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Case Report

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New Treatment's Strategies of Dissociative Symptoms in Bipolar Disorder

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Abstract

Depersonalization (DP) and derealization (DR) are experiences in which the individuals feel respectively a sense of unreality and detachment from him/herself, then an alteration in the perception of the reality of the external world is lost. These conditions may be detected both in healthy and pathological conditions, but the prevalence and clinical correlates of dissociative symptoms in bipolar disorder have received limited attention in literature. Moreover, this association is often underdiagnosed or misunderstood. Four different case reports of bipolar patients with different expressions of derealization and depersonalization symptoms are explained. We underline the difference clinical presentation and the impact of dissociative symptoms and we suggested four different line of treatment. The aim of this study is to discuss new treatment possibilities of derealization and depersonalization in bipolar disorder.

Keywords: *"Bipolar disorder" OR/AND "depersonalization disorder" OR/AND "drug", "pharmacotherapy" OR/AND "medication", OR/AND "treatment", OR/AND "atypical antipsychotics".*

Introduction

Depersonalization (DP) and derealization (DR) are experiences in which the individuals feel respectively a sense of unreality and detachment from him/herself, then an alteration in the perception of the reality of the external world is lost. These conditions may be detected in healthy individuals often under condition of stress, fatigue or drug abuse, and has been described in a number of psychiatric (panic disorder, major depression, posttraumatic stress disorder, schizophrenia, bipolar disorder) and neurological conditions (migraine, epilepsy, etc.). Dissociative disorders are often studied through psycho-trauma issues and literature is rare on affective illness comorbid with dissociative disorders (Mula M et al., 2009; Montant J et al., 2014). In surveys conducted among non-clinical respondents lifetime prevalence of DP and DR symptoms were found between 31 and 66% compared to a lifetime prevalence of DP and DR symptoms in psychiatric settings of 42 to 91% (Hunter et al. 2004b). In our precedent study we suggest that lifetime prevalence of dissociative symptoms in bipolar disorder (BD) was 25.6% in BDI, 25% in BDII, and we highlight the link between BD and dissociative disorders (Mula M et al., 2009). Moreover, comorbidity often refers to an early onset subtype with also comorbid panic and DP-DR disorder (McKinnon DF et al., 2006; Montant J et al., 2014). Besides, unipolar patients suffering from dissociative symptoms have more often cyclothymic affective temperament (Montant J et al., 2014), as well as cyclothymic bipolar II patients, who are often misclassified as borderline personality disorder because of their extreme mood instability (Perugi G et al., 2002), present DP symptoms.

DP and DR are very common in BD and may represent a clinical index of disease severity, poorer response to treatment and high level of comorbidity, in mood and anxiety disorders (Mula M et al., 2007). Moreover high levels of anxiety inside DP disorder seem characterised by additional non-specific perceptual symptoms. Despite DR and DP are little studied in BD forms, the presence of these symptoms is far from absent.

DP 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 (Sierra M, 2008). Historical reports in the treatment of DP refer the use of amphetamines like methylphenidate (Foguet et al. 2011), antipsychotics (Ackner 1954; Shorvon 1946), atypical antipsychotics like clozapine (Nuller 1982), barbiturates, benzodiazepines like phenazepam (Nuller 1982) and clonazepam (Stein & Uhde 1989), tricyclic anti-depressants like desipramine (Noyes et al. 1987), clomipramine (Simenon D et al, 1998) and imipramine (Hollander E et al., 1989), Selective Serotonin Reuptake Inhibitors like fluoxetine (Fichtner et al. 1992; Ratliff & Kerski 1995) and buspirone (Abbas et al. 1995), SNRIs like venlafaxine (Preve et al. 2011), a combination of benzodiazepines and serotonergic activity drugs like citalopram- clonazepam (Sachdev 2002), anti-convulsants like lamotrigine (Sierra et al. 2006; Aliyev NA et al., 2011), opiate antagonists like naltrexone (Ginsberg 2005). Several small open-label studies have also been conducted. The aim of this study is to discuss a possible neurobiological mechanism of DP and new pharmacological approaches, in particular atypical antipsychotics augmentation of lamotrigine, of DR and DP in BD patients.

Method

Literature Review

We conducted a systematic literature review with the principal scientific databases (PubMed, Embase, PsycINFO, MEDLINE) including papers, papers containing case reports of patient with DP and/or BD, all articles written and published in English between 1954 and 2015 were included. The key words or terms included in this search were: "Bipolar disorder", "depersonalization disorder", "derealization",

"depersonalization", "dissociation", "therapy", "drug", "pharmacotherapy" "medication", "treatment", "atypical antipsychotics", "antidepressant", "benzodiazepine", "neuroleptics", "mood stabilizer".

Case Reports

Four inpatients presenting with BD and DP were assessed with the SCID-P for Axis I diagnosis. As regards psychopathological evaluation, the patients were also administered the Structured Clinical Interview for Derealization and Depersonalization Spectrum (SCI-DER), the Depersonalization Severity Scale (DSS) for dissociative spectrum symptoms, the Hamilton Rating Scale for Depression (HRSD) to quantify depressive features as well as the Young Mania Rating Scale (YMRS) to measure manic symptoms. We assessed the patients at the first visit, at 1 month, 2 and 6 months. All patients received a neurological and general medicine review as well as a first-level brain imaging examination (CT and/or MRI).

Case 1: a 26-year-old white Caucasian gentleman developed depressive mixed phase characterized by sadness, anhedonia, psychomotor retardation, cognitive impairment with lack of attention, insomnia, with concomitant persistence dissociative symptoms (derealization, affective and autopsychic depersonalization). The patient had previous personal or family history of mental illness (bipolar disorder) and had not for substance abuse, neurological and general medicine review, Electro Encephalo Gram (EEG) as well as Brain CT were negative; she was treated with ziprasidone (40 mg) augmentation of lamotrigine (100 mg).

Case 2: a 32-year-old white Caucasian lady developed depressive mixed phase characterized by asthenia, apathy, psychomotor activation, insomnia, lack of libido, anxiety with depersonalization symptom (derealization and somatopsychic depersonalization). The patient had no previous personal or family history of mental illness and substance abuse. Neurological and general medicine review, Electro Encephalo Gram (EEG) as well as Brain MRI were negative; she improved with brexpiprazole (2 mg) augmentation of lamotrigine (100 mg).

Case 3: a 38-year-old white Caucasian Lady developed depressive mixed phase characterized by sadness, asthenia, anhedonia, psychomotor retardation, cognitive impairment with rapid thoughts, lack of attention, logorrhoea, insomnia, in association with a Depersonalization disorder. The patient had previous personal or family history of mental illness (bipolar disorder in mother and father line) and had for substance abuse (cocaine); neurological and general medicine review, Electro Encephalo Gram (EEG) as well as Brain CT were negative; she was treated with aripiprazole (5 mg) augmentation of lamotrigine (100 mg).

Case 4: a 33-year-old white Caucasian Lady present an agitated depression characterized by asthenia, sadness, reduction of the energy, agitation, anxiety, panic attack, insomnia, lack of libido, cognitive impairment with depersonalization symptom (derealization, autopsychic and affective depersonalization). The patient had previous personal or family history of mental illness (bipolar disorder in mother line) and substance abuse (alcohol and cocaine). Neurological and general medicine review, Electro Encephalo Gram (EEG) as well as Brain MRI were negative; she improved with lurasidone (80 mg) augmentation of lamotrigine (150 mg).

During the hospitalization we assessed DP and DR symptoms as well as the reduction of the dissociative severity in all the patient after the introduction of the different atypical antipsychotics. These patients were followed for 6 months after the discharge from our Award and there were no mood switching as well as side effects. DP symptoms improved during the hospitalization and we observe a progressive improvement of these symptomatology after the discharge. Atypical Antipsychotics augmentation of lamotrigine was accompanied by a good response and resolution of dissociative symptoms over the next six months in the four case reports reported.

Discussion and conclusion

Sierra and Berrios (1998) postulated an interesting similarity between the sensory–limbic disconnection syndrome as defined by Geschwind (1965a,b), that is well characterized in some animal models (Downer, 1961), and the neurobiology of DP. According to their model, DP results from the combination of two mechanisms: an inhibitory component mediated by left-sided MPC hyperactivation that inhibits amygdala and indirectly the ACC (with a functional sensory– limbic disconnection) and an excitatory component driven by uninhibited amygdala circuits controlling both cholinergic and monoaminergic ascending arousal systems leading to the activation of the right prefrontal cortex (with a state of vigilant attention) (Fig. 1).

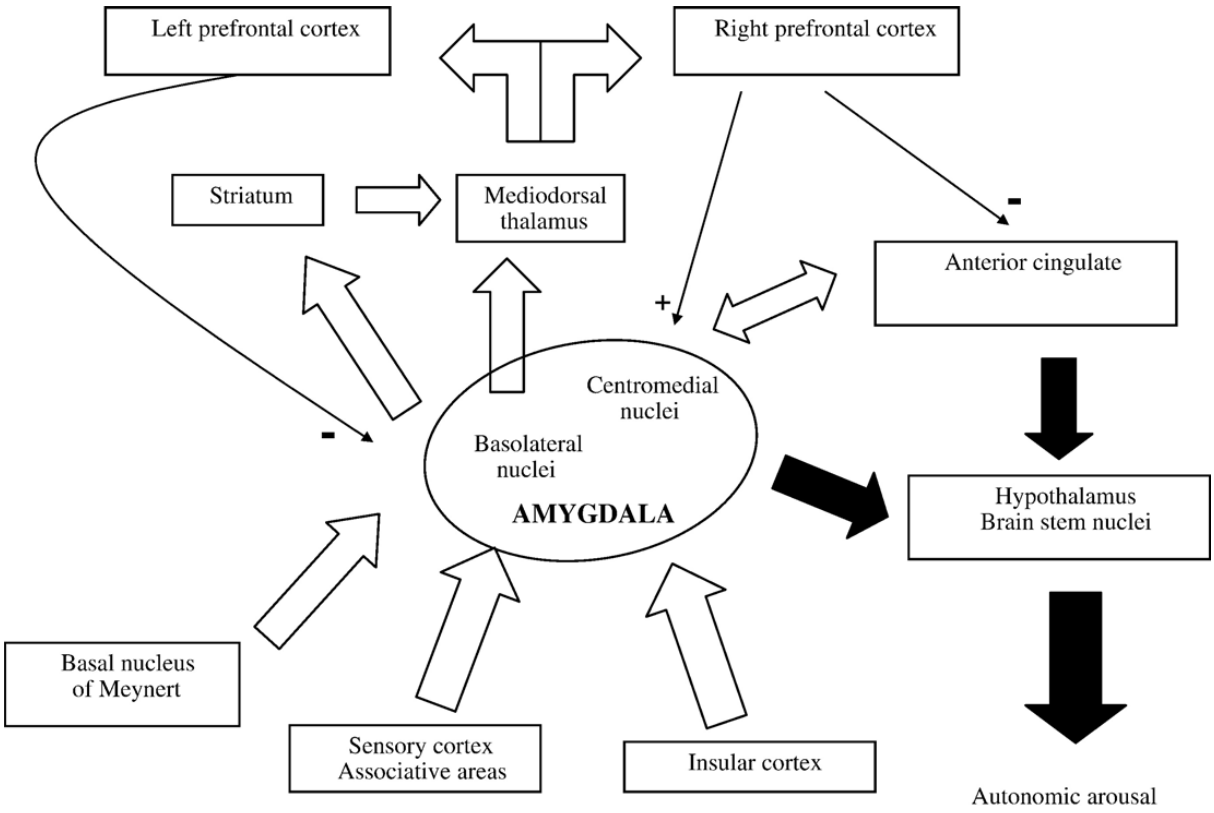

Fig. 1: A possible neurobiological model of depersonalization. Bold arrows represent disconnected pathways by left prefrontal cortex hyperactivation(modified from Sierra and Berrios, 1998).

A neurobiological model of DPD has also been proposed (Sierra M et al.,1998), hypothesizing dysfunctionally increased fronto-insula/limbic inhibitory regulation. This model is consistent with neurological case studies (Sierra M et al., 2002) and has been refined by neuroimaging research using fMRI (Phillips ML et al., 2001; Medford N et al., 2006), which has demonstrated reduced insula, limbic and visual association cortical activation in response to emotive pictures, and increased VLPFC activation. A Functional magnetic resonance imaging (fMRI) study has pointed to ventrolateral prefrontal cortex (VLPFC) inhibition of insula as a neurocognitive correlate of the disorder (Jay EL et al., 2014).

Treatment recommendations and guidelines for DP disorder have not been established and no studies specifically investigated the role of pharmacotherapy in ameliorating DP symptoms in mood and anxiety disorders. Only for lamotrigine were more consistent result about the efficacy to treat depersonalization. (Sierra m, 2008; Aliyev NA et al., 2011)

The use of atypical antipsychotics in addition to lamotrigine, only drug with proven efficacy in the treatment of depersonalization, (Sierra M, 2008) in these four case reports was accompanied by a good response, resolution and better clinical outcome of dissociative symptoms over the next six months and after the suspension of lamotrigine in the next 6 months.

Aripiprazole, brexpiprazole, lurasidone and ziprasidone have a relevant 5HT$_{1A}$ partial agonism, and the activation of 5-HT$_{1A}$ improve the release of dopamine in medial prefrontal cortex, striatum and hippocampus (Li Z et al., 2004; Bantick RA et al., 2005; Pau Celada, M. et al., 2004), like antidepressants such as MAOIs and TCAs, SSRIs, lithium, valproate, all increase postsynaptic 5-HT$_{1A}$ signaling, either through direct or indirect mechanisms in humans (Savitz J, 2009).

The efficacy of atypical antipsychotics in bipolar disorder is now a mainstay in the international guidelines for treatment of bipolar disorder, and it seems that the addition of atypical antipsychotics to lamotrigine (only drug with proven efficacy in the treatment of depersonalization) lead to a resolution of dissociative symptoms, most likely due to stimulation of serotonin, like happens with aripiprazole (Uguz F et al., 2014).

The 5-HT1A receptor is a subtype of serotonin receptor located in presynaptic and postsynaptic regions. Activation of this receptor is invoved in anxiolotic, antidepressant and antipsychotic medication. It is possible that partial agonism at the 5-HT$_{1A}$ receptor has been postulated as a potential therapeutic mechanism in the alleviation of depression, anxiety, negative symptoms, and extrapyramidal side effects (Millan MJ, 2000). Postsynaptic 5-HT$_{1A}$ receptors are found in those regions of the brain that are implicated in the control of mood, cognition and memory. It has become clear that these receptors can be a useful target in the management of various neuropsychiatric disorders (Newman-Tancredi a et al., 2011). Moreover, the serotoninergic potentiation resulted in an improvement of dissociative symptoms and the blockade of postsynaptic 5-HT$_{1A}$ receptors may impart complementary anxiolytic properties and, in analogy to stimulation of 5-HT$_{1A}$ autoreceptors, facilitate cortical and hippocampal glutamatergic and, possibly,

cholinergic activity (Millan MJ, 2000; Uguz F et al., 2014). Modulation of cholinergic function by serotonin due to 5-HT1a receptor, establish the connection between hippocampal dependent memories and It will then focus on a brain region and a neuropharmacological substrate that have been poorly studied as regards serotonergic modulation of memory functions, namely the medial septum and its 5-HT(1A) receptors. Based on recent findings of our laboratory, we suggest that these receptors, located on both cholinergic and GABAergic septal neurons, take part in a mechanism that controls encoding, to some extent consolidation, but not retrieval, of hippocampal-dependent memories. (Jeltsch-David).

The interconnection of different brain area plays a role in the clinical presentation of DP and DR symptoms in BD and, 5-HT_{1A} receptors regulate and modulate gabaergic, cholinergic, glutammaergic, and dopaminergic as well as serotoninergic function. All the different system and pathway are interconnected to develop the dissociative experiences, and in particular the stimulation of 5-HT1A receptors could activate the firing of Dopamine from the cortex, improve cholinergic function in memory process, re-establish normal monoaminergic function. It is therefore crucial to achieve the right balance of agonism at both pre and post synaptic $5HT_{1A}$ receptors in order to obtain the desired effect (Schatzberg and Nemeroff, Book), in order to obtain the resolution of DP and DR symptoms.

Further research is warranted to replicate our clinical observations and, in general terms, controlled studies are needed to confirm the efficacy of this treatment.

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