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Moderators and mediators of antipsychotic response in delusional disorder: Further steps are needed

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Abstract

Delusional disorder (DD) has been traditionally considered a relatively rare and treatment-resistant psychotic disorder. In the last decade, increasing attention has focused on therapeutic outcomes of individuals affected by this disorder. The aim of this paper is to provide a synthesis of the literature addressing two very important questions arising from DD research: (1) For which patients with DD do antipsychotic medications work best (the moderators of response); and (2) What variables best explain the relationship between such treatments and their effectiveness (the mediators of response). We searched PubMed and Google Scholar databases for English, German, French and Spanish language papers published since 2000. We also included a few classic earlier papers addressing this topic. Variables potentially moderating antipsychotic response in DD are gender, reproductive status, age, duration of illness, the presence of comorbidity (especially psychiatric comorbidity) and its treatment, brain structure, and genetics of neurochemical receptors and drug metabolizing enzymes. Antipsychotic and hormonal blood levels during treatment, as well as functional brain changes, are potential mediating variables. Some, but not all, patients with DD benefit from antipsychotic treatment. Understanding the circumstances under which treatment works best can serve to guide optimal management.

Key words: Delusional disorder; Psychosis; Moderators; Mediators; Antipsychotic response

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Core tip: Although patients with delusional disorder have traditionally been viewed as treatment-resistant, many do experience benefits from antipsychotic medications, but not all respond similarly. The identification of mediators and moderators of treatment

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response is clinically useful in that understanding under what circumstances treatment works best provides a reliable guide to effective management.

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INTRODUCTION

Delusional disorder (DD) is defined in DSM-5 as a psychotic disorder characterized by the persistence, for at least one month, of one or more delusions that do not markedly impair personal, social or occupational function and that are present independently of schizophrenia, affective disorder or substance abuse disorder^[1]. The disorder is characterized by a high prevalence of psychiatric morbidity. Delusional beliefs in this condition are encapsulated and usually monothematic; they lack the bizarreness of delusions found in schizophrenia^[2]. The various commonly seen delusional themes designate subtypes of DD - *e.g.*, erotomania, grandiosity, delusional jealousy, paranoia, and somatization^[3]. DD has been widely considered a relatively rare disorder with a cited lifetime prevalence of 0.02%^[1,4]. It is a disorder that starts relatively late in life; the mean onset age is 40, but this ranges from 18 to the nineties. The disorder is somewhat more common in women than in men^[5,6]. The individual's ethnic and religious background is an important consideration when making a diagnosis; it determines whether a strongly held irrational belief is a delusion or a traditional mindset.

DD has been described by Kendler^[7] as an inherently treatment-resistant disorder but others have challenged this view, attributing most of the failure to respond to treatment to widespread non-adherence. Individuals with this disorder characteristically do not see themselves as ill, and, therefore, often do not take prescribed drugs^[8-10].

As in other diseases, there has been a growing interest in the field of DD studies to enable the monitoring of both adherence and response to therapeutic drugs^[11]. However, to the best of our knowledge, to date, no clinical trials have been conducted on the effectiveness of currently used medications, which renders specific treatment recommendations impossible to make at this time^[10]. Only one randomized controlled trial of treatment effectiveness exists in DD and this has evaluated a psychotherapeutic approach rather than a pharmacological one. The trial evaluated group cognitive-behavioral therapy *vs* supportive group therapy conducted over a 24-wk period^[12]. Cognitive-behavioral therapy proved to be more effective than the control measure on 3 of 7 dimensions of the Maudsley Assessment of Delusion Schedule, but the participant sample was very small (12 participants per group).

One problem in investigating treatment outcomes in DD is the lack of consensus on the definition of antipsychotic response as it applies to this disorder^[13]. Different investigators use different definitions of response and many base their judgement solely on a clinical evaluation, which is, by its nature, necessarily subjective. Cut-off points on assessment scales are sometimes used, but the scales differ^[14]. Adding to the problem is the difficulty of accurately assessing issues of adherence^[11,15].

Despite difficulties in evaluating treatment outcomes, most reports agree that response is variable and heavily dependent on patient factors, such as adherence to the prescribed regimen^[16].

Patient pre-existing characteristics that influence response are referred to as moderators. Several have been suggested in the context of DD. Identifying a moderator helps to determine when and under what conditions treatment is most effective, and for whom^[17-19]. In contrast, a mediator, or intervening variable, is one that can alter the relationship between the independent and dependent variables, in this case, antipsychotic treatment and outcome^[18,19]. Moderators are in place before treatment begins. Mediators mediate the process during treatment. Moderators of treatment efficacy are inherent in the patient or the patient's environment. Mediators of treatment efficacy are measurable changes in the patient that occur during the course of treatment^[20] (Figure 1).

Moderators and mediators of an intervention are important to identify. They have

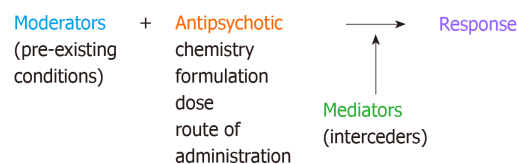


Figure 1 Moderators and mediators.

never been reported for DD but have been specifically addressed in other psychiatric domains, for instance, in affective disorders and substance abuse^[21-23].

Specifying moderator and mediator factors in DD clarifies such questions as: For whom do available treatments work, how do they work, and when do they work.

LITERATURE SEARCH

We searched PubMed and Google Scholar databases for English, German, French and Spanish language papers published since 2000 that pertained to the role of moderators and mediators of antipsychotic response in DD. Several thousand abstracts were initially screened. Most were excluded because, although they addressed predictors, mediators, and moderators of antipsychotic response, they did so for schizophrenia only. In the end, by consensus, 40 primary articles were selected as relevant to our goals. These included a few classic earlier papers on the topic that we considered to be still relevant. For purposes of comparison, additional papers addressing moderators/mediators in psychoses other than DD were also included. After the screening and selection process, the collected information was divided into the following sections: (1) Moderators of treatment response in DD; and (2) Mediators of treatment response in DD.

MODERATORS OF TREATMENT RESPONSE

In other psychotic disorders, moderating variables, or pre-treatment characteristics of patients that predict response to drugs, have included gender, reproductive status, age at treatment, duration of illness, psychiatric comorbidity, abnormalities of brain structure or function, aberrant biochemistry, and gene variants, especially those coding for neurochemical receptors and drug metabolizing enzymes (Table 1). In DD, consideration of moderating variables involved in antipsychotic response has not been previously attempted.

Gender and hormonal status

There is a literature on gender differences in DD. As part of the Halle Delusional Syndromes Study, Wustmann *et al*^[24] investigated gender-related features of DD in a carefully diagnosed sample of 43 inpatients (22 men and 21 women) consecutively admitted to one hospital over a long period of years. Thirty-three patients were re-interviewed from 3 to 24 years after the onset of their symptoms. Gender distribution in this sample was almost equal; age of onset was significantly later in women; the diagnosis persisted in women whereas, in a third of the men, it was changed to schizophrenia over time. Women were more compliant with treatment and, thus, received medication more often than men. Paradoxically, while over 80% of the women remained unremitted at follow up, this was true for only half of the men. The authors concluded that DD in women is more severe and more persistent than in men, but this study does not directly address the effect of gender on treatment response^[24].

Román Avezuela *et al*^[25] investigated gender differences in DD in a sample of 50 first admission inpatients. All were diagnosed according to DSM-IV criteria and were retrospectively evaluated by review of medical records, the OPCRIT 4.0, and a symptom inventory specially designed for the study. The proportion of women to men was 1.27:1. As in the Wustmann *et al*^[24] study, the age of first admission was higher in women. Men misused substances more than women and women suffered depression more often than men. Men were more likely to present with grandiose, jealous or persecutory delusions whereas women more frequently had erotomaniac delusions. No gender differences in the course of illness were observed but, again, treatment response was not directly examined^[25].

These two studies yielded some similar and some contradictory results, which is to be expected because sample sizes were small and methodologies differed. Even with

Table 1 Potential moderators and mediators of antipsychotic response in delusional disorder

Moderators	Mediators
Gender	Antipsychotic plasma concentrations
Reproductive status	Blood flow to brain
Age	Brain glucose metabolism
Comorbidity	Dopamine receptor occupancy
Brain lesions	Estrogen levels
Genetic factors	
D2 receptor genes	
Metabolizing enzyme genes	

identical methodology, results of gender studies can easily diverge because a variety of potential moderating variables differ by gender, comorbid substance use and treatment adherence for instance, and this can skew group gender response in opposing directions depending on the composition of the sample^[5].

In patients with psychoses other than DD, women have been observed to respond more robustly to antipsychotics than men, but only during their reproductive years^[26,27]. This has been attributed to estrogens potentiating treatment response^[28-30], a potentiation that has been shown to end at menopause^[31]. DD begins relatively later in life than schizophrenia so that most women with this disorder cannot count on circulating estrogens to assist with antipsychotic response. In fact, the drop of estrogen at menopause may be what determines the higher prevalence of DD in women than in men^[6].

When studies that control for potentially confounding factors are conducted in DD, it seems likely that gender will prove to be a moderator of antipsychotic response, as it is in other psychoses.

Age

Age is known to moderate antipsychotic response in many psychotic illnesses. Both age at treatment and also age at onset of illness, often a proxy for illness duration, can impact therapeutic outcomes in psychosis.

Mangoni *et al*^[32] have highlighted a person's age at treatment as a moderator of medication response. Age changes the bioavailability, distribution, metabolism and elimination of drugs. As people age, there is a gradual reduction in renal and hepatic clearance, as well as a relative increase in the volume of drug distribution^[33]. The net effect for lipophilic drugs such as antipsychotics is a tendency for drug accumulation in lipid stores^[34], which can lead to drug toxicity. Toxic drug levels impair subsequent adherence, thereby undermining treatment effectiveness. To date, no studies have specifically investigated the impact of age at treatment on therapeutic outcomes in DD. Conclusions can only be inferred from studies in schizophrenia populations and from other pharmacological research in aging populations.

Age at onset of illness has been considered a moderator of antipsychotic response in schizophrenia^[35]. Usually, the younger the onset, the more severe the illness, which equates with poor response to treatment^[35]. With respect to DD, the severity of symptoms has not generally been seen as varying with onset age although the results of the Wustmann *et al*^[24]'s study do suggest that later onset correlates with symptom severity. DD almost always starts relatively late in adult life when the physiological and psychological process of aging and age-related co-morbidities make recovery from any illness increasingly challenging. This undoubtedly contributes to the generally poor antipsychotic response in DD. It is possible that larger samples will, nevertheless, find that, here too, younger onset correlates with illness severity. Young onset age usually means longer duration of illness at the time of ascertainment. In most illnesses, long untreated duration makes recovery less likely^[36], but the relevant studies in DD have not been done. Interestingly, DD subtypes seem to differ with respect to age at onset. Out of 51 outpatients diagnosed with DD at one psychiatric clinic, the persecutory subtype showed the oldest onset age while the youngest onset age was associated with the somatic subtype^[37].

In general, age, whether at the time of treatment or at the time of onset of symptoms, is a powerful moderator of treatment outcome in psychosis^[38] and may prove to be so in DD as well.

Comorbid psychiatric disorders

It is known that patients with DD suffer from many psychiatric comorbidities,

especially depressive disorders^[39]. Mood disorders are reportedly seen in one half of patients with DD^[40].

Maina *et al*^[39] investigated the occurrence and clinical correlations of comorbid psychiatric diagnoses in 64 patients with DD. Patients with one comorbid psychiatric disorder (as compared to those with no co-morbidity) showed an earlier age of DD symptom onset, came to psychiatric attention at an earlier age, and were, as a group, younger. Antipsychotic response was, however, not evaluated^[39]. Other research groups have confirmed the extent of comorbidity in DD. In a study of 86 outpatients with DSM-IV DD, and using the Mini International Neuropsychiatry Interview as a diagnostic tool, de Portugal *et al*^[40] found that 46.5% of study participants suffered from at least one additional lifetime psychiatric diagnosis, depressive disorder being the most common one. This is in agreement with Marino *et al*^[41] who reported that, in 42% of 67 patients with DD (44 women and 23 men), a mood disorder had preceded the onset of DD.

Substance abuse may also precede DD. Román Avezuela *et al*^[25], in the study referred to earlier, showed that men frequently suffered from alcohol or cannabis dependence at least one month prior to the diagnosis of DD. Depression and substance abuse comorbidity are both associated with a worse prognosis in DD^[25,41], especially if the comorbid condition precedes the onset of DD symptoms.

In psychotic illness in general, substance abuse is a frequently seen secondary condition^[42,43], a way, some have speculated, of coping with disturbing thoughts or with medication side effects. In one study from India, 11 out of 13 first episode, drug-naïve DD patients from a tertiary care center were found to suffer from at least one psychoactive substance use disorder^[43]. Since these patients were unmedicated, the substances were probably used to drown out disturbing thoughts, although it is also possible that the effect of early onset substance use may have contributed to the induction of DD.

The connection between comorbid psychiatric diagnoses and antipsychotic treatment response has not been sufficiently investigated in DD. When it is, it may prove to significantly moderate antipsychotic response, as it does in related illnesses.

Brain changes on neuroimaging

Structural and functional brain changes have been reported in neuroimaging case studies of patients with DD^[44], giving rise to the possibility that such changes may moderate treatment response.

In 1989, Miller and co-workers carried out a prospective study on a sample of patients with late-life onset psychosis. Five patients (3 diagnosed with DD, 1 with schizophrenia, and 1 with bipolar disorder) underwent either magnetic resonance imaging or computed tomography. The investigators found that multiple lacunar infarcts were associated with poor neuropsychological performance and non-response to treatment. They suggested that the presence of brain structural lesions could predict treatment response^[45]. A similar correlation between brain lesion and treatment failure has been seen in schizophrenia^[46,47]. Freudenmann *et al*^[48] have reported fronto-striato-thalamo-parietal network lesions that correlated with antipsychotic response in one patient with delusional parasitosis.

Other neuroimaging studies in DD, however, have been unable to show a correlation between brain structure and therapeutic response^[49,50]. Howard and collaborators, for instance, found that lateral ventricle volumes in DD were greater than in schizophrenia, but they could not show an association between this finding and response to antipsychotic medications^[50].

As of now, it is unclear what brain lesion, if any, predicts antipsychotic response in DD patients.

Biological factors: Biochemistry and genetics of receptors and enzymes

Hyperdopaminergic states have been implicated in many psychoses^[51], buttressed by the fact that all antipsychotic drugs currently in use block D2 dopamine receptors, as elucidated by the pioneering work of Philip Seeman^[52] and reconfirmed many times over the years^[53,54]. Since one-third of patients with schizophrenia show poor response to available antipsychotics, the implication is that the dysregulation of other neurochemical pathways (serotonergic, cholinergic, glutaminergic) may also, to varying degrees, lead to psychosis^[55-58].

Morimoto *et al*^[59] investigated the relationship between antipsychotic response, plasma homovanillic acid (pHVA), dopamine receptor (DR) genes and tyrosine hydroxylase (TH) in 57 patients with DD, 48 patients with schizophrenia, and 48 healthy controls. DD patients homozygous for the Ser9Ser dopamine D3 receptor (DRD3) genetic variant showed higher pretreatment levels of pHVA, *-i.e.* higher dopamine function, than heterozygous (Ser9Gly) patients. The pHVA level fell (by nearly 30 pmol/mL) after 8 weeks of treatment with the antipsychotic, haloperidol,

suggesting that polymorphisms in the DRD3 gene can moderate response to antipsychotics.

It has been reported that genetic variants of cytochrome P450 enzymes responsible for antipsychotic drug metabolism either raise or lower antipsychotic plasma levels of specific drugs, and can thus contribute to treatment response^[60]. Recent work has investigated the benefits of pharmacogenetics in maximizing antipsychotic treatment effectiveness in psychosis. The study sample included 58 patients with DD. When dose adjustments were made to antipsychotic drugs according to the presence of relevant polymorphisms in CYP1A2, CYP2C19, CYP2D6 and CYP3A5 enzymes, an improved symptom response was expected. Unfortunately, this was not found^[60]. Genetic variants of CYP2D6 enzymes have been able, however, to predict which doses of which drugs result in side effects^[61].

Subtherapeutic plasma levels of antipsychotics, attributable to activity differences in CYP enzymes (among other factors that occur during the course of treatment), are held to be a major cause of treatment resistance in most psychoses^[62]. The investigation of genetic variants of genes encoding for cytochrome P450 enzymes has revealed that some patients are fast or ultra-fast metabolizers, while others metabolize drugs much more slowly. Speed of metabolism affects serum concentration and subsequent entry into the brain.

Therapeutic drug monitoring is a promising new area in DD. As early as 1998, Silva and co-workers explored the effect of giving pimozide at increasing doses to 7 patients with DD over a 6-wk period. Pimozide levels and psychopathology scores as per the Brief Psychiatric Rating Scale (BPRS) were assessed every week^[63]. Had some patients improved, this study could have yielded a plasma concentration/therapeutic response index. Unfortunately, pimozide had no effect on any dimension of the BPRS, although pimozide levels confirmed that patients were taking their medication.

Therapeutic effectiveness can, as mentioned earlier, be defined in a variety of ways. Herbel and Stelmach conducted a study where they defined effectiveness as the restoration of decisional competence in previously incompetent patients with DD^[64]. This outcome was determined in their study by retrospective chart review. Where the plasma level of haloperidol was done (only one case), a low level (2.9 ng/mL) was associated with failure to achieve competence.

More recently, antipsychotic plasma concentrations obtained by high-performance liquid chromatography in 27 patients with DD and 27 patients with schizophrenia were used to examine treatment both adherence and response^[65]. The association between antipsychotic response and plasma levels of antipsychotics could not be determined, however, due to the naturalistic design, the several antipsychotics with which patients were treated, and the relatively small sample size^[65].

The serum concentration of a drug is affected, of course, by more than genetic variants of metabolizing enzymes. Given strict adherence to a prescribed regimen, it is primarily determined by drug dose, but also by route of administration, by liver and kidney health, volume of distribution, and by interaction with concomitant drugs, tobacco, and the ingestion of specific foods^[66]. Some of these factors are moderators of response; some are mediators.

Available evidence from patients with other psychoses^[62,67,68] suggests that the determination of plasma drug concentrations, especially when the antipsychotic in question is clozapine, is very useful in predicting treatment outcome. If, in the future, antipsychotic plasma concentration are linked to response in DD, then genetic variants of cytochrome P450 enzymes that help to determine antipsychotic blood levels will be categorized as moderators of response, as they are in other psychoses.

MEDIATORS OF TREATMENT RESPONSE IN DD

Several mediators of response (factors that emerge from the interaction of patient and antipsychotic treatment) have been identified in patients with DD: Antipsychotic drug levels, functional changes in the brain, and hormonal levels (see [Table 1](#)).

Plasma level of the drug

As mentioned, and as is well known, the blood level of an antipsychotic drug predicts how much of it will enter the brain and, thus, how effective it will be at its target site. Blood level is determined by many factors, some of which are moderators (genetics of metabolizing enzymes, genetics of drug receptors, genetics of body mass, genetics of liver and kidney health) because they characterize the person prior to treatment, and some of which are mediators because they occur during treatment (drug dose, route of administration, smoking status, concomitant drugs, ingestion of certain foods such as grapefruit, which can raise the blood level of some drugs and lower the level of

others).

As described earlier, plasma levels of antipsychotics have been examined in DD but it has not yet been possible to correlate them with treatment response.

Functional brain changes during treatment

In schizophrenia, many investigations have been conducted into the relationship between changes in regional blood glucose metabolism (measured by single-photon emission tomography - SPECT) and clinical response to antipsychotic treatment. Cerebral blood flow (CBF) to different regions of the brain has also been studied in a variety of patients undergoing treatments with antidepressants, antipsychotics, and electroconvulsive therapy^[69-73].

In DD, specifically in delusional parasitosis, cerebral blood flow changes before and after successful treatment with antipsychotics have also been reported. Narumoto and colleagues described the case of an 82 year old man who had had symptoms of delusional parasitosis for 5 years beginning one month after he suffered a stroke in the right temporoparietal region of the brain^[74]. Cerebral blood flow in the patient was assessed at baseline by SPECT and again after 6 weeks of risperidone therapy, by which time the patient had fully recovered from his delusional symptoms. At baseline, there was a global decrease of CBF, which the investigators attributed to the influence of the prior stroke. Post-treatment SPECT, however, showed a marked increase in regional cerebral blood flow (rCBF) in bilateral frontal and left temporoparietal regions. The decreased rCBF in the right temporoparietal region remained unchanged. Increased blood flow to large brain regions other than the lesion area seems to have mediated the improvement of clinical symptoms^[74].

Freudenmann *et al*^[48] described another case of a 27 year old woman with delusional parasitosis who was treated with aripiprazole. She achieved full remission when dopamine 2 receptor occupancy reached 63%-78% occupancy, as measured by photon emission tomography^[48]. Using SPECT, cerebral glucose metabolism was also investigated in this patient. Before treatment, glucose metabolism in the thalamus and putamen was left dominant. This remained unchanged after treatment.

Although only individual case reports exist at this time, functional neuroimaging changes may prove, in the future, to be quantifiable mediators of antipsychotic response in DD (Table 2).

Changes in hormonal levels

In other psychoses, various hormonal levels have been investigated as potential mediators of treatment response. Many preclinical, clinical and epidemiological studies have concluded that elevated estrogen levels are neuroprotective in psychosis^[75-78], which would partly explain why schizophrenia in women, until the age of menopause, is, on the whole, a less severe disease than it is in men^[26,79]. Hypothetically, normal fluctuations of estrogen levels influence the response of psychotic symptoms to antipsychotic treatment either by action at the dopamine 2 receptor or by modification of the activity of drug metabolizing agents.

During the reproductive years, the level of estrogen in women fluctuates with menstrual phase and also with pregnancy stage^[78,79]. This is reflected in clinical measures of the severity of symptoms; the higher the level of estrogen, the more attenuated the symptoms^[80].

Because DD is a disorder of older age, fluctuating estrogen levels may not be as relevant as they are in schizophrenia^[81,82] but, by checking hormone levels, one would be able to determine whether exogenous estrogens (and perhaps other hormones) can boost antipsychotic response in DD.

CONCLUSION

Although many patients with DD experience benefits from treatment with antipsychotics, this is not true for all patients. Understanding for whom and under what circumstances treatment works best can guide management strategies for DD patients. Based on the literature on DD and other psychoses, moderators of antipsychotic response probably include gender, reproductive status, age, comorbid psychiatric disorders, baseline brain abnormalities, biochemistry, and genes coding, for instance, for brain receptors and drug metabolizing enzymes. Suggested mediating variables include measurable functional brain alterations during treatment, such as changes in neuronal receptor occupancies, blood flow to the brain, brain glucose metabolism, and blood hormone levels.

Understanding moderators has substantial clinical relevance. For instance, knowing that comorbid psychiatric illness such as mood disorders and substance abuse disorders often precede DD opens an avenue to early intervention. Understanding

Table 2 Therapeutic implications of brain lesions in delusional disorder

Ref.	Study design	Imaging method	Age	Contrast group	DD type	Main findings
Moderators of treatment response (structural brain findings)						
Miller <i>et al</i> ^[45] , 1989	Prospect	CT, MRI	Case 1: 86 Case 2: 72 Case 3: 62	Schizophr (<i>n</i> = 1) Bipolar disorder (<i>n</i> = 1)	Persecutory	Structural brain disease in all 3 cases contributed to treatment resistance
Mediators of treatment response (changes in functional brain findings)						
Wada <i>et al</i> ^[69] , 1999	Case report	SPECT	Age = 78	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes improved at remission
Ota <i>et al</i> ^[70] , 2003	Case report	SPECT	Age = 72	-	Somatic	Decreased perfusion in the left temporal and parietal lobes improved after treatment
Hayashi <i>et al</i> ^[71] , 2004	Case report	SPECT	Age = 77	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes improved after treatment
Narumoto <i>et al</i> ^[74] , 2006	Case report	SPECT	Age = 82	-	Somatic	Global decrease in rCBF Reversed in all non-stroke areas after remission
Hayashi <i>et al</i> ^[72] , 2010	Case report	SPECT	Age = 42	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes normalized after treatment
Freudenmann <i>et al</i> ^[48] , 2010	Prospect.	PET SPECT	Age = 27	Organic DD (<i>n</i> = 1)	Somatic	<i>SPECT</i> : D2R occupancy predicted remission <i>PET</i> : Glucose metabolism in putamen and thalamus did not normalize with remission
Uezato <i>et al</i> ^[73] , 2012	Case report	SPECT	Age = 53	-	Somatic	Hyperperfusion in the right temporal lobe normalized after electroconvulsive therapy

DD: Delusional disorder; CT: Computerized tomography; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; rCBF: Regional cerebral blood flow; PET: Positron emission tomography. DaT: Striatal dopamine transporter; D2R: D2 receptor.

mediating factors in DD patients who are adherent to medication but nevertheless not responding helps clinicians by suggesting different ways (other than raising the dose) by which plasma levels can be increased, for instance via smoking cessation, changes in diet or drug regimes, or by the addition of adjunctive hormones.

DDs have been traditionally difficult to treat. Awareness of the moderators and mediators of treatment response can help to make recovery possible.

FUTURE DIRECTIONS

The identification of moderators and mediators of response in delusional disorders, which traditionally do not respond well to standard antipsychotic treatment, facilitates the development of personalized treatments. A better understanding of

these factors will help clinicians decide which form of treatment works best for which patient^[60].

Several moderators of antipsychotic response in delusional disorder have been suggested: Gender, reproductive status, age and comorbid medical disorders, comorbid psychiatric disorders, baseline brain abnormalities, biochemical factors, genetics of both liver enzymes and neurochemical receptors in the brain^[39,44,59]. In the future, randomized controlled trials will need to ascertain whether these or other factors do, indeed, moderate response in DD.

Future studies will also need to investigate potential mediating variables of antipsychotic response in DD, such as functional brain changes, antipsychotic plasma levels and estrogen and other hormone levels.

Delusional disorder may respond better to psychotherapeutic interventions than to medications. Moderators and mediators of cognitive behavioral therapies, for instance, will need to be investigated in the future.

All subcategories of DD may not respond in the same way to treatment. Currently, most studies have only researched the somatic subtype^[48,49]. It is possible that patients with erotomania or delusional jealousy respond differently than those with delusional parasitosis – this question needs to be thoroughly examined.

The future will undoubtedly be able to overcome the problem of research sample availability of relatively rare conditions such as delusional disorders. Large international collaborations will almost certainly be part of the solution.

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