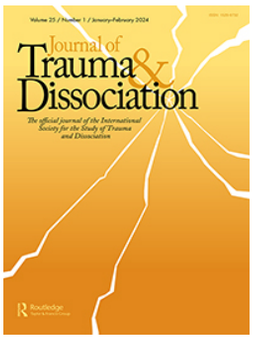

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# The Treatment of Depersonalization-Derealization Disorder: A Systematic Review

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**ABSTRACT**

Depersonalization-derealization disorder (DPD) is characterized by persistent or recurrent experiences of detachment from oneself and surroundings, as well as a sense of unreality. Considering the inadequacy of current research on treatment, we performed a systematic review of the available pharmacotherapies, neuromodulations, and psychotherapies for DPD. The systematic review protocol was based on PRISMA 2020 guidelines and preregistered. The PubMed, Web of Science, PsycINFO, Embase, the Cochrane Library, Scopus, and ScienceDirect databases were searched from inception to June 2021. All treatments for DPD and all study types, including controlled and observational studies as well as case reports, were assessed. Of the identified 17,540 studies, 41 studies (four randomized controlled trials, one non-randomized controlled trial, 10 case series, and 26 case reports) involving 300 participants met the eligibility criteria. We identified 30 methods that have been applied independently or in combination to treat DPD since 1955. The quality of these studies was considered. The relationship between individual differences, such as symptoms, comorbidities, history, and duration since onset, and treatment effects was explored. The results suggest that a series of treatments, such as pharmacotherapies, neuromodulation, and psychotherapies, could be considered in combination. However, the quality and quantity of studies were generally low considering the high prevalence of DPD. The review concludes with suggestions for future research and an urgent call for more high-quality research.

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**KEYWORDS**
Depersonalization; dissociative disorders; pharmacotherapy; neuromodulation; psychotherapy

## Introduction

Depersonalization disorder/depersonalization-derealization disorder (DPD) is a mental disorder that, according to the Diagnostic and Statistical Manual of

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Mental Disorders 5th (DSM-5) and International Classification of Diseases 11th (ICD-11), is characterized by feeling unreal or detached from oneself or one's surroundings, as suggested by metaphors like "I seem to be living in a dream" or "I am just like a machine, like a robot". Depersonalization or derealization symptoms are common, affecting 8.7% of 13,182 participants in the Gutenberg health study (Schlax et al., 2020), 11.9% of 3,809 surveyed students aged 12–18 year in German in 2011 (Michal et al., 2015), and 19.1% of 1008 adults in a phone survey in the US (Aderibigbe et al., 2001). If the symptoms are persistent or affect social functioning it can become a disorder, with prevalence rates reported as high as 0.95% in a cohort of 3,275 participants in the UK and 1.9% in a sample of 1,287 members of the general population in Germany (Lee et al., 2012; Michal et al., 2016) Incidence is accompanied by damage to individuals' life and work, mainly due to increased suicidal ideation and related mental stress (Michal et al., 2010; Solano et al., 2016), elevated depression and anxiety symptoms (Schlax et al., 2020), association with first-rank symptoms of schizophrenia-spectrum psychoses (Humpston et al., 2020), and impaired cognition (attentional and perceptual systems) (Guralnik et al., 2000, 2007), which also poses a tremendous burden on society. With recent developments in psychopathology and neuroimaging, therapeutic treatments for DPD have undergone a transformation and expansion from operative therapy to pharmacotherapies, psychotherapies, and neuromodulation.

Given the incidence and economic burden of DPD, there is urgent need for effective treatment measures. However, there is a lack of clinical guidance for treating DPD. For example, a previous systematic review of DPD treatment identified only four randomized controlled trials (RCTs), one of which was later retracted (Somer et al., 2013). Another systematic review concentrated on transcranial magnetic stimulation (TMS), but had issues with duplicates and missing data (Orrù et al., 2021). A 2017 article provided clinical guidance for assessment and measurement in the form of a narrative review – rather than a systematic review – of treatment (E. C. M. Hunter et al., 2017). Due to the limitations of previous systematic reviews, it is hard to develop guidelines for DPD treatment, which limits appropriate clinical decision-making for DPD.

A complete review is important for DPD given its approximately 1% incidence. To robustly review different types of clinical interventions (Gurevitch et al., 2018), we gathered as much evidence as possible for this systematical review and provide clear descriptions of the interventions (e.g., dose, add-on treatment, efficacy). Considering that individual differences (e.g., psychological trauma, affective temperament, and biological changes) might be associated with patients' behavior, emotion, and outcomes (Baldessarini et al., 2017), case reports and case series that provide detailed information (e.g., history of trauma, family details, and treatment) were combed to inspire future studies. In addition, this review carefully evaluated the quality of extant studies. In response to the identified issues and deficiencies, we offer some suggestions for future research.

Overall, this review examines clinical evidence for various methods along with their curative and side effects to develop a clear landscape of DPD healthcare, inform appropriate treatment options, and develop robust research.

## Method

This systematic review adhered to PRISMA 2020 guidelines and followed a predetermined published protocol (Page et al., 2021). Details of the systematic review protocol were registered on PROSPERO.

### *Search strategy*

To gather articles for this review, we searched the PubMed, Web of Science, PsycINFO, Embase, the Cochrane Library, Scopus, and ScienceDirect databases from inception to June 2021. The named databases were searched using combinations of two key concepts from MeSH, namely: depersonalization (such as depersonali#ation, dereali#ation) and treatment (such as treatment*, therap*, drug, pharmacotherap*, chemotherap*, psychotherap*, CBT, EMDR, hypno*, cognitive behavior*, NIBS, noninvasive brain stimulation, ECT, rTMS, transcranial magnetic stimulation*, tDCS, cathodal stimulation). The within-concept subject headings and keywords were combined with the "OR" command, while the two search strings were combined with the "AND" command in each database. The complete search strategy is provided in Table S1.

We also combed through the references sections of relevant review articles to identify any relevant studies. The corresponding authors were contacted to obtain additional data, when required.

### *Inclusion and exclusion criteria*

The inclusion criteria were as follows: studies where participants were assessed using at least one diagnostic basis for DPD, including the ICD or DSM, or diagnosis by a specific clinical institution or physician. Any single or combined ethical intervention was accepted when compared with another kind of treatment, usual care, placebo, or none. Response to therapies should be recorded using standardized rating scales, clinical interviews, or self-report. Studies using electroencephalogram (EEG), magnetic resonance imaging (MRI), and other measurements were considered. We included case reports, case series, RCTs, and quasi-experimental studies. Only studies written in English were included.

Studies were excluded when participants had DPD symptoms secondary to organic brain disorders and other diseases (e.g., epilepsy, schizophrenia

spectrum disorders, depressive disorders, anxiety disorders, substance-related and addictive disorders, etc.). Therapeutic methods that do not meet current ethical norms were also excluded. Moreover, studies where the outcomes were not quantified or described, retracted articles, and studies lacking full text (where the authors could not be contacted) were excluded.

### *Study selection*

After summarizing the retrieved articles and references to critical reviews, results with the same author and similar titles were confirmed by reading the complete text and excluded. All remaining studies were reviewed by the lead authors (WS and ZS) who read the study titles to exclude any nonrelevant articles based on the criteria listed above. All reviews/studies deemed potentially relevant were read in full and independently judged against the inclusion and exclusion criteria by two reviewers (WS and ZS). When necessary, disputes were resolved by consensus and consultation with a third reviewer (FS). Hand searches of the references from all included reviews/studies were performed to identify studies missed by the bibliographic searches. The corresponding authors of the papers were contacted to request additional information if needed.

### *Data extraction, synthesis, and presentation*

Considering the differences between studies, case reports, case series, and controlled studies, the studies are presented separately in two tables. Information about participants, interventions, comparisons, and outcomes were extracted. We adopted the Cochrane (Higgins et al., 2019) for RCTs, the methodological index for non-randomized studies (MINORS) (Slim et al., 2003), the JBI critical appraisal tool (JBI) (Munn et al., 2020) for case series, and M. H. Murad's methodological quality and synthesis approach for case reports (MHM) (Murad et al., 2018) to assess studies. We compared the effectiveness of different treatments and one treatment using different doses and/or frequencies, and identified the efficacy evaluation tools used and study quality. The specific symptoms and comorbidities were summarized in another table.

## Results

A total of 40 citations, including 41 studies with 300 participants, were identified by the PRISMA 2020 guidelines, as illustrated in Figure 1.

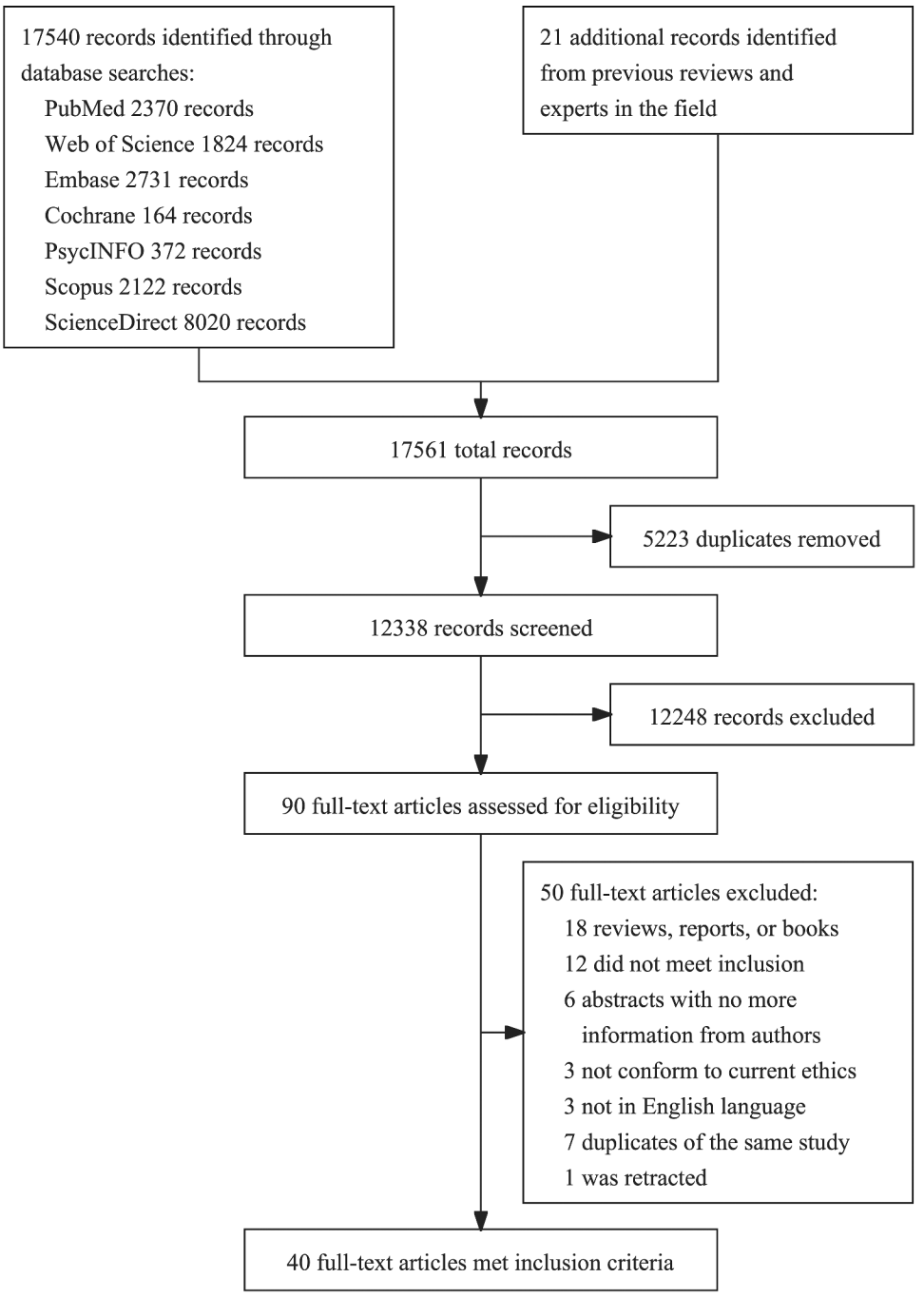


**Figure 1.** Prisma.

### *Study characteristics and methodological quality*

The 14 articles that included more than three cases, which are recorded in Table 1, involved a total of 273 participants and were published between 1982

**Table 1.** Studies involving more than three participants.

| Authors, year | N | Gender (M/F) | Mean age | Mean months of illness | Disease subtype | Diagnosis basis | Study type | Form of therapy | Treatment | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| (Nuller, 1982) | 15 | 6/9 | 35 | N/A | 1 | 3 | Case series | 1 | clozapine | 2/10 |
| (Nuller, 1982) | 42 | 8/34 | 18–67 | 2–18 | 1 | 3 | Case series | 1 | phenazepam | 2/10 |
| (E. Hollander et al., 1990) | 8 | 3/5 | 30·3 | N/A | 1 | 2 | Case series | 1 | fluoxetine or fluvoxamine | 5/10 |
| (Simeon, Guralnik, et al., 1998) | 8 | 2/6 | 30·1 | N/A | 1 | 2 | Crossover RCT | 1 | clomipramine vs desipramine | 7/21 |
| (Nuller et al., 2001) | 14 | 5/9 | 32 | N/A | 1 | 1 | Crossover controlled trial | 1 | naloxone | 17/24 |
| (Sierra et al., 2001) | 11 | NA | NA | 24–180 | 1 | 1 | Case series | 1 | lamotrigine with SSRIs | 7/10 |
| (Sierra et al., 2003) | 14 | 8/6 | 35·2 | 24–120 | 1 | 1 | Crossover RCT | 1 | lamotrigine | 19/21 |
| (Simeon et al., 2004) | 50 | 29/21 | 35·7 | 212·4 | 1 | 1 | RCT | 1 | fluoxetine | 19/21 |
| (E. C. M. Hunter et al., 2005) | 21 | 17/4 | 38·0 | 144·0 | 3 | 3 | Case series | 3 | CBT | 7/10 |
| (Simeon & Knutelska, 2005) | 14 | 12/2 | 30·9 | N/A | 1 | 3 | Case series | 1 | naltrexone | 7/10 |
| (Sierra et al., 2006) | 32 | 19/13 | 37·1 | 145·2 | 1 | 1 | Case series | 1 | lamotrigine with SSRIs | 8/10 |
| (H. E. Hollander, 2009) | 8 | N/A | NA | N/A | 1 | 1 | Case series | 3 | EMDR | 2/10 |
| (Mantovani et al., 2010) | 12 | 9/3 | 33·6 | 9·8 | 1 | 1 | Case series | 2 | rTMS | 7/10 |
| (Jay et al., 2014) | 17 | 13/4 | 37·5 | 164·0 | 3 | 3 | RCT | 2 | rTMS | 7/21 |
| (Jay et al., 2016) | 7 | 5/2 | 36·1 | 232·8 | 3 | 1 | Case series | 2 | rTMS | 7/10 |

and 2016. Nine of these articles were about pharmacotherapy, followed by three about neuromodulation, and two about psychotherapy. The diagnostic criteria for DPD varied from physician judgment to DSM 5 criteria. The study type also varied from case reports to single-arm studies and crossover or simple controlled trials, with improving research quality. The sample sizes of these 14 studies averaged 18.2, with the largest study involving 50 individuals. Differences were reported for effectiveness, which may relate to the use of different assessment methods.

To objectively understand the status quo of DPD research, the quality of studies was evaluated using the Cochrane, MINORS, JBI, or MHM approaches, as shown in Figure 2. For the four RCTs, the Cochrane results were not satisfactory, mainly due to attrition bias, performance bias, and detection bias. Since these four studies used the Clinical Global Impression Scale (CGI) (Busner & Targum, 2007), Dissociative Experiences Scale (DES) (Carlson & Putnam, 1993), Cambridge Depersonalization Scale (CDS) (Sierra & Berrios, 2000) and other tools to evaluate efficacy, it is difficult to compare the results further. One non-RCT assessed by MINORS showed deficiencies in patient inclusion, sample size estimation, and statistical analysis. The quality of the 10 case series evaluated by JBI was generally low, lacking clear inclusion criteria, valid methods for the condition measured, complete or consecutive inclusion of participants, and clear reporting of the presenting site(s)/clinic(s) demographic information. The shortcomings of the 26 case reports evaluated

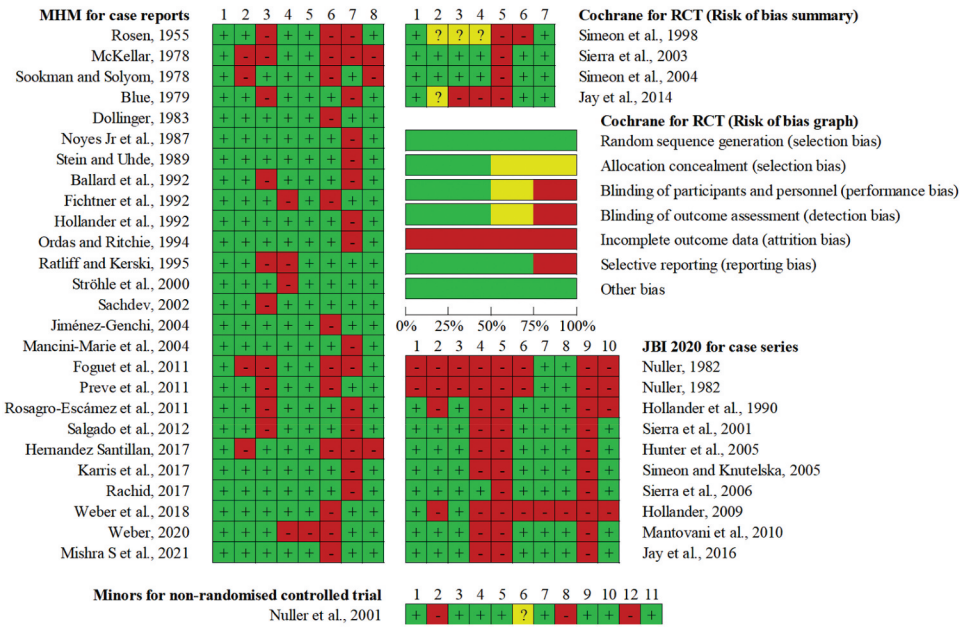


**Figure 2.** Quality of case series (JBI) and RCT (Cochrane).

by MHM related to causality, meaning that studies cannot provide a clear explanation of the relationship between the treatment methods and results.

Disease subtype: 1=depersonalization; 2=derealization; 3=depersonalization and derealization. Diagnosis basis:1=DSM-4 (R,TR), 2=DSM-3-R, 3=doctors' judgment; Form of therapy: 1=Pharmacotherapy, 2=Neuromodulation, 3=Psychotherapy, 4=Operation; NA, not applicable; SSRIs, selective serotonin reuptake inhibitors; CBT, Cognitive Behavioral Therapy; EMDR, eye movement desensitization and reprocessing; rTMS, repetitive Transcranial Magnetic Stimulation

### *Treatment for DPD*

Early studies involving lobotomy (Freeman et al., 1942), hallucinogens like mescaline (Guttmann & Maclay, 1936), and medically induced convulsions (Schilder, 1939) were excluded, leaving a total of 30 treatment methods in 40 studies covering the period 1955–2021. These methods are reported in Table 2.

Treatment: SSRIs, selective serotonin reuptake inhibitors; rTMS, repetitive transcranial magnetic stimulation; TPJ, temporo-parietal junction; VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; CBT, Cognitive Behavioral Therapy; EMDR, eye movement desensitization and reprocessing; MBCT, Mindfulness-Based Cognitive Therapy.

Assessment: CGI: Clinical Global Impressions Scale; DES: Dissociative Experiences Scale; PSE, Present State Examination; CDS, Cambridge Depersonalization Scale; BDI, Beck Depression Inventory; HRSA, Hamilton Rating Scale for Anxiety; YBOCS, Yale-Brown Obsessive Compulsive Severity scale; SADS-L, Schedule for Affective Disorders and Schizophrenia-Lifetime version; SPECT, Single Photon Emission Computed Tomography.Effect: different evaluation methods were used for independent case reports and multicase studies: the former for the degree of change in a single patient, while the latter for the proportion of positive reactions (the former: 1=invalid, 2=partly improved or scores of CDS or other scales for DPD dropped 20%-50%, 3=significantly improved or scores of CDS or other scales for DPD dropped 50%-80%, 4=completely improved or scores of CDS or other scales for DPD dropped more than 80%). Specific manifestation: N=numbing, S=unreality of self, and R=unreality of surroundings.Specific psychological symptom: DD=Depressive Disorders, AD=Anxiety Disorders, OCRD=Obsessive-Compulsive and Related Disorders, SSRD=Somatic Symptom and Related Disorders.Quality: Cochrane is for randomized controlled trials, MINORS is for non-randomized controlled trials, JBI is for case series, and MHM is for case reports. MHM, Tool for evaluating the methodological quality of case reports by Mohammad Hassan Murad.

Twenty-eight studies including 229 participants used drugs as the major therapy. These drugs included include mood stabilizers (lamotrigine, as an

**Table 2.** Treatment for DPD.

| Treatment | Author, year | Number of participants | Dose | Second treatment | Assessment | Effect | Specific manifestation | Specific psychological symptoms | Side effect | Study type | Quality | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Pharmacotherapies** | | | | | | | |
| **Antidepressants** | | | | | | | | | | | | |
| Fluoxetine | (E. Hollander et al., 1990) | 7 | 5-80mg/d | none | self report | 85.7% (6/7) | A, N, R, S, T | AD, DD, OCRD | insomnia | Case series | JBI | 5/10 |
| | (Simeon et al., 2004) | 50 | 10-60mg/day | not allowed | CGI, DES | No carryover effect | N/A | AD, DD, TSRD, SSRD,PD | fatigue, insomnia, decreased libido, et al. | RCT | Cochrane | 19/21 |
| | (Fichtner et al., 1992) | 1 | 20mg/d | none | self report | 2 | N, S, A, R | AD | N/A | Case report | TEMQCR | 6/8 |
| | (E. Hollander et al., 1992) | 1 | 80mg/d | none | self report | 4 | N, S, A, R | SSRD, OCRD, DD | N/A | Case report | MHM | 7/8 |
| | (Ratliff & Kerski, 1995) | 1 | 20mg/d | Alprazolam | self report | 2 | N, S, A | AD,DD | N/A | Case report | MHM | 6/8 |
| Fluvoxamine | (E. Hollander et al., 1990) | 1 | 300mg/d | Clomipramine | self report | 1 | A, S, R | OCRD | none | Case series | JBI | 5/10 |
| Clomipramine | (Simeon, Guralnik, et al., 1998) | 7 | 250 mg/d | not allowed | CGI | 28·6% (2/7) | N/A | DD, AD, OCRD | sedation, weight gain | RCT | Cochrane | 7/21 |
| Desipramine | (Simeon, Guralnik, et al., 1998) | 6 | 250 mg/d | not allowed | CGI | 16.7% (1/6) | N/A | DD, AD, OCRD | N/A | RCT | Cochrane | 7/21 |
| | (Noyes et al., 1987) | 1 | 200mg/d | none | self report | 3 | N, S, R | AD, DD | Drowsiness, dry mouth and constipation | Case report | MHM | 7/8 |
| Paroxetine | (Ströhle et al., 2000) | 1 | 40 mg/d | none | self report | 2 | N/A | none | restlessness, sleep disturbances | Case report | MHM | 7/8 |
| Venlafaxine | (Preve et al., 2011) | 1 | 112·5mg/d | none | CDS | 4 | S | DD, AD, OCRD | none | Case report | MHM | 6/8 |
| | | | | | **Antiepileptics** | | | | | | | |
| Lamotrigine | (Sierra et al., 2001) | 11 | 250mg/d | SSRIs only | PSE, DES | 54·5% (6/11) | N/A | AD | none | Case series | JBI | 7/10 |
| | (Sierra et al., 2003) | 14 | 250mg/d | none | PSE, CDS, DES, BDI | No carryover effect | N/A | N/A | dizziness, muscle aches, nausea | RCT | Cochrane | 19/21 |

(*Continued*)

**Table 2.** (Continued).

| Treatment | Author, year | Number of participants | Dose | Second treatment | Assessment | Effect | Specific manifestation | Specific psychological symptoms | Side effect | Study type | Quality | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (Sierra et al., 2006) | 32 | 25-600mg/d | unlimited | CDS, DES | 56·3% (18/32) | N/A | N/A | nausea, diarrhea, visual disturbance, tremor and cognitive impairment | Case series | JBI | 8/10 |
| | (Rosagro-Escámez et al., 2011) | 1 | 100mg/d | Sertraline, Clomipramine | CDS, DES | 3 | S, R | AD, OCRD, DD, BPD | N/A | Case report | MHM | 6/8 |
| | (Salgado et al., 2012) | 1 | 200mg/d | none | CDS | 2 | N, S | AD, DD | N/A | Case report | MHM | 6/8 |
| Clonazepam | (Stein & Uhde, 1989) | 1 | 1mg/d | Carbamazepine | SADS-L | 4 | R | none | N/A | Case report | MHM | 7/8 |
| | (Sachdev, 2002) | 1 | 3mg/d | Citalopram | self report | 4 | N, R, S, A | DD, OCRD | N/A | Case report | MHM | 7/8 |
| | (J. V. Weber et al., 2018) | 1 | 1mg/d | none | CDS | 3 | N, S, R | AD, DD, TSRD, SSRD | N/A | Case report | MHM | 7/8 |
| Phenazepam | (Nuller, 1982) | 42 | 3–30 mg/d | none | self report | 59.5% (25/42) | N/A | AD | N/A | Case series | JBI | 2/10 |
| Carbamazepine | (Stein & Uhde, 1989) | 1 | 1200mg/d | none | SADS-L | 1 | N/A | N/A | panic attacks | Case report | MHM | 7/8 |
| | | | | | **Antipsychotics** | | | | | | | |
| Clozapine | (Nuller, 1982) | 15 | 150–600 mg/day | none | self report | 60·0%(9/15) | N/A | AD, DD | perculiar confusion, loss orientation | Case series | JBI | 2/10 |
| Quetiapine | (Mancini-Marie et al., 2004) | 1 | 700mg/d | none | CDS, DES | 2 | N | N/A | N/A | Case report | MHM | 7/8 |
| | | | | | **Opioid receptor antagonists** | | | | | | | |
| Naloxone | (Nuller et al., 2001) | 14 | 1.6–10 mg i.v. | benzodiazepine | depersonalization scale | 71.4% (10/14) | N/A | DD, AD | none | non-randomised controlled trial | Minors | 17/24 |
| Naltrexone | (Simeon & Knutelska, 2005) | 14 | 100-250mg/d | baseline treatment | CGI, CDS, DES | | N/A | N/A | sedation, fatigue, et al. | Case series | JBI | 7/10 |

(*Continued*)

**Table 2.** (Continued).

| Treatment | Author, year | Number of participants | Dose | Second treatment | Assessment | Effect | Specific manifestation | Specific psychological symptoms | Side effect | Study type | Quality | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Others** | | | | | | | |
| Methylphenidate | (Foguet et al., 2011) | 1 | 54mg/d | baseline treatment | self report | 4 | N/A | DD | N/A | Case report | MHM | 4/8 |
| Mixed amphetamine salts | (S. R. Weber, 2020) | 1 | 20mg/d | baseline treatment | CDS | 2 | N/A | N/A | N/A | Case report | MHM | 5/8 |
| | | | | | **Neuromodulations** | | | | | | | |
| rTMS (TPJ) | (Mantovani et al., 2010) | 12 | 1Hz, 1800 pulses (100% MT) | lorazepam | CDS, DES | 50% (6/12) | N/A | DD, AD | N/A | Case series | JBI | 7/10 |
| | (Jay et al., 2014) | 9 | 1Hz, 900 pulses (110% MT) | baseline treatment | CDS, DES, skin conduction | 55.6% (5/9) | N/A | DD, AD | "twitching or jerking" sensations, headache, difficulties concentrating | RCT | Cochrane | 7/21 |
| | (Rachid, 2017) | 1 | 1Hz, 1800 pulses (100% MT) | Paroxetine +Trazodone +Lamotrigine | CDS | 3 | N, S, R, T | DD | N/A | Case report | MHM | 7/8 |
| rTMS (VLPFC) | (Jay et al., 2014) | 8 | 1Hz, 900 pulses (110% MT) | baseline treatment | CDS, DES, skin conduction | 62.5% (5/8) | N/A | DD, AD | "drunk-like" feelings, headache, difficulties concentrating | RCT | Jadad | 5/5 |
| | (Jay et al., 2016) | 7 | 1Hz, 900 pulses (110% MT) | baseline treatment | CDS, DES | 85.7% (6/7) | N/A | AD | headache, pain above left eye | Case series | JBI | 7/10 |
| rTMS (DLPFC) | (Jiménez-Genchi, 2004) | 1 | 20Hz | Clomipramine | CDS, BDI, SPECT | 3 | N, S, R | DD | N/A | Case report | MHM | 7/8 |
| | (Karris et al., 2017) | 1 | 1-10Hz, 3000 pulses (110% MT) | Bupropion | CDS, HRSA | 3 | N, S, R | DD | N/A | Case report | MHM | 7/8 |
| ECT | (Ordas & Ritchie, 1994) | 1 | 12 sessions | Fluoxetine | self report | 2 | S | DD, SSRD, PD | mild short-term memory loss | Case report | MHM | 7/8 |

(*Continued*)

**Table 2.** (Continued).

| Treatment | Author, year | Number of participants | Dose | Second treatment | Assessment | Effect | Specific manifestation | Specific psychological symptoms | Side effect | Study type | Quality | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Psychotherapies** | | | | | | | |
| CBT | (E. C. M. Hunter et al., 2005) | 21 | 13 sessions | baseline treatment | PSE, DES, CDS | 29% (6/21) | N/A | AD,DD | none | Case series | JBI | 7/10 |
| EMDR | (H. E. Hollander, 2009) | 8 | 20 sessions | not limited | self report | 2 | N/A | AD | none | Case series | JBI | 2/10 |
| vis-à-vis therapy | (Rosen, 1955) | 1 | 70 sessions | none | self report | 2 | S, R, A | none | N/A | Case report | MHM | 5/8 |
| Supportive therapy | (McKellar, 1978) | 1 | 2 weeks | none | self report | 4 | S, R | N/A | N/A | Case report | MHM | 3/8 |
| Behaviour therapy | (Sookman & Solyom, 1978) | 2 | 20–50 sessions | Flooding treatment | self report | 3, 4 | S, R, A, T | AD, OCRD | N/A | Case report | MHM | 5/8 |
| Directive therapy | (Blue, 1979) | 1 | 6 sessions | none | self report | 4 | A, S, R | SSRD | N/A | Case report | MHM | 6/8 |
| Family therapy | (Dollinger, 1983) | 1 | 16 weeks | none | self report | 4 | A, R | N/A | N/A | Case report | MHM | 7/8 |
| Dynamic psychotherapy | (Ballard et al., 1992) | 1 | 12 sessions | none | self report | 4 | R, S, A | AD | N/A | Case report | MHM | 6/8 |
| MBCT | (Mishra et al., 2021) | 1 | 24 sessions | Paroxetine | CDS | 3 | N, S, R, A | AD | none | Case report | MHM | 7/8 |

adjunct to selective serotonin reuptake inhibitors (SSRIs), 25–600 mg/day, etc.), SSRIs (fluoxetine, 5–80 mg/day, etc.), tricyclic antidepressants (clomipramine, 250 mg/day, etc.), benzodiazepines (clonazepam, 1–3 mg/day, etc.), antipsychotics (clozapine, 150–600 mg/day, etc.), opioid receptor antagonists (naltrexone, 100–250 mg/day, etc.), and other medications. Most of these 19 drugs showed positive evidence on scales such as the CDS and DES. Sedation, nausea, fatigue, and dizziness were consistently reported as side effects.

Lamotrigine and fluoxetine attracted great concern. The former proved to be effective for DPD as an adjunct to SSRIs in an open trial (Sierra et al., 2001) and a retrospective study (Sierra et al., 2006), while a placebo-controlled crossover trial (Sierra et al., 2003) did not support beneficial effects as a sole medication. The latter showed no obvious effect in a RCT (Simeon, 2004), contradicting the results of a previous case series (E. Hollander et al., 1990).

Forty participants from eight studies were treated by neuromodulation. Repetitive transcranial magnetic stimulation (rTMS) has been a research focus since 2004, mainly using a figure-of-eight coil held tangentially to the scalp of the head with the handle pointing backward from the midline at 45° to stimulate specific positions at a frequency of 1 Hz and 800 to 1800 pulses per session. The stimulus positions were always set to the temporo-parietal junction (TPJ), ventrolateral prefrontal cortex (VLPFC), and dorsolateral prefrontal cortex (DLPFC). According to the scale measurements, patients improved in terms of DPD as well as comorbidities such as anxiety disorders, depressive disorders, and suicidal thoughts. Some patients experienced side effects of rTMS, such as mild headaches. Electroconvulsive therapy (ECT) was also applied in a case report (Ordas & Ritchie, 1994) without the desired result.

Nine studies involving 37 participants focused on psychotherapies, especially cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR). Of note, 29% of 21 participants did not meet the DPD diagnostic criteria after an average of 13 CBT sessions (E. C. M. Hunter et al., 2005). It was reported that simultaneous use of psychotherapies can improve the overall condition of patients. However, the side effects were not mentioned.

Four randomized controlled studies have focused on the therapeutic effects of fluoxetine, lamotrigine, desipramine, clomipramine, and rTMS on depersonalization (Jay et al., 2014; Sierra et al., 2003; Simeon et al., 2004; Simeon, Guralnik, et al., 1998). No significant efficacy was found for fluoxetine and lamotrigine (Sierra et al., 2003; Simeon et al., 2004). With “much improved” or “very much improved” in the CGI results as effective, the effectiveness of desipramine and clomipramine was 16.7% and 28.6% (Simeon, Guralnik, et al., 1998). Using a 25% reduction in CDS-S score as effective, rTMS stimulation of TPJ and VPLFC brain regions was 55.6% and 62.5% effective (Jay et al., 2014).

**Table 3.** Main symptoms of DPD and co-morbid mental disorders.

| Symptoms | Specific manifestations |
|---|---|
| Unreality of self | detachment from body (robotic); observe oneself as another (float) |
| Unreality of surroundings | detachment from surroundings; things were unreal; living in a fog/a dream/a strange world/a parallel world |
| Numbing | inability to feel emotions |
| Perceptual alterations | visual, olfactory, auditory, spatial, and proprioceptive distortions |
| Temporal disintegration | time distortions; déjà vu experiences |
| Others | dizziness; headache; suicide thoughts or attempt; mind emptiness; mind fullness; decline of concentration, cognition, judgment, and capability; socially withdrawn |
| **Co-morbid mental disorders** | **Specific psychological symptoms** |
| Depressive disorders | depressed mood, persistent depressive disorder, major depressive disorder |
| Anxiety disorders | social phobia, agoraphobia, specific phobia, panic attack, panic disorder, generalized anxiety disorder |
| Obsessive-compulsive and related disorders | obsessive-compulsive disorder, obsessive-compulsive personality traits |
| Somatic symptom and related disorders | somatic symptom disorder, illness anxiety disorder, conversion disorder |
| Personality disorders | paranoid personality disorder, schizoid personality disorder, narcissistic personality disorder, borderline personality disorder |
| Trauma-and stressor-related disorders | posttraumatic stress disorder |

### *Symptoms of DPD*

To make deep use of the available information, we summarized the characteristics of the patients from 26 case reports. The specific clinical information is listed in Table S2, including symptoms, accompanying diseases, personality, trauma history, family history, and treatment history. The main manifestations of DPD symptoms and detailed comorbidities are sorted based on Sierra (Munn et al., 2020; Sierra et al., 2005) and the DSM-5, as shown in Table 2.

Main symptoms of DPD and co-morbid mental disorders were summarized in Table 3. Unreality of self is the most common symptom of DPD (24 times), followed by unreality of the surroundings (23 times), and numbing (13 times). Most participants had other mental disorders: almost half had anxiety disorders or depressive disorders, while one-third had obsessive-compulsive and related disorders. Notably, all showed a sensitive and perfectionist personality when dispositions were reported. Histories of psychological trauma, substance abuse, and family abuse were common, too.

The symptoms were extracted from the Cambridge Depersonalization Scale. The co-morbid mental disorders were extracted from DSM-5. The specific manifestations and psychological symptoms were summarized from the literatures.

## Discussion

There are problems with previous systematic and narrative reviews of DPD treatment, such as the singularity of the research field, low quantity and quality of included studies, and an early publication time (E. C. M. Hunter et al., 2017;

Orrù et al., 2021; Somer et al., 2013). This review has performed an updated search of the relevant databases and assessed the methodological quality of the identified studies.

Considering the quality and quantity of evidence, medication is the main treatment for DPD. Drugs currently used to treat DPD include antidepressants, antiepileptics, antipsychotics, opioid receptor antagonists, etc. Serotonin reuptake blockers play a mediating role in serotonergic dysregulation, which is a possible mechanism for DPD. Serotonergic effects and pharmacokinetic/pharmacodynamic interactions between lamotrigine and SSRIs have been considered in multiple mental disorders (Dursun & Deakin, 2001; Normann et al., 2002; Southam et al., 1998), suggesting a link between glutamate, GABA, and the serotonergic system (Sanacora et al., 2002). Hypoalgesia (Moroz et al., 1990) and low cortisol levels (Nuller et al., 2001) in patients with DPD indicate a possible role of the opioid system. Naloxone and naltrexone also help with dissociation on a larger scale (Bohus et al., 1999; Glover, 1993), which may be related to augmentation of cortisol production.

Neuromodulation is another promising therapeutic option, particularly with the TPJ and VLPFC being in the spotlight. Possible causes for DPD include fronto-limbic imbalance, hyperactivity of prefrontal structures and hypoactivation of limbic regions (Lemche et al., 2008; Medford et al., 2006; Phillips et al., 2001; Sierra & Berrios, 1998), and altered functional connectivity, can be explained by TPJ imbalance (E. Hollander et al., 1992; Locatelli et al., 1993; Sierk et al., 2018). The VLPFC plays a role in physical and social pain, emotional attribution (Vucurovic et al., 2020), object recognition (Romanski & Chafee, 2021), and representation and integration of auditory and visual stimuli (Romanski, 2012), which correlates with DPD symptoms such as numbing, unreality of surroundings, and perceptual alterations. TMS as a noninvasive brain stimulation technique that can modify the underlying neural activity (Kluger & Triggs, 2007; Rossini & Rossi, 2007), resulting in a decrement in cortical excitability when at low frequency (1 Hz) (Chen et al., 1997). This method has been applied to stimulate the TPJ and VLPFC for the treatment of DPD. Meanwhile, TMS in healthy individuals can induce illusions or perception of self, disrupted mental transformation of the body (Blanke et al., 2005), proprioceptive abilities (Tsakiris et al., 2008) and resolution of intersensory conflicts (Papeo et al., 2010).

Studies on psychotherapy are empirical without a mature paradigm. From a cognitive behavioral perspective, transient depersonalization symptoms could be exacerbated and perpetuated by a maintenance cycle resulting from catastrophic misinterpretations of serious mental illness (E. C. Hunter et al., 2003), which could be a path to chronic DPD. Models of panic (Clark, 1986) and health anxiety (Warwick & Salkovskis, 1990) can provide similar evidence for DPD treatment. From the perspective of the nervous system, inhibited thalamic activity due to excessive suppression by the medial PCF and anterior

cingulate could explain some characteristics of DPD patients (Critchley et al., 2002; Frewen & Lanius, 2006). Dysfunctional breathing patterns, as represented by breath-holding, were associated with EMDR to reverse sensory and cognitive numbing and recover a sense of familiar self, ultimately addressing the core DPD symptoms (H. E. Hollander, 2009).

Previous studies cannot provide satisfactory evidence supporting clinical treatment. First, according to the Cochrane, MINORS, JBI, and MHM assessment results, the quality of studies was not high. Most trials did not report adequate information about the outcomes. It should be noted that double-blinding is difficult when using psychotherapy or rTMS. Second, incomplete outcome data indicate that an effect may be more likely to be overestimated from a "per-protocol" analysis compared with "ITT" analysis of the same trials (Porta et al., 2007). Third, a lack of information in the original studies prevented us from quantifying outcomes such as adverse events. Finally, outcomes were measured with various rating scales, resulting in strong heterogeneity. Therefore, future researchers should carry out methodological evaluation of trial design and result evaluation to support research on DPD.

Furthermore, the design of clinical trials should be improved. The choice of the control and blinding should be carefully considered. In a study of the potential role of the VLPFC in DPD, researchers used the TPJ as an active control, since TPJ stimulation could be therapeutically beneficial for patients but through an unrelated mechanism to that under investigation (Jay et al., 2014). The stimulus scheme should be described in detail to ensure that the trial is reproducible. The combination of drugs, starting dose, maximum dose, schedule of dose escalation, and duration of the dose should be fully described. For rTMS, it is recommended that the coil be placed according to the standard international 10–20 EEG system of electrode placement.

The method of evaluating efficacy should be further standardized. CGI has been used to quantify results since it was first published in 1976, although it has been criticized for inconsistency, unreliability, and poor specificity (Bech, 1981; Beneke & Rasmus, 1992; Forkmann et al., 2011). DES – especially its depersonalization subscale – is sensitive to the detection of DPD (Daphne Simeon et al., 2003; Simeon, Guralnik, et al., 1998). Compared with DES, which covers dissociative diseases, the subsequently published CDS shows better selectivity and captures the clinical aspects of DPD in a comprehensive manner (Sierra & Berrios, 2000). CDS has state and trait versions (CDS-S and CDS-T), the latter of which helps with diagnosis and the former clarifies the patient's status as a percentage to assess the "here and now" rates of patients. A partial responder means a 25% or more reduction in CDS-S score, whereas a full responder means a 50% or more reduction (Jay et al., 2016; Mantovani et al., 2010). Therefore, the percentage change in CDS

score from baseline to the end of the trial can be used to assess treatment efficacy.

In summary, this study has highlighted the low volume of studies and small sample sizes in research relative to the high prevalence of DPD. Moreover, heterogeneity among the studies hinders disease research. As DPD is a stressor to society and a burden to 1% of the population without a knowledgeable doctor or guidelines, there is a need for research focused on identifying and combining evidence-based strategies to treat DPD through robust designs that aid symptom alleviation and healing.

## Limitations

This review is subject to several limitations. First, the identified studies were not of high quality and lacked sufficient information. The quantity of evidence is not enough to support a robust conclusion. Additionally, conflicts of interest of evidence were not analyzed, which may give rise to present biased data, resulting in low robustness of the conclusion. The number of studies focusing on the combination of different types of treatment is insufficient to confirm robust combination strategies.

## Conclusion

Relative to previous studies, this review has advanced our understanding of DPD research in terms of both breadth and depth. By comprehensively evaluating previous clinical studies in this area, we have provided a reference for future clinical trial designs and guideline writing. We summarized the existing treatment methods and proposed three strategies as references: collaborative treatment strategies, personalized therapeutic schedules, and expectations for high-quality research. Meanwhile, we made a summary of the main manifestations and comorbidities of DPD, which can construct the characteristics of DPD to a supplementary diagnostic basis, and provide clues to the relationship between symptom propensity, comorbidity propensity, and treatment effectiveness.

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