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Late-Onset Schizophrenia: Do Recent Studies Support Categorizing LOS as a Subtype of Schizophrenia?

Jeanne E. Maglione, MD, PhD, **Scot E. Thomas, MD**, and **Dilip V. Jeste, MD**

Department of Psychiatry, University of California, San Diego, La Jolla, CA

Abstract

Purpose—To review recent literature about late-onset schizophrenia (LOS): schizophrenia with onset between ages 40–60 years. New findings are presented in the context of the previous literature.

Recent findings—Newer studies continue to suggest that early-onset schizophrenia (EOS) and LOS share fundamental clinical features (i.e. positive symptoms, negative symptoms, functional deficits). One larger recent study confirmed earlier findings that LOS differs from EOS in several important ways including predominance of women, lower severity of positive symptoms, and lower average antipsychotic dose requirement. However, this study did not find LOS patients were more likely to have the paranoid subtype or to have less severe negative symptoms compared to EOS patients. New neuroimaging and molecular studies are identifying possible differences in the underlying pathophysiology of EOS and schizophrenia developing in mid- to late-life; however, more research is needed to confirm these findings and determine their significance. No studies evaluated treatment strategies specifically in LOS.

Summary—LOS continues to be an understudied area. Recent studies add support to the idea that LOS may be a distinct subtype of schizophrenia. Studies designed to elucidate the pathophysiology of LOS in comparison with EOS and to assess treatment strategies in this population are needed.

Keywords

Late onset schizophrenia; schizophrenia; older adult

Introduction

Although schizophrenia most commonly presents early in life, at least 20% of patients have onset after the age of 40 years. Some have proposed that schizophrenia with onset between the ages of 40 and 60 years is a distinct subtype of schizophrenia, late-onset schizophrenia (LOS)(1). However, there has been debate regarding the importance of age of onset and the term LOS has not been incorporated into the Diagnostic and Statistical Manuel of Mental Disorders (DSM)-5 (2) which states “late-onset cases can meet the diagnostic criteria for

Corresponding Author: Dilip V. Jeste, MD, Estelle and Edgar Levi Chair in Aging, Sam and Rose Stein Institute for Research on Aging, Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive #0664, La Jolla, CA 92093. Phone: (858)-534-4020. Fax: (858)-543-5475. djeste@ucsd.edu..

schizophrenia, but it is not yet clear whether this is the same condition as schizophrenia diagnosed prior to mid-life." We reviewed papers published over the past few years pertaining to this debate and present these studies in the context of what was previously known about schizophrenia with later onset.

History

Onset in early adulthood was, at one point, considered a central characteristic of schizophrenia. Historically, the idea that symptoms emerged in early adulthood is reflected in the name coined by Emil Kraeplin - *dementia praecox* - which suggested that the illness was associated with progressive decline (dementia) and sought to distinguish it from organic disorders arising in late-life (praecox) (3). Kraeplin himself, among others, later observed that some cases arose in later-life and that, unlike dementia, cases were not always associated with progressive decline. He used two other terms for psychotic illnesses manifesting in middle to late-life, *paraphrenia* for patients with symptomology similar to *dementia praecox*, but with predominantly paranoid features and later onset, and *paranoia* for patients with paranoid delusions manifesting in middle to late adulthood without the other symptoms of *dementia praecox* (i.e. perceptual disturbances, formal thought disorder) (4).

A substantial literature has since documented an evolving thought process regarding schizophrenia presenting in mid to late adulthood. Some important points of consideration have been: 1) whether there is enough evidence to support categorizing cases with later onset as a distinct subtype of schizophrenia, and 2) whether later-onset cases of schizophrenia-like symptoms represent a pathophysiological process completely separate from schizophrenia (i.e. a neurodegenerative process). Early versions of DSM included no upper age limit in the criteria for schizophrenia (5, 6). In the DSM-III, a diagnosis of schizophrenia was not permitted if onset occurred after the age of 45 years. DSM-III-R allowed a diagnosis of schizophrenia at any age but included a specifier of "late-onset" for onset after the age of 45 years (7). Later editions of the DSM have not includes age-related criteria or specifiers (8, 9).

In the late 1990s an international conference including a panel of experts (1) reviewed the available evidence and concluded that cases with onset of symptoms between the ages of 40 and 60 years should be conceptualized as a subtype of schizophrenia and recommended the use of the term LOS. The panel also concluded that schizophrenia-like symptoms arising after the age of 60 years, when the risk of primary neurodegenerative dementias is greater, are more likely to have a distinct underlying (i.e. degenerative rather than neurodevelopmental) pathology. The name very-late-onset-schizophrenia-like-psychosis (VLOSLP) was recommended to describe this group (1, 10).

Demographic Characteristics

A minority of patients with schizophrenia, 20%–29%, have onset after the age of 40 (1). The fact that EOS and LOS are similar with respect to many risk factors is consistent with the idea that they are forms of the same illness (11, 12). Family history is present in approximately 10%–15% of individuals with schizophrenia regardless of age of onset (4).

EOS and LOS are also associated with similarly elevated risks for childhood maladjustment and minor physical anomalies, and having fewer years of education (4, 10) compared with individuals without schizophrenia. A greater proportion of LOS patients have successful occupational and marital histories compared with EOS patients (10). Further, women predominate among LOS but not EOS patients (10, 12, 13). The reasons for this consistently reported finding are not yet clear.

Clinical Characteristics

Both patients with EOS and LOS suffer from what we commonly think of as schizophrenia-related psychopathology (i.e. positive and negative symptoms), cognitive impairment, and functional disability at greater levels than those without schizophrenia (10, 14). It has been reported that LOS patients are more likely to have certain symptoms including well-organized and persecutory delusions and certain types of hallucinations including visual, tactile, and auditory hallucinations with a running commentary (1, 4, 12, 15, 16). One recent study found that among those with delusions, LOS patients have greater belief conviction and poorer insight (14). Some studies have reported that LOS is associated with less severe negative symptomology (17) and greater frequency of the paranoid subtype compared with EOS (4, 12). However, a larger study recently completed at the University of California, San Diego (UCSD) including data collected over 20 years comparing 744 EOS and 110 LOS patients found no differences in severity of negative symptoms and similar relative proportions of patients with the paranoid subtype (10). Consistent with most previous studies, LOS was associated with a lower level of positive symptoms and a lower daily antipsychotic dose requirement (10). Another study recently reported that the prodromal phase of EOS is characterized by more negative symptoms compared to LOS (17).

Cognitive symptoms are one of the strongest predictors of functioning in schizophrenia (18). Both EOS and LOS are associated with cognitive deficits. Further, in both EOS and LOS the level of cognitive impairment tends to be stable over time (4, 19) suggesting that neither is a dementing process. Findings regarding differences in the severity and nature of cognitive deficits have been variable with some studies reporting that LOS is associated with less severe cognitive deficits (4) and others reporting no differences (10, 12, 20). A meta-analysis in 2009 reported that some cognitive functions were relatively preserved in LOS compared with EOS: arithmetic, processing speed (digit symbol) and vocabulary. Importantly, it was noted that the number of studies focusing specifically on LOS was limited and sample sizes tended to be small. Therefore important possible confounding factors including duration of illness, education level, premorbid intellectual abilities or comorbid diseases could not be considered (21). The larger subsequent UCSD study described above found that after adjustment for age and severity of negative/deficit symptoms, LOS was associated with less impairment in abstraction, flexibility of thinking, processing speed (digit symbol), one of two measures of perceptual organization (Block Design), and verbal memory, but no differences in arithmetic or crystallized verbal knowledge (10) compared with EOS. When duration of illness was also considered only the differences in processing speed and perceptual organization remained significant. A single study has compared social cognition measures in patients with EOS and LOS. In this small study including 15 patients with EOS, 15 patients with LOS, and 30 healthy controls,

patients with LOS scored significantly better on one Theory of Mind ability (Hinting Task) compared to those with EOS (22).

These studies suggest that EOS and LOS are similar with respect to major fundamental features, consistent with the idea that they are both forms of the same disease. However, several distinguishing characteristics of schizophrenia with later onset, particularly the consistent finding that LOS patients have lower daily antipsychotic dose requirements, support the utility of considering LOS a distinct subcategory of schizophrenia.

Genetic Studies

Family history is present in 10%–15% of individuals with EOS or LOS (4). One recent study assessed for a 32 base-pair deletion allele in the chemokine receptor CCR5 in 268 patients with schizophrenia and 323 controls. Although there was no association between the deletion allele and a schizophrenia diagnosis there was an association between the allele and a later age of onset (as approximated by first hospitalization) (23). The deletion allele was observed with greater frequency in patients with first hospitalization after the age of 40 compared to those with earlier first hospitalizations. CCR5 binds a number of chemokines and serves as a co-receptor for retroviruses. The investigators postulate that in people at risk for serious mental illness, the deletion allele could have a protective effect against more severe forms (i.e. earlier onset) of the illness via an altered cytokine response to viral infections either in prenatal or early development. Alternatively they suggest that the deletion allele could result in a decreased ability to clear common infections leading to neuronal damage and development of LOS. Another study assessed for the presence of dopamine D2 receptor gene polymorphisms in 157 patients with schizophrenia and 250 control participants and found that one (rs2734829) was associated with schizophrenia and with later age of onset (24). More research is required to both replicate these findings and to fully understand their implications. However, these studies suggest that there may be differences between EOS or LOS with respect to genetic profiles influencing susceptibility and that specific genes may influence age of onset.

Inflammation

A number of studies have found associations between inflammatory conditions, such as autoimmune diseases and infections, and schizophrenia (25). Given that aging is associated with an overall increase in inflammation (26), inflammation could play a role in the pathophysiology of LOS. C-reactive protein (CRP) is a commonly utilized serum marker of inflammation. Some (27–30) but not all (31, 32) studies have reported cross-sectional associations between elevated levels of CRP and schizophrenia. A recent prospective population-based study of more than 70,000 individuals found that elevated plasma levels of CRP were associated with a 6- to 11-fold increased risk of developing schizophrenia in middle to late life. The study design did not allow authors to test for an association between CRP levels and development of EOS.

Neuroimaging Studies

Quantitative neuroimaging studies have shown that EOS and LOS are associated with reductions in the volume of specific brain regions including the medial temporal lobe and anterior temporal gyri (33). One study found that EOS patients had smaller thalamic volumes compared with LOS patients (34). More modern neuroimaging studies employing diffusion tensor imaging (DTI) to assess cerebral white matter abnormalities in schizophrenia have identified white matter abnormalities in the internal capsule, middle frontal gyrus, superior temporal gyrus, and corpus callosum. One small study has employed these techniques to specifically evaluate white matter abnormalities in LOS. The investigators found evidence of abnormal white matter integrity in the left parietal lobe and right posterior cingulum in LOS patients (N=17, mean age 46.9 years) compared with age matched controls (N=17), although there were no associations between these abnormalities and symptomology (35). More research is required to determine whether there are specific differences in the patterns of white matter alterations between patients with EOS and LOS and how this relates to other disease characteristics.

Pharmacological Treatment

Antipsychotic medications are widely employed to treat psychotic symptoms in schizophrenia. Most randomized controlled trials to support this practice were conducted on younger adults. A Cochrane Review conducted in 2012 regarding the use of antipsychotics in LOS (36) found only one study meeting the review's inclusion criteria, an eight week-randomized controlled trial comparing risperidone and olanzapine in 44 in-patients with LOS. The only symptom outcome measure, the Brief Psychiatric Rating Scale (BPRS), was similarly decreased in both treatment arms (37). In short, there was not enough trial-based evidence upon which to base guidelines for use of antipsychotics in LOS. The short-term benefit of risperidone and olanzapine for treatment of psychotic symptoms in middle-aged and older adults with schizophrenia has been supported in multiple double-blind trials (38–41). There have also been single short-term trials suggesting that aripiprazole and paloperidone are of benefit (42).

Recent data has raised concerns about the long-term safety and effectiveness of antipsychotics in middle-aged and older adults. A study recently completed at UCSD compared four commonly prescribed atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in 332 outpatients over the age of 40 years, with psychotic symptoms related to schizophrenia, mood disorders, PTSD, or dementia, over 2 years of treatment (43). An equipoise-stratified randomized study design was employed to mimic clinical practice whereby each participant and their clinician could exclude up to two of the four study medications due to past experience, or anticipated risks. Participants were then randomized with equal probability to receive one of the remaining medications. There was no placebo group. Concerning findings included a high one-year cumulative incidence of metabolic syndrome (36% in 1 year) and high rates of both serious (23.7%) and non-serious (50.8%) adverse events. No significant improvement in psychopathology was found as measured by the BPRS. Over half of the study participants discontinued their assigned medication within 6 months, most often due to side-effects (51.6%) or lack of efficacy

(26%). The quetiapine arm of the study was discontinued early because the incidence of serious adverse events was found to be twice that of the other three atypical antipsychotics included in the study (44). These findings suggest that the commonly used atypical antipsychotic medications may be helpful short-term but neither safe nor effective over longer periods of treatment in middle-aged and older adults.

Psychosocial Treatment

Our review didn't identify any studies testing non-pharmacological interventions specifically in LOS. There are, however, several interventions which are beneficial for older adults with psychotic disorders. Cognitive Behavioral Social Skills Training (CBSST) is a 36-session, weekly group therapy program combining cognitive behavioral therapy with both social skills training and problem-solving training. Compared with a goal-focused supportive group therapy control, CBSST improved functioning and defeatist attitudes in of middle-aged and older patients with schizophrenia or schizoaffective disorder (N=79, ages 45–78 years) (45). A 12 month long program combining social skills training and a nurse-administered preventive healthcare program (HOPES: Helping Older People Experience Success) was associated with improved community living skills and functioning, greater self-efficacy, and lower levels of negative symptoms in a sample of 183 adults over the age of 50 years with serious mental illness, more than half of whom had schizophrenia or schizoaffective disorder(46) (47) and the improvement in community living skills persisted at follow-up 3-years later. Functional Adaptation and Skills Training (FAST), which consists of 24 weekly group-based functional skills classes, was associated with improvement in functioning and decrease in utilization of emergency medical services, particularly emergency psychiatric services, in older adults with schizophrenia (N=240). Studies specifically testing these interventions in LOS patients are needed.

Conclusions

Although the pathobiology of schizophrenia developing later in life continues to be understudied, some new studies addressing age of onset are being done. Recently published studies continue to show that EOS and LOS share most fundamental demographic and core clinical characteristics and therefore support the idea that they represent forms of the same illness. However there are also several important ways in which schizophrenia with onset between the ages of 40 and 60 differs from EOS including: gender distribution, lower average severity of positive symptoms, and lower average antipsychotic dose requirement, which support the utility of considering LOS a distinct subcategory of schizophrenia. New neuroimaging and molecular studies are identifying possible differences in the underlying biology of EOS and LOS, however more research is needed to confirm and interpret these findings. Studies testing treatment strategies specifically in patients with LOS are needed to provide a basis for the development of treatment guidelines.

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23395192] * This study compared Cognitive Behavioral Social Skills Training (CBSST) with a goal-focused supportive contact intervention to improve functioning in patients with schizophrenia over the age of 45 years. CBSST resulted in greater improvements in functioning over time particularly for patients with more severe defeatist performance attitudes. The authors conclude that CBSST can effectively improve function in middle-aged and older adults with schizophrenia. Age of onset was not examined.

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Key Points

1. Published studies continue to show that early- and late-onset schizophrenia share most of the core demographic and clinical characteristics, and therefore, support the notion that they represent forms of the same illness.
2. At the same time, schizophrenia with onset between the ages of 40 and 60 years differs from early-onset schizophrenia in some important ways including greater female preponderance, lower severity of positive symptoms, and lower antipsychotic dose requirement, consistent with the proposal that it may be a distinct subtype of schizophrenia.
3. New genetic and molecular studies are identifying possible differences in the underlying pathophysiology of early-onset schizophrenia and schizophrenia developing in mid- to late-life; however, more research is needed to confirm these findings and determine their significance.
4. Literature on pharmacologic treatment strategies specifically for patients with late-onset schizophrenia is limited, but suggests that the dose requirements are generally lower than those in patients with early-onset illness.
5. Psychosocial interventions are promising although studies specifically testing their efficacy in patients with late-onset schizophrenia are lacking.