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Pharmacotherapy of depersonalization/derealization disorder

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INTRODUCTION

Depersonalization/derealization disorder (DDD) is characterized by persistent or recurrent depersonalization and/or derealization that causes clinically significant distress, while reality testing remains intact [1].

DDD has a prevalence of approximately 2 percent and is associated with significant morbidity, but often goes undetected or misdiagnosed, leading to delays in treatment.

This topic discusses pharmacotherapy for DDD. The epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of DDD are discussed separately. Psychotherapy for DDD is also discussed separately. (See "Depersonalization/derealization disorder: Epidemiology, clinical features, assessment, and diagnosis" and "Depersonalization/derealization disorder: Psychotherapy".)

APPROACH TO TREATMENT

Our approach to selecting among treatments for depersonalization/derealization disorder, including the use of pharmacotherapy and psychotherapy, is discussed separately. (See "Approach to treating depersonalization/derealization disorder".)

DEFINITIONS

Depersonalization — Depersonalization is a persistent or recurrent feeling of detachment or estrangement from one's self. An individual experiencing depersonalization may report feeling like an automaton or as if in a dream or as if watching himself or herself in a movie. Depersonalized individuals may report the sense of being an outside observer of their mental processes or their body. They often report feeling a loss of control over their thoughts, perceptions, and actions.

Derealization — Derealization is a subjective sense of detachment or unreality regarding the world around them (eg, individuals or objects are experienced as unreal, dreamlike, foggy, lifeless, or visually distorted).

OVERVIEW OF PHARMACOTHERAPY

There is limited robust evidence from randomized trials on the efficacy of medication for depersonalization/derealization disorder. Benzodiazepines, serotonin reuptake inhibitors, or naltrexone may be useful to treat specific target or comorbid symptoms as an adjunct to psychotherapy [2].

SEROTONIN REUPTAKE INHIBITORS

Selective serotonergic reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants are unlikely to be of major benefit for depersonalization/derealization disorder (DDD) symptoms, but may be useful to reduce comorbid anxiety and depressive symptoms if prominent. It has been postulated that these symptoms, if untreated, can fuel an intensification of depersonalization and derealization symptoms [2].

Efficacy — The only randomized trial comparing an SSRI with placebo in patients with DDD did not find the SSRI to be efficacious [3]. The trial compared fluoxetine with placebo in 50 patients with DDD. Ratings by clinicians and patients did not find clinically significant differences in depersonalization or dissociation change scores between the fluoxetine and placebo-treated groups. No difference was seen between the two groups on ratings of depression or anxiety.

An earlier, uncontrolled trial reported that two of seven patients with DDD showed improvement following enrollment in an eight-week course of treatment with clomipramine [4].

A retrospective report of patients with DDD found [2]:

- Of 60 patients with DDD treated with an SSRI, nine patients reported their symptoms had definitely improved, 14 patients reported "slightly improved," and 37 reported "stayed the same or worsened."
- Of nine patients with DDD treated with an SNRI, all of the patients reported that their symptoms stayed the same or worsened.
- Of three patients with DDD treated with clomipramine, all of the patients reported that their symptoms stayed the same or worsened.

In our clinical experience, patients with DDD who experience reduction in anxiety and depression with SSRI treatment often report that although the depersonalization has not changed, they are less distressed by it and better able to ignore it.

Administration — No individual serotonergic reuptake inhibitor (SRI) has been shown to have superior efficacy over another for depression or anxiety; the selection among them for patients with DDD and associated symptoms can be customized to the patient based on the drug's side effect profile, drug-drug interactions, and/or patient treatment history/preference.

Therapeutic doses of SSRI and SNRIs in the treatment of DDD are approximately the same as for the treatment of depression (table 1). Time to onset of clinically meaningful action for an SRI varies by patient, but can be as long as four to six weeks, or longer. If the patient does not show a robust response, the SRI should be increased in one- to two-week increments until sufficient improvement is seen or the maximum recommended or highest tolerated dose is reached.

As an example, paroxetine can be used at an initial therapeutic dose of 20 mg/day. If the patient does not experience a robust clinical response after four to six weeks, paroxetine can be titrated up to a maximum of 80 mg/day.

Side effects — Common side effects of SSRIs include sexual dysfunction, nausea, diarrhea, insomnia, and withdrawal on discontinuation. SSRIs can also cause drug interactions, weight gain, and agitation and/or hyperactivation.

Common side effects of SNRIs are nausea, dizziness, insomnia, sedation, constipation, and sweating. Venlafaxine may increase blood pressure, usually to a small extent.

NALTREXONE

Naltrexone is a nonselective opioid antagonist used to treat opioid use disorder and alcohol use disorder.

Efficacy — An uncontrolled trial of naltrexone in 14 patients with depersonalization/derealization disorder (DDD) found an average 30 percent reduction in symptoms, with four patients showing marked improvement [5]. (See "Depersonalization/derealization disorder: Epidemiology, clinical features, assessment, and diagnosis", section on 'Neurobiology'.)

In our clinical experience, patients with pronounced emotional numbing that does not respond to psychotherapy may benefit from oral naltrexone.

Administration — Naltrexone can be started at a dose of 50 mg/day, and increased by 50/mg every one to two weeks as tolerated until an adequate response is achieved, to a maximum of 250 mg/day. Naltrexone is a nonselective opioid antagonist; higher dosing may be required for kappa receptor blockade. However, this has not been studied in treatment for DDD.

Liver function tests (liver function test; aspartate aminotransferase test [AST], alanine aminotransferase test [ALT], and total bilirubin) should be checked at baseline. The medication should not be started if values are greater than five times the upper limit of normal. AST and ALT should be repeated 8 to 12 weeks after initiating the drug, and then quarterly unless clinically indicated before then. Tests for human immunodeficiency virus, hepatitis C virus, and hepatitis B chronic infection should be checked before or soon after starting medication.

Side effects — Common side effects of oral naltrexone are nausea, headache, and dizziness, which subside with continued use. Higher doses of naltrexone are associated with an increased risk of hepatotoxicity. Use of naltrexone, like any medication, should be preceded by a discussion of potential risks and benefits and accompanied by frequent monitoring with liver function tests.

LAMOTRIGINE

Lamotrigine, a mood stabilizing anticonvulsant, has shown mostly positive results in three trials for depersonalization/derealization disorder (DDD) (two with small samples).

- A randomized trial of 80 patients with DDD found that participants treated with lamotrigine were more likely to respond compared with patients receiving placebo (72 versus 16 percent) [6]. A concern about this study was the description of enrolled patients as “without psychiatric comorbidity,” which is unusual given the high rates of comorbidity

in this population. (See "Depersonalization/derealization disorder: Epidemiology, clinical features, assessment, and diagnosis", section on 'Comorbid conditions'.)

- Two small studies from a single research group came to conflicting findings:
  - Four of four patients with DDD experienced a reduction in depersonalization in an uncontrolled study of lamotrigine [7].
  - None of nine patients with DDD responded to lamotrigine in a placebo-controlled, cross-over trial [8].

BENZODIAZEPINES

Benzodiazepines do not appear to be efficacious for the symptoms of depersonalization or derealization, but in our clinical experience, these medications can be used to treat prominent anxiety symptoms in patients with depersonalization/derealization disorder (DDD) and without a history of substance use disorder.

There are no controlled trials of benzodiazepines in these patients. In a retrospective report of 35 patients with DDD treated with benzodiazepines, patients reported they had definitely improved in 10 cases, slightly improved in 8 cases, and stayed the same or worsened in 17 cases [2].

As an example, clonazepam can be used, starting at an initial dose of 0.5 mg/day two or three times daily and increasing in increments of 0.5 mg/day until an adequate response is achieved, side effects occur, or a maximum of 4 mg/day is reached. A table provides dosing information on these medications (table 2).

Side effects of benzodiazepines include impairment of psychomotor performance, amnesia, dependence and withdrawal symptoms after long-term treatment, and rebound anxiety after short-term treatment.

ANTIPSYCHOTIC MEDICATIONS

There are no controlled trials on the efficacy of first- or second-generation antipsychotic medications in depersonalization/derealization disorder (DDD) [2]. In uncontrolled sample of 13 patients with DDD treated with an antipsychotic drug across multiple trials, all 13 patients reported that they had stayed the same or worsened [2]. In our clinical experience, patients often report feeling more dissociated and “cloudy” with these agents. Anecdotal report

suggests that antipsychotics may benefit patients whose DDD is subsumed by intense underlying dysregulation and shifting self states. A case report of three patients reported significant improvement with aripiprazole; however, these patients had comorbid major depression and obsessive-compulsive disorder [9].

Antipsychotic medications may be indicated for the treatment of DDD accompanied by psychosis. In clinical experience, the more sedating antipsychotics often worsen the cloudiness of depersonalization in these patients, while less sedating medications, such as aripiprazole, can reduce symptoms of anxiety and depression (table 3).

STIMULANTS

Stimulants and related medications (including methylphenidate, bupropion, atomoxetine, modafinil, and donepezil) are used to treat symptoms of depersonalization/derealization disorder (DDD); however, there are no randomized trials supporting their use.

A retrospective report that described stimulant treatment in patients with DDD found that symptoms generally remained the same or worsened [2]:

- Of nine cases treated with stimulants, no patients reported that their symptoms had definitely improved; two patients reported their symptoms had slightly improved, and seven patients reported that their symptoms stayed the same or worsened.
- Of 11 cases treated with bupropion, 10 patients reported that their symptoms stayed the same or worsened.
- Of 15 cases treated with buspirone, all of the patients reported that their symptoms stayed the same or worsened.

TRANSCRANIAL MAGNETIC STIMULATION

Small open trials of transcranial magnetic stimulation (TMS) in patients with depersonalization/derealization disorder (DDD) have shown promising results [10,11]. Prefrontal and temporoparietal sites have been tested in DDD. In clinical treatment, some patients opt for combined targeting; however, reports of these cases have not been published.

As examples:

- TMS provided daily for three weeks (five sessions/week) was associated with decreased DDD symptoms in 6 of 12 patients studied. Five of the six patients received three additional weeks of treatment, experiencing a 68 percent reduction in DDD symptoms from baseline; TMS targeted the right inferior parietal lobule [10].

- In a smaller open trial [11], seven patients with medication-resistant DDD were treated with up to 20 sessions of right-sided TMS to the ventrolateral prefrontal cortex for 10 weeks, with an average 44 percent reduction in symptoms.

OTHER INTERVENTIONS

There are no controlled trials of electroconvulsive therapy in depersonalization/derealization disorder (DDD) patients. In the retrospective report of three patients with DDD treated with electroconvulsive therapy, all three reported that they stayed the same or worsened [2]. (See "Depersonalization/derealization disorder: Epidemiology, clinical features, assessment, and diagnosis", section on 'Neurobiology'.)

There is no published study of stellate ganglion block or vagus nerve stimulation. One might speculate that further sympathetic blockade would not ameliorate, or could worsen the condition. Deep brain stimulation targets have not been explored in DDD, but could be of potential interest in stimulating limbic and associated brain regions.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Dissociative disorders".)

SUMMARY AND RECOMMENDATIONS

- Our approach to selecting among treatments for depersonalization/derealization disorder (DDD), including the use of pharmacotherapy and psychotherapy, is discussed separately. (See "Approach to treating depersonalization/derealization disorder".)

- Selective serotonergic reuptake inhibitor and serotonin–norepinephrine reuptake inhibitor antidepressants are unlikely to be of major benefit for DDD symptoms, but may be useful to reduce comorbid anxiety and depressive symptoms if prominent (table 1). (See 'Serotonin reuptake inhibitors' above.)

- A small, uncontrolled trial and our clinical experience support the use of naltrexone, an opioid antagonist, for pronounced emotional numbing in patients with DDD. Naltrexone is given orally starting at a dose of 50 mg/day, and gradually increased up to 250 mg/day if tolerated. (See 'Naltrexone' above.)

- Benzodiazepines do not appear to be efficacious for the symptoms of depersonalization or derealization, but in our clinical experience, these medications can be used reduce anxiety in patients with DDD and without a history of substance use disorder (table 2). As an example, clonazepam can be used, starting at an initial dose of 0.5 mg/day two or three times daily. (See 'Benzodiazepines' above.)

- Antipsychotic medications do not appear to be helpful for patient with DDD. If used to treat co-occurring psychosis in a patient with DDD, less sedating antipsychotics such as aripiprazole may be preferable. In our clinical experience, more sedating antipsychotics often worsen the cloudiness of depersonalization in these patients. (See 'Antipsychotic medications' above.)

- Stimulants and related medications (including methylphenidate, bupropion, atomoxetine, modafinil, and donepezil) are used to treat symptoms of DDD; however, there are no randomized trials supporting their use. (See 'Stimulants' above.)

- Lamotrigine has shown promising results in a few trials. (See 'Lamotrigine' above and 'Other interventions' above.)

- Transcranial magnetic stimulation to both a prefrontal and temporoparietal target has shown preliminary promise and could be clinically combined pending further research. (See 'Transcranial magnetic stimulation' above.)

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