Optimizing treatment of delusional disorder: new goals for a new era

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ABSTRACT
Delusional disorder (DD) is an underresearched psychotic disorder characterized by the presence of monosymptomatic delusions on a background of relatively well-preserved global functioning. Prominent hallucinations and significant affective symptoms are absent and response to treatment is poor due at least partially to a lack of adherence to antipsychotic (AP) medications. More recently, several studies have found a degree of cognitive impairment in DD patients, and affective symptoms are now more frequently reported. Treatment specifically addressing the different clinical domains of DD has not been sufficiently investigated and comprehensive treatment goals remain poorly defined. For this reason, the aim of this review is to summarize the current evidence on the following: efficacy and adverse events associated with antipsychotic medications, prediction of response, treatment of comorbidity, and prevention and promotion of mental wellbeing. This review focuses on optimizing treatment for this hard-to-treat condition and on discovering predictors of response. APs are the first-line treatment of DD. Second-generation APs are used most often because of their tolerability profiles. Evidence concerning pharmacological treatment is nevertheless scarce; clinical trial evidence of cognitive behavioral therapy effects is paradoxically more robust. Because of age-induced pharmacodynamic and pharmacokinetic alterations, adverse events of APs are most frequent in this population than in other psychotic conditions, perhaps because the onset of DD is usually in middle-to-old age. Some findings suggest that separately treating affective and cognitive comorbidity improves clinical outcomes. Targeting specific symptom domains and altering doses to suit the demands of age (and reproductive status in women) holds clinical promise. Recommendations are for a) combined psychosocial and pharmacologic intervention, b) health promotion and c) prevention of psychiatric comorbidity. Rehabilitative strategies that enhance recovery need further investigation. Research in this area needs to target specific, well-defined goals.

KEYWORDS: psychosis, delusional disorder, treatment, antipsychotic response.

ABBREVIATIONS:
- AP: Antipsychotics
- CYP: Cytochrome P450 enzymes
- DD: Delusional Disorder
- FGA: First-Generation Antipsychotics
- OPCRIT: Operational Criteria Checklist for Psychotic Illness and Affective Illness
- PANSS: Positive and Negative Syndrome Scale
- RCT: Randomized Clinical Trial
- SGA: Second Generation Antipsychotics
- WHO: World Health Organization

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INTRODUCTION

Delusional disorder (DD) is a severe and complex mental illness that affects the information processing of the brain. It is mainly manifested by the presence of monosymptomatic delusions [1]. Although delusional thoughts are the prevalent symptom, there are others, less prominent and perhaps less relevant to treatment goals [2]. These can be classified by domain: depressive symptoms, non-prominent hallucinations, irritability, behavioral or cognitive symptoms [3]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of DD requires the presence of one or more delusions lasting one month or longer, with subtyping by delusional theme [2]. The subtypes or delusional categories are: delusions of persecution, erotomania, delusions of jealousy, grandiose delusions, somatic delusions, plus mixed and unspecified subtypes [4]. A number of studies report high rates of affective comorbidity in patients with DD, significant depressive symptoms being frequently found [5]. Non-prominent hallucinations and behavioral symptoms are also included in DSM-5 [2]. To qualify, they need to be relatively mild and related to the main delusional theme. Although previous research concluded that DD patients were cognitively intact, more recently, some studies report that some patients with DD exhibit cognitive dysfunctions [6]. Compared to patients with schizophrenia, Grover et al. report that those with DD perform worse in attention, visual learning and verbal working memory tasks [6]. More recent studies confirm that cognitive symptoms such as impaired verbal memory negatively impact functionality in patients with DD [3].

Little is known about epidemiological data in DD, very few studies having investigated this topic [7, 8]. Manschreck reported that the vast majority of work shows a DD prevalence of 24-40 per 100,000 population, with incident cases numbering 0.7 to 3.0 [4]. In a cohort study of community residents aged 65 years and over, Copeland and co-workers found a prevalence of DD of 0.04% and an annual incidence of 15.6 in a population of 100,000 [8]. In a recent study of DD patients attending an emergency department, González-Rodríguez and colleagues found a prevalence of 10 per 100,000 cases, with 4 being new onset cases [9].

Dopamine dysregulation has been hypothesized as a final common pathway to psychotic disorders [10]. In the particular case of DD, Morimoto and colleagues addressed this issue by looking at genes of a dopamine metabolite, plasma homovanillic acid (pHVA), of a dopamine precursor, tyrosine hydroxylase (TH), as well as at genes of D2, D3 dopamine receptors in patients with DD [11]. Their conclusion was that polymorphisms in DRD2, DRD3 and TH genes in the persecutory subtype of DD could lead to hyperdopaminergic states associated with delusional symptoms [11]. The biological underpinnings of treatment response in DD have also been recently reviewed. Monoaminergic systems, particularly dopaminergic and serotonergic neurotransmitter systems, are reportedly very strong determinants of response to AP [12]. Nevertheless, the variability in treatment response indicates a need to look beyond neurotransmitters and examine structural and functional brain imaging findings.

With respect to AP, pimozide used to be considered as the gold standard for DD [13, 14], but is no longer used because of its cardiovascular toxicity [15]. Second-generation antipsychotics as well as non-pharmacological interventions are currently used, and clinical trials have shown some promising results [16]. Very few studies, however, have investigated the efficacy of available therapies for symptoms other than delusions.

In our opinion, it is time to redefine the goals of treatment. Depression, cognitive impairment, and behavioral symptoms also need to be addressed and their treatments evaluated for efficacy. Recovery from DD is more than the elimination of delusions; it needs to also target function and quality of life. Thus, in this review, our aim is to summarize the current evidence on the efficacy (and side effects) of all treatments for all aspects of DD and to reformulate treatment goals.

METHODS

We carried out a non-systematic comprehensive narrative review focusing on all treatments of DD, evaluating their efficacy as well as adverse outcomes. We were interested in data pertaining to outcomes associated with comorbidity, mental illness prevention, mental health promotion, psychological and rehabilitative interventions. Our main aim was to reformulate the ultimate goals of treatment in this disorder. We searched
the PubMed and Google Scholar databases for papers published in the last 10 years that addressed treatment of DD. The following search terms were used: “delusional disorder”, “paranoia”, “therapy”, “treatment”, “treatment goals” and “treatment objectives”. A few older classic papers were also selected for inclusion because we considered them relevant to our stated aim. Included studies were limited to those published in English, German, French or Spanish. The review was divided into five sections: (1) evidence on efficacy and response rates to treatment in DD, (2) evidence on safety and adverse events of treatments in DD, (3) evidence on the role of comorbidity and clinical phenotype in DD, (4) evidence of efficacy of prevention and mental health promotion measures in DD, and (5) new goals for the treatment of DD.

Efficacy and response rates in DD

Based on scientific evidence gathered over many years, the main treatment for patients with DD became AP medications [13, 15]. One of the most relevant early reviews in the field of DD was carried out by Munro and Mok [13]. These investigators analyzed over 1,000 articles on patients with DSM-defined DD and reported that the response to AP treatment and the consequent prognosis of this illness was relatively good, irrespective of the specific delusion. This 1995 paper, in fact, marks one of the most important milestones of DD research because it showed that the content of a delusion was not predictive of response and had no prognostic value. Among the APs available at that time, pimozide reportedly obtained the best results.

Manschreck and Khan [14] conducted an updated review to determine whether the use of second-generation antipsychotics impacted treatment response and prognosis. They found that adherence to medication had been poorly reported in past studies and that depressive comorbidity was more frequent than had been reported by Munro and Mok [13]. They also reported that the use of all available AP resulted in a similarly good response (50% of cases); no AP was superior to others.

A more recent systematic review evaluated the effectiveness of several psychotropic medications as well as psychological interventions in patients with DD, comparing each treatment with placebo [16]. Relevant randomized controlled trials were included if they investigated antipsychotic medications, antidepressants, mood stabilizers or psychotherapy in the context of DD. Only 1 randomized clinical trial (RCT) met their inclusion criteria [17]. This was a trial comparing the effectiveness of add-on cognitive-behavioral therapy (CBT) to an add-on attention placebo control (APC) group over 24 weeks. Patients in both groups were first stabilized on AP. Both treatment and control groups showed an improvement on strength of delusional conviction, preoccupation, and affect related to belief, as well as a diminution of factors contributing to belief maintenance. Patients receiving CBT, however, improved more than the APC group on affect related to belief, actions taken on the basis of beliefs and strength of belief conviction. This was a very small trial – 11 patients in the CBT group and 6 in the APC group - and yet it was the only RCT in the whole DD field. It led to the conclusion that psychotherapies worked in DD when combined with AP and that further RCTs were badly needed [16].

In a more recent systematic review, González-Rodríguez and collaborators examined and critically analyzed operational definitions of AP response in DD [18]. Nearly half of the studies they reviewed evaluated AP response by chart review and subjective criteria. The other half used observer-rated scales. Only one study used a definition combining results from the Clinical Global Impression Improvement scale with a mean change from baseline symptom score, and only one other study reported response rates based on a scale-derived cut-off, as recommended in schizophrenia research [19]. Muñoz-Negro and colleagues did an updated systematic review that compared the effectiveness of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) in all DD studies that used clinician-rated scales. FGAs turned out to be slightly superior to SGAs [15]. However, group differences were marginal, and pimozide, once the gold standard, did not provide any advantage over other drugs.

A wise clinician once said, “Use drugs when they first come on the market. That’s when they work best.” Understanding the full circumstances under
which AP are most effective helps clinicians optimally treat their patients. Recent work has described established moderators of AP response: gender, reproductive status, age, duration of illness, presence of psychiatric comorbidity, brain structure, and polymorphisms of dopamine receptor and drug metabolizing enzyme genes [20-22]. There are also mediating factors: AP and hormonal blood levels and functional brain changes [20].

Safety and tolerability of AP in DD

Despite extensive use, evidence-based reports on AP safety and tolerability in DD are sparse [14, 23]. Recent research has emphasized that menopause in women and ageing in general exerts a major influence on both tolerability and safety of AP [20]. Pharmacokinetics and pharmacodynamics are altered, and the probability of drug-drug interactions increases [24]. This is important in DD, which is a disorder that starts relatively late in life.

Current evidence indicates that SGAs are better tolerated than FGAs [15]. The incidence of extrapyramidal side-effects is lower with SGAs, and cognitive impairment is rarer [25]. Long-term safety, however, is a major problem with SGAs because of weight gain and metabolic effects, although some SGAs show comparably safer metabolic profiles than others. Many experts recommend that a combined efficacy/safety score should determine AP choice.

Given the morbidity and mortality associated with psychosis in older populations, regular monitoring of AP effects is necessary [26]. Adjunctive nonpharmacological strategies are effective in DD and their use can decrease dosing requirements for AP, while maintaining efficacy [26]. A recent study in patients with schizophrenia and DD [27] found that the individual determination of key cytochrome P450 (CYP) enzyme genetic polymorphisms may, in the future, be able to personalize AP treatment and thus increase both efficacy and safety.

Comorbidity and clinical phenotypes in DD

Comorbid depression has always figured in descriptions of DD [13]; its prevalence is estimated to lie between 21% and 58% [20, 28]. The presence of nonprominent hallucinations and comorbid substance use has also been described but is less frequent than depression [29]. A recent cross-sectional study compared clinical characteristics of patients with DD and those with schizophrenia [30]. Results confirmed that patients with DD function better in the world; the psychopathological is milder.

In 1999, Serretti and collaborators analyzed the factorial structure of psychopathological symptoms in inpatients with DD using the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT) [31]. They identified four independent factors: 1) delusion factor, 2) depressive symptoms, 3) hallucinations and 4) irritability, suggesting that DD may be a heterogeneous disorder, with different individuals expressing different clinical profiles. Following the same line of thinking, de Portugal and coworkers explored psychopathological factors in a sample of outpatients with DD using the Positive and Negative Syndrome Scale (PANSS) [32]. Four consistent factors were identified: 1) Paranoid (mainly delusional), 2) cognitive, 3) schizoid and 4) affective. The affective dimension was associated with the presence of somatic delusions and risk of suicide; the cognitive dimension positively correlated with non-prominent hallucinations and the paranoid dimension with poor adherence to treatment and poor response. Such clinical differentiation suggests that treatment and rehabilitation measures, as well as prognosis, need to be individualized.

Prevention and promotion of mental health in DD

In 2013, the World Health Organization (WHO) developed a 7-year Mental Health Action Plan and made important recommendations about the integration of health and social care services, and the implementation of strategies to promote and prevent mental ill health and to support research and training in psychologic/psychiatric disease [33]. These core mental health strategies are applicable to all patients with DD, but women in particular, because women have health needs that differ from those of men [34]. According to WHO, providing mental health care after symptoms appear is important but insufficient; mental health providers also ought to actively promote mental health principles by paying attention to physical health, providing patients with adequate housing.
and appropriate employment, and protecting them against the adverse effects of treatment. Preventing suicide by optimal treatment of depressive symptoms is a critical mental health goal.

Prevention of potential risk factors for DD also needs consideration. Porras-Segovia and collaborators found a 5.7% prevalence of sensory deficit (vision and hearing loss) in a case register of DD patients, a significantly higher prevalence than that found in the general population [35]. It is possible (though not proven) that deficits such as these in the aging population contribute to the formation of delusions, which then becomes potentially preventable.

Once delusions have emerged, their early identification becomes vital. Self-report questionnaires completed by primary-care patients revealed that patients were opened to being asked about delusions, stress, and psychosocial factors that increase risk of mental illness. One example is a recent case report by Weise and collaborators [37]. Building a patient-clinician therapeutic alliance prevents unacceptable outcomes such as suicide or violence in DD and promotes adherence to treatment and potential for recovery. The role of partial hospitalization programs (PHPs) as a bridge between hospitals and outpatient services has been recently addressed. PHPs are multidisciplinary and can offer flexible programs which include prevention and promotion strategies [34].

New goals for the treatment of DD

Recent work has recommended new goals for the treatment of DD [38-40]. Because this is a treatment resistant disorder, improving response rates is imperative, and this can be done by specifically targeting the different domains or psychopathological dimensions that factor analysis has uncovered [31, 32]. The frequently noted affective dimension [13, 32] needs to be identified and treated with appropriate antidepressants and psychological approaches in order to reduce the risk of suicide and improve clinical outcomes [32].

Despite the fact that DD is usually considered to spare cognition, the presence of cognitive impairment has been noted in some patients [3, 6]. Cognitive remediation has not been tested in this population but needs consideration. Treating cognitive symptoms may be a new goal for the treatment of DD.

It has been shown that the paranoid dimension responds not only to AP but also to cognitive-behavioral therapy [16], which can diminish the strength of delusional conviction, reduce preoccupation with the delusion, change the negative affect associated with the delusion, and eliminate some of the factors that help maintain the delusion. In doing so, it can make possible a reduction of AP dose and consequently decrease adverse effects and increase treatment adherence.

The problem of adherence has not been adequately investigated in DD although, since 1995 [13], nonadherence in DD has been attributed to disorder-related lack of insight. Antipsychotic plasma monitoring may prove useful in detecting antipsychotic nonadherence and determining its relationship to the patient’s clinical state [20, 27]. Research is needed to reach a consensus on operational definitions of adherence, how best to assess it, and what interventions are best able to ensure full cooperation between patient and doctor.

Sleep disturbances are another aspect of DD. They have been associated with relapse and exacerbation of delusions in DD [41]. Research is needed into potential correlations between treatment of insomnia and clinical status.

The gut-brain axis has become a popular new target of investigation. AP changes the composition of gut bacteria and this may affect symptoms directly via changes in neurotransmission or indirectly via diminished response to AP or, alternately, increased side effects [42].

Searching for biomarkers of specific symptoms or syndromes is another promising area of research in psychosis. This involves the identification of genetic and also non-genetic risk factors [43], which has never been done specifically for DD.

Table 1 summarizes our proposals for new treatment goals for patients with DD based on current evidence in the field. AP is helpful for some aspects of this disorder but other, perhaps less obvious, aspects also need attention and should help patients achieve subjectively meaningful outcomes.
Table 1. New goals for the treatment of delusional disorder.

<table>
<thead>
<tr>
<th>General objective</th>
<th>Specific objective</th>
<th>Procedure</th>
</tr>
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<tbody>
<tr>
<td>Improve response rates</td>
<td>Treating depressive symptoms</td>
<td>Combination of antidepressants and nonpharmacological interventions</td>
</tr>
<tr>
<td></td>
<td>Treating cognitive symptoms</td>
<td>Psychological interventions and cognitive remediation (still to be tested)</td>
</tr>
<tr>
<td></td>
<td>Treating non-prominent hallucinations</td>
<td>Combination of antipsychotics and psychological interventions</td>
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<tr>
<td>Improve adherence rates</td>
<td>Improve operational definitions for adherence</td>
<td>Testing the correlation between objective and subjective measures</td>
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<td></td>
<td>Improve adherence to medications</td>
<td>Designing studies to control moderators of adherence</td>
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<tr>
<td>Treatment of sleep disturbances</td>
<td>Treating insomnia and other sleep disorders</td>
<td>Non-pharmacological interventions and optimizing AP treatment</td>
</tr>
<tr>
<td>Treatment of medical comorbidities</td>
<td>Treating comorbid physical illness and avoiding drug-drug interactions</td>
<td>Liaison with other medical specialties</td>
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<tr>
<td>Promotion and prevention of mental health problems</td>
<td>Identification of mental health risk factors and life-style risk factors</td>
<td>Smoking and substance abuse cessation therapies</td>
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<tr>
<td>Investigation of gut-brain axis</td>
<td>Exploring the role of the microbiome and gut brain axis</td>
<td>Investigating the role of the microbiome and gut-brain axis in AP effects</td>
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CONCLUSIONS
Much remains to be researched in DD. Mainly characterized by monosymptomatic delusions, but now recognized as encompassing affective and cognitive and perceptual symptoms as well, it is a disorder in search of effective treatment. Response to antipsychotic is generally considered relatively poor, in large part because of the high rate of treatment nonadherence. This review suggests that targeting the varied clinical domains within DD via domain-specific treatment strategies will improve outcomes. In general, combinations of biological and psychosocial treatments work best. Paying attention to both physical and psychiatric comorbidity is important and, perhaps even more important is the integration of prevention and health promotion into the comprehensive care plan for DD.

CONFLICT OF INTEREST STATEMENT
A. González-Rodriguez and A. Guàrdia have received honoraria, registration for congresses and/or travel cost compensation from Janssen Pharmaceuticals and Lundbeck-Otsuka. JA. Monreal has received consultancy and/or lecture honoraria from Sanofi, Pfizer, Servier, Janssen and Lundbeck-Otsuka.

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