Late-Onset Schizophrenia

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Symptoms of psychosis, including delusions, hallucinations, loosening of associations, and thought disorder, are prevalent in geriatric populations. In a Swedish community sample of 347 non-demented adults who were 85 years old at study entry, 10.1% were found to have at least 1 psychotic-type symptom. The most common of these were hallucinations (6.9%), paranoid ideation (6.9%), and delusions (5.5%) [1]. Earlier studies reported that psychosis was present in more than 25% of older patients admitted to inpatient geropsychiatric units [2] and more than 33% of older adults admitted to a hospital for psychiatric treatment for the first time [3]. Psychosis can occur in a variety of conditions and disorders of late life with etiologies including acute conditions such as delirium or the effects of substance use or withdrawal. Alternatively, psychotic symptoms may arise from chronic degenerative conditions such as moderate to severe Alzheimer's disease or Lewy body dementia. Finally, a variety of late-life psychiatric illnesses including delusional disorder, mood disorder with psychotic features, bipolar disorder, and both early- and late-onset schizophrenia (LOS) can also be accompanied by prominent psychotic features.

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History and Terminology

Most individuals with schizophrenia develop symptoms of psychosis in late adolescence or early adulthood. As a result, our understanding of thought disorders primarily stems from these early-onset patients. However, it has long been recognized that such symptoms can emerge for the first time later in life. Unfortunately, late-life psychosis has historically been inconsistently described, imprecisely defined, and understudied. Manfred Bleuler, who first brought attention to the study of late-life psychosis, crystallized these difficulties with an often-cited quote [4, 5]:

> One can hardly deal with late onset schizophrenic pictures without being reminded again and again how right Kraepelin was when he called the science of psychoses of old age 'the darkest area of psychiatry'. Indeed, today as in earlier times the ground seems to shake under our feet, and our basic psychiatric terms seem to lose their meaning, when one grapples with late onset schizophrenias. (p. 259)

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In fact, the rigorous study of late-onset psychotic symptoms started with M. Bleuler who, in 1943, observed that 15% of the patients with schizophrenia he examined had an onset of symptoms after 40 years of age and another 4% developed symptoms after age 60 [5]. Noting that nearly half of his late-onset cases evidenced symptoms that were consistent with those seen in the early-onset schizophrenia, Bleuler coined the term "late-onset schizophrenia" to reflect a disorder with an onset of schizophrenia-like symptoms occurring at age 40 years or later. However, this classification did not immediately take hold in the USA or Great Britain. Rather, the term "late paraphrenia" was more commonly used to reference onset of all schizophrenia-like symptoms and delusional disorders with onset after age 55 or 60 [6, 7].

Late paraphrenia was included as a diagnosis in ICD-9, and in ICD-10, the term was included as a part of the diagnosis of delusional disorder. Despite the lack of data to support an age cutoff, in the DSM-III, schizophrenia was defined as having an onset *before* age 45, thus reflecting the "praecox" view of Kraepelin with typical disease onset in late adolescence and early adulthood. As evidence that schizophrenia can emerge after age 44 accumulated, the age cutoff was eliminated and replaced with a late-onset specifier in the DSM-III-R. Subsequent revisions removed the late-onset specifier, and DSM-IV-TR simply noted that an onset after age 45 is both possible and associated with certain characteristics including female preponderance, better premorbid functioning, more paranoid delusions and hallucinations, and less disorganization and negative symptoms than are characteristic of early-onset schizophrenia. Neither the most recent iteration of the DSM (DSM-5) nor ICD-10 contains separate codes differentiating the late-onset of symptoms.

An International Late-Onset Schizophrenia Group met in 1998 in order to encourage greater consistency in the recognition, classification, and treatment of late-life schizophrenia. Although there were still no data to justify specific age cut points for diagnostic classification, it was felt that some delineation of age groups was necessary in order to stimulate further research in this area. In the resulting consensus statement [8], it was concluded that there was sufficient evidence to justify the adoption of two illness classifications: LOS and very-late-onset schizophrenia-like psychosis (VLOSLP). The former was conceptualized as a subtype of schizophrenia with an onset occurring after age 40 years. VLOSLP was defined as having an onset after age 60 and applies when the symptoms cannot be attributed to an affective disorder or a progressive structural brain abnormality. It was so named in order to reflect the relative diagnostic uncertainty that arises when attempting to identify a primary psychotic disorder at an age in which the risk for dementia-related psychoses begins to rise.

Epidemiology

Despite the findings and age cutoffs recommended by the consensus conference statement, the terms LOS and VLOSLP have yet to be uniformly adopted, and the ages used to define "late onset" still vary across studies. Not surprisingly, gaining an accurate estimate of the incidence of LOS and VLOSLP has proven difficult. The issue is further complicated by the fact that many studies assessing the epidemiology of schizophrenia do not include older adults, and those that do make varying levels of effort to exclude individuals whose psychotic symptoms might be due to such causes as dementias or delirium. Other studies that do focus on psychosis in adulthood often collapse across non-affective psychotic conditions, making it impossible to determine which characteristics are specific to LOS/VLOSLP.

The available evidence suggests that the 1-year prevalence rate of schizophrenia, irrespective of age of onset, in people ages 45–64 is 0.6% [9]. The proportion of individuals with schizophrenia whose symptoms emerge after age 40 (i.e., LOS) has most recently been estimated to be 36.4% [10] with only 3% developing symptoms after age 60 (i.e., VLOSLP) [11]. The community prevalence estimates for those age 65 and older range from 0.1 to 0.5% [12–14], and the incidence of VLOSLP is estimated to be in the

Table 42.1 Comparison of patient characteristics by age of onset

Characteristic	Early-onset schizophrenia	Late-onset schizophrenia	Very-late-onset schizophrenia-like psychosis
Age	<40	41–59	60+
Sex differences	M > W	W > M	W > M
Negative symptoms	Prominent	Perhaps less prominent	Uncommon
Positive symptoms	Prominent	Prominent	Prominent
Thought disorder	Prominent	Uncommon	Uncommon
Partition delusion	Uncommon	Less common	Common
Family history of schizophrenia	Common	Less common	Uncommon
Early-life maladjustment	Common	Less severe	Uncommon
Cognitive dysfunction	Common	Uncommon	Uncommon
Cognitive decline over time	Absent	Uncommon	Uncommon
Efficacious antipsychotic dose	Greater	Lower	Lower

Adopted from Reeves and Brister [18] and Palmer and colleagues [19]

range of 17–24 per 100,000 [15]. Greater age tends to confer greater risk for the disorder, as data from first admission reports for patients age 60 and above indicate the annual incidence of schizophrenia-like psychosis increases by 11% with each 5-year increase in age [16]. Further, while most individuals with LOS or VLOSLP first develop symptoms in their 50s, 60s, and 70s, Cervantes, Rabins, and Slavney [17] reported a woman who, after detailed examination, was found to have developed LOS at the age of 100. Thus, it appears that LOS/VLOSLP can develop at any age in late adulthood.

Clinical Features

The symptoms of schizophrenia, regardless of the age of onset, can include the positive symptoms of delusions, hallucinations, and disorganized speech and behavior, along with negative symptoms such as affective flattening, alogia, and avolition. According to DSM criteria, in order to justify the diagnosis of schizophrenia, these symptoms must disrupt a person's ability to function in major life roles, not be accompanied by prominent mood symptoms and not be due to substance use. Numerous similarities have been noted between the clinical presentation of LOS/VLOSLP and early-onset schizophrenia. In fact, they are often described as being more similar than different, particularly with respect to their positive symptom presentation [8]. On the other hand, evidence suggests that early- and late-onset cases are not identical conditions in terms of their clinical phenomenology (see Table 42.1).

Late-Onset Schizophrenia

There are a number of relative, and sometimes subtle, differences in symptom presentation that differentiate early- and late-onset schizophrenia. One of the most notable and reliably reported differences, particularly among earlier studies, is the relative paucity of classic negative symptoms such as affective flattening or blunting in persons with LOS [20–22]. Almeida and colleagues [23] found that only 8.5% of participants in their cohort evinced negative symptoms, and those that did appeared only mildly affected. In contrast, more recent investigations of large numbers of well-characterized subjects suggest that while individuals with LOS still show greater negative symptoms than age-matched healthy controls [19], EOS and LOS groups show similar negative symptom severity [2, 3, 24, 25], suggesting that early- and late-onset groups may be more similar in this regard than has previously been appreciated.

Individuals with LOS have historically been found to be markedly less likely to experience formal thought disorder (e.g., loosening associations, circumstantiality, etc.) than those who

develop schizophrenia in adolescence or early adulthood [20, 22]. For example, Pearlson and colleagues [20] looked at individuals who had an onset of symptoms after age 45 and found that formal thought disorder was present in only 5.6% of cases. In contrast, thought disorder was present in 51.9% of young adults with early-onset schizophrenia and in 54.5% of older early-onset cases. Pearlson et al. also found that the overall occurrence of formal thought disorder decreased as age of onset increased, such that individuals with the latest onset (i.e., VLOSLP) showed markedly lower rates of disordered thinking.

With respect to positive symptoms, patients with LOS are more likely to report visual, tactile, and olfactory hallucinations than are those with early-onset schizophrenia [20, 26], Alzheimer-type dementia with psychosis, or major depression [27]. When auditory hallucinations are present in LOS, they are more likely to consist of a third person, running commentary and accusatory or abusive content [22]. The content of the delusions in early- and late-onset schizophrenia may also differ, with LOS patients being more likely to experience persecutory and partition delusions (i.e., the belief that people, objects, or radiation can pass through what would normally constitute a barrier to such passage) [20, 22]. Such delusions frequently involve the belief that people or animals invade one's residence at night. For example, we had one patient with VLOSLP who was convinced that the light on a distant power line actually was a device being used to monitor her behavior at home. It has also been reported that some Schneiderian first-rank symptoms, such as delusions of control and thought insertion, thought withdrawal, or thought broadcasting, are far more likely to occur in LOS than in dementia-related psychosis [27].

Very-Late-Onset Schizophrenia-Like Psychosis

Relatively few studies have focused on the presentation of patients who develop psychoses for the first time in very late life and whose symptoms meet criteria for VLOSLP. Nonetheless, available evidence does suggest some unique and identifying symptoms in these patients. For example, there is a high prevalence of sensory deficits including a notable preponderance of conduction deafness [7, 28] and social isolation in those with VLOSLP [7].

Perhaps even more so than in LOS, formal thought disorder and negative symptoms are extremely rare in those with onset at age 60 or later [4, 23, 29]. Nevertheless, most, if not all, positive symptoms of early-onset schizophrenia can also appear in those with VLOSLP. Helping to differentiate VLOSLP from psychotic symptoms arising due to other etiologies are the partition delusions that occur in up to 70% of VLOSLP cases [20, 30, 31] but are less common in early-onset schizophrenia. The nature and pattern of positive symptoms of schizophrenia seen in VLOSLP also tend to be rather unlike the psychotic symptoms seen in the so-called *organic* psychoses of aging such as Alzheimer's disease and Lewy body dementia. A more characteristic delusion of patients with Alzheimer-type dementia is that others are stealing personal effects that the patient actually has misplaced or hidden and forgotten. Unlike dementing conditions wherein delusions and hallucinations tend to be less organized and persistent, the psychotic symptoms of VLOSLP tend to be more organized, fully formed, and stable features of the condition. As is discussed below, also unlike psychoses in dementia, the psychotic symptoms of VLOSLP are not invariably associated with a decline in cognition over time.

When considering the positive symptoms of schizophrenia evident in VLOSLP, there is a high prevalence of visual hallucinations [22, 29, 32]. Multimodal hallucinations are also quite common in this group. In a well-characterized cohort of persons with VLOSLP from south London, Howard [4] found visual hallucinations in 40% of the sample, with 32% experiencing these as well-formed visual hallucinations. Further, approximately 20% had what were described as Charles Bonnet-type complex recurrent visual hallucinations (sometimes described as "Charles Bonnet syndrome plus" [33]). Also common,

reported in 59.4% of the sample, were visual misinterpretations and misidentifications. In comparison with the prominent visual disturbances, auditory hallucinations were even more common in the London cohort, as 70% of those with VLOSLP were noted to have nonverbal auditory hallucinations. Another sizable proportion of participants (49.5%) endorsed auditory hallucinations consisting of third-person voices or voices speaking directly to the patient. Hallucinations in other modalities were common as well, with 30–32% reporting olfactory, gustatory, or tactile hallucinations with delusional elaboration. Finally, equally notable were the high rates of delusions of persecution (84.2%) and reference (76.3%) seen in VLOSLP.

Risk Factors and Associated Features

A number of studies have examined risk factors for the development of LOS and VLOSLP including gender, age, premorbid functioning, family history of schizophrenia and dementia, APOE genotype, pharmacological treatment response, and neuroimaging characteristics.

Gender

Perhaps the most consistent risk factor for the development of schizophrenia or psychotic symptoms in late life is gender. Unlike early-onset schizophrenia in which there is a male predominance, considerable evidence indicates that a disproportionate number of individuals diagnosed with LOS and VLOSLP are female [14, 23, 24, 29, 30]. In one early study of gender differences in schizophrenia onset across the lifespan, Castle and Murray [14] found a male to female ratio of 1.56:1 in the 16- to 25-year age group. The ratio was roughly equal among those with onset around age 30. However, for those whose psychosis emerged for the first time between 66 and 75 years of age, the male to female ratio declined to just 0.38:1.0. Further, this difference appears to persist even after accounting for gender differences in social role expectations and care-seeking behavior [34, 35].

Age

Age also appears to be a risk factor, particularly for developing VLOSLP. The risk of developing schizophrenia is highest in adolescence and early adulthood. It declines during mid-adulthood but then increases again after age 60, at which time very LOS-like psychoses occur with increasing frequency. VLOSLP has been found to occur in 10 individuals per 100,000 adults in the 60–65 age bracket. Thereafter, the rates rise steadily to 25 per 100,000 among adults aged 90 and above [16].

Premorbid Functioning

Although some studies suggest poor childhood adjustment in both early- and late-onset schizophrenia [36], many investigations have found notable differences in rates of successful social and role functioning between early- and late-onset cases. Generally, individuals who develop psychosis late in life tend to have better premorbid educational attainment, greater occupational success, and less impaired psychosocial functioning than is seen in early-onset schizophrenia [21, 37, 38]. For example, in one study [14], half of those with early-onset schizophrenia were judged to have poor premorbid work adjustment as compared to only 15% of the LOS group. Similarly, while 43% of early-onset subjects were rated as showing poor premorbid social adjustment, only 22% of those with LOS were rated as such. Rates of marriage were also twice as high among LOS compared to early-onset cases (66% vs. 33%).

While later onset of schizophrenia and psychosis may be associated with better psychosocial functioning and perhaps a less severe form of the disease, evidence suggests that those who do develop schizophrenia/VLOSLP in late life are more likely to have a history of mild premorbid

schizoid or paranoid personality traits that do not meet criteria for a personality disorder [7, 20, 21]. Further, evidence suggests that while their psychosocial deficits are not as severe as those with early-onset schizophrenia, they still have greater rates of general psychopathology and functional disability than healthy normal controls [24].

Family History

Family studies of LOS and VLOSLP tend to be small and have methodological shortcomings. There is some evidence that those with LOS may have higher rates of schizophrenia among relatives than unaffected individuals [37]. However, studies also have found lower rates of schizophrenia among relatives of those with late-onset compared to early-onset schizophrenia [20, 39]. There does not appear to be an increased rate of schizophrenia among relatives of patients with VLOSLP [19] nor does there appear to be an increased prevalence of family history of Alzheimer's disease, vascular dementia, Lewy body dementia, or APOE ε4 alleles in LOS or VLOSLP [40]. Consistent with this, LOS patients do not show the hallmark neuropathological indicators associated with neurodegenerative dementias on autopsy [41].

Pharmacological Treatment Response

At present, there is no good randomized clinical trial evidence on which to base treatment guidelines for LOS/VLOSLP [4, 42]. Despite the lack of well-controlled, double-blind trials and overreliance on case reports or series, available evidence indicates that LOS and VLOSLP often respond well to antipsychotic medications. Further, effective treatment can often be reached at doses that are a fraction of those used for early-onset cases. Based on open-label observations, Howard [8] found that LOS can often be effectively managed on antipsychotic doses that are approximately 40% as high as that needed for younger patients. Similarly, Barak [38] reported that 71.4% of individuals with VLOSLP reached a favorable response to an atypical antipsychotic (risperidone) as compared to just 57.1% of older patients with early-onset schizophrenia. Despite its apparent efficacy, recent data suggests that less than half of VLOSLP patients are started on an antipsychotic at time of diagnosis and only about one quarter are receiving pharmacological treatment at 1 year post-diagnosis [43]. More careful monitoring and greater efforts to enhance treatment engagement may be warranted in this population. As in all populations, antipsychotic side effects can include sedation, anticholinergic effects, extrapyramidal effects, weight gain/diabetes, hyperglycemia, tardive dyskinesia, and neuroleptic malignant syndrome.

Neuroimaging

Neuroanatomic investigations of individuals with schizophrenia have generally failed to detect consistent characteristics that differentiate LOS cases from early-onset schizophrenia. Anatomic brain imaging studies of individuals with LOS have found increased ventricle-to-brain ratios in LOS/VLOSLP compared to matched healthy controls [38, 44, 45]. Semiquantitative analyses of brain MRI scans have demonstrated larger thalamic volume in LOS compared to early-onset schizophrenia [46] and smaller third ventricle volumes compared to age-matched controls [47]. Focal changes, such as reduced volumes of the left temporal lobe and superior temporal gyrus, are also similar to those found in early-onset cases [45, 48]. With respect to white matter abnormalities, some early studies reported that large subcortical white matter hyperintensities were common in LOS [49]. However, subsequent studies that carefully controlled for organic cerebral disorders failed to replicate these earlier findings among late-onset cases [38, 50, 51]. More recent diffusion tensor imaging findings also failed to find significant differences in fractional anisotropy or mean diffusivity between those with VLOSLP and age-matched unaffected adults, arguing further against structural white

matter abnormalities as a potential etiology for psychotic symptoms late in life [52].

Early functional neuroimaging studies found lower perfusion of the frontal and temporal lobes in LOS as compared to EOS and healthy controls [53], as well as preliminary evidence of higher D2 receptor density in those with LOS compared to age and gender norms [45]. More recently, Wake [54] compared regional cerebral blood flow (rCBF) in EOS in their 30s to LOS patients and found different patterns of rCBF between the patient groups. While the EOS group showed reduced precentral and inferior frontal gyri rCBF, those with LOS demonstrated bilateral postcentral gyri reductions. The LOS group generally demonstrated more strongly localized temporal lobe hypoperfusion. While these findings suggest that differences in rCBF may be related to the age of disease onset, the age difference between the patient groups introduces a significant methodological limitation. Furthermore, the study was cross-sectional in nature, and it remains unclear whether any LOS participants showed signs of an incipient dementia syndrome that might account for the observed temporal hypoperfusion.

In light of the known association between elevated inflammatory biomarkers and risk of schizophrenia, Wium-Anderson and colleagues [55] conducted a large case registry review and found that elevated C-reactive protein at baseline was associated with a 6- to 11-fold increase in the risk of LOS and VLOSLP in the general population. These associations held even after removal of participants who went on to develop dementia in the 2 years following their diagnosis of schizophrenia.

Cognitive Profile and Course

Contrary to Kraepelin's notion that schizophrenia involves a progressive "dementia praecox," there is now compelling evidence that early-onset schizophrenia is a neurodevelopmental disorder that rarely involves progressive dementia. While the development of schizophrenia in early life certainly is associated with widespread cognitive dysfunction, it does not predict worsening cognitive decline in late life relative to age-matched controls [56, 57]. Some experts have suggested that the emergence of psychotic symptoms late in life may signal the onset of a neurodegenerative process [58]. Further, given that LOS/VLOSLP arises at a time in which rates of dementia begin to rise, differentiating the cognitive pattern of a primary psychiatric disease from the psychoses that can accompany dementia is important from a treatment planning perspective.

Persons with early-onset schizophrenia show severe and pervasive deficits across virtually all domains of cognitive functioning. The most pronounced impairments typically appear to involve psychomotor speed, verbal memory, and attention [59, 60]. Beginning in the mid-1990s, studies began finding that both early- and late-onset schizophrenia involve cognitive dysfunction [21, 56] and that early- and late-onset groups tended to perform quite similarly to one another on cognitive testing. In these early studies, the primary differences seen between the early- and late-onset groups tended to occur on tests of learning/memory and abstraction/mental flexibility, with later age of onset being associated with better performance on these tasks.

Vahia and colleagues [24] replicated the finding that outpatients with both early- and late-onset schizophrenia performed more poorly than healthy controls on most cognitive tests but that those with LOS showed less severe dysfunction on most measures and these differences in cognitive impairment were accompanied by notable functional differences. Their early- and late-onset groups were equivalent in terms of crystallized verbal abilities and working memory as assessed by Wechsler subtests (Wechsler Information, Vocabulary, Similarities, and Arithmetic subtests). However, the LOS patients showed less severe impairment than early-onset cases on tests of processing speed (Digit Symbol), visuoconstruction (Block Design), executive functioning (WCST perseverative responses), and verbal memory as assessed by CVLT long-delay free recall (when adjusted for Trial 5 learning). In addition to showing less severe cognitive deficits, the LOS group performed better than early-onset patients on performance-based measures of functional capacities, social skills, and health-related

quality of life. More recent work by Brichant-Petitjean and colleagues [61] found similar results when comparing a group with EOS, those with LOS who were <65 years old and had MMSE >27, and healthy matched controls across a brief cognitive battery. Here the LOS group demonstrated intermediate cognitive functioning, outperforming the EOS group on Digit Span forward, phonemic verbal fluency, and delayed recall of the Rey Complex figure while consistently underperforming relative to the controls.

Most studies examining the cognitive profile of schizophrenia emerging in late life have combined patients with LOS and VLOSLP or combined across late-life psychosis diagnostic categories. As a result, less is known about whether there are any unique VLOSLP-related cognitive deficits. Those studies that do address this issue have found that the cognitive deficits associated with VLOSLP are widespread, with no pronounced differences in cognition between LOS and VLOSLP [8]. Similarly, when considering the full spectrum of schizophrenia-spectrum disorders (i.e., schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder, and psychotic disorder NOS), Hanssen [62] found that non-demented very late-onset patients were similar to non-demented early-onset patients in terms of IQ, attention, memory, and executive functioning.

Of critical importance is determining whether the onset of psychosis late in life signals the presence or onset of a dementing condition. Available evidence suggests that the pattern of cognitive deficits seen in early- and late-onset schizophrenia differ from those seen in Alzheimer's disease, with schizophrenia of any age of onset showing a pattern of deficient learning coupled with intact retention [21, 56, 63, 64]. This contrasts with the impairments seen in Alzheimer's disease, which involve both learning and retention.

Several longitudinal studies have sought to determine whether LOS/VLOSLP might herald the development of a progressive dementia syndrome. Most of these [57, 65, 66] have found a pattern of stable cognition over a period of several years. For example, a careful review of the longitudinal cognitive literature failed to yield any conclusive evidence that cognitive trajectory of EOS and LOS patients differs over time [67]. A longitudinal [68] study of patients with early- or late-onset schizophrenia, mild Alzheimer's disease, Alzheimer's disease with psychotic features, and healthy controls found that both dementia groups showed steep cognitive declines over a 2-year period, whereas both schizophrenia groups and the normal controls remained cognitively stable over the same interval. However, the finding of stable cognitive functioning over time in LOS is not uniform. A few studies with longer follow-up periods have reported that a proportion of patients decline over time. For example, Holden [15] conducted a retrospective chart review and found that 35% of people with LOS developed dementia within a 3-year follow-up period. Brodaty and colleagues [58] reported that 9 of 19 (47%) older adults with LOS subjects developed dementia over a period of 5 years, whereas none of the 24 healthy controls developed dementia over the same period. In the largest study to date, Korner and colleagues [69] conducted a retrospective cohort study of patients in Denmark who were first hospitalized with a diagnosis of schizophrenia late in life. Both late and very late first-contact patients were several times more likely to develop a dementia syndrome over the 3–4.5 years following hospitalization when compared to both the general population and to a somatic (osteoarthritis) control group. Finally, a longitudinal study of psychogeriatric clinic patients, Rabins and Lavrisha [27] examined the rates of conversion to dementia (as indicated by declines in MMSE of ≥4 points and fulfillment of DSM-IV criteria for dementia) in 28 cognitively intact, non-depressed patients with LOS; 48 patients with depression but not dementia or psychosis; and 47 patients with dementia and psychosis. While approximately half the LOS cases developed dementia by 10-year follow-up, those with LOS were no more likely to develop dementia than those with late-life major depression. These findings suggest it may be the late-onset of a psychiatric disorder, rather than the late-onset of schizophrenia specifically, which may portend the onset of a dementia syndrome in some individuals.

Taken together, cross-sectional and longitudinal studies suggest that while individuals with LOS may perform more poorly than normal controls on tests of learning and memory, they can be differentiated from those with primary dementing conditions by the relative preservation of retention and recognition skills. Further, the psychosis of LOS and VLOSLP is not invariably associated with deteriorating cognitive abilities, and some patients remain cognitively stable over time. Given the variability in cognitive outcomes, a progressive dementia syndrome does not appear to be the primary underlying etiology of most cases of LOS/VLOSLP. Further research is needed to determine the pathology of most commonly experienced by those individuals with LOS/VLOSLP who do ultimately convert to a dementia syndrome.

Assessment

Given the age of the population in question, when a patient presents with symptoms of psychosis late in life, the referral question tends to focus on differentiating between late-life psychosis and a primary dementing illness. However, psychosis in late life can stem from several etiologies including acute conditions such as a delirium, degenerative conditions like moderate to severe dementia, or any of several psychiatric illnesses, including delusional disorder, mood disorder with psychotic features, bipolar disorder, and either early- or late-onset schizophrenia (see Table 42.2). In light of the differential course and survival rates for these various etiologies, an accurate diagnostic formulation is crucial to formulating the most effective treatment plan.

Table 42.2 Common differential diagnoses

Delirium
Substance use or withdrawal
Alzheimer's disease, moderate to severe
Lewy body dementia
Delusional disorder
Mood disorder with psychotic features
Bipolar disorder
Schizophrenia (early onset)

Clinical Interview and Symptom Assessment

As described above, the cognitive deficits of LOS/VLOSLP are relatively nonspecific and usually milder than those seen in older adults with early-onset schizophrenia. Thus, evaluation and proper diagnosis of these patients rely heavily on taking a thorough history of the patient's premorbid functioning and the nature and course of the psychotic symptoms. We have found that a knowledgeable informant can provide critically important data. This is particularly the case if a patient is experiencing intrusive psychotic symptoms at the time of the evaluation. However, the absence of an identifiable family member, friend, or caregiver who knows the patient well enough to provide such input suggests a level of social isolation that is fairly common in LOS patients. Determining the duration of symptoms can itself be a challenge given that these patients often lead relatively solitary lives. In fact, many such individuals only come to the attention of care providers after a neighbor becomes concerned about paranoid or other floridly psychotic behavior. For example, one of our patients repeatedly and angrily confronted the neighbor that she believed was breaking in and stealing money from her home. It was only after repeated unsuccessful attempts to convince the patient otherwise that the neighbor contacted the local police, which prompted the patient's admission to our geriatric psychiatry service.

As LOS and VLOSLP are associated with various premorbid characteristics, when taking a clinical history, particular attention should be paid to the individual's occupational and social functioning during midlife. Did the patient achieve a reasonable degree of occupational success by mid-adulthood, or is their work history characterized by difficulty maintaining employment, "underemployment" (working at jobs for which they are clearly overqualified), or recurrent problems working with others so that they quit jobs or were terminated? Since LOS and VLOSLP are associated with the presence of mild premorbid schizoid or paranoid personality traits, it can also be helpful to determine whether an individual has

a full and socially connected existence or gravitated toward solitary activities in their adulthood. Similarly, it is helpful to determine whether an individual's history suggests a lack of interest or success in forming romantic relationships or a general lack of relationships that could be characterized as close or warm. It is helpful to determine if the patient is described as mistrustful of others, quick to perceive slights or threats, or frankly suspicious. Although this is informative, the paranoia that often characterizes LOS/VLOSLP makes it difficult to obtain these details directly from the patient and sometimes from others as well. Rather, these individuals are often suspicious of the assessment procedures, reticent to disclose personal information, or unwilling to allow a knowledgeable informant to speak to the neuropsychologist or treatment team.

As was outlined above, LOS and VLOSLP are associated with common but not pathognomonic clinical features. These include prominent positive symptoms, such as auditory hallucinations of accusatory or abusive voices, visual hallucinations, and paranoid, persecutory, or partition delusions. Negative symptoms (i.e., alogia, avolition, and affective blunting) tend to be less prominent, and formal thought disorder is relatively rare. In our clinic, we augment our clinical interview with the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS). These semistructured interview/observation rating scales [70] can help quantify the severity of positive and negative symptoms. The SANS is a 25-item scale with five subscales: affective flattening, alogia, avolition/apathy, anhedonia/asociality, and inattention. The SAPS consists of 35 items and 4 subscales: hallucinations, delusions, bizarreness, and formal thought disorder. Both scales include a global rating, and symptoms are rated as they occurred over the preceding month.

Differentiating LOS/VLOSLP from Other Psychiatric Disorders

A thorough review of a patient's clinical and psychiatric history is essential to diagnosis, as the symptom presentation and cognitive deficits can be similar to other disorders. Affective disorders, including bipolar disorder and unipolar depression, also are common in older adults and can be accompanied by frank psychosis. The symptoms of LOS/VLOSLP do not couple tightly with fluctuations in a patient's mood. If psychotic symptoms resolve with return to a euthymic state or a patient exhibits mood-congruent psychotic features in manic and depressed states, LOS/VLOSLP should not be diagnosed, and consideration should be given to a diagnosis of depression with psychotic features or bipolar disorder. In our clinic, we routinely administer the 15-item Geriatric Depression Scale [71]. The diagnostic validity and reliability of this version are comparable to those of the original 30-item version [72, 73], and this appears to be the case for middle-aged adults as well [74]. Finally, although delusions can be a feature of LOS and VLOSLP, they differ from a late-life delusional disorder in that the latter is characterized by the presence of a nonbizarre delusion that occurs in the absence of prominent auditory or visual hallucinations. Further, delusional disorders are often associated with preserved premorbid personality, intact intelligence, and intact functioning in matters that are unrelated to the content of the delusion. This contrasts with the symptoms of LOS and VLOSLP in that the delusions may be bizarre, multimodal hallucinations are common, and both cognitive and functional deficits may be present.

Differentiating LOS/VLOSLP from Dementia Syndromes

Psychosis can occur in a variety of dementia syndromes such as Alzheimer's disease, Lewy body dementia, Parkinson's disease, and vascular dementia. However, there are several means of differentiating a primary psychiatric disorder from a primary degenerative cognitive disorder in an older patient. Because of the high rates of sensory deficits in LOS/VLOSLP, we often find it helpful to begin by evaluating the patient's auditory and basic visual-perceptual abilities. Hearing can be informally assessed during the clinical interview by performing basic comprehension and repetition tasks or by having the patient close

his or her eyes and indicate in which ear they hear the examiner's fingers rubbing lightly. If auditory deficits are present but mild to moderate, we often use a microphone and amplifier worn in the ear during cognitive assessment. More severe deficits may warrant delaying neuropsychological testing until after an audiology consultation. A pocket vision screener can be used to screen for problems with near visual acuity. We find it useful to keep a selection of magnifying reading glasses in various strengths for patients with decreased near visual acuity to use during testing. Finally, we often rely on the Judgment of Line Orientation, Hooper Visual Organization Test, and Boston Naming Test to detect the presence of visual misperceptions, which are common in LOS and VLOSLP.

Differentiating the psychosis of late-life schizophrenia from the psychosis that can accompany dementia should include a characterization of the initial symptoms and the temporal course of the condition. Hallucinations and delusions are rarely an initial symptom of dementia. Rather, in primary dementia syndromes, early cognitive decline is often the first indication of a disorder. These cognitive impairments tend to be at least moderately severe by the time psychotic symptoms emerge in patients with a primary dementing illness. In contrast, the psychotic symptoms of LOS and VLOSLP are often the first and most prominent manifestations of these conditions. While cognitive deficits often co-occur with the hallucinations and delusions, these deficits are usually not severe enough by themselves to bring a patient to clinical attention. Qualitatively, the hallucinations and delusions of LOS and VLOSLP tend to be more organized, elaborate, and stable than those seen in dementia. Finally, while not an essential feature of dementing illnesses, it is helpful to assess whether the patient has experienced a decline in cognition and if so, over what period of time. A decline in cognition and functioning over a period of months to years is often a sign of dementia. The cognitive weaknesses seen in LOS and VLOSLP, in contrast, tend to be stable features of the disorder and generally do not worsen over time, particularly when symptoms emerge between age 40 and 60 (i.e., LOS).

When attempting to diagnose an older patient with psychosis, it is also important to assess the presence of other symptoms that are characteristic of particular dementia syndromes, as their presence decreases the likelihood that the patient has LOS. Both LOS and VLOSLP are associated with a broad, generalized pattern of mild cognitive dysfunction. However, some features are generally not seen in these patients. Apraxia and naming deficits are not typical of LOS/VLOSLP, whereas they are prominent in Alzheimer's disease. Similarly, in a patient with visual hallucinations, the presence of axial rigidity, disproportionate impairment on tests of visual-perceptual or visual-constructional ability, and other Parkinsonian features would raise the suspicion for a Lewy body dementia and reduce the likelihood of LOS in the differential diagnosis. Several studies have found that patients with LOS or VLOSLP also be differentiated from those with dementia by their relatively preserved retention of newly acquired information as demonstrated by tests such as the HVLT-R or CVLT-II.

Medical Rule Outs and Recommendations

As with many conditions warranting a clinical neuropsychological evaluation in older adults, particular care must be taken to rule out the presence of delirium or another organic cause of psychosis when LOS/VLOSLP is in the differential. Learning about the course of the patient's symptoms can be illuminating. Unlike delirium in which hallucinations and delusions appear to wax and wane, the psychotic symptoms of LOS/VLOSLP tend to be stable and persistent. They rarely show marked fluctuations over time. We often recommend the patient undergo standard laboratory blood studies (e.g., complete blood count, glucose, TSH, electrolytes, BUN, creatinine, liver function, B12, folate, RPR, etc.) in order to rule out thyroid conditions, infections, glucose or electrolyte abnormalities, vitamin deficiencies, and other metabolic abnormalities. A toxicology screen should be considered, particularly if there is a suspected history of substance abuse. Any recent changes in drug use

should also be considered, as older adults can be particularly vulnerable to drug withdrawal. Similarly, it can be helpful to review the patient's medication history to assess for the potential effects of anticholinergic medications and adverse drug interactions. Brain imaging can be informative in determining whether any strokes, tumors, or other cerebral abnormalities might account for the late-onset of psychotic symptoms. Finally, given the increased rates of sensory deficits in patients with LOS/VLOSLP relative to older patients with affective disorder, early-onset schizophrenia, and age-matched controls [4, 20], recommendations for formal audiology and ophthalmology workups are often helpful to assess the extent to which sensory deficits might contribute to misinterpretations in older patients with psychosis. See Table 42.2 for common considerations in the differential diagnosis.

Treatment Recommendations

As outlined above, a substantial proportion of patients with LOS/VLOSLP show effective treatment response to relatively low-dose neuroleptics. For some patients, such treatment can limit their experience to a single acute episode. We have found that a geriatric psychiatrist is the most appropriate person to manage a patient's psychotropic medications. Further, if sensory impairments are present, attempts should be made to remedy these as well as possible, as they might contribute to perceptual aberrations. Even if full correction of sensory impairments is not possible, it can be helpful to educate patients about the potential contribution of hearing or vision impairments to their symptoms and difficulties with everyday functioning.

There are also a number of psychosocial interventions and recommendations appropriate in this population. These include supportive and cognitive-behavioral therapies. Aguera-Ortiz and Renese-Prieto [4] outlined a number of "tips and tricks" for the psychological management of patients with late-life schizophrenia. Even though patients may have difficulty forming an initial attachment to their treatment providers, attempts should be made to establish a good therapeutic relationship and a supportive atmosphere. It is not necessary to agree with a patient's delusional system, but rather to be empathic and understanding. Listening to psychotic complaints in a nonjudgmental manner may lessen the likelihood that they will act on their agitation (e.g., by confronting neighbors). It can also help address a patient's social isolation, especially if it leads to entry into a larger social sphere. More generally, we have found it important to educate family members and caregivers and to help create a network of persons (e.g., family members, friends, neighbors, church members) who can help ensure a patient's ongoing safety. In some instances, the establishment of a conservatorship or guardianship may be in the patient's best interest.

Clinical Pearls

- LOS/VLOSLP is associated with female gender, increased age, premorbid schizoid or paranoid personality traits, poor premorbid social and occupational functioning, social isolation, and sensory deficits.
- Symptoms tend to consist primarily of positive symptoms such as auditory or visual hallucinations or paranoid delusions. Partition delusions are particularly common and are fairly unique to LOS/VLOSLP. There is also often a lack of negative symptoms and formal thought disorder, particularly in those with very late onset.
- Similar to early-onset schizophrenia, LOS/VLOSLP is associated with a generalized, nonspecific pattern of cognitive dysfunction. However, the cognitive impairment tends to be less severe than early-onset schizophrenia. It differs from that seen in patients with dementia with psychosis by virtue of the relative sparing of memory abilities and the absence of cortical features and extrapyramidal signs. LOS and VLOSLP have been conceptualized as primarily non-dementing disorders, but patients with late onset of schizophrenia

probably are at increased risk of developing dementia.

- When an older patient presents with psychotic symptoms, it is important to first rule out delirium, identifiable medical etiologies, and the effects of medications or toxins, as well as prominent mood symptoms.
- Treatment, both psychosocial and pharmacological, can be successful in helping affected individuals maintain maximal functional independence and remain safe.

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