EXPERT REVIEWS

Depersonalization disorder: pharmacological approaches

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Depersonalization disorder (DPD) is a chronic and distressing condition with a prevalence in the general population between 0.8 and 2%. Several neurobiological studies in the last decade have shown that patients have suppressed limbic activation to emotional stimuli. Such findings are in line with a model which suggests that the condition is generated by an anxiety-triggered, 'hard-wired' inhibitory response to threat. Such a mechanism would ensure the preservation of adaptive behavior, during situations normally associated with overwhelming and potentially disorganizing anxiety. In DPD, such a response would become chronic and dysfunctional. Depersonalization remains a condition for which no definitive treatment exists, and for which conventional medications, such as antidepressants or antipsychotics, have been found to be of little value. Fortunately, a few promising lines of pharmacological treatment have emerged in recent years, although more rigorous studies are needed. For example, a number of studies suggest that opioid receptor antagonists such as naltrexone and naloxone are useful in at least a subgroup of patients. In spite of initial expectations, the use of lamotrigine as a sole medication has not been found useful. However, open-label trials suggest that its use as an add-on treatment with selective serotonin reuptake inhibitors (SSRIs) is beneficial in a substantial number of patients. Similarly, the use of clonazepam, particularly in conjunction with SSRI antidepressants, appears to be beneficial in patients with high levels of background anxiety. In line with the stress-related model of depersonalization, those neurotransmitter systems of relevance to depersonalization are known to play important inhibitory roles in the regulation of the stress response.

KEYWORDS: cannabis • clonazepam • depersonalization • derealization • dissociation • ketamine • lamotrigine • opioid receptor antagonists • stress response

Depersonalization is a fascinating phenomenon characterized by an alteration in the perception or experience of the self [1,2]. Patients typically complain of four types of symptoms: detachment from their bodies; emotional numbing; feelings of estrangement and detachment from personal memories; and a feeling that the external world looks unreal [3]. In spite of the dramatic nature of the experience, patients "remain aware of the unreality of the change. The sensorium is normal and the capacity for emotional expression intact" [2].

As a comorbid condition, the prevalence of depersonalization has been found to range between 40 and 80% in psychiatric patients [4]. In such cases, there is evidence which suggests that the presence of depersonalization signals more intense clinical severity of the accompanying condition [5]. For example, panic disorder patients who depersonalize seem to be characterized by an earlier onset of and a more severe course of the condition than those without depersonalization [6]. A recent report also found that patients with schizophrenia and accompanying depersonalization had more prominent cognitive dysfunction and alexythymia than those without depersonalization [7]. It has also been suggested that depersonalization in the context of depression constitutes a clinical marker of resistance to pharmacotherapy [8].

Depersonalization also occurs as a condition in its own right and as such shows an independent course from any comorbid disorder. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) names such a chronic form as 'depersonalization disorder' (DPD) and classifies it as a dissociative condition [1]. The WHO International Classification of Diseases (ICD)-10 in turn, uses the term 'depersonalization–derealization syndrome' and views it as an independent neurotic condition separate from dissociative conditions [2]. Both contentions emphasize different valid observations. On the one hand, it is clear that DPD has

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an intimate relationship with anxiety states, which seems specific enough to as to set it apart from other dissociative conditions. On the other hand, it is clear that the profound disruption of self awareness that characterizes the condition can be best conceptualized as being dissociative in nature. Indeed, the common core affecting all dissociative disorders is an alteration in the integrative function of consciousness, memory and identity [1,2]. The condition usually starts in adolescence or early adult life and, although it may be episodic, more frequently it follows a chronic and persistent course. In most cases, depersonalization generates high subjective distress and can become quite incapacitating [9,10].

DPD is still assumed to be a rare condition by most clinicians, despite the fact that a number of recent epidemiologic studies have shown its prevalence in the general population to be between 0.8 and 2% [4,11]; not unlike that of schizophrenia or manic depressive illness. Unfortunately, most psychiatrists are still trained to believe that DPD is extremely rare and that whenever depersonalization is present, it represents an almost irrelevant symptom stemming from a primary condition such as major depression, an anxiety disorder or even impending psychosis. Not surprisingly, the rate of misdiagnosis has been found to be very high [9,10]. Another possible cause for underdiagnosis comes from the fact that sufferers are often hesitant to talk about their experience. Such reluctance stems from the ineffable nature of the experience and from fears of being thought 'mad' by others [9,10].

Neurobiological aspects

Depersonalization has been shown to correlate with anxiety measures, and patients with a diagnosis of DPD are often found to have significant levels of anxiety [9,10]. Additionally, the onset of depersonalization often coincides with stressful life events or even life-threatening situations. This has been interpreted as suggesting that depersonalization represents an anxiety-triggered 'hard-wired' inhibitory response intended to ensure the preservation of adaptive behavior during situations normally associated with overwhelming and potentially disorganizing anxiety [12]. It has been proposed that such inhibitory response is mediated by a fronto–limbic suppressive mechanism, which would generate a state of emotional numbing and disable the process by means of which perception (including that of one's own body) as well as cognition become emotionally colored. Such 'decoloring' will result in a 'qualitative change' of conscious awareness, which is then reported by the subject as "unreal or detached". In patients with DPD, this experience would become abnormally persistent and dysfunctional [12].

Recent functional neuroimaging [13–15] and psychophysiological studies [16,17] support the aforementioned model and have indicated that patients with DPD show medial prefrontal activation and under-activation of limbic areas to aversive and arousing emotional stimuli. It has also been found that patients show attenuation of autonomic sympathetic responses [16,17], and a negative correlation between intensity of depersonalization and urine norepinephrine levels has also been identified [18].

Towards pharmacological treament of depersonalization

Little is known about useful pharmacological treatments for DPD, and the condition has been generally considered refractory to most medications. There are historical reports of the use of barbiturates, amphetamines and neuroleptics, all with no consistent benefit. Although no systematic studies have been carried out with antipsychotics, retrospective reports on large series of patients do not show them to be useful [10]. Fortunately, the above bleak and rather hopeless scenario has gradually begun to change during the last decade. Indeed, a number of studies involving both challenge and therapeutic trials suggest that a few key neurotransmitter systems may be of particular relevance to the pathophysiology of depersonalization and a few promising medications have been identified (Table 1).

Depersonalization & serotonin

Evidence pointing to a serotonergic involvement in depersonalization comes from challenge studies, as well as therapeutic trials with serotonergic antidepressants.

Challenge studies

A number of substances with predominant serotonergic effects have been reported to induce depersonalization-like experiences and suggest that serotonergic mechanisms are important in the neurobiology of depersonalization.

The most relevant study in this regard was carried out by Simeon *et al.* using the 5-hydroxytryptamine $(5\text{-HT})_{2C}$ agonist meta-chlorophenylpiperazine (m-CPP) in an attempt to induce depersonalization in 67 subjects under double-blind placebo-controlled conditions [19]. It was found that, when challenged with m-CPP, 18% of the participants experienced depersonalization or derealization. However, a potential confounder with m-CPP is that it can induce panic attacks which, as it is known, frequently triggers depersonalization symptoms. Indeed, the authors found a striking correlation of 0.7 between the induction of depersonalization and the development of panic symptoms, which makes it unclear whether the induction of depersonalization was a direct effect of a serotonergic challenge, or indirectly mediated by an ensuing panic attack.

Psilocybin, a powerful serotonergic agonist at $5\text{-HT}_{2A/1A}$ receptors, has also been found to induce depersonalization in a dose-dependent manner under placebo-controlled conditions. Interestingly, it was found that the presence of depersonalization correlated with a subjective feeling of time distortion and impairment in working memory [20]. Such relationship between depersonalization and distorted time experience had been noticed in previous studies focusing on

Table 1. Studies that have targeted chronic depersonalization according to study type, medication used and sample size.

Study	Type of study	Drug and dose	n	Outome
Serotonergic antidepressants				
Hollander *et al.* (1990)	Patient series	Different selective serotonin reuptake inhibitors (20–60 mg/day)	8	Significant improvement in those with comorbid anxiety or obsessive–compulsive disorder
Simeon *et al.* (2004)	Double-blind, placebo-controlled	Fluoxetine (10–60 mg/day)	54	Fluoxetine was not more effective than placebo
Simeon *et al.* (1998)	Double blind, crossover	Clomipramine (300 mg/day) versus desipramine	8	Two cases showed substantial improvement on clomipramine
Lamotrigine				
Sierra *et al.* (2001)	Series of patients	Add-on lamotrigine (250 mg/day)	11	Six patients showed significant improvement
Sierra *et al.* (2003)	Double-blind, placebo-controlled	Lamotrigine (250 mg/day)	9	No patients improved on either lamotrigine or placebo
Sierra *et al.* (2006)	Retrospective	Add-on lamotrigine (50–800 mg/day)	32	56% of patients showed a 30% reduction
Clonazepam				
Stein *et al.* (1989)	Single-blind, single-case	Clonazepam (0.75 mg) versus carbamazepine (1200 mg)	1	Clonazepam but not carbamazepine brought about a dramatic improvement of depersonalization
Sachdev (2002)	Single-case report	Clonazepam (3 mg) plus citalopram (30 mg/day)	1	Substantial improvement
Opioid receptor antagonists				
Nuller *et al.* (2001)	Single-blind, placebo-controlled	Naloxone, single to several intravenous infusions (total dose: 1.6–10 mg)	14	71% of patients experienced a significant reduction in the intensity of depersonalization
Simeon and Knutelska (2005)	Open-label	Naltrexone (100–250 mg)	14	30% mean intensity reduction as measured by three dissociation scales

the effects of cannabis on cognition [21]. In fact, cannabis has been shown to be a potent inducer of depersonalization experiences (see later). Although the main pharmacological effects of cannabis are mediated through cannabinoid receptors, it is known to severely disrupt serotonergic neurotransmission. For example, functional electrophysiological studies have shown that activation of presynaptic cannabinoid CB1 receptors results in decreased 5-HT release in the neocortex [22]. It would seem, in fact, that most of cannabis' effects on cognition and perception are mediated by its disruptive effect on serotonergic neurotransmission [23,24], and it is likely that its ability to induced depersonalization is related to this effect. Matthew *et al.* found that marijuana smoking, but not placebo smoking, was able to produce depersonalization feelings in 62% of 35 healthy subjects [25]. The intensity of depersonalization reached a peak after 30 min and returned to the baseline after 120 min. A comparison of the effects of high- versus low-potency marijuana cigarettes established that the ability of cannabis to induce depersonalization was dose dependent rather than an idiosyncratic response to the drug.

Therapeutic effects of serotonergic antidepressants

Several reports on the use of selective serotonin reuptake inhibitors (SSRIs) on single cases or small series of patients with DPD have suggested that these medications have a promising role in the treatment of DPD. For example, Hollander *et al.* used SSRIs on a sample of eight consecutive patients with long-standing prominent depersonalization symptoms, most of whom met criteria for DPD [26]. The authors noted high levels of comorbidity with anxiety disorders or obsessive–compulsive disorder, and in fact, the presence of either seemed to predict a better response to SSRIs. Other retrospective accounts of the effectiveness of SSRIs on DPD were less conclusive and suggestive of only marginal beneficial effects [10]. Unfortunately, this

initial promise of SSRIs has not been supported by a recent double-blind study, in which fluoxetine was not found to be more effective than placebo in 54 patients with DSM-IV DPD [27]. However, in line with Hollander *et al.,* it was found that those patients with a comorbid diagnosis of depressive or anxiety disorder tended to fare better on fluoxetine than on placebo. Thus, in nine patients who had an additional diagnosis of anxiety disorder, improvement of the anxiety condition was invariably associated with an improvement in depersonalization. However, those experiencing some improvement clarified that the depersonalization had not really changed but that "they seemed somehow to take less notice or be less bothered by them" [27].

In another attempt to test the serotonergic hypothesis of depersonalization, Simeon *et al.* carried out a double-blind, crossover trial to compare the efficacy of clomipramine (a selective serotonin tricyclic antidepressant) and desipramine (a selective norepinephrine tricyclic antidepressant) on eight patients with DPD during an 8-week trial. Of seven subjects who completed the clomipramine phase of the trial, two showed significant improvement in depersonalization. Although one of the latter responded to both medications, she claimed that clomipramine had a more substantial effect on depersonalization [28]. Of interest, none of the responders had depression, but one had a comorbid diagnosis of social phobia.

In view of the above results, it has to be concluded that the use of SSRIs or clomipramine as sole medications is not indicated for the treatment of DPD. It is possible, however, that their use on patients with prominent anxiety and depression symptoms may result in improved tolerance of depersonalization symptoms.

Further support for an underlying relationship between DPD and anxiety disorders comes from anecdotal reports showing that clonazepam, either on its own or in association with SSRIs, has beneficial effects on DPD [29,30]. Stein *et al.* carried out a detailed pharmacological investigation on a patient with a 6-year history of continuous depersonalization (i.e., DPD) and no history of anxiety or affective disorders [31]. A challenge phase of the study revealed that the administration of caffeine, but not of placebo, produced a consistent increase in depersonalization, and also triggered panic attacks which the patient had never experienced before. It was also found that the single-blind administration of clonazepam, but not of carbamazepine, brought about a dramatic improvement of depersonalization. Furthermore, a rechallenge with caffeine while under the effects of clonazepam failed to increase depersonalization intensity [31].

Depersonalization & glutamate

Other researchers have suggested that excitatory amino acids such as glutamate might be relevant in general to the pathophysiology of depersonalization and dissociation [32]. For example, subanesthetic doses of ketamine, whose effects might be mediated through increased glutamate release, can induce many of the subjective experiences characteristic of depersonalization, including a sense of detachment and emotional numbing [33]. Interestingly, a recent functional MRI study found that subjects with ketamine-induced depersonalization showed abnormalities in the processing of emotional stimuli, which were similar to those previously reported in patients with DPD [34]. Thus, subjects with ketamine-induced depersonalization and those with DPD showed a lack of activity in limbic areas and hyperactivity in prefrontal cortical regions that may be important for mood regulation [13,34]. It is believed that ketamine-induced depersonalization is mediated by increased glutamate release in response to NMDA receptor blockade, with a consequent excess of glutamate activity at non-NMDA glutamate receptors [33]. In keeping with this hypothesis, it has been found that pretreatment with lamotrigine, a drug reported to inhibit glutamate release by action at the presynaptic membrane, attenuates the effects of ketamine on conscious experience and cognition [35].

In order to test the hypothesis that depersonalization is glutamate mediated, Sierra *et al.* carried out a small double-blind, crossover, placebo-controlled trial on nine patients with DPD. Unfortunately, the results failed to show any positive effects of lamotrigine when taken as a sole medication [36]. In spite of these negative results, two open-label trials using lamotrigine as an add-on medication with antidepressants, particularly of the SSRI type, suggest that 50–70% of patients with DPD experience varying degrees of improvement [37,38]. Although these two studies did not control for placebo effects, it is worth noticing that double-blind studies have found negligible placebo effects in DPD [27,36]. Such findings suggest that rather than acting on its own, lamotrigine works better as an add-on therapy with SSRI antidepressants. This possibility is not surprising in view of the circumstantial evidence reviewed earlier, which points to an involvement of both serotonergic and glutamatergic mechanisms in depersonalization. If that is indeed the case, it may be that successful pharmacological interventions need to target both neurotransmitter systems. It is clear that these promising results warrant further, more rigorous research.

Depersonalization & the opioid system

Ample evidence supports the view that the endogenous opioid system is involved in the regulation of emotional and behavioral responses to stress [39]. Indeed, activation of this system has been shown to lead to increased pain threshold, suppressed emotional experience and repression of negative affective states [40]. It is believed that a stress-driven activation of the opioid system would have adaptational value through blunting the potentially deleterious effect of aversive stimuli, thus enabling the individual to deal more effectively with adverse situations [41]. From a neurobiological point of view, it has recently been demonstrated that activation of opioid receptors within limbic system structures leads to a marked decrease of blood flow within the same areas [42]. In addition to stress-driven activation of the opioid system, there is also evidence that chronic conditions, such as depression and anxiety disorders, may involve a dysregulation in the opioid system [43,44]. For example, it has been found that patients with panic disorder have abnormally high levels of endogenous opioids in cerebrospinal fluid [44], and that their

concentration increases after the induction of a panic attack with lactate [45]. This panic-induced release of endogenous opioids is potentially relevant to depersonalization given that the latter is itself a prominent and frequent symptom of panic attacks [46]. Moreover, recent findings suggest that the experience of panic is indeed a mediating mechanism capable of triggering dissociative responses during acute trauma [47,48]. Could it be that panic-induced opioid activation may in some circumstances elicit depersonalization symptoms? Interestingly enough, it has been found that exposure to selective κ-receptor agonists reliably elicit depersonalization–derealization symptoms and dysphoria in a dose-dependent manner under placebo-controlled conditions [49,50].

Effect of opioid antagonists on dissociative & depersonalization symptoms

One of the interesting properties of opioid receptor antagonists is that, in the absence of concurrent opioid system activation (e.g., opiate administration or stress), they produce few discernible effects in healthy volunteers [51]. As a corollary, the occurrence of marked behavioral effects following the administration of opioid antagonists may constitute an indirect sign, which suggests underlying opioid activation. In this respect, it is intriguing that opioid antagonists have been found to improve a range of dissociative symptoms in patients from different diagnostic groups. For example, in order to test the hypothesis that emotional numbing is an opiate-mediated phenomenon, Glover administered nalmefene to 18 patients with post-traumatic stress disorder (PTSD), and found that eight showed a marked improvement of this and other dissociative symptoms [52]. A similar, albeit less dramatic, reduction of dissociative symptoms was observed in eight PTSD patients treated with naltrexone [53]. Another study tested the beneficial effect of naltrexone on 18 patients with borderline personality disorder (BPD), and found a marked reduction in both the intensity and duration of dissociative symptoms including depersonalization, emotional numbing and flashbacks [54]. Although the authors did not control for placebo effects, the fact that improvements took a few days to become apparent was interpreted as suggestive of a genuine, rather than placebo, effect. Philipsen *et al.* carried out a placebo-controlled, double-blind crossover study to test the effects of a single dose of intravenous naloxone (0.4 mg) on nine BPD patients whilst in an acute dissociative state [55]. Although most patients showed significant improvement, there were no significant differences between naloxone and placebo.

An interesting feature of depersonalization that may be indicative of an overactive opioid system is the finding of an increased pain detection threshold in patients with chronic depersonalization [56,57], as well as in subjects with hypnotically induced depersonalization [58]. Given that the endogenous opioid system can cause suppression of both emotional and physiological pain in stress-related situations [59], it is tempting to speculate that it could mediate such symptoms in depersonalization. In this regard, Nuller *et al.* tested the hypothesis that long-lasing depersonalization stems from a dysregulation in the opioid system [60]. They carried out a single-blind, placebo-controlled trial with naloxone in 14 patients suffering with long-lasting depersonalization of 1–16 years duration. Six of their patients met the DSM-IV criteria for DPD with no comorbid conditions, while in eight depersonalization existed concomitantly with depression. Naloxone was administered intravenously as a single dose of 1.6–4 mg in 11 patients. Three patients who failed to show any initial response were administered subsequent doses up to a maximum 10 mg. Remarkably, the authors reported that three patients had a complete and lasting remission of depersonalization, while seven experienced significant improvement (>50% symptom reduction on a depersonalization scale). Only one patient showed moderate improvement, while in two it was minimal and short-lasting. Altogether, only one patient failed to experience any kind of symptom amelioration. In summary, 71% of their patients experienced a significant reduction in the intensity of depersonalization. Surprisingly, in most cases, symptom improvement was reported to occur within the first 20–40 min following naloxone administration. In keeping with the hypothesis that depersonalization represents an opioid-driven suppressive effect on the stress response, patients were found to have low basal plasma cortisol levels, which subsequently increased after naloxone administration.

In an attempt to further test the opioid depersonalization-model, Simeon *et al.* carried out an open-label trial with naltrexone on 14 subjects with DPD [61]. Whilst seven subjects received a maximum dose of 100 mg/day for 6 weeks, the other seven went on to receive 250 mg/day for 10 weeks. It was found that three patients reported a marked improvement, with a more than 70% reduction in symptoms. The mean intensity reduction for the whole sample was 30% (as measured by three dissociation scales). Although these results are far less dramatic than those reported by Nuller *et al.* [60], it is worth bearing in mind that naloxone and naltrexone have different pharmacokinetic profiles, which could have an effect on results. Thus, whilst naltrexone is twice as potent as naloxone and has a considerably longer half-life, its bioavailability is more unreliable given that it undergoes a significant first-pass effect and only 5–12% of a dose reaches the systemic circulation [52]. It is clear that more research is needed in this promising area.

Expert commentary

Although depersonalization remains a condition for which no definitive treatment exists, promising lines of pharmacological research have emerged in recent years, and a number of promising drugs have been identified. In keeping with views of depersonalization as a stress-related inhibitory response, it is worth noting that those neurotransmitter systems found to be of relevance to the condition seem to all play important inhibitory functions in the regulation of the stress response. Thus, in addition to the increasingly well-known stress-related modulatory effect of the opioid [59] and serotonergic systems [62], recent research has

identified a glutamate-dependent fronto–limbic inhibitory mechanism on emotional behavior [63]. Indeed, glutamatergic neurons originating in the medial prefrontal cortex are thought to inhibit emotional responses, through NMDA-dependent activation of inhibitory GABAergic neurons in the amygdala.

Five-year view

It is clear that pharmacological research on depersonalization is still in its infancy, and some of the drugs showing promising results in open-label trials need to be tested under placebo-controlled conditions in larger samples of patients. A related and needed research endeavor is to clarify the existence of clinical subgroups of depersonalization, which may show preferential response to some medications. As reviewed previously, it may be that cases with a prominent background of anxiety or obsessions may respond better to SSRIs or clonazepam. Likewise, unpublished anecdotal observations suggests that a subgroup of patients who complained of prominent attentional symptoms, under-arousal and hypersomnia may respond to stimulants such as modafinil [64].

In regards to the search for new pharmacological treatments, two new drugs loom in the horizon as potentially useful: cannabis receptor antagonists and selective κ-opioid receptor antagonists. Indeed, the fact that cannabis can induce depersonalization in a dose-dependent manner would make the cannabinoid CB1 receptor antagonist rimonabant an intriguing research candidate with potential antidepersonalization effects. In line with other depersonalization-relevant neurotransmitters, the endocannabinoid system is currently thought to play a role in the modulation of emotional processes, and particularly in the mediation of adaptive responses to unavoidable stressful stimuli [63]. Current research in rodents has shown rimonabant to have anxiolytic properties and to improve the deleterious effects produced by chronic stress [65].

In view of the promising results with opioid antagonists, it is worth bearing in mind that while the induction of depersonalization is exclusive to κ-agonists, all of the antagonists tested to date are nonspecific and with a preference for μ-receptors at low doses. Although κ-opioid antagonists have not yet been developed for human use, it is likely they will become available in the next few years [66].

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Key issues

- Depersonalization disorder (DPD) is a distressing and often disabling condition, which follows a chronic and persistent course.
- Recent epidemiologic studies show the prevalence of DPD in the general population to be between 0.8 and 2%.
- Neuroimaging and psychophysiological studies have detected anomalous brain activation to emotional stimuli, which is inline with views that depersonalization is generated by a threat-triggered fronto–limbic inhibition on emotional processing.
- DPD is highly resistant to pharmacological treatments, and conventional medications, such as antidepressants or antipsychotics, have been found to be of little value.
- Open-label trials suggest that lamotrigine as an add-on medication with selective serotonin reuptake inhibitor (SSRI) antidepressants is a useful treatment option in some patients.
- The use of clonazepam as an add-on medication with SSRIs, appears useful, particularly in patients with prominentbackground anxiety.
- A few promising studies show the use of opioid receptor antagonists to be beneficial to at least a subgroup of patients.
- The recent availability of cannabis receptor antagonists, as well as the ongoing development of selective κ-opioid antagonists, might constitute new promising research areas for future therapeutic developments.

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