



Review Article

Primary and Secondary Prevention in Delusional Disorder



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Abstract

Delusional disorder (DD), once entrenched, responds poorly to currently available treatment. This calls for community and individual preventive measures. Our goal was to conduct a literature review exploring the possibilities of prevention. This narrative review is based on a search of the PubMed database from its inception until July 2022. While not specific to DD, the search found evidence for primary and secondary strategies used to protect against or ameliorate psychotic illness characterized by prominent delusions. Community preventive strategies included addressing socioeconomic disadvantage and mental health stigma, improving mental health service accessibility, screening for and treating potential precursors to DD, such as sensory and cognitive deficits, as well as psychiatric symptoms, such as depression, anxiety, sleep disturbance, and substance abuse. Secondary community prevention relied on early detection programs and specialized services for early treatment of DD symptoms and their co-morbidities. Individual forms of secondary prevention were interventions geared toward illness denial, treatment nonresponse and antipsychotic (AP) refusal. Effective secondary prevention reduced symptom intensity and diminished the risk for fatal outcomes such as suicide. Based mostly on the evidence from related disorders, preventive and early treatment strategies, when put into effect, promise to reduce morbidity and allow for the recovery of patients with DD.

Introduction

Delusional disorder (DD) is a schizophrenia-related disorder characterized by the presence of monosymptomatic delusions and distinguished from schizophrenia by a relative absence of hallucinations and negative symptoms such as apathy, anhedonia, and

avolition. Importantly, DD first occurs in middle to late age. In addition to prominent delusional symptoms, its presentation most often includes significant depressive symptoms and relatively intact global functioning.¹ DD has traditionally been considered difficult to cure. In large part, this has been because patients did not believe that they were ill and, therefore, did not adhere to long-term treatment.²

DD is currently classified into subtypes according to its main delusional theme, e.g., persecutory, erotomanic, jealous, grandiose, somatic, mixed, and unspecified.^{1,3} Although the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)¹ does not report on its demographics, DD is more prevalent in women than men, and the mean age at onset is approximately 45 years, which would correspond to the beginning of the decline of estrogen, or pre-menopause in women. Men with DD are more likely than women to be unmarried, and women, to be widowed.³

The etiology of DD is essentially unknown. Molecular genetic investigations have been limited to small association studies of dopamine receptor (DR) polymorphisms.⁴ Because DD is a late-occurring condition, large family studies have not been feasible. Morimoto *et al.* examined the plasma levels of homovanillic acid (pHVA) and DR genes and their synthesizing enzyme, tyrosine hydroxylase (TH) in patients with DD and schizophrenia, as well as in healthy controls.⁴ The conclusion of their study was that DD, especially the persecutory type, was a hyperdopaminergic psychosis

Keywords: Delusional disorder; Prevention; Psychosis; Treatment; Pharmacotherapy; Psychosocial management.

Abbreviations: AMDP, Manual for Assessment and Documentation of Psychopathology; AP, antipsychotics or antipsychotic medication; AUDIT, Alcohol Use Disorders Identification Test; BPRS, Brief Psychiatric Rating Scale; CBT, Cognitive Behavioral Therapy; CNV, copy number variation; CPAP, continuous positive airway pressure; DD, delusional disorder; DI, delusional infestation; DR, dopamine receptor; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DUP, duration of untreated psychosis; FDA, Food and Drug Administration; GAF, Global Assessment of Functioning Scale; GMV, gray matter volume; HADES, Halle Delusional Syndromes Study; HLA, human leukocyte antigen; LOI, long-acting injectable antipsychotics; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; OSA, obstructive sleep apnea; pHVA, plasma homovanillic acid; SAD, social anxiety disorder; SNP, single-nucleotide polymorphism; SNV, single-nucleotide variant; SSRI, selective serotonin reuptake inhibitor; TH, tyrosine hydroxylase; WHO, World Health Organization.

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in which polymorphisms of dopamine receptors D2 and D3 played a part. Likewise, a study by Debnath *et al.*⁵ confirmed the importance of human leukocyte antigen (HLA) genes in DD and emphasized the evidence for the shared nature of etiological mechanisms in this disorder and schizophrenia. Neurotransmitter abnormalities similar to those in schizophrenia (dopamine dysregulation and elevated dopamine synthesis) has also been found in DD.⁶ In addition, rare copy number variations (CNVs), rare single-nucleotide variants (SNVs), and commonly found single-nucleotide polymorphisms (SNPs) are currently being investigated in schizophrenia and its several related disorders.⁷ CNVs tend to be expressed in the developing brain, and they could predispose to a variety of psychiatric disorders with little diagnostic specificity. It has also been found that major psychiatric disorders share common genetic variations in neuronal, immune, and histone pathways.⁷ This is consistent with clinical trials that show the symptoms of all major psychotic disorders to be responsive to the same antipsychotic medications (AP).⁸

A variety of structural brain abnormalities (relative to healthy controls) have been noted in the paranoid type of DD by Wolf *et al.*⁹ They found aberrant gray matter volume (GMV) in right prefrontal regions implicated in the emotions of fear and anxiety, and in circumstances of threat. Brain abnormalities in the medial frontal and anterior cingulate cortex were also found in DD.¹⁰ Prefrontal, parietal, temporal, thalamic, and striatal dysfunctions have been reported in delusional infestation (DI), whereas white matter volume dysfunctions were seen in patients with accompanying organic lesions.^{9,11} Additionally, cerebellar dysfunctions have been specifically reported in somatic type DD.¹²

The standard treatment of DD is AP with, sometimes, adjunct antidepressants.¹³ As is the case for psychotic disorders in general, current evidence favors treatment in the community as opposed to treatment in hospital¹⁴ although a combination of both has often been necessary.¹⁵ Furthermore, community care has been reported to significantly reduce relapses and hospital admissions, to improve medication adherence, and to result in clinical improvement more often than hospital care.¹⁶ Community care allows for multidisciplinary psychosocial interventions, such as patient and family psychoeducation, cognitive therapy, and social skills training. Interventions such as these reduce self-stigma and are known to improve treatment effectiveness in related disorders. Family support, provision of employment opportunities, and a variety of rehabilitative strategies are offered in many community services for psychosis; they improve global functioning and aid subjectively defined recovery.¹⁴

Primary prevention measures, when offered to all members of a community, aim at suspected causes and known risk factors for mental illness.¹⁷ Alternatively, specific preventive strategies are directed at groups at high risk for specific disorders. Secondary prevention addresses early detection and early intervention after symptom onset.

As in all psychiatric disorders, biological causes interact with exposures and responses to life stress. Genes and environment interact, so that modifying the environment can prevent the expression of disorder-determining genes.^{18,19} Results of a recent study support the effectiveness of such preventive measures.²⁰

Thus, the aim of this narrative review was to summarize the literature that examined:

1. Community level preventive strategies in DD, especially those targeting demographically vulnerable populations.
2. Individual level primary preventive strategies in DD, i.e., pharmacological and psychosocial treatment of pre-delusional

psychiatric symptoms (mood, anxiety, sleep disturbance, and substance abuse), as well as potentially pre-delusional medical symptoms (sensory and cognitive deficits).

3. Secondary prevention at the community level, i.e., early detection, and at the individual level, i.e., early intensive and comprehensive treatment of the symptoms, both pharmacological and psychosocial.
4. Additional secondary strategies on an individual level, i.e., intervention directed at illness denial, treatment resistance, and AP refusal.

We conducted the review by searching the PubMed database from its inception until July 2022. Search terms were “delusional disorder” OR “delusional psychosis”, AND “prevention,” OR “early detection,” OR “early treatment.” The literature was sparse; we cite all the papers we found that addressed prevention in delusional syndromes.

Primary and secondary preventive strategies at the community level.

The World Health Organization (WHO) has defined health as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity”.²¹ This definition is based on the understanding that many precursors to mental ill health, such as socioeconomic disadvantage, air and water pollution, discrimination and stigmatization, are, in theory, preventable. Therefore, the WHO has promoted comprehensive strategies for mental health prevention.²¹ Determinants of mental health go beyond the individual; they include the social, cultural, economic, and environmental milieu in which a person lives. The WHO has also acknowledged special vulnerability factors in specific populations, e.g., the physically or intellectually disabled, the frail elderly, or persons living in poverty, suffering chronic health conditions, or belonging to stigmatized minority groups.²¹

Mental and physical health are considered inseparable. Mental disabilities are disproportionately accompanied by comorbid malignancies and cardiovascular diseases. Additionally, mortality rates are high among the mentally ill because of increases in physical ill health, but also because of high rates of suicide, which is one of the leading causes of premature death in patients suffering from persistent delusions.²² Moreover, a significant association has been found between positive psychotic symptoms (delusions and hallucinations) and suicidal ideation.²³ Nevertheless, this can be prevented by prompt treatment of psychotic symptoms with effective doses of AP. It is well known that mental illness often leads to unhealthy life choices - poor nutrition, poor hygiene, excessive alcohol and drug use, lack of sufficient physical, mental, or social activity, all of which contribute to poor health and poor quality of life. In this sense, preventive intervention, such as exercise programs, have been investigated and found effective as secondary prevention in the first episodes of psychosis.²⁴ Moderate exercise training was found to induce changes in the markers of oxidative stress and antioxidant concentration, with subsequent improvements in psychotic symptoms. One example of a primary prevention strategy is community infection control. It has been shown that SARS-CoV2 infection is able to induce psychosis,²⁵ thus implying that promotion of hygiene measures could potentially reduce the incidence of disorders such as DD.

The WHO's Comprehensive Mental Health Action Plan 2013–2030 has focused on the promotion and protection of mental health, and the prevention of mental disorders.²¹ This is based on six principles and approaches: 1) universal health coverage, 2) hu-

man rights, 3) evidence-based-practice, 4) a life-course approach, 5) a multisectoral approach, and 6) empowerment of persons with mental disorders and psychosocial disabilities.

Evidence-based practice recognizes the need for robust trial methodology and reproducibility of results. The life-course approach recognizes that risk and protective factors for mental illness vary across the different life stages.

In the context of DD, a study carried out by Tizon *et al.* investigated two cohorts of patients from two different neighborhoods in Barcelona, Spain.²⁶ The objective of the study was to compare the prevalence, socio-demographic, and clinical factors in a catchment area consisting of 103,615 inhabitants in two neighborhoods that differed with respect to socioeconomic level and degree of psychosocial risk factors for mental illness. Tizon *et al.*²⁶ found that the prevalence of DD was higher in the less advantaged neighborhood. This implied that eradicating inequities in social capital could reduce the risk of DD. The study concluded by highlighting the political feasibility of such intervention and its vital importance to public health.

Wustmann *et al.*²⁷ conducted a project called the Halle Delusional Syndromes (HADES) study, a cross-sectional and longitudinal study investigating a sample of patients with DD, in order to determine prevalence, socio-demographics, and clinical features. Forty-three patients were recruited who fulfilled the International Classification of Diseases, Tenth Revision (ICD-10) and DSM-IV criteria for a DD diagnosis. The Brief Psychiatric Rating Scale (BPRS) and the Manual for Assessment and Documentation of Psychopathology (AMPD system) were used to evaluate symptoms, and the Global Assessment of Functioning Scale (GAF) was used to assess function. The study found some gender differences. Men tended to be single, had a history of more frequent perinatal and developmental disturbances, and came more often from lower socioeconomic classes. These findings implied that DD prevention needs to take gender into account.

Routine community screening programs for conditions that predispose to DD, such as neurological or sensory impairment, form part of primary prevention. Early detection and treatment of sensory impairments were shown to prevent not only DD, but also depressive illness and dementia in a psychiatric outpatient clinic in Ghana.²⁸ The paranoid subtype of DD was found in this study to be positively associated with both blindness and deafness and to be more common in women than in men.²⁸ More recent studies have also investigated the prevalence of vision and hearing loss in DD.²⁹ In a sample of 1,452 patients fulfilling DSM-5 DD criteria, 7.4% were found to have sensory deficits: vision loss (3.5%) and hearing loss (3.9%). These findings were in line with previous reports from de Portugal *et al.* who found a 5.7% prevalence of sensory deficits in DD.³⁰ A recent systematic review and meta-analysis also confirmed an increased risk of psychosis in patients with hearing impairment.³¹ Likewise, loneliness, diminished ability to place oneself in another's shoes (impairment in the theory of mind), and disturbances of source monitoring (memory errors where the source of a memory is misattributed) were all found to be potential mechanisms underlying the association between psychosis and hearing loss.³¹

In addition, sensory impairment is known to be intimately connected with low socioeconomic status,³² thereby doubling the risk for psychotic disorder. Effective treatment of vision and hearing loss has thus served as a potential primary preventive measure against DD. Vision rehabilitation in a general population of visually impaired adults was recently shown to improve quality of life.³³ However, no similar studies have been done in DD patients.

An important and prevalent community preventive mental health measure is the attempt to reduce mental health stigma among the public at large, in the healthcare sector, and in the workplace.²¹ This strategy has shown beneficial effects in the context of severe mental illness.³⁴ A systematic review carried out by Hanisch *et al.* investigated the effectiveness of interventions targeting the stigma of mental illness in the workplace.³⁵ Employee knowledge and supportive behavior were targeted, and the results were judged successful.

The WHO's Comprehensive Mental Health Plan 2013–2030 included strategies for combating stigma in schools and in the workplace.²¹ In contrast to other psychotic disorders, such as schizophrenia where patients are often too disabled to hold jobs, DD patients are very frequently employed, so that combating workplace stigma becomes particularly important.³⁶

Suicidal preoccupation, which occurs in DD in 8–21% of cases³⁷ is critical to prevent. Cutting suicide rates by one third has, for instance, been a prime WHO target.²¹ Nonetheless, the SARS-CoV-2 pandemic has increased suicide attempts in DD. Weise *et al.* reported the case of a 60-year-old woman whose first psychiatric admission was caused by an attempted suicide during the COVID pandemic.³⁸ The pandemic was, and continues to be, known for its potential to aggravate mental health symptoms. This implies that community level preventive measures (use of digital monitoring systems and distress phone lines), when put into effect, are able, to some extent, to reduce suicide rates. Older patients, postmenopausal women in particular, are at special risk and require extra monitoring.³⁹

Another potential community strategy to prevent the development of severe mental illness such as DD is to institute programs for family psychoeducation, in order to help family members address delusional beliefs.⁴⁰ A recent review pointed out that some family responses to psychiatric symptoms appear to be more constructive than others. Stigmatization of delusional beliefs, guilt, withdrawal, anger, and fear were found counterproductive,⁴¹ whereas calm and empathic understanding of the affect behind the delusion prevented the crystallization of delusions. It was also important for families to become acquainted with the mental health system, so that they could access the appropriate services promptly. Hence, organizing educational family group sessions relevant to mental health is considered a useful community intervention, as it is in schizophrenia.⁴²

In summary, numerous community preventive strategies are possible in this population (Table 1). Combating socioeconomic disadvantage, reducing mental illness stigma, routinely screening for sensory impairment, instituting community suicide prevention, and family psychoeducation programs have been shown to be relevant preventive measures for disorders such as DD.

Primary and secondary preventive strategies on an individual level

Many of the same measures apply to individuals determined to be at risk for psychotic illness. Helping to attenuate the disadvantages of poverty by providing at-risk individuals with educational bursaries, skills training and supported employment opportunities form part of comprehensive social services. Referral to ophthalmology and otolaryngology whenever sensory impairment are suspected is standard medical practice. One study of 104 outpatients with chronic schizophrenia-spectrum disorders (which included DD) examined the factors that contributed to self-stigma, such as coping styles and symptom severity.⁴³ A significant positive associa-

Table 1. Community-level and individual-level strategies for prevention of delusional disorder

Target	Strategies
Community level	
Socioeconomic disadvantage	Subsidized skills training, supportive employment, affordable housing, disability benefits, and health insurance. ²¹
Stigmatization of mental illness	Mental health advocacy, combating stigma in schools, workplaces, health system, and the general public. ^{34,36}
Health screening	Screening programs for sensory impairment and provision of treatment. ²⁹
Suicide prevention	Distress phone lines and public health announcements. ^{37,38}
Individual level	
Physical health	Early treatment of all physical illnesses, especially sensory and neurological that contribute to delusion formation. ³²
Suicide prevention	Close monitoring, liaison with family, recognition of warning signs, and access to immediate care for persons at risk. ³⁷
Life Style	Intervention and promotion (nutrition, alcohol and drug use, physical activity, and meaningful occupation). ⁴²
Family interventions	Family liaison and psychoeducation. ⁴⁰

tion was found between self-stigma and disorder severity, thus inferring that the effective treatment of psychotic symptoms reduced patients' tendencies to be ashamed of and blame themselves for their illness.

Treating pre-existing psychiatric conditions is an important component of prevention. Several study results have shown that patients with DD often experience a variety of non-psychotic psychiatric symptoms before they are diagnosed with DD. These were pre-morbidities whose treatment serves as primary prevention of DD. When they occur alongside DD, their early treatment serves as secondary prevention of DD severity and primary prevention of fatal outcomes such as suicide.

Early researchers who investigated this topic were Opjordsmoen and Retterstøll who, in 1993, compared clinical outcomes in two cohorts of 72 first-admission patients with DD. The first cohort was hospitalized between 1946 and 1948 (called the long-term group); the second was admitted between 1958 and 1961 (the short-term group).⁴⁴ The second group, treated in hospital with antidepressants and AP, showed no improvement in outcome over that of the first group, whose hospitalizations predated the introduction of either of these classes of drugs. These findings implied that patients with DD were not better off when treated with AP + antidepressants. However, it is possible that treatment non-adherence – usually considered particularly high in DD – could have influenced these results.

The coexistence of mood disorders occurs in approximately half of all DD patients according to a study conducted by Marino *et al.*⁴⁵ This study also found a familial risk for both DD and mood disorder and reported that mood symptoms, when present, preceded DD about half the time. This is important clinical information that can serve preventive ends.

Furthermore, in a cohort of 64 DD patients, Maina *et al.*⁴⁶ found that 72% suffered from at least one comorbid psychiatric disorder. In their study, comorbid affective disorders only preceded the onset of DD in younger patients with relatively early DD onset. Likewise, de Portugal *et al.*⁴⁷ found that, out of 86 DD outpatients, 46% presented with signs of depression or anxiety. Patients with

comorbidity had more somatic delusions, non-prominent hallucinations, and exhibited a higher suicide risk than those without comorbidity.⁴⁷ The implication was that active treatment of comorbidity could reduce psychotic symptom severity and, perhaps, lower the risk of suicide.

González-Rodríguez *et al.* carried out a cross-sectional study of 44 patients with DD who fulfilled DSM-IV-TR criteria.⁴⁸ From the total sample, 15 patients (34.1%) presented with comorbid depressive symptoms, 14 (31.8%) showed suicidal ideation, and seven (15.9%) showed recent (within the prior two years) suicidal behavior. Patients with comorbid depression had an earlier age at onset and suffered a greater intensity of suicidal ideation, again implying that early treatment of depression could reduce the risk of suicide. The results of a recent review were also consistent with these findings.⁴⁹

Veras *et al.* reported four cases of patients first diagnosed with social anxiety disorder (SAD) that was followed, after a period of time, by a diagnosis of DD.⁵⁰ SAD, in some cases, can be a prodromal form of DD.

Panic attacks have also been associated with psychoticism,⁵¹ but this possibility has not been systematically addressed in DD. Gupta and Kulhara⁵² reported one case of a woman who first presented with a history of panic attacks, and subsequently developed persecutory delusions that fulfilled the DD criteria. The patient suffered from anticipatory anxiety and systematized persecutory delusions and received a diagnosis of a DD persecutory type with comorbid panic attacks, which remitted with AP treatment. While this was only one case, it was consistent with other studies that pointed to anxiety disorders in general as being potentially a pre-morbid manifestation of DD.

Substance use disorder is a further important co-morbidity that, when treated, could prevent or reduce the severity of DD, as was demonstrated in patients with first-episode psychosis.⁵³ de Portugal *et al.*, using DSM-IV-TR criteria, carried out a cross-sectional study of 86 DD outpatients with and without pre-morbid substance use disorder.³ They found that men had a significantly higher frequency of premorbid substance use than women (30.3%

Table 2. Early detection of non-psychotic psychiatric comorbidities

	Hypotheses	Strategies
<i>Affective comorbidities</i>		
Affective symptoms prior to the onset of DD	Could increase risk of DD and self-injury or suicide. ⁴⁹	Early antidepressant Rx to reduce symptoms and suicide risk. ⁴⁸
Affective symptoms after the onset of DD	Early Rx, especially in somatic DD, can reduce the severity of symptoms. ⁷⁷	Early Rx to prevent poor outcomes. ⁴⁴
<i>Anxiety comorbidities</i>		
Social anxiety disorder (SAD)	SAD could lead to delusions. ⁵⁰	CBT for SAD. ⁵⁰
Panic attacks	Anticipatory anxiety and panic could lead to DD. ⁵²	CBT for panic. ⁵²
<i>Sleep disorders</i>		
Insomnia	Insomnia can worsen DD symptoms. ^{62,63}	Rx of insomnia improves outcome. ⁶²
Sleep apnea (OSA)	OSA can increase symptom severity, especially negative symptoms. ⁶⁰	Screening and Rx for OSA. ⁶⁰
<i>Substance use disorders</i>		
Alcohol and other drug use disorders	Substance use can worsen DD symptoms. ^{55,57}	Early detection of substance use, esp. targeting men, and prompt Rx. ⁵⁵

vs. 11.3%). This confirmed the results of Román-Avezuela *et al.*⁵⁴ who, in a study of 50 inpatients with DD, also showed that men far more often than women were diagnosed with comorbid substance use disorders (40.9% vs. 3.6%). This was true for alcohol (22.7% vs. 3.6%) and for cannabis (22.7% vs. 0%), thus indicating that prevention and early treatment of substance abuse could be an effective risk management technique in men.

Kulkarni *et al.* investigated a cohort of 445 patients with persistent DD (men: 236, women: 219) from a tertiary center in India.⁵⁵ Men more often than women presented with comorbid substance use disorders (24.1% vs. 1.8%). The most common psychotic content in the context of this comorbidity was the delusional convictions of partner infidelity or Othello syndrome, which has long been associated with alcohol use disorders.⁵⁶ These findings were consistent with the results of a cross-sectional study of patients with first-episode of psychosis from Northern India.⁴² A semi-structured interview was used in this latter research to assess clinical variables as well as information regarding the use of substances: age at first consumption, type of substance used, and duration and pattern of substance use. Cannabis use was assessed by urine testing, whereas alcohol use was evaluated using the Alcohol Use Disorder Identification Test (AUDIT). In accordance with the studies listed previously, men were significantly more frequently diagnosed than women with alcohol use disorders. Treating substance abuse early can also prevent medical sequelae secondary to an excessive intake of alcohol.⁵⁷ Substance use treatment should also be able to increase adherence to DD management.

Another frequent premorbid as well as comorbid condition in psychotic disorders is sleep disorder⁵⁸ and its treatment has been shown to reduce the severity of psychosis.⁵⁹ Moreover, insomnia and nightmares have been called out as potential risk factors for the onset and persistence of psychotic symptoms.⁶⁰ Kasanova *et al.*⁶¹ investigated the temporal relationship between sleep disturbances, sleep quality and occurrence of paranoid ideation in 42 acutely paranoid and 32 non-paranoid individuals, and 41 further study participants with schizotypal traits. Poor subjective sleep

quality at night was associated with greater paranoid ideation the following morning.⁶¹ Sleep disturbances specifically in DD have not been investigated but a review conducted by our team⁶² has recommended early identification and treatment of sleep problems because of the link with not only with paranoid ideation but also with cognitive impairment and suicidal ideation.

As has been previously mentioned, DD usually begins at middle age, which, in women, corresponds to the period of menopausal transition. This period, and the postmenopausal stage that follows, are associated with a significant increase in sleep disturbances such as sleep apnea, insomnia and restless leg syndrome, all of which impact quality of life, health, and social and personal functioning.⁶³ During perimenopause, insomnia is the most frequently experienced and treatable sleep disorder.⁶⁴ Effective treatment of pre-existing sleep problems could prevent the onset of psychotic thinking and can reduce symptom severity if diagnosed after the onset of psychosis⁶⁵ although this has not yet been specifically studied in DD.

In summary, treating associated psychiatric disorders early, whether they precede or are comorbid with DD, could serve as a protective measure (Table 2).

Benefits of starting DD treatment early

The early identification and treatment of psychotic symptoms has been widely considered to benefit patients suffering from psychotic disorders. Several studies have reported that early intervention services are superior to standard care in terms of remission rates, hospitalization rates, and social and personal functioning.⁶⁶ These studies, however, have usually been done in early onset schizophrenia with patients who were adolescents or young adults. Very few studies had addressed the potential benefits of treating DD patients (usually middle aged and elderly adults) as early as possible after the onset of psychotic symptoms.

Age is an important variable. A case register study of 236 patients with delusional infestation who attended four special-

Table 3. Management of treatment resistant DD and antipsychotic refusal

Clinical scenario	Hypotheses	Strategies
<i>Treatment resistant DD</i>	Drugs with affinity for multiple receptors may overcome resistance. ⁸	Check adherence. Motivate adherence. Try clozapine. Try LAIs. ⁷⁴
<i>Antipsychotic refusal</i>	Denial of illness and intolerance of side-effects can result in drug refusal. ⁷⁷	Explain the wide application of APs. Try antidepressants ⁸ and psychoRx. ⁷³

ized clinics in the United Kingdom, Italy, and Russia⁶⁷ described clinical outcomes and compared them with those of previous cohort studies. A total of 189 patients were followed longitudinally and classified according to age: <55 years, 56–75 years, and >75 years. Younger age was associated with better clinical outcomes. A longer duration of untreated psychosis (DUP) correlated positively with worse outcomes, which suggested that early detection and treatment of DD could improve prognosis, at least for the delusional infestation form of the disorder. These findings were consistent with previous studies in delusional parasitosis,⁶⁸ notably with those from specialty clinics in Austria.⁶⁹ Two recent studies also confirmed that later age at onset and longer DUP in delusional infestation was associated with poor outcome.^{70,71}

In summary, the very scant available literature suggests that early AP intervention in DD can produce several benefits. Early treatment with antidepressants, as noted earlier, reduces suicidal ideation.

What can be done for treatment resistance or antipsychotic refusal?

Approximately one third of patients with schizophrenia are treatment resistant, meaning that positive symptoms persist despite two or more trials of an adequate dose and duration of AP (with documented adherence).⁷² Strong evidence does not exist for DD, but the mode of action of AP has been deemed analogous in the two conditions, which would make treatment resistance equally likely. An observational registry cohort study from Sweden compared the effectiveness of various pharmacotherapies in the prevention of hospitalization and work disability in DD populations.⁷³ The results showed that the use of clozapine and a long-acting injectable (LOA) AP was associated with the lowest risk of hospitalization. The use of both LOA and oral aripiprazole correlated positively with the lowest risk of work disability. The relatively superior performance of LOAs suggests that a lack of adherence could explain a large part of the failure to respond to treatment. The reason for the superiority of clozapine over other AP still remains unknown but several hypotheses exist, such as clozapine's affinity for the serotonin receptor (5-HT_{2R}), for the dopamine 1 receptor (D1), for the adrenoceptor (α 2c), and for muscarinic receptors (M1-M4).⁷⁴

In addition, there is evidence that many DD patients refuse AP treatment, chiefly because they do not consider themselves 'psychotic,' but also because they cannot tolerate the side effects.⁷³ Brownstone *et al.*⁷⁵ have provided some tips on how best to address the issue of AP refusal in the context of delusional parasitosis, sometimes referred to as delusional infestation (DI). They recommend introducing the use of an AP by explaining that medications are often used for symptoms and not necessarily for their original indication. They stated that: "One way to get the patient to accept AP treatment is to offer a medication that has no US Food and Drug Administration (FDA) psychiatric indication because DI patients are universally opposed to taking medications involving mental illness." Because the AP, pimozide, is only FDA indicated

for Tourette's syndrome and not psychosis they reported being able to convince their patients to take it.

In the same spirit, clinicians offer antidepressants instead of AP because many patients with DD readily admit that they are depressed. Though the available evidence for antidepressant effectiveness in most cases of DD is weak, there are reports of the efficacy of clomipramine and other antidepressants in the treatment of the somatic subtype (Table 3).^{8,76,77}

Previous studies have reported that cognitive-behavioral therapy (CBT) is effective in treating delusional symptoms in schizophrenia patients, as well as in DD.^{72,78} One trial compared patients with DD who received CBT with a placebo-control group who received an equal amount of medical attention. The results showed that CBT had a higher impact than placebo on the affect relating to delusional belief, strength of conviction, and on proneness to act on delusional beliefs.⁷⁸ This suggests that secondary prevention in the form of psychotherapy, when added to pharmacological treatment, might can shorten the duration of symptoms and prevent negative sequelae.

Discussion

The goal of primary prevention in mental health is to reduce incidence by intervening prior to the onset of illness.⁷⁹ Through early detection and prompt treatment, secondary prevention aims to reduce severity and disability, as well as prevent recurrence and, thus, reduce prevalence.⁸⁰ Poor mental health in a community is a concern because it leads to widespread disability and mortality; it is also an economic concern⁸¹ as well as a cause of major personal and family distress. Prevention, therefore, addresses public health as well as individual health and quality of life.⁸⁰

Delusional disorder (DD) is considered a schizophrenia-related disorder, and, by implication, a severe mental illness associated with disability and suicide, sometimes homicide.⁸¹ It is an understudied disorder, which is why we chose to review the literature pertaining to its primary and secondary prevention.

To address our three aims, we examined the literature on community and individual opportunities for preventive interventions. In considering the establishment of a clinical service to prevent psychosis, Salazar de Pablo *et al.*⁸² systematically reviewed the relevant prevention literature. Although the evidence came mostly from the field of schizophrenia, especially first episode schizophrenia, the conclusions of the review were that clinical monitoring, psychoeducation, antidepressants, psychosocial support, and family intervention were the most effective prevention strategies. Less effective but still recommended measures were anxiolytics, mood stabilizers, and physical health interventions. The authors recommended a multidisciplinary approach, a rapid response to referrals, and flexibility with regard to assessment times and settings (e.g. possibility of home visits after office hours). They also supported a transdiagnostic approach.⁸³ A transdiagnostic approach is consistent with our findings that DD can follow from prior mood and anxiety dysregulation or substance abuse, or sleep disturbance,

or sensory impairment.

At the individual level, the literature emphasizes that lifestyle issues are important in prevention - healthy living, diet, exercise, social activity, solid relationships, social and personal functioning and occupation. Exploring personal stress reduction techniques is also relevant.⁸⁴ Greater accessibility to mental health and social services to rural communities, impoverished and immigrant communities, patients with physical disabilities, women with childcare responsibilities, and workers unable to take time off work are also vital.⁸⁵

The literature has described modifiable and nonmodifiable risk factors and primary prevention strategies for major depressive disorders and for suicidal patients and for elderly psychiatric patients.⁸⁶ These strategies apply to DD patients.

Comorbidities (depression, anxiety, sleep disturbance, substance abuse, and sensory impairment) are often present in DD and their early and comprehensive treatment reduces DD symptoms and prevents sequelae such as injury to self and other.⁶⁸

Demographic factors, such as age, gender, minority status, employment, marriage, parental, or immigrant status require specially tailored and targeted interventions.^{86,87}

Future directions

Because delusional disorder (DD) is a less well-recognized disorder than schizophrenia or depression or dementia, preventive clinical services have not been devoted to this disorder, or the age group most at risk for this disorder, the same way that has been done^{82,86} for more prevalent forms of psychiatric disease. Similar preventive measures apply – psychoeducation, screening, early intervention and psychosocial support for individuals most at risk. Telepsychiatry and outreach to remote communities is the way of the future and has already begun. With respect to improved early treatment effectiveness, genotyping and matching patient to a personally effective therapeutic drug is now underway in many medical specialties. Psychiatric disorders are more complex, but psychiatry will, in the near future, also become the beneficiary of precision medicine.

Conclusions

Because DD is universally considered a relatively treatment-resistant disorder, it is important to prevent this disorder whenever possible by vigorously screening for and treating delusion-inducing medical and psychiatric conditions. Once the disorder has been diagnosed, antipsychotic medication is the treatment of choice. Patients, however, often do not perceive themselves as ill and, therefore refuse psychiatric intervention. Psychosocial treatments are more readily accepted. Although the literature is sparse, the evidence for the success of preventive measures is growing.

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Conflict of interest

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Author contributions

AGR and MVS wrote parts of the first draft of the manuscript and worked together to improve the subsequent versions. Both authors approved the final version of the manuscript.

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