**Title:** Psychosis in Multiple Sclerosis: A Complex Neuropsychiatric Association

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## Introduction:

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system that may be associated with a broad spectrum of neuropsychiatric manifestations. Although psychosis is considered an uncommon complication of MS, increasing evidence suggests that psychotic symptoms may occur more frequently in individuals with MS than in the general population.

## Objectives:

Our aim is to perform a narrative review of the literature regarding psychosis in patients with multiple sclerosis.

## Methods:

A semi-structured search was conducted on PubMed and other major scientific databases concerning the association between psychosis and multiple sclerosis, with particular emphasis on systematic reviews, meta-analyses, and recent relevant studies.

## Results:

Psychosis is an uncommon, but clinically significant manifestation of MS, with reported prevalence ranging from 0.4% to 7.4%. Psychiatric symptoms may precede, coincide with, or develop after the diagnosis of MS, potentially complicating the recognition of an underlying neurological disorder.

Schizophrenia-spectrum disorders, bipolar disorder and mood disorders with psychotic symptoms have been reported among affected patients. Common clinical manifestations include delusions, particularly persecutory and polymorphic delusions, as well as auditory and visual hallucinations.

Several mechanisms have been proposed to explain the association between MS and psychosis. Structural brain abnormalities, particularly extensive periventricular, temporal, frontal, cerebellar

and cerebellar peduncular lesions, may contribute to the development of psychotic symptoms. Neuroinflammatory and autoimmune processes, disruption of neurotransmitter pathways, and corticosteroid treatment may also play a role.

Recent evidence suggests that psychosis emerging after MS diagnosis may be associated with specific lesion patterns, while psychosis preceding or coinciding with MS may represent an early manifestation of the disease.

Treatment-resistant psychosis should raise suspicion of an underlying neurological condition, particularly when accompanied by atypical clinical features or neurological symptoms. Although antipsychotic medication remains central to symptomatic management, treatment of the underlying inflammatory activity of MS may be crucial in selected cases.

## Conclusion:

Psychosis in MS is an uncommon but clinically relevant neuropsychiatric manifestation that may represent a direct consequence of inflammatory and structural brain involvement or coexist with a primary psychiatric disorder. The temporal relationship between psychosis and MS, neuroimaging findings, neurological examination, and treatment response are important in establishing an accurate diagnosis. Clinicians should maintain a high index of suspicion for MS in patients presenting with atypical or treatment-resistant psychosis, particularly in the presence of neurological or radiological abnormalities. Further prospective studies are needed to clarify the underlying mechanisms and establish evidence-based diagnostic and therapeutic strategies.