Psychiatry Research 281 (2019) 112529

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

# Pharmacotherapy for dissociative disorders: A systematic review

Roshan Sutar*, Sandhaya Sahu

*Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), Bhopal, India*

ARTICLE INFO

*Keywords:*
Dissociative disorders
Pharmacotherapy
Systematic review
Placebo

ABSTRACT

*Background:* Dissociative Disorder (DD) is a large group of disorders that shares common psychopathology. Psychopharmacological agents have sparse evidence in the treatment of DD in general. Multiple pharmacotherapy options have been used without conclusive evidence.

*Methods:* We conducted a systematic review of data in English language from 1967 to 2019 the protocol of which was registered under PROSPERO (Study ID CRD42019127235). Using PRISMA guidelines, 5 RCTs reporting data on 214 participants providing data on response to pharmacotherapy in dissociative disorder were included.

*Results:* The treatment response rate of pharmacotherapy group as measured in reduction in dissociative symptoms was 68.42% ($n$ = 65/95), significantly higher than that of 39.49% ($n$ = 47/119) in the control group. And, the pooled RR was 1.59 (95% CI, 0.76–3.30; $P$ = 0.21). The overall effect estimates are favourable to pharmacotherapy group over placebo.

*Conclusion:* It would be apt to conclude that Paroxetine and Naloxone are the only pharmacological agents studied through RCTs and found to have modest evidence for controlling depersonalization symptoms and dissociative symptoms that are comorbid with PTSD and BPD. Results of this meta-analysis should be interpreted with caution in view of high heterogeneity and scanty literature on RCTs on various subtypes of DD.

## 1. Introduction

Dissociative disorders (DD) continue to challenge psychiatrists in the background of limited understanding and dearth of established neurobiological mechanisms for their treatment. Wide spectrum of dissociative disorders includes Dissociative Amnesia, Dissociative Fugue, Dissociative Identity Disorder, Dissociative convulsion, Dissociative Motor Disorder, Trance- Possession disorder and Depersonalisation-Derealisation Disorder (Spiegel et al., 2011; World Health Organization, 1993). There are hardly any targeted pharmacological approaches for DD unlike other psychiatric disorders (Somer et al., 2013). Utility of psychodynamic therapies to address core unconscious conflicts in addition to cognitive and supportive psychotherapy had been a standard treatment in most of the institutes across India as well as in the west (LaFrance et al., 2014). Despite unclear neurobiological understanding of DD, the use of psycho-pharmacological agents has never stopped among treatment armamentarium of a psychiatrist. In the resource limited countries like India, it is not uncommon to find patients with isolated DD receiving only pharmacological treatment in the absence of available treatment guidelines. Selective serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake inhibitors (SNRI), Antiepileptic drugs, Benzodiazepines (BZD) are frequently utilised treatment options for DD (Gentile et al., 2014). More so, the over diagnosing such patients with depression and anxiety disorders is possible in order to escape the ethical dilemma of choosing pharmacotherapy that is an undermined aspect of DD. Dissociative spectrum disorders and dissociative symptoms are often comorbid with range of psychiatric disorders like Post traumatic stress disorder, anxiety, depressive and adjustment disorders. So the available evidence on pharmacotherapy for dissociative disorders mostly comes from studies that describe isolated case reports, case series, and open trial on specific subcategories of DD or comorbid dissociative symptoms.

In this article author summarizes various psycho-pharmacological evidences on the available treatment options for dissociative disorders. There is neither an existing guideline on pharmacological treatment of DD nor a systematic review describing rationale of contemporary practice of using medications. This systematic review is an attempt to trouble shoot clinical decision making regarding pharmacological treatment options for DD in routine clinical situations. It also questions to further enhance neurobiological understanding of DD in terms of formulating targeted treatment protocol.

* Corresponding author.
*E-mail address:* roshidoc@gmail.com (R. Sutar).

https://doi.org/10.1016/j.psychres.2019.112529
Received 29 May 2019; Received in revised form 20 August 2019; Accepted 22 August 2019
Available online 23 August 2019
0165-1781/ 

## 2. Methods

### 2.1. Search strategy

All English-language published studies from 1967 to 2019 were included. All subcategories of DD- Dissociative Amnesia, Dissociative Fugue, Dissociative Identity Disorder, Dissociative convulsions, Dissociative Motor Disorder, Trance- Possession disorder and Depersonalisation–Derealisation Disorder as per ICD-10 or DSM-III and DSM-IV were included. The protocol was registered on PROSPERO (Study ID CRD42019127235). Relevant studies were identified on Medline, PubMed and Google Scholar. In addition, writing to authors for the articles where full text was not available and search of the references in published articles was carried out. MeSH terms used for the search were, dissociative disorders AND pharmacotherapy OR treatment, dissociative disorders AND drug treatment, dissociative disorders AND pharmacology OR psychopharmacology, dissociative Amnesia AND pharmacotherapy, dissociative fugue AND pharmacotherapy, dissociative identity disorder AND pharmacotherapy, dissociative convulsions AND pharmacotherapy, dissociative motor disorder AND pharmacotherapy, trance- possession disorder AND pharmacotherapy and Depersonalisation-Derealisation disorder AND pharmacotherapy, conversion disorder AND pharmacotherapy, Hysteria AND pharmacotherapy. There were 7 randomized placebo-controlled trials (RCTs) on pharmacological treatment options for DD which were included for meta-analysis (Nuller et al., 2001, Sierra et al., 2003, Philipsen et al., 2004a,b, Simeon et al., 2004, Marshall et al., 2007, Aliyev and Aliyev, 2011, Schmahl et al., 2012). Two independent reviewers did the preliminary search matching, tabulation of included and excluded studies and selection of studies for meta-analysis. Critical and qualitative review was preferred to summarize the findings. Response to pharmacotherapy was measured in terms of reduction in scores on Dissociative Experience Scale, Cambridge Dissociation Scale and subjective improvement reported across different studies. Although heterogeneous, all 7 studies were included for qualitative synthesis and 5 studies were included for quantitative synthesis (meta-analysis).

### 2.2. Data collection and analysis

Revman 4.2.7 statistical programmer by Cochrane collaboration was used for carrying out the meta-analysis. The effect sizes (ES) for the response to pharmacotherapy in DD were expressed as weighted mean differences using Hedges g and 95% Confidence Interval (CI). Heterogeneity was removed by $\chi^2$ test and $I^2$ test. Results were synthesized using random effect model for heterogeneous data. Forest plots were generated for the effect estimates and Confidence Intervals for individual studies and Meta-analyses.

## 3. Results

### 3.1. Results of search

A total of 1028 studies met the preliminary search criteria and additionally 43 relevant studies were newly found with handheld search of references, out of which 62 studies were duplicate hence removed. After title screening, among 1009 studies, 864 studies were not relevant to treatment hence excluded. Among 145 studies, 28 were excluded as they were about dissociative symptoms as an adverse effect of pharmacotherapy. Remaining 117 studies were screened for full text on randomized placebo controlled trial in English language. Seven studies met the inclusion criteria and were subsequently included in qualitative synthesis as shown in Fig. 1. Among excluded studies, 37 studies had no abstract, 28 studies were in language other than English and 45 comprised of case reports, case series, open trials, expert review etc. which are described under Table 2.

### 3.2. Description of included studies

Among seven included RCTs in English-language, 214 participants were included as shown in Fig. 1. Trials had placebo comparison with Fluoxetine, Paroxetine, Lamotrigine, Naltrexone and Naloxone. Four studies included depersonalization disorder (Nuller et al., 2001, Sierra et al., 2003, Aliyev and Aliyev, 2011, Simeon et al., 2004), two studies included dissociative symptoms in borderline personality disorder (Philipsen et al., 2004a,b, Schmahl et al., 2012) and one study included dissociative symptoms in Post-traumatic stress disorder (Marshall et al., 2007). All studies included age range from 18 to 45 years, both genders except one study (Philipsen et al., 2004a,b). All studies had duration of 8–12 weeks except two studies where acute dissociative symptoms were treated in 30 min to 4 weeks (Philipsen et al., 2004a,b, Nuller et al., 2001). All studies used DSM IV criteria for diagnosis. Two studies mentioned adverse effects of Lamotrigine and Fluoxetine. Drop out were minimal in all the studies. Most of the studies had included Dissociative Experience Scale (DES), Cambridge Depersonalization Scale (CDS), and Dissociative Symptom Scale (DSS) for measuring DD symptoms. Secondary outcome measures included Clinical Global Improvement-Severity (CGI-S), Hamilton Depression rating scale (HAMD), Beck Depression Inventory (BDI) and Hamilton Anxiety rating scale (HAMA). One study used cross over design (Philipsen et al., 2004a,b). Lamotrigine dose used was up to 250 mg/day, Fluoxetine (60 mg/day), Naloxone (0.4 mg), Paroxetine (max. 60 mg/day) and Naltrexone (50–200 mg/day) as depicted in Table 2. The characteristics of the included studies and response to pharmacotherapy are described in Table 3 and Fig. 2.

### 3.3. Description of excluded studies

Among 45 excluded studies comprised of 22 case reports, 5 case series, 5 expert reviews, 4 open label trials, a single case control study, 5 Randomized Control Trails (RCTs), 1 meta-analysis, 1 survey and 1 letter to editor. Around 21 studies (50%) mentioned comorbid psychiatric conditions with DD. Majority of studies were positive about outcome. Details of the drugs that were proven to be effective in reducing dissociative symptoms are mentioned in Table 1. Three studies were on Low frequency repetitive Transcranial Magnetic Stimulation. (rTMS) with positive outcome in reducing dissociative symptoms. Most common psychiatric comorbidity included Borderline personality disorder while most common dissociative disorder included was Depersonalisation disorder. Among 28 studies excluded due to dissociation as an adverse effect of pharmacotherapy comprised of ketamine as most common agent followed by clarithromycin and Pregabalin.

### 3.4. Meta-analysis

The results in the meta-analysis were not estimable for the study by Sierra et al. (2003) due to zero events in treatment and control arm while one published study was found retracted from the journal publisher. Hence only remaining 5 studies were taken into account for estimation of effect size and quantitative synthesis. There were five RCTs on pharmacotherapy for subjects with dissociative disorder with high heterogeneity ($Tau^2 = 0.49$) existed among the results ($P < 0.00001$, $I^2 = 97\%$). The treatment response rate of pharmacotherapy group was 68.42% ($n = 65/95$), significantly higher than that of 39.49% ($n = 47/119$) in the control group. And, the pooled RR was 1.59 (95% CI, 0.76–3.30; $P = 0.21$). There are four RCTs after excluding one study with skewed confidence interval (Nuller et al., 2001) leading to high heterogeneity, and revised low heterogeneity ($Tau^2 = 0.10$) was found among the results ($P < 0.00001$, $I^2 = 90\%$). The treatment response rate in the pharmacotherapy group was 67.90% ($n = 55/81$), not significantly higher than response rate of 56.62% ($n = 47/83$) in the control group. And, the pooled RR was 1.18 (95% CI, 0.80–1.73; $P = 0.40$).

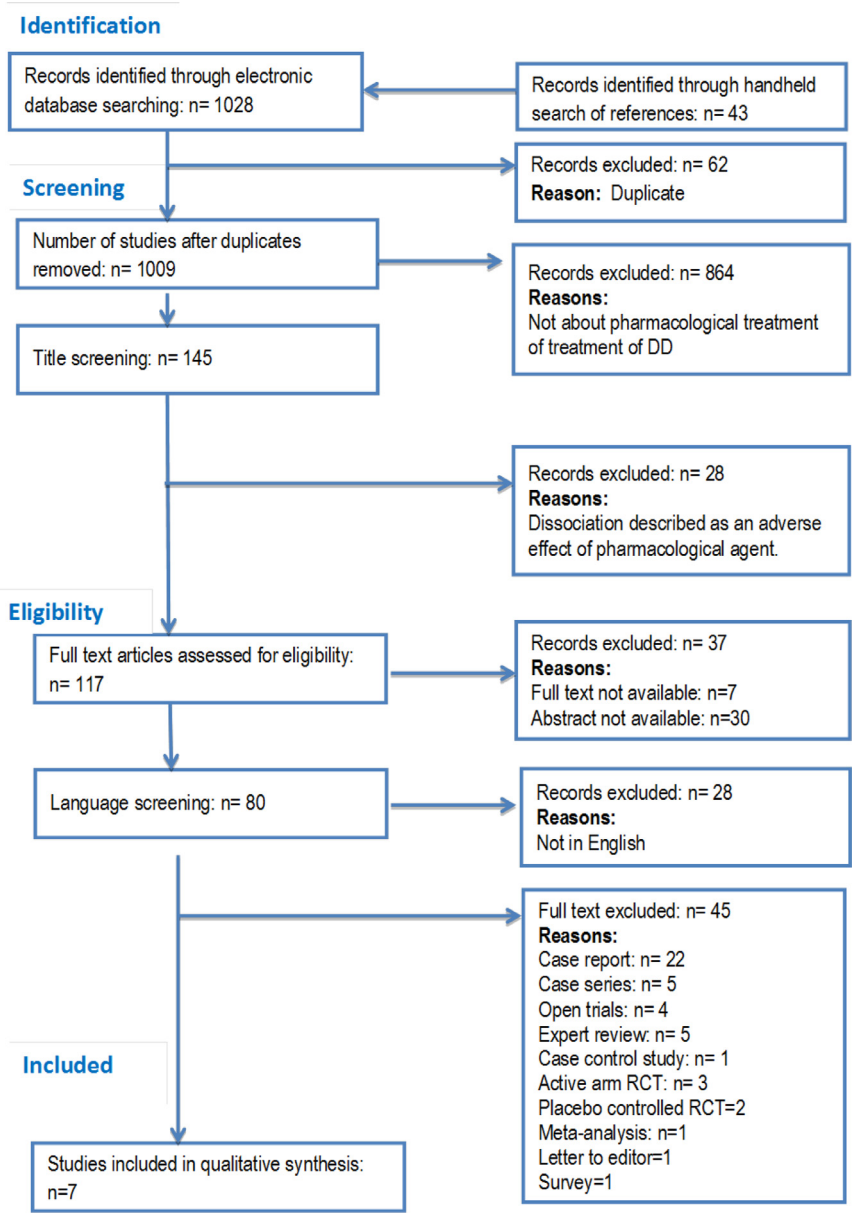


**Fig. 1.** PRISMA flow of information through various stages of review (Moher et al., 2009).


**Fig. 2.** Forest plot showing comparison between pharmacotherapy and placebo response to dissociative symptoms.

**Table 1**
Studies which are excluded from the review.

| Sr. No | Study author and year | Dissociative subgroup | Comorbid disorder | Psychopharmacological agent | Outcome |
|---|---|---|---|---|---|
| **Case reports** | | | | | |
| 1 | Jha (2017) (2 Case reports) | Dissociative Convulsions | – | Eperisone (50 −150 mg/day) | Improved |
| 2 | Scarella and Franzen (2017) | Depersonalisation and Derealisation | Attention Deficit Hyperactivity Disorder (ADHD) and Dysthymia | Mixed Amphetamine salts (30 mg/day) | Improved |
| 3 | Liu-Barbaro and Stein, (2015) | Dissociative fugue | Post-Traumatic Stress Disorder (PTSD) | Sertaline150 mg Prazosin 4 mg | Improved |
| 4 | Perales-Blum et al., (2015) | Dissociative identity disorder (DID) | Major Depressive Disorder (MDD), PTSD, and anxiety disorder without agoraphobia | Quetiapine 50 mg | Improved |
| 5 | Lai CH et al., 2012 | Dissociative identity disorder | Mild MDD | Risperidone 2 mg and Mirtazapine 30 mg | Improved |
| 6 | Ilechukwu and Henry, (2006) | Dissociative fugue | – | Lorazepam 6 mg I.V | Improved |
| 7 | Desarkar et al., (2006) | Dissociative disorder-mixed type | MDD | Duloxetine 60 mg | Improved |
| 8 | Ballew and Morgan, (2003) | Acute dissociative amnesia | – | Diazepam I.V 30 mg | Improved |
| 9 | Hale and Pinninti, (1994) | Dissociative possession | Paranoid schizophrenia | Trifluperazine and clopenthixol | Improved |
| 10 | Coons, (1992) (2 Case reports) | Dissociative identity disorder | Borderline personality disorder (BPD) | Carbamazepine 300 mg/day | Improved |
| 11 | Fichtner et al., (1990) | Dissociative identity disorder | BPD | Carbamazepine 1500 mg/day | Improved |
| 12 | Khouzam, (1987) | Dissociative trance state | Recurrent MDD | Trimipramine 150 mg/day | Improved |
| 13 | Foguet et al., 2010 | Depersonalisation | MDD | Methylphenidate 54 mg/day | Improved |
| 14 | M.B. and T.W., (1989) (Single blind single case) | Depersonalisation | – | Clonazepam 0.75 mg versus Carbamazepine 1200 mg/day | Clonazepam showed improvement |
| 15 | Sachdev, (2002) | Depersonalisation | – | Clonazepam and citalopram | Substantial improvement |
| 16 | Karris et al., (2017) | Depersonalisation | MDD | Low frequency rTMS to the right DLPFC followed by high frequency rTMS to the left DLPFC (6 sessions). | Significant reduction in depersonalization symptoms |
| 17 | Saitis et al., (2008) | Depersonalisation | – | Fluoxetine 40 mg/day | Improved |
| 18 | Salgado et al., (2012) | Depersonalization and Derealisation Syndrome | – | Add on Lamotrigine 200 mg/day to Venlafaxine 225 mg and Risperidone 2 mg | Improved |
| 19 | Miljevic et al., (2011) | Conversion disorder | – | Amitriptyline (25 mg daily,tds) and lorazepam (1 mg daily tds) | Improved |
| 20 | Oulis et al., (2009) | motor conversion disorder | – | Amisulpride 200 mg/day | Improved |
| 21 | Stiebel and Kirby, (2018) | Conversion disorder or hysteria | – | Amytal interview | Improved |
| 22 | Hurwitz, (1988) | Conversion symptoms | – | IV amobarbital and methylphenidate | Improved |
| **LONGITUDINAL OPEN STUDY** | | | | | |
| 1 | Ural et al., (2015) | Caseness based on Dissociation Questionnaire (DIS-Q) | Panic disorder | Venlafaxine 150 mg | Response to Venlafaxine in Panic disorder can be negatively influenced by comorbid dissociative symptoms. |
| 2 | Simeon and Knutelska, (2005) ($N = 14$) | Depersonalization disorder | – | Naltrexone mean dose 120 mg/day | Three patients were very much improved, and 1 patient was slightly improved with Naltrexone treatment. |
| 3 | Mantovani et al., (2011) Open-label cross-over study ($N = 12$) | Depersonalisation | Depression and Anxiety | Iinhibitory low-frequency rTMS administered to right and left Temporo-parietal junctions. | 6 patients responded at the end of 3 weeks after right TPJ rTMS. |
| 4 | Bohus et al., (1999) $N = 13$ | Self-rated questionnaire measuring dissociation, analgesia, tonic immobility, and tension (DAISS) | BPD | Naltrexone 25 to 100 mg q. i.d. | Significant reduction of the duration and the intensity of dissociative phenomena were noted. |
| **CASE SERIES** | | | | | |
| 1 | Pape and Wöller, (2015) ($N = 15$) | Dissociative amnesia and stupor | PTSD | Naltrexone in doses of 2–6 mg/day | 11 reported immediate positive effects, 7 described a sustained beneficial effect. |
| 2 | Sierra et al., (2003) ($N = 32$) | Depersonalisation | – | Add on Lamotrigine (50 to 800 mg/day) | 56% patients showed 30% reduction in symptoms of Depersonalisation |
| 3 | Hollander et al., (1990) | Depersonalisation | Obsessive Compulsive Disorder (OCD) and Anxiety | Different SSRIs | Improvement in those with comorbid conditions. |
| 4 | Sierra et al., (2001) ($N = 11$) | Depersonalisation | – | Add on Lamotrigine 250 mg/day | 6 patients responded. |
| 5 | White et al., (1988) | Non organic locomotor disorder | – | Thiopentone 20–100 mg IV | |
| **EXPERT REVIEW** | | | | | |

(*continued on next page*)

**Table 1** (*continued*)

| Sr. No | Study author and year | Dissociative subgroup | Comorbid disorder | Psychopharmacological agent | Outcome |
|---|---|---|---|---|---|
| 1 | Gentile et al., (2014) | Depersonalization- Derealisation disorder | – | Pharmacotherapy and psychotherapy | Psychotherapy should be considered with or without medications. |
| 2 | Gentile et al., (2013) | Dissociative identity disorder | – | Pharmacotherapy and psychotherapy | Pharmacotherapy is useful to treat comorbid psychiatric disorders |
| 3 | Sierra et al., (2005) | Depersonalisation | – | Pharmacotherapy and psychotherapy | Combination treatment requires more evidence |
| 4 | Sierra, (2008) | Depersonalisation | – | Naltrexone, Naloxone, Lamotrigine, Clonazepam | Requires good study designs to build evidence. |
| 5 | Bravo et al., (2013)Bravo et al., 2013 | Psychogenic Non Epileptic Seizure (PNES) | – | Sertraline 200 mg/day | SSRI are helpful in reducing symptoms of PNES. Studies with large sample size and different outcome measures are needed. |
| **RANDOMISED CONTROLLED TRIAL** | | | | | |
| 1 | McCarthy et al., (1994) Placebo controlled trial ($N = 35$) | Caseness based on Dissociative Experiences Scale | Bulimia nervosa | Fluoxetine 60 mg | Good response may be predicted for nonspecific symptoms like depression |
| 2 | Simeon et al., (1998) Double blind crossover ($N = 8$) | Depersonalisation | – | Clomipramine 300 mg versus Desipramine | 2 cases improved on clomipramine |
| 3 | LaFrance et al., (2014) | PNES | – | Sertraline (flexible dose UPTO 200 mg) and CBT-ip | Cognitive Behavioural Therapy (CBT) with or without Sertaline is superior to Sertaline. |
| 4 | DEARY and WILSON, (1994) | Globus Pharyngeus | – | Amitriptyline verses placebo | Amitriptyline was not helpful in the dissociative symptoms. |
| 5 | BO et al., (2010) | Globus hystericus | – | Modified banxia houpu decoction | Benefits in relieving dissociative symptoms. |
| **CASE CONTROL STUDY** | | | | | |
| 1 | Jay et al., (2014) Case control type ($N = 37$) | Depersonalisation | – | Inhibition to right Ventrolateral Pre Frontal Cortex (VLPFC) using repetitive transcranial magnetic stimulation (rTMS) | rTMS to both sites led to reduced depersonalization scores but can be nonspecific physiological effect too. |
| OBSERVATIONAL STUDY | | | | | |
| 1 | Kasap et al., (2012) | Globus hystericus | – | Proton pump inhibitor | Improved |
| OTHERS (Survey and letter) | | | | | |
| 1 | Sno and Schalken, (1999) (Systematic survey) | Dissociative Identity disorder | – | Fluoxetine and Paroxetine were the most frequently reported serotonin reuptake inhibitors. | Along with medications, psychotherapeutic explanatory framework is mandatory. |
| 2 | Markowitz and Gill, (1996) | Dissociative identity disorder | – | – | Until definitive answers are awaited through multimodality research, the decision to treat DID with medications is based largely on isolated case reports with nonexistent outcome data. |
| **META-ANALYSIS** | | | | | |
| 1 | Somer et al., (2013) (Meta-analysis of 4 RCTs) | Depersonalisation | Anxiety | Lamotrigine, Fluoxetine, Naltrexone and Biofeedback | Inconsistent evidence for the efficacy of lamotrigine, Fluoxetine and Naltrexone. |

**Table 2**
Studies included for the review:.

| RCT | Author and year | Characteristic of the study | Pharmacotherapy response |
|---|---|---|---|
| 1 | Nuller et al., (2001) Single blind placebo controlled ($N$ = 14) | In patient setting, single centre, Naloxone (1.6 to 4 mg stat), placebo comparison, DSM-IV diagnosis of depersonalization disorder, duration: 4 weeks; 9 male, 4 female, mean age 32 years, subjective reporting of depersonalization score and also by measuring plasma cortisol, cortisone and corticosterone for stress response as measured pre and post Naloxone/placebo injection. Limitation includes to Naloxone over 4 weeks only as compared to other studies and inclusion of single subtype of DD that is Depersonalization. | Naloxone (1.6 to 4 mg) was superior to placebo statistically also corroborated with involvement of corticosteroid in the stress response to depersonalization symptoms by measuring plasma cortisol, cortisone corticosterone. 71% patients experienced significant improvement. |
| 2 | Simeon et al., (2004) Randomised controlled trail ($N$ = 54) | Out patients setting, single centre, Fluoxetine (60 mg/day), placebo comparison, DSM-IV diagnosis of depersonalization disorder, duration: 10 weeks, outcome measures- CGI-I scores, DES scores, DSS scores; 52% females in treatment group and 32% female in control group, 50 were randomized, mean age 34.5 ($S.D$ = 11.4) in treatment group and 36.8 ($S.D$ = 10.1) in control group, the study was supported in part by NIMH grant MH055582 to D.S. The Fluoxetine and placebo capsules were provided by Eli Lilly. Comorbid anxiety and depression was measured. Limitation includes a single subtype of DD that is Depersonalization. | Fluoxetine (60 mg/day) was not statistically superior to placebo though improvement in CGI-I scores were noted in Fluoxetine group over placebo in comorbid depression and anxiety. |
| 3 | (A.Philipsen et al., 2004a,b) Placebo controlled study ($N$ = 9) | Seven in patients and 2 outpatients from singe centre of University of Freiburg, Germany, Single dose Naloxone (0.4 mg I.V), placebo comparison, acute dissociative state in DSM-IV diagnosis of Borderline Personality Disorder, duration: 15 min to 30 min, Outcome measures: DSS, DES, CADSS, 9 female, no males. Limitation includes measurement of acute response to Naloxone as compared to other studies and a single subtype of DD that is Depersonalization. | Single dose Naloxone (0.4 mg I.V) was not superior to placebo in acute dissociative state in Borderline Personality Disorder. |
| 4 | Marshall et al., (2007) single-blind placebo ($N$ = 70) | Hispanic (65.4%), African American (9.6%) and Caucasian (25%) Out patients, Single centre, Paroxetine (maximum 60 mg/day), placebo comparison, 10 weeks, dissociative symptoms in DSM-IV diagnosis of PTSD. Outcome measures: CGI-I and DES, 67% female, mean age: 39.87 years (S.D. = 11.2). Limitation includes subjects with diagnosis of PTSD and not DD; measuring response to treatment in non-specific dissociative symptoms that are comorbid with PTSD. | Paroxetine (maximum 60 mg/day) was statistically significant over placebo in a 12 weeks trial of treatment of dissociation comorbid with chronic PTSD. Paroxetine was well tolerated. Scores over CGI-I and DES were significantly correlated with improvement. |
| 5 | Aliyev and Aliyev, (2011) Double-blind placebo-controlled design ($N$ = 80) | Azerbaijani outpatients, single centre, lamotrigine (25–300 mg/day), placebo comparison, DSM-IV diagnosis of depersonalization disorder, 12 weeks, 80 randomised, mean age 37.7; 0% female, outcome measures: CDS | Lamotrigine was statistically superior to placebo in a 12 week trial. However study was excluded from the qualitative synthesis as the original article was retracted by the journal. |
| 6 | Schmahl et al., (2012) double-blind placebo-controlled randomized trials (total $n$ = 29). | Multicentre: Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim; the Department of Psychiatry and Psychotherapy, University of Rostock and the Centre for Psychosomatic Medicine, Bad Wiessee, Inpatient as well as outpatients, duration: 8 weeks, Naltrexone (50–200 mg/day), placebo comparison, Outcome measures: DSS, German adaptation of DES, dissociative symptoms in DSM-IV diagnosis of Borderline Personality Disorder, male 0%, mean age: before cross over: 28.3 years (S.D = 8)before cross over: 29.2 years (S.D = 8.9). Limitation includes only female subjects, specific diagnosis of BPD and measuring response to treatment in non-specific dissociative symptoms that are comorbid with BPD. | Intensity and duration of dissociative symptoms were numerically lower under Naltrexone than under placebo group. Dissociative symptoms responded to 3 weeks of Naltrexone (50–200 mg/day) over placebo in 29 patients with Borderline Personality Disorder. However the difference was not statistically significant. |
| 7 | Sierra et al., 2003 | Out patients, single centre-Maudsley hospital clinic, Lamotrigine up to 250 mg/day over 7–8 weeks period, placebo comparison, DSM-IV diagnosis of depersonalization disorder, duration: 12 weeks cross over study, 8 male, 6 female, mean age 35.2 years (SD = 3.4), outcome measures-Cambridge Depersonalization Scale (CDS) and Present State Examination (PSE). Limitation includes measurement of response to Lamotrigine in a single subtype of DD that is Depersonalization | Lamotrigine (up to 250 mg/day over 7–8 weeks period) was not better than placebo in Depersonalisation Derealisation disorder in a cross over study. However the results in the meta-analysis were not estimable for the study due to zero events in treatment and control arm. |

Subgroup analysis was done for the studies with treatment duration of at least 8 to 12 weeks. The heterogeneity reduced to 0.03 with $P$ = 0.0009 and $I^2$ = 70%. The treatment response rate in the pharmacotherapy group was 80.24% ($n$ = 65/81), significantly higher than response rate of 44.76% ($n$ = 47/105) in the control group. And, the pooled RR was 1.13 (95% CI, 0.88–1.44; $P$ = 0.34). The results are depicted in Fig. 3.

There was modest evidence for Paroxetine (RR = 2.44 CI [1.16, 5.16]) in reducing dissociative symptoms in PTSD but the results are not generalized due to unavailability of results on dissociative disorders per se or other specific subtypes of DD. Two studies on Lamotrigine were on depersonalization disorder but the one had to be excluded from analyses while other study was not supportive for Lamotrigine efficacy in Depersonalisation disorder. The two studies on Naloxone were positive (RR = 1.33, CI [3.24, 829.04]) but for two very different groups of patients – depersonalization disorder and acute dissociative states in borderline personality disorder and limits the interpretation of results to dissociative disorders in general. The single negative study on

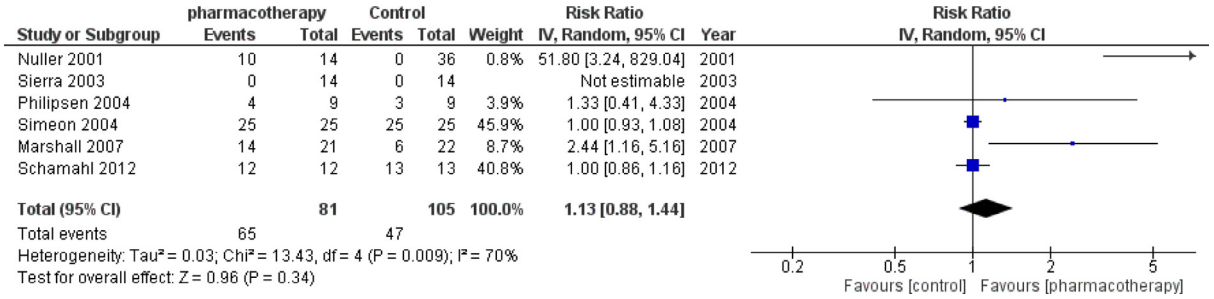


**Fig. 3.** Forest plot comparing subgroup analysis with duration of treatment more than 8 weeks.

**Table. 3**
Risk of bias in selected studies.

| Study ID | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Nuller et al., 2001 | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Simeon et al., 2004 | low | Low | Unclear | Low | Low | Unclear |
| Philipsen et al., 2004a,b | High | Unclear | Unclear | Unclear | Unclear | Unclear |
| Marshall et al., 2007 | Unclear | Unclear | Low | Low | Low | Low |
| Schamahl et al., 2012 | Low | Low | Low | Low | Low | Low |

Fluoxetine was on depersonalization disorder while the single negative study on Naltrexone was for dissociative symptoms in borderline personality disorder. This is depicted in Figs. 2 and 3. Cochrane risk of bias table was used for analysis of bias among selected studies.

The overall risk of bias was evaluated as "low" according to the five criteria stipulated by the Cochrane Handbook for systematic reviews of Interventions as described in Table 3. On exclusion of one RCTs (Nuller et al., 2001) there was significant reduction in heterogeneity of the sample may be due to the skewed confidence interval [3.24 829.04], no mention of funding source and less robust methodology in terms of description leading to unclear risk of bias. Naloxone had modest efficacy (RR = 1.33, CI [3.24, 829.04]) in terms of reducing depersonalization symptoms over placebo (Nuller et al., 2001). Lamotrigine had good efficacy in depersonalization subtype of dissociative disorders (RR = 4.57, CI [2.14, 9.80]) but results had to be omitted as original study was retracted by the journal after publication (Aliyev and Aliyev, 2011). Paroxetine also had good evidence (RR = 2.44 CI [1.16, 5.16]) for reducing dissociative symptoms in PTSD with good tolerability over placebo but being an only RCT in PTSD, it is difficult to generalize the results for other DD (Marshall et al., 2007). Naloxone was not superior to placebo though the trial was not conducted in dissociative disorders per se but acute dissociative state in PTSD (Philipsen et al., 2004a,b). More number of studies on Lamotrigine, Paroxetine and Naloxone are warranted to conclusively state the efficacy in specific subtype of DD. In terms of efficacy in reducing dissociative symptoms, Fluoxetine and Naltrexone touched line of no effect though study of Fluoxetine was on subjects with depersonalization (Simeon et al., 2004) and Naltrexone on subjects with dissociative symptoms in BPD (Schmahl et al., 2012). Table 4 shows GRADE recommendation using GRADE profiling (GRADEpro GDT).

## 4. Discussions

The limited data from this meta-analysis reflects insufficient information on the use of pharmacotherapy in specific subtypes of DD. In an open label trial of Venlafaxine in panic disorder with and without dissociative symptoms, good response to treatment was observed in patients without dissociative symptoms (Ural et al., 2015). In Two open label trial of Naltrexone in patients with BPD and depersonalization disorder respectively shown significant improvement in dissociative symptoms suggesting involvement of opioid system in symptom manifestation (Bohus et al., 1999, Simeon and Knutelska, 2005). In a placebo controlled RCT, Fluoxetine was studied in the context of response to childhood trauma and dissociative experience in bulimic patients and treatment response was found to be nonspecific (McCarthy et al., 1994). In a 16 week double blind crossover trial for depersonalization disorder, Clomipramine was found to be marginally better than Desipramine (Simeon et al., 1998). Sertaline was found to be ineffective against CBT in psychogenic nonepileptic seizures. Another 2 RCTs reflected Amitriptyline to be ineffective while modified banxia houpu decoction (Chinese herb) effective in Globus Pharyngeus symptoms (Deary and Wilson, 1994; Bo et al., 2010). In nutshell, open label studies and some RCTs on Lamotrigine and Fluoxetine have taken into account of depersonalization disorders predominantly while Naloxone, Paroxetine and Naltrexone have included nonspecific category of dissociative symptoms in PTSD and BPD suggesting strong limitation of this meta-

**Table. 4**
GRADE profiling.

| Certainty assessment № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | № of patients Pharmacotherapy | placebo | Effect Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment response** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | not serious | not serious | none | 65/95 (68.4%) | 47/119 (39.5%) | **RR 1.59** (0.76 to 3.30) | **233 more per 1000** (from 95 fewer to 908 more) | ⨁⨁⨁⨁ HIGH | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio.

analysis. In the dearth of information on pharmacotherapy in specific subtype of DD, it is noteworthy to discuss the available evidence with caution as single RCT exist considering drug-disorder subtype combination. Modest evidence for Paroxetine and Naloxone exists that too in dissociative symptoms of PTSD and Depersonalisation disorder respectively. There is no evidence for Fluoxetine and Naltrexone. The results of the meta-analysis show heterogeneous and surprisingly insufficient literature on RCTs on various subtypes of DD like Dissociative Amnesia, Dissociative Fugue, Dissociative Identity Disorder, Dissociative convulsion, Dissociative Motor Disorder, Trance- Possession disorder. In fact not all the subtypes were included in final analyses as a result of insufficient number of published studies. Overall it appears satisfactory to reflect upon that at least this meta-analysis generates some evidence for the use of pharmacotherapy in depersonalization subtype of dissociative disorders but the results of single pharmacological agent in a specific DD needs to be replicated in larger RCTs. It would be apt to conclude that Lamotrigine, Paroxetine and Naloxone are the only pharmacological agents studied and only Naloxone and Paroxetine were found to have modest evidence for controlling depersonalization symptoms and dissociative symptoms that are comorbid with PTSD and BPD. There is a strong possibility that dissociative symptoms frequently co-occur with another psychiatric condition like PTSD or BPD making it a heterogeneous sample naturally which can be addressed upon in future studies. It may seem unrealistic to study DD and single pharmacological agent in isolated placebo controlled RCT but that is probably the most important outcome surfacing through this meta-analysis. It is surprising that despite several decades of research on DD, only case reports and open trials with few RCTs have tested efficacy of pharmacotherapy in DD. The unavailability of single treatment for single disorder subtype of DD makes is difficult to comment upon utility of any single agent in treatment of DD. At the most comorbid psychiatric disorders can be included in such trials for better evidence generation against single pharmacological agent and keeping good patient follow up rates if dropout remains a concern.

The strength of our study is inclusion of all the DD in the literature and comprehensive review of all the studies which were missing in earlier meta-analysis (Somer et al., 2013). We have looked into an umbrella of DD in a single review which is a unique characteristic though that eventually appeared as a limitation due to existing insufficient RCTs in DD. We have justified the inclusion and exclusion of comorbid conditions and non RCTs in this review based on search items and number of excluded studies. Few other limitations include small number of trials with small sample size and large heterogeneity, nonconcealment of funding source and variability on primary outcome measures across RCTs. It would be interesting to know which pharmacotherapy suits best for different subcategories of DD as most of the current evidence exists only for depersonalization disorder. In the dearth of conclusive evidence, the future research in the area of pharmacotherapy for DD seems promising option. Moreover since no single pharmacotherapy has been replicated till now suggest potentially ignored area of psychiatric research. The future research should focus on building evidence for Paroxetine and Naloxone and probably Lamotrigine in a single subtype of DD while understanding the neurobiological substrates of it.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112529.

## References


Aliyev, N.A., Aliyev, Z.N., 2011. Lamotrigine in the immediate treatment of outpatients with depersonalization disorder without psychiatric comorbidity: randomized, double-blind, placebo-controlled study. J. Clin. Psychopharmacol. https://doi.org/10.1097/JCP.0b013e31820428e1.

Ballew, L., Morgan, Y., Yasser, L., 2003. Intravenous diazepam for dissociative disorder: memory lost and found. Psychosom. J. Consult. Liaison Psychiatry 44, 346–347. https://doi.org/10.1176/appi.psy.44.4.346.

Bo, P., Chen, Q., Zhu, H., Zhang, X., Xu, H., Zhang, Y., Cao, Y., 2010. Clinical observations on 46 cases of globus hystericus treated with modified banxia houpu decoction. J. Tradit. Chin. Med. https://doi.org/10.1016/s0254-6272(10)60023-4.

Bohus, M.J., Landwehrmeyer, G.B., Stiglmayr, C.E., Limberger, M.F., Böhme, R., Schmahl, C.G., 1999. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: an open-label trial. J. Clin. Psychiatry 60, 598–603.

Bravo, T.P., Hoffman-Snyder, C.R., Wellik, K.E., Martin, K.A., Hoerth, M.T., Demaerschalk, B.M., Wingerchuk, D.M., 2013. The effect of selective serotonin reuptake inhibitors on the frequency of psychogenic nonepileptic seizures: a critically appraised topic. Neurologist. https://doi.org/10.1097/NRL.0b013e31827c6bfd.

Coons, P.M., 1992. The use of carbamazepine for episodic violence in multiple personality disorder and dissociative disorder not otherwise specified: two additional cases. Biol. Psychiatry 32, 717–720. https://doi.org/10.1016/0006-3223(92)90302-G.

Deary, I.J., Wilson, J.A., 1994. Problems in treating globus pharyngis. Clin. Otolaryngol. Allied Sci. https://doi.org/10.1111/j.1365-2273.1994.tb01148.x.

Desarkar, P., Das, A., Sinha, V.K., 2006. Duloxetine for childhood depression with pain and dissociative symptoms. Eur. Child Adolesc. Psychiatry. https://doi.org/10.1007/s00787-006-0553-4.

Fichtner, C.G., Kuhlman, D.T., Gruenfeld, M.J., Hughes, J.R., 1990. Decreased episodic violence and increased control of dissociation in a carbamazepine-treated case of multiple personality. Biol. Psychiatry 27, 1045–1052. https://doi.org/10.1016/0006-3223(90)90040-9.

Gentile, J.P., Dillon, K.S., Gillig, P.M., 2013. Psychotherapy and pharmacotherapy for patients with dissociative identity disorder. Innov. Clin. Neurosci. 10, 22–29.

Gentile, J.P., Snyder, M., Gillig, P.M., 2014. Stress and trauma: psychotherapy and pharmacotherapy for depersonalization/derealization disorder. Innov. Clin. Neurosci. 11, 37–41.

Hale, A.S., Pinninti, N.R., 1994. Exorcism-resistant ghost possession treated with clopenthixol. Br. J. Psychiatry 165, 386–388.

Hollander, E., Liebowitz, M.R., DeCaria, C.M., Fairbanks, J., et al., 1990. Treatment of depersonalization with serotonin reuptake blockers. J. Clin. Psychopharmacol.

Hurwitz, T.A., 1988. Narcosuggestion in chronic conversion symptoms using combined intravenous amobarbital and methylphenidate. Can. J. Psychiatry. https://doi.org/10.1177/070674378803300214.

Ilechukwu, S.T.C., Henry, T., 2006. Amytal interview using intravenous lorazepam in a patient with dissociative fugue. Gen. Hosp. Psychiatry. https://doi.org/10.1016/j.genhosppsych.2006.08.001.

Jay, E.L., Sierra, M., Van Den Eynde, F., Rothwell, J.C., David, A.S., 2014. Testing a neurobiological model of depersonalization disorder using repetitive transcranial magnetic stimulation. Brain Stimul. https://doi.org/10.1016/j.brs.2013.12.002.

Jha, V.N., 2017. Response to eperisone in patients of therapy-resistant dissociative convulsions: a report of two cases. Indian J. Pharmacol. 49, 121–123. https://doi.org/10.4103/0253-7613.201033.

Karris, B.C., Capobianco, M., Wei, X., Ross, L., 2017. Treatment of depersonalization disorder with repetitive transcranial magnetic stimulation. J. Psychiatr. Pract. https://doi.org/10.1097/PRA.0000000000000215.

Kasap, E., Ayhan, S., Yüceyar, H., 2012. Does *Helicobacter pylori* treatment improve the symptoms of globus hystericus? Turkish J. Gastroenterol. https://doi.org/10.4318/tjg.2012.0507.

Khouzam, H.R., 1987. Treatment of recurrent major depression agitation and dissociative state with trimipramine. Can. J. Psychiatry. https://doi.org/10.1177/070674378703200927.

LaFrance, W.C., Baird, G.L., Barry, J.J., Blum, A.S., Webb, A.F., Keitner, G.I., Machan, J.T., Miller, I., Szaflarski, J.P., 2014. Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2014.817.

Liu-Barbaro, D., Stein, M., 2015. Psychopharmacologic treatment of dissociative fugue and PTSD in an Ethiopian refugee. J. Clin. Psychiatry 76, 958. https://doi.org/10.4088/JCP.14cr09334.

Mantovani, A., Simeon, D., Urban, N., Bulow, P., Allart, A., Lisanby, S., 2011. Temporoparietal junction stimulation in the treatment of depersonalization disorder. Psychiatry Res. https://doi.org/10.1016/j.psychres.2010.08.022.

Markowitz, J.S., Gill, H.S., 1996. Pharmacotherapy of dissociative identity disorder. Ann. Pharmacother. https://doi.org/10.1177/106002809603001225.

Marshall, R.D., Lewis-Fernandez, R., Blanco, C., Simpson, H.B., Lin, S.H., Vermes, D., Garcia, W., Schneier, F., Neria, Y., Sanchez-Lacay, A., Liebowitz, M.R., 2007. A controlled trial of Paroxetine for chronic PTSD, dissociation, and interpersonal problems in mostly minority adults. Depress. Anxiety. https://doi.org/10.1002/da.20176.

McCarthy, M.K., Goff, D.C., Baer, L., Cioffi, J., Herzog, D.B., 1994. Dissociation, childhood trauma, and the response to Fluoxetine in bulimic patients. Int. J. Eat. Disord. 15, 219–226. https://doi.org/10.1002/1098-108X(199404)15:3<219::AID-EAT2260150304>3.0.CO;2-F.

Miljevic, C.D., Kecojevic-Miljevic, S., Crnobaric, C., Lecic-Tosevski, D., 2011. A rare case of male hysteria - hemiparesis successfully treated with amitriptyline. Psychiatr. Danub 23, 281–284.

Nuller, Y.L., Morozova, M.G., Kushnir, O.N., Hamper, N., 2001. Effect of naloxone therapy on depersonalization: a pilot study. J. Psychopharmacol. https://doi.org/10.1177/026988110101500205.

Oulis, P., Kokras, N., Papadimitriou, G.N., Masdrakis, V.G., 2009. Adjunctive low-dose amisulpride in motor conversion disorder. Clin. Neuropharmacol. https://doi.org/10.1097/WNF.0b013e3181b20144.

Pape, W., Wöller, W., 2015. Low dose naltrexone in the treatment of dissociative symptoms. Nervenarzt 86, 346–351. https://doi.org/10.1007/s00115-014-4015-9.
Perales-Blum, L., Ibarra-Yruegas, B., Cuéllar-Barboza, A., 2015. Successful treatment of dissociative identity disorder in an adolescent with quetiapine. J. Child Adolesc. Psychopharmacol. https://doi.org/10.1089/cap.2014.0133.
Philipsen, A., Schmahl, C., Lieb, K., 2004b. Naloxone in the treatment of acute dissociative states in female patients with borderline personality disorder. Pharmacopsychiatry. https://doi.org/10.1055/s-2004-827243.
Philipsen, A., Schmahl, C., Lieb, K., 2004a. Naloxone in the treatment of acute dissociative states in female patients with borderline personality disorder. Pharmacopsychiatry 37, 196–199. https://doi.org/10.1055/s-2004-827243.
S., M.B., U., T.W., 1989. Depersonalization disorder: effects of caffeine and response to pharmacotherapy. Biol. Psychiatry.
Sachdev, P., 2002. Citalopram-clonazepam combination for primary depersonalization disorder: a case report. Aust. N. Z. J. Psychiatry. https://doi.org/10.1046/j.1440-1614.2001.t01-1-01030.x.
Saitis, M., Katsigiannopoulos, K., Papazisis, G., 2008. Treatment of depersonalization disorder with Fluoxetine: a case report. Ann. Gen. Psychiatry. https://doi.org/10.1186/1744-859x-7-s1-s208.
Salgado, A., Oliveira, L., Sierra-Siegert, M., Salgado, J.V., 2012. Depersonalization and derealization syndrome: report on a case study and pharmacological management. Rev. Bras. Psiquiatr. https://doi.org/10.1016/j.rbp.2012.04.006.
Scarella, T.M., Franzen, J.R., 2017. Case report: improvement in dissociative symptoms with mixed amphetamine salts. J. Trauma Dissoc. 18, 649–662. https://doi.org/10.1080/15299732.2016.1259195.
Schmahl, C., Kleindienst, N., Limberger, M., Ludäscher, P., Mauchnik, J., Deibler, P., Brünen, S., Hiemke, C., Lieb, K., Herpertz, S., Reicherzer, M., Berger, M., Bohus, M., 2012. Evaluation of Naltrexone for dissociative symptoms in borderline personality disorder. Int. Clin. Psychopharmacol. 27, 61–68. https://doi.org/10.1097/YIC.0b013e32834d0e50.
Sierra, M., 2008. Depersonalization disorder: pharmacological approaches. Expert Rev. Neurother. https://doi.org/10.1586/14737175.8.1.19.
Sierra, M., Baker, D., Medford, N., David, A.S., 2005. Unpacking the depersonalization syndrome: an exploratory factor analysis on the Cambridge Depersonalization Scale. Psychol. Med. https://doi.org/10.1017/S0033291705005325.
Sierra, M., Phillips, M.L., Ivin, G., Krystal, J., David, A.S., 2003. A placebo-controlled, cross-over trial of lamotrigine in depersonalization disorder. J. Psychopharmacol. https://doi.org/10.1177/0269881103017001712.
Sierra, M., Phillips, M.L., Lambert, M.V., Senior, C., David, A.S., Krystal, J.H., 2001. Lamotrigine in the treatment of depersonalization disorder. J. Clin. Psychiatry. https://doi.org/10.4088/JCP.v62n1012b.
Simeon, D., Guralnik, O., Schmeidler, J., Knutelska, M., 2004. Fluoxetine therapy in Depersonalisation disorder: randomised controlled trial. Br. J. Psychiatry. https://doi.org/10.1192/bjp.185.1.31.
Simeon, D., Knutelska, M., 2005. An open trial of Naltrexone in the treatment of depersonalization disorder. J. Clin. Psychopharmacol. 25, 267–270. https://doi.org/10.1097/01.jcp.0000162803.61700.4f.
Simeon, D., Stein, D.J., Hollander, E., 1998. Treatment of depersonalization disorder with clomipramine. Biol. Psychiatry. https://doi.org/10.1016/S0006-3223(98)00023-7.
Sno, H.N., Schalken, H.F., 1999. Dissociative identity disorder: diagnosis and treatment in the Netherlands. Eur. Psychiatry 14, 270–277. https://doi.org/10.1016/S0924-9338(99)00171-6.
Somer, E., Amos-Williams, T., Stein, D.J., 2013. Evidence-based treatment for Depersonalisation-Derealisation disorder (DPRD). BMC Psychol. https://doi.org/10.1186/2050-7283-1-20.
Spiegel, D., Loewenstein, R.J., Lewis-Fernández, R., Sar, V., Simeon, D., Vermetten, E., Cardeña, E., Dell, P.F., 2011. Dissociative disorders in DSM-5. Depress. Anxiety. https://doi.org/10.1002/da.20874.
Stiebel, V.G., Kirby, J.V., 2018. The amytal interview in the treatment of conversion disorder: three case reports. Mil. Med. https://doi.org/10.1093/milmed/159.4.350.
Ural, C., Belli, H., Tabo, A., Akbudak, M., 2015. Open-longitudinal study of the effect of dissociative symptoms on the response of patients with panic disorder to venlafaxine. Compr. Psychiatry 57, 112–116. https://doi.org/10.1016/j.comppsych.2014.11.016.
White, A., Corbin, D.O.C., Coope, B., 1988. The use of thiopentone in the treatment of non-organic locomotor disorders. J. Psychosom. Res. https://doi.org/10.1016/0022-3999(88)90065-7.
World Health Organization, 1993. The ICD-10 Classification of Mental and Behavioural Disorders. Nonserial Publication WHO.