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Differences between delusional disorder and schizophrenia: A mini narrative review

González-Rodríguez A *et al.* Differences among psychoses

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Abstract

Psychotic syndromes are divided into affective and non-affective forms. Even among the non-affective forms, substantial differences exist. The aim of this relatively brief review is to synthesize what is known about the differences between two non-affective psychoses, schizophrenia and delusional disorder (DD), with respect to clinical, epidemiological, sociodemographic, and treatment response characteristics. A PubMed literature search revealed the following: in schizophrenia, hallucinations, negative symptoms and cognitive symptoms are prominent. They are rare in DD. Compared to schizophrenia patients, individuals with DD maintain relatively good function, and their delusions are believable; many are beliefs that are widely held in the general population. Treatments are generally similar in these two forms of psychosis, with the exception that antidepressants are used more frequently in DD and, for acute treatment, effective antipsychotic doses are lower in DD than in schizophrenia. It is with the hope that the contrasts between these two conditions will aid in the provision of safe and effective treatment for both that this review has been conducted.

Key Words: Non-affective psychosis; Delusional disorder; Schizophrenia; Epidemiology; Symptoms; Treatment response

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Core Tip: Although patients with delusional disorder and schizophrenia share clinical similarities, epidemiological and treatment outcomes suggest that these two conditions belong to different diagnostic categories. The onset of delusional disorder (DD) occurs at a relatively late age and, in contrast to schizophrenia, everyday functioning is preserved. Treatment is similar, with more frequent use of antidepressants in DD. Effective targeting of symptomatic domains is important in both these forms of psychosis.

INTRODUCTION

Schizophrenia and delusional disorder (DD) are both non-affective psychoses and symptoms overlap in many ways. Both conditions are characterized by the presence of delusions although, in schizophrenia, hallucinations, cognitive deficits, and features such as thought disorder, apathy, and social isolation are as much in evidence as are delusions. In both disorders, delusions are usually centered around themes of persecution, but grandiosity, morbid jealousy, erotomania, and delusionally interpreted somatic sensations are also very common^[1] (Table 1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delusions, in whatever psychotic illness they are found, are defined as fixed beliefs that are not easily amenable to correction, despite proof to the contrary.

Although Table 1 represents the current sub-classification of DD, several investigators have attempted to introduce different groupings within this diagnostic category. Wustmann and collaborators^[2] classified DD patients into three groups: erotocentric (erotomantic delusions and delusions of jealousy), somatocentric (delusions of health threat and somatic delusions) and securocentric (persecutory, querulous, litigious delusions, and delusions of reference). Some patients present with two or more different types of delusion over time. In the schizophrenia literature, although some

contemporary writers still refer to paranoid schizophrenia as a subtype, sub-grouping according to delusional content is largely obsolete.

The aim of this brief narrative review is to search the existing psychiatric literature in order to address the following questions: (1) Do epidemiological data differentiate DD from schizophrenia? (2) Do clinical features or psychiatric comorbidities differ in DD and schizophrenia? And (3) Are there data that show differences between DD and schizophrenia with respect to treatment response to treatment, both pharmacological and psychosocial?

THEORETICAL SPECULATIONS ON THE ORIGIN OF DELUSIONS

How delusions take root and grow in a human mind is a much-debated topic, which, it is agreed, results from the interaction of biological, psychological and environmental factors.

Theorists believe that delusions arise from chance exposure to an event that feels special, out of the ordinary^[3]. A preoccupation with “how could this possibly have happened to me?” begins to torment the individual until a ‘eureka’ moment is reached when everything falls into place^[4]. This has been called the “aha” experience^[5] when an explanation, sometimes seemingly outlandish, has at last been found.

Despite the fact that the eureka explanation sounds, when shared, implausible to others, it can germinate and plant itself firmly in the mind of a biologically vulnerable individual and become a quasi-permanent, salient feature in that person’s life^[6]. Family members and friends question the explanation, argue against it, which frequently leads to conflicts that culminate in the social isolation of the deluded person^[7]. To account for this process in the context of schizophrenia, most of the literature assumes a genetic predisposition inherent in the deluded person; in DD, on the other hand, because delusions emerge later in life, they are often attributed to acquired brain pathology^[7]. In both conditions, biological underpinnings that make the ground fertile to delusions are assumed, but clear evidence of brain structure/function impairment is usually lacking^[8].

Psychological origin theories are not excluded^[9,10], especially not in DD. Formative traumatic experiences are thought to lead to negative emotions such as shame, guilt, or fear, resulting in a “be on your guard” attitude that transforms ordinary events into threats that grow to become convictions of deliberate persecution^[11]. Some have argued that emotionally aroused states facilitate hypervigilance to threat, and that such states of mind lead to both misinterpretations and, especially in schizophrenia, misperceptions^[12].

It is possible that phenomena such as these arise frequently in many people but are then aborted by feedback from trusted others. Individuals who are socially isolated may not have access to such feedback. It is also possible that, occasionally, delusional explanations for extraordinary events persist because they are reinforced by external affirmation^[13].

There is a school of thought that attributes the persistence of a delusion not only to outside reinforcement but also to the susceptible person’s habitual form of reasoning, or cognitive biases. Such biases have biological underpinnings but may also represent learned phenomena. One example of a cognitive bias is the tendency to jump too quickly to unwarranted conclusions^[14]. As described by Laukkonen *et al*^[4], the more that a person comes to faulty conclusions about everyday events, the more ‘proofs of concept’ are incorporated into an ever-expanding delusional system. It is psychologically easy to attribute mistakes and disappointments to perceived foes and conspirators^[15]. Gunn and Bortolotti^[16] note that paranoid delusions, by placing blame for missteps on outside persecutors, serve as ‘secondary gain,’ allaying the guilt and shame of personal failings. In cultural anthropology, an important distinction has been made between guilt cultures, shame cultures, and cultures of fear^[17], classified on the basis of traditionally preferred ways by which parents socialize their children. In this context, Matos *et al*^[18] speak of shame memories as central to the development of paranoia. Carvalho *et al*^[19] emphasize instead the influence of family narratives and childhood memories on the emergence of paranoid ideation. In a much-cited paper, Kirmayer and Ryder^[20] conclude that cultural habits are embedded in the brain as

neural correlates of emotion^[21], and can thus predispose to different forms of mental symptoms in different cultures.

The literature continues to leave the issue of the origin of delusions open. It is possible, however, to arrive at a conclusion that delusional thinking in psychoses that begin at older ages (such as DD) is likely to originate mainly in life experiences whereas delusions that begin in youth (as in schizophrenia) are rooted in neurodevelopment, with most current research centered on aberrations of neurotransmission, especially dopamine transmission^[22-24]. A recent positron emission tomography study found dopamine dysregulation in both schizophrenia and DD^[25]. This suggests a neurocognitive model for delusion formation that links aberrant salience of a chance stimulus, often threat-related, with mesostriatal dopamine signaling. Secondary cognitive processes are recruited to try to make sense of what is perceived as a highly unusual, highly significant experience. These processes, namely jumping to conclusions, unswerving attachment to one's original conclusions, and inattention to counterarguments, for which dopamine dysregulation may also be responsible, maintain and sustain the delusion^[26]. This is a model of delusion formation that also leaves room for a major contributory role for prior experience of trauma and sociocultural input^[27].

EPIDEMIOLOGY

The lifetime prevalence of schizophrenia, despite variations in study design, geographic source, and study quality, is estimated at 0.48%-1%^[28]. This is in contrast to the lifetime prevalence of DD, rated as 0.2%^[1], but reported by some researchers to be a decimal place rarer - 24 to 30 per 100000^[29]. Prevalence varies with the characteristics of the study sample and the setting of the investigation^[30].

A major difference between schizophrenia and DD is the age of onset, late teens and early adulthood in schizophrenia, middle age and above in DD^[30]. Onset age is critical in many ways. For example, the fact that DD first occurs, for the large part, in postmenopausal women may explain why gender differences during the reproductive

years are not as marked in this disorder as they are in schizophrenia, where circulating estrogen levels protect the brains of reproductive age women^[30,31]. Onset age may also affect the thematic content of delusions. In DD, erotomania, for instance, has been found to be more frequent in women with premenopausal onset while somatic and jealous delusions are more common in women whose onset is postmenopausal^[32].

Epidemiological differences between DD and schizophrenia depend to a significant degree on the diagnostic instrument and the diagnostic criteria and the specific syndromes that are included under the two categories. Some syndromes within the schizophrenia spectrum, such as paranoia querulans (incessant legal actions to obtain compensation for perceived wrongs) and paraphrenia (psychotic symptoms first diagnosed in the elderly) have been removed from current classification systems and are now subsumed under either DD or schizophrenia. This is notably the case for paraphrenia, which is now variably categorized as late onset schizophrenia, atypical psychosis, schizoaffective disorder or DD^[33]. Shifts such as these in diagnostic labeling contribute to changes in reported prevalence of the two disorders.

With respect to the prevalence of subtypes, most investigations agree that persecutory delusions are the most common in both conditions^[34], followed, in DD, by jealous, somatic and erotomaniac delusions^[32,35].

In contrast to schizophrenia which, in addition to delusions, comes with prominent hallucinations, negative, and cognitive symptoms, DD is usually considered a disorder of delusions only. Phenotypic factorial analyses of DD, however, have identified 4 independent symptom areas: delusions, hallucinations, depression, and irritability^[36]. This suggests that DD, as diagnosed today, is symptomatically heterogeneous, with symptoms that overlap to a considerable degree with those of schizophrenia. de Portugal and co-workers^[37], who also investigated this question, found 4 symptom categories in DD, paranoid, cognitive, schizoid and affective, which, together, explained 59% of the variance in symptomatology.

In clinical practice, both schizophrenia and DD patients frequently present with psychiatric comorbidities, mainly affective disorders. In DD, depressive disorders have

been found in 21%-55.8% of patients^[38]. Women may present with more mood symptoms than men, but findings in this area are controversial^[2,35]. In schizophrenia, it has been noted that delusional themes can change over time in approximately one-third of cases^[39]. In terms of functional ability, patients with DD show a significantly superior global functioning than patients with schizophrenia, suggesting that DD is distinct from schizophrenia, and, on the whole, less severe^[40].

CLINICAL APPROACH TO PATIENTS WITH DELUSIONS

The literature strongly suggests that, when beginning treatment with a person who is delusional, whatever the specific diagnosis, the first concern must be safety - safety for the patient, for persons who the patient believes are enemies and for family members and treating personnel who may become incorporated into the patient's delusional system. Suicide is a risk because low self-esteem often lies at the core of delusions. Adding to the concern for safety is the fact that, depending on a jurisdiction's mental health legislation, involuntary treatment can be difficult for the family to arrange, even in situations of imminent danger^[41].

Once safety concerns have been allayed, the next challenge is to build a therapeutic alliance by patient and clinician working together toward common goals^[42]. Clinical practice suggests that initial goals need not be ambitious but must have patient buy-in. For instance, because delusions take their toll on sleep quality, working together to improve sleep by using sleep hygiene techniques and sedatives is likely to engage initially treatment-resistant patients^[43].

Succeeding at something together builds trust and paves the way to information-sharing and, ultimately, to discussion of sensitive topics such as the objective veracity of a delusional belief. But this can wait^[44]. Experienced clinicians always acknowledge the subjective veracity of the belief.

When engaging patients who have difficulty with trust, many therapists recommend starting by discussing early childhood because patients are less likely to perceive past issues as threatening compared to the potential threat of the therapist dismissing their

accounts of current history^[45]. Whereas experience and skill are always clinically useful, there is a consensus that a therapist's genuineness is the most important ingredient in forging a trusting therapeutic bond^[46].

Ongoing therapy largely consists of enhancing the patient's self-esteem, bolstering resilience and improving metacognitive skills^[47]. ¹ Judiciously planting seeds of doubt about the reality of a delusion by exploring alternate explanations is a key metacognitive technique^[48]. ¹ Cognitive-behavioral techniques have successfully eliminated delusional ruminations, negative beliefs about the self, interpersonal oversensitivity, as well as sleep disturbance, each of which has been shown capable of reinforcing delusions^[49].

Techniques recommended for delusional jealousy consist of targeting common tendencies found in such patients, *e.g.*, inferring the emotions and intentions of others, personalizing chance occurrences, overgeneralizing from one or two experiences, and persistently anticipating catastrophe^[50]. Other therapeutic targets are hypervigilance, negative self-esteem, and the inclination to mistrust others. Reframing a patient's view of a situation is an important therapeutic technique^[51] *e.g.*, "He does go out a lot, but it might be because you give him a hard time at home rather than because he's seeing another woman." Experienced clinicians believe that therapists do well to embrace the role of educator, teaching patients about emotions and the many ways in which strong feelings can drive behavior^[52]. Practice sessions and homework assignments relevant to the expression of emotions are cited as a vital part of cognitive therapy and rehabilitation protocols for all forms of delusions^[53].

These recommendations apply to the initial approach to patients with both DD and schizophrenia, but are less effective when the patient's cognition is impaired. Table 2 summarizes the main recommendations for an initial approach to DD.

PHARMACOLOGICAL TREATMENT

Definitions of response to antipsychotic or other pharmacological treatment vary. Response criteria based on reduction in standard rating scale scores, as is done in

schizophrenia^[54], have been recommended in DD^[55] where, thus far, response has been defined on the basis of clinical opinion.

The most recent study in this area was an observational registry- based cohort study in a Swedish population diagnosed with DD^[56]. Hospitalization and work disability were found to be less likely occurrences when antipsychotic were prescribed, compared to when they were not. Protection was best conferred by clozapine, olanzapine and all long-acting injectable antipsychotics. When comparisons were made between DD and schizophrenia, ³ a relatively smaller dose of haloperidol (4.7 mg/d) was effective in suppressing delusional symptoms in DD than in schizophrenia (12.7 mg/d)^[57]. Treatment was shorter (65 d) in DD compared to 104 d in schizophrenia. At hospital discharge, the global assessment of functioning score was also significantly higher in DD^[57]. Although more studies are needed, this suggests that an acute episode of DD may respond to treatment at lower doses and within a shorter time period than an acute episode of schizophrenia. Studies on comparative longer-term response to antipsychotics are, however, lacking.

Factors influencing drug response

Adherence to prescribed drug regimens is generally acknowledged as a critical factor influencing therapeutic response. In turn, adherence is influenced by the patient's gender, age, duration of illness, comorbidities, number of concomitantly prescribed drugs, simplicity of the drug regimen, and quality of the therapeutic relationship^[2,58]. Thomas and colleagues^[59] have studied these factors as they pertain to schizophrenia, but this has not yet been done in DD.

Specific host genes may enhance or diminish drug response. Morimoto *et al*^[57] investigated the relationship between variants of dopamine receptor genes and the tyrosine hydroxylase gene in DD patients, schizophrenia patients, and healthy controls. They found an association between genetic variability in DRD3 and plasma homovanillic acid (pHVA). Specifically, patients with DD ⁶ homozygous for the DRD3 gene Ser9Ser showed higher pretreatment levels of pHVA than others, an effect

especially marked, in this sample, among patients with the persecutory subtype of DD. Aided by structural and functional neuroimaging, work on the genetics of drug response in DD and schizophrenia is underway.

A multicenter positron emission tomography and magnetic resonance spectroscopy study (STRATA) tested whether striatal dopamine synthesis capacity and/or elevated anterior cingulate cortex glutamate levels can differentiate between patients with psychosis who do and do not respond to antipsychotic medications^[60]. The findings revealed a potential ⁵ role of glutamate levels (but not striatal dopamine synthesis) in the prediction of response.

Very few studies have investigated the biological basis of treatment response in DD. In the case of the delusional infestation subtype of DD, one study, however, identified distinct patterns of prefrontal, temporal, parietal, insular, thalamic and striatal dysfunction implicated in response^[61].

Therapeutic drug monitoring is currently a promising technique that can evaluate treatment efficacy, correlate adverse events to prescribed doses and assess adherence. While it is often used in the treatment of schizophrenia, it is still rarely done when treating DD patients.

Use of antidepressants

Antidepressants have been used as monotherapy in DD when clinicians believe that the delusion is caused by depression. Paroxetine and clomipramine are examples of antidepressants commonly used^[62]. Antidepressants used as an adjunct to antipsychotics is a frequent treatment strategy in both DD and schizophrenia.

NON-PHARMACOLOGICAL TREATMENTS

Cognitive therapy has been shown to be helpful in DD^[63], as it is in schizophrenia^[64,65]. Patients receiving CBT show a significant reduction in the strength of their delusional conviction, in the intensity of the affect associated with their delusion, and in the frequency of behaviors resulting from their delusion.

Table 3 presents the main pharmacological and psychosocial interventions used in the management of patients with DD and schizophrenia.

RISK OF SUICIDE

Neither suicide antecedents nor suicide rates have, to date, been compared in DD and schizophrenia. Existing studies have established the percentage of suicidal behavior in patients with DD to be between 8% and 21%^[66]. In schizophrenia, it hovers around 10%^[67]. In both disorders, men are more at risk for completing suicide than women^[38]. The somatic subtype and the persecutory subtype of DD are most associated with suicide^[30] whereas, in schizophrenia, suicide appears to depend not on delusional theme but on the presence of command hallucinations^[68].

DISCUSSION

When we began our review, we wanted to address 3 questions: (1) Do epidemiological data differentiate DD from schizophrenia? (2) Do clinical features or psychiatric comorbidities differ in DD and schizophrenia? And (3) Are there data that show differences between DD and schizophrenia with respect to treatment response to either pharmacological or non-pharmacological treatment?

We found an overlap between the diagnosis of DD and schizophrenia, with boundaries often very blurred. As characterized in DSM-5, the middle age onset of DD distinguishes it from the earlier onset in schizophrenia. The literature gives a prototypical picture of schizophrenia as one of hallucinations, cognitive, and negative symptoms in addition to delusions, with function deteriorating over time. Relatively good function is maintained in DD. While this disorder is also characterized by symptoms other than delusions (mainly affective symptoms), delusions predominate. Treatment response to antipsychotic medication appears to be similar in the two conditions, although DD patients, as a group, are older, and would be expected, as one study has shown, to require comparatively lower doses to achieve symptom reduction. When compared to younger age, older age, however, can limit the benefits of

pharmacotherapy because of an increased frequency of potential drug interactions and adverse events. An adequate long term comparison of drug response in the two conditions is lacking. Clinical reports recommend the addition of antidepressants to the medication regimen of patients with DD, but large-scale trials to prove the usefulness of this strategy have not yet been conducted. Specific symptoms, when targeted by cognitive behavioral therapies, respond in both DD and schizophrenia, although efficacy trials in DD are, to date, limited.

The content of delusions seem more understandable in DD than they often are in schizophrenia but the major theme is one of persecution in both conditions. In general, the prevalence rate for delusional disorder is significantly lower than that for schizophrenia.

Importantly, a persecutory delusion is such a firmly held belief that it can often lead to behavior which endangers the believer and the persons implicated in the delusion. Safety is a paramount concern; suicide is an important risk. Evidence for the success of current interventions into prevention of suicide and aggression remains relatively weak. There are many limitations to this narrative review. There is an extremely large literature on schizophrenia, with well-controlled randomized trials of treatment options. This does not yet exist for delusional disorders. Because of the symptom overlap and the prevalence disparity as well as the age discrepancy, well-defined comparative groups are difficult to recruit. Much of the literature on delusional disorders consists of small case series or reports of individual cases. To accurately answer the questions posed in this review, methodologically well-conducted, multicenter trials are required. The review should nonetheless be helpful for clinicians, especially with respect to initial approaches to patients with delusions, and the cautions about safety.

CONCLUSION

This brief review covers the recent literature on difference between two non-affective psychoses, DD and schizophrenia. The former is much rarer and presents at older ages.

More often than schizophrenia, DD is accompanied by depression, which increases the risk for suicide. Acting out against imagined persecutors is a potential danger in both disorders. While delusions are prominent in both schizophrenia and DD, other psychiatric symptoms may also be present and may require targeted treatment. In contrast to schizophrenia, outside the sphere of the delusion, cognitive functions are usually not impaired in DD, so that a therapeutic alliance is possible and is essential for treatment to succeed. Research into the efficacy of specific treatments is, however, sparse in DD.

This review covers what is known and not known about similarities and differences between schizophrenia and DD, with the hope that highlighting contrasts between these two overlapping conditions will ultimately improve the treatment of both. Future research must address the difficult task of designing rigorous clinical trials that compare response to therapeutic interventions for delusions in individuals whose primary diagnoses may vary.

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