included (Gainer et al., 2021). Initially, based on existing literature that suggested an association between dissociative symptoms and substance use disorders (Ghafarinezhad et al., 2013), it was hypothesised that the subjects prescribed methadone would have higher dissociation scores than prescribed with naltrexone. However, their results indicated that in the subjects treated with methadone or naltrexone the dissociative symptoms were lower, while in those treated with buprenorphine they were higher (Gainer et al., 2021). The study examined the relationship between dissociative symptoms and opioid use disorder using the Dissociative Experiences Scale (DES). They studied subjects who were taking prescribed methadone, buprenorphine, or naltrexone for opioid use disorder. The authors suggested that these findings may have been because patients treated with buprenorphine had more severe dissociation symptoms and indicates the importance of the diagnosis and monitoring of dissociative symptoms in people undergoing treatment for substance use disorder, since these symptoms can interfere with treatment (Gainer et al., 2021). Other possible explanation for the lower levels of dissociation in the subjects with methadone prescription it would be 'chemical dissociation' hypothesis, which proposes substance use as substitutive method of dissociation, and this implies differences in DES score compared to psychogenic dissociation (Somer et al., 2010). On other side, lower dissociative symptoms with naltrexone could be associated to the antagonistic effect of naltrexone for MOR, DOR and KOR receptors, understanding dissociation is partly a consequence of unstable endopioid activity and, therefore, opioid antagonism improves dissociative symptoms (Bohus

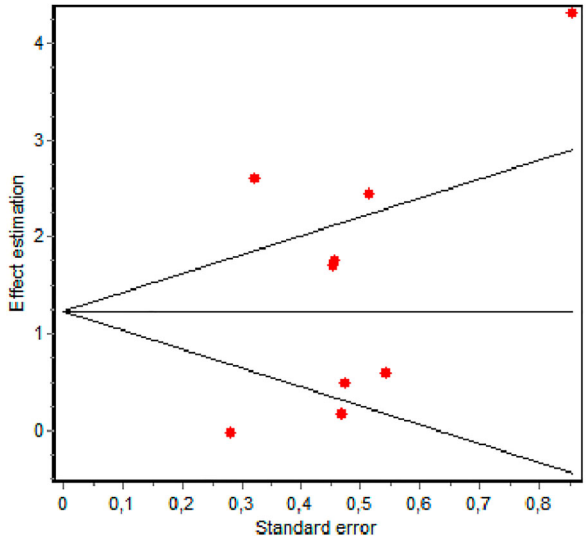

Figure 5. Funnel plot.

et al., 1999; Simeon & Knutelska, 2005). Higher dissociation with buprenorphine may be since the drug acts as a partial MOR agonist, which differentiates it from naltrexone and could explain a lesser effect on dissociative symptoms (García, 2020). Finally, it is important to note that the participants in the study by Gainer et al. (2021) were in treatment for opioid use disorder, which limits the generalizability of their results. As they themselves comment in their article: 'It is difficult to discern from our data if methadone and naltrexone improve dissociative symptoms, if buprenorphine or side effects of buprenorphine worsens dissociative symptoms, or if the subjects who were taking prescribed buprenorphine have more severe dissociative symptoms independent of the prescribed medication' (Gainer et al., 2021).

All the results regarding naltrexone that we included in this study suggested its usefulness in reducing dissociative symptoms, in line with the publication bias indicated by the funnel plot shown in Figure 5. However, it is worth noting that one trial that could not be included (Schmahl et al., 2012) indicated that, although treatment with naltrexone led to a decrease in the intensity and duration of dissociation in patients with BPD compared to the placebo, this effect was too small to reach statistical significance (Schmahl et al., 2012). Nonetheless, the overall impression was that naltrexone is a promising candidate for the treatment of dissociative symptoms. In addition, it has the advantage that it is well documented that, in humans with no history of drug abuse, its use does not alter behaviour, perception, mood, or cognition (Berg et al., 1996).

Only one of the included studies (Philipsen et al., 2004) focused on naloxone, a nonspecific competitive opioid antagonist of the MOR, DOR, and KOR receptors (García, 2020). The objective of this clinical trial was to show that the use of naloxone leads to an improvement in acute dissociative states in patients with BPD. However, the results were not significant because there were no differences between the use of the placebo and the drug and the improvement in both cases could be explained by the anti-dissociative effect of the injection (Philipsen et al., 2004). Although, some investigations demonstrate that injections cause pain, and pain activates the endogenous opioid system (Holden et al., 2005) and may induce a dissociated state (Bob, 2008). However, Philipsen et al. (2004) support that pain has an anti-dissociative effect, agree with the anti-dissociative model that emphasises the role of pain to generate bodily sensations to maintain contact with reality (Klonsky, 2007). Contrary to these findings, another clinical trial by Nuller et al. (2001) that could not be included in this current work, showed a decrease in the intensity of dissociative symptoms with the use of naloxone, as measured with validated scales and quantified by an increase in plasmatic cortisol levels.

In turn, no research with nalmefene, a selective modulator of the opioid system (a MOR and DOR antagonist and KOR partial agonist; García, 2020) met our inclusion criteria, even though, because of its similar mechanism to naltrexone and naloxone, this drug could represent a future pharmacological alternative. Indeed, several studies have provided evidence in support this statement. First, Martín-Blanco et al. (2017) found significant results indicating that nalmefene can reduce the symptoms of patients with BPD, although they did not specifically measure dissociative symptoms. Second, Enning and Schmahl (2022) conducted a study in which nalmefene showed promising results as a possible alternative to naltrexone, particularly in the case of intolerance or insufficient naltrexone efficacy.

Based on the literature reviewed, it should be noted that, in addition to the improvement in different clinical manifestations of dissociative disorder, opioid antagonists have also shown promising results in the treatment of other disorders that include dissociation as a symptom (PTSD, BPD or substance use disorder) and other symptoms of these disorders, which have in common a relationship with dysphoric mood, anhedonia and feelings of emptiness (Bandelow et al., 2010). For instance, opioid antagonists have demonstrated to be useful in the treatment of BPD-related symptoms (Timäus et al., 2021) and diagnostic criteria such as non-suicidal self-injurious behaviours (Roth et al., 1996), suicidal ideation (Martín-Blanco et al., 2017), and some impulsive behaviours such as binge eating (Marrazzi et al., 1995) or substance abuse (García, 2020). This is because the neurobiological mechanisms underlying these clinical symptoms may be like those of dissociative clinical symptoms, that is, dysfunction of the EOS. Dysphoric mood, anhedonia and feelings of emptiness may be expressions of decreased EOS activity, as well as the attempt of

affected patients to compensate with stimulating actions of EOS (Bandelow et al., 2010). This would allow considering the use of opioid receptors as therapeutic targets (García, 2020). Thus, transdiagnostically, the experience of dissociative symptoms could be understood as an activation of the opioid system driven by acute or chronic stress. This would mean an attempt by the organism to mobilise the last reserves of EOS with the purpose to mitigate the harmful effect of aversive stimuli (Lyssenko et al., 2018). Therefore, the use of opioid antagonists could allow a decrease in the intensity and duration of the dissociative symptoms and other maladaptive behaviours to mitigate emotional discomfort.

Even though opioid antagonists seem to be a promising option for the treatment of dissociative symptoms, the result of this present meta-analysis must be interpreted with great caution because of its three main limitations: the limited amount of data considered, heterogeneity of the studies included, and their methodological quality. First, only a small number of studies with small sample sizes met our inclusion criteria. Furthermore, only one of the included studies was placebo-controlled. In addition, data could not be obtained from some articles that could have been included, partly because these publications were so old. In this sense, this meta-analysis highlighted the absence of current research on the subject, with exceptions such as Gainer et al. (2021) and Enning and Schmahl (2022). This paucity of data and sample also entails the lack of statistical power for analysis of race and sex-related differences in effects. Second, there was high heterogeneity between the studies we considered, as reflected in the Q index. There was wide variability in terms of the population studied, dissociation measurement scales, follow-up time, form of drug administration, and study designs. Special mention should also be made regarding the variety in the methodological quality of the studies we considered given that cross-over and intra-subject studies were included. Although the inclusion of this type of research in meta-analyses is sometimes discouraged, the type of error they can produce is underweighting (Higgins & Green, 2011); in other words, having too little weight in the final result. Thus, for this reason we decided to include these studies given the general paucity of such work. Although the heterogeneity limits the reliability of the results obtained and could even discourage their quantitative synthesis, we chose to synthesise them to obtain a reference value that serves to assess whether it would be worth continuing this line of research. Even insisting on the caution with which this quantitative synthesis must be taken given its little strength, we believe that, with all the abovementioned reservations based on these major limitations, the result obtained in this meta-analysis was promising.

Previous reviews, such as the one by Sutar and Sahu (2019), analysed the treatments used for dissociative symptoms and applied stricter inclusion criteria, meaning that studies without a control group were excluded. Other studies, such as the one by García (2020), reviewed treatment of BPD with opioid antagonists, excluding all other clinical presentations of dissociation from the investigation. Our study was the first to review all the published evidence on the treatment of dissociative symptoms with opioid antagonists. However, we were unable to collect data from many more studies than those included in previous reviews, indicating the scarcity of research on this topic in recent years.

Given the results of previous reviews as well as those from this meta-analysis, this research highlights the importance of studying the treatment of dissociative symptoms with opioid antagonists, since dissociation symptoms frequently coexist with other psychiatric conditions such as PTSD or BPD and have been associated with a poorer treatment response (Lanius et al., 2014). This reduced response is because dissociative symptoms interfere with information processing, learning, and memory; so, dissociation treatment is important even when the dissociative scores are not high (Lyssenko et al., 2018). There are currently clinical guidelines that support the benefit of psychotherapeutic treatment in dissociative symptoms (ISSTD, 2011), however, there is a lack of conclusive evidence in favour of any specific psychoactive drug (Sutar & Sahu, 2019). Future research in pharmacotherapy, added to that from the field of psychotherapy, seems to be a promising alternative and, specifically, study of the use of opioid antagonists seems to be a very reasonable option, given its neurobiological justification.

In this sense, we believe that further clinical trials employing high-quality methodologies, i.e. randomised studies with a control group, must be conducted. As mentioned by Bolm and Piegler (2001), this type of work would make it possible to achieve official approval for this indication. This is particularly important given that medications for dissociative symptoms are already being used in clinical practice (Brand et al., 2009) and so it is essential to have adequate evidence to support recommendations and clinical guidelines in this regard. It would also be useful if future studies used the same dissociation measurement scale, given the high heterogeneity produced by the different forms of measurement used to date. Other possible lines of future research could involve, on the one hand, carrying out studies focused on the use of naltrexone and nalmefene, given that the expectations for their use are promising and current research is scarce. On the other hand, the in-depth study of opioid receptors would be also useful, for example, to try to develop selective KOR agents with improved pharmacological affinities respect the currently existing opioid antagonists (Carlezon et al., 2009).

In conclusion, opioid antagonists (particularly naltrexone, for which the most quantitative data is currently available) are promising candidates for the treatment of dissociative symptoms and show a moderate–large effect size in their reduction.

Contributors

I.E. N.J., and A.B. designed the study; I.E. performed the database search; N.J., I.E. C.P.; J.R., and M.S.L. selected the articles and extracted the information; A.B. and G.H. assessed the study quality, resolved disagreements, and supervised the study; G.H. obtained the resources and funding for the work; A.B. performed the data analysis and wrote Experimental Procedures and Results; N.J., I.E. C.P., M.S.L., J.R., and G.H wrote Introduction and Discussion. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author, A.B., upon reasonable request.

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