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Introduction

The literature on late-onset schizophrenia (LOS) is growing, although slowly. It points to important diagnostic, treatment, and prognostic differences from the more common early-onset schizophrenia (EOS). Yet, there remain some gaps in our understanding (Jeste and Nasrallah, 2003), suggesting a need for further research. As of 2000, it was estimated that only 1% of the literature on schizophrenia focused on the older population, with an even smaller proportion specific to the late-onset subgroup (Cohen et al., 2000). Unsurprisingly, schizophrenia with onset in late life remains a challenge to both clinicians and researchers, despite the one-year prevalence rates of 0.6% and 0.2% among individuals aged 45–64 years and 65 years and over, respectively, and lifetime prevalence of 1% and 0.3% reported by the Epidemiologic Catchment Area (ECA) study (Robins and Regier, 1991) and the rising numbers of older adults.

Research on this topic has been hampered by lack of consensus regarding nomenclature and diagnostic criteria as well as heterogeneity in clinical samples, often resulting in a variety of clinical syndromes included under the same broad diagnostic category (Castle and Morgan, 2008). For example, ‘late-life schizophrenia’ is an umbrella term that can be applied to two different groups of individuals: those diagnosed with schizophrenia in early adulthood and those who developed the illness in middle or late life (Palmer et al., 1999).

A significant increase in the older population is expected, resulting in a doubling of the number of seniors with severe mental illnesses by 2050 (Cohen et al., 2000). More frequent cases of LOS are to be expected, but it needs to be emphasized that individuals with onset of symptoms prior to age 45 will still account for approximately 85% of patients with schizophrenia encountered in clinical settings (Cohen et al., 2000). In this chapter, we focus primarily on schizophrenia first manifesting in late life, and subsequently on chronic schizophrenia in older people and its distinction from LOS.

Nomenclature

Historical background

While the current terms late-onset schizophrenia (LOS) and very-late-onset schizophrenia-like psychosis (VLOSLP) have gained acceptance in recent years, previous terms such as late paraphrenia and the French term *psychose hallucinatoire chronique* remain in use occasionally in the world literature and are commonly used by clinicians, especially outside the US (Dubertret et al., 2004; Harris and Jeste, 1988; Howard et al., 1994; Riecher-Rössler et al., 2003).

In his use of the term ‘dementia praecox’, Kraepelin (1899) implies an early onset and rapidly deteriorating course. A decade later, Eugen Bleuler (1950) de-emphasized age of onset as a defining feature. Kraepelin later recognized that sometimes the illness presented later in life and he described cases with onset as late as the seventh decade, although these accounted for only 0.2% of the 1,054 patients he studied.

Manfred Bleuler, Eugen’s son, may be considered the first to explicitly introduce in 1943 the concept of LOS. Setting the ground with criteria still applied today, he stated that these cases should begin after age 40, with symptoms not fundamentally different to those seen in schizophrenia with an earlier onset, and that there should be no amnestic syndrome or physical sign that indicated a degenerative brain disease as the most likely aetiology (Bleuler, 1943). Using this definition, he found that 15% of schizophrenic disorders began between 40 and 60 years of age, with only a small number of cases presenting later. Prior to Manfred Bleuler’s work, others in Germany had attempted to distinguish cases of later onset, including Gaupp in 1905, followed by Stransky (‘dementia tardiva’), Berger (‘paranoia chronica’), Kleist (‘involutional paranoia), Albrecht

('presenile paraphrenia'), Serko ('involutional paraphrenia'), and Medow ('stiffening involutional psychosis'). British psychiatrists employed the term 'late paraphrenia' to describe 'a well-organized system of paranoid delusions with onset after age 45, with or without hallucinations existing in the setting of a well-preserved personality and affective response' (Roth, 1955). Post (1966) doubted the frequency of schizophrenia with onset in late life and felt that a heterogeneous group of disorders were more likely, hence the expression 'persistent persecutory states of late-life'.

The *Diagnostic and Statistical Manual (DSM)* has changed its stance on distinguishing late-onset from earlier-onset schizophrenia over the past four editions. Published in 1980, the DSM-III had eliminated the category 'involutional paranoid states/paraphrenia' and did not allow for the diagnosis of schizophrenia if symptoms emerged after the age of 45 (American Psychiatric Association, 1980). This criterion was modified in the revised edition with the introduction of the 'late-onset' specifier for onset after 44 years old (American Psychiatric Association, 1987). However, the term was eliminated from the DSM-IV (American Psychiatric Association, 1994) and the DSM-5, which notes, 'Such late-onset cases can still meet the diagnostic criteria for schizophrenia, but it is not yet clear whether this is the same condition as schizophrenia diagnostic prior to mid-life (e.g., prior to age 55 years)' (American Psychiatric Association, 2013, p. 103). The World Health Organization included no qualifier for late-onset in its *International Classification of Diseases, 8th edition* (ICD-8). In the ICD-9, however, the category of 'paranoid schizophrenia' included the subtype of 'paraphrenic schizophrenia'. In the ICD-10 the entity was included as 'paraphrenia (late)' in the delusional disorders group (World Health Organization, 1992).

Current terminology: International consensus

In 2000, the International Late-Onset Schizophrenia Group proposed the terms 'late-onset schizophrenia (LOS)' for cases with onset between 40 and 60 years and 'very-late-onset schizophrenia-like psychosis (VLOSLP)' for those presenting first after age 60. The panel concluded that evidence supported these age cut-offs and that these diagnoses had face validity (Howard et al., 2000). The distinction of the VLSOLP was supported by strong empirical evidence, with the LOS age criteria of 40 years more arbitrary; however, the experts felt that both had clinical usefulness and were intended to promote research in the field (Howard et al., 2000). Despite initial concerns, subsequent research has not shown a significant likelihood of affective disorders misclassified as LOS or VLOSLP. Moreover, EOS and LOS appear to be very stable diagnoses; they remained unchanged in as many as 93% of cases in a recent follow-up and only rarely were they reclassified as mood disorders (Taylor, 2001; Vahia et al., 2010). Although stronger evidence supports the distinction of VLOSLP as opposed to LOS, few studies have focused on this diagnosis specifically. In this chapter, we use the term LOS to indicate both LOS

and VLOSLP, except where specified. We also omit use of the term ‘late paraphrenia’, unless specified.

Epidemiology

Poorly defined diagnostic criteria, diverse terminology, and heterogeneity of samples have limited epidemiological data on psychotic symptoms in older people.

The prevalence of paranoid ideation in individuals over age 65 has been reported to be as high as 6%, although symptoms arising in the context of cognitive impairment account for most of these cases. Forsell and Henderson (1998) found an overall prevalence of 12.1% in those with cognitive dysfunction, compared to 2.6% in those without (Christenson and Blazer, 1984). Older individuals also seem to be more susceptible to both visual and auditory hallucinations, although women appear to be the most at risk in later age than men and they experience a later peak prevalence (Tien, 1991). Rates of one-year psychotic symptom prevalence in the oldest old (over 95 years) have been estimated to be as high as 7.4%. The risk of psychosis appears directly proportional to age in the geriatric population. Van Os and colleagues (1995) suggested that incidence rates increase by 11% every 5 years after age 60. From 10 per 100,000 person-years between 60 and 65 years, the incidence rate reached 25 per 100,000 person-years in people 90 years and older. These rates reflect incidence for all nonaffective, nonorganic psychoses, including schizophrenia.

The incidence rates of schizophrenia peak between ages 16 and 25 years and then again in the 46–55 years age group, and there may in fact be a third peak in incidence rates in individuals aged 65 and older (Castle and Murray, 1993). A considerable overlap between late-onset psychosis and schizophrenia exists in epidemiologic studies. In a prospective study assessing new cases of schizophrenia fulfilling DSM-IV criteria, Mats Bogren and colleagues (2010a) found an incidence rate of 8 per 100,000 person-years in the age group of 65 + years (American Psychiatric Association, 1994). Rates of 15.6 and 17 per 100,000 person-years have been suggested for delusional disorder (based on DSM-III-R) and late-paraphrenia (as per Kay and Roth’s criteria), respectively (American Psychiatric Association, 1987; Copeland et al., 1998; Holden, 1987; Kay and Roth, 1961). New onset of psychosis in late-adulthood therefore frequently occurs outside the context of schizophrenia or schizoaffective disorder. One-year prevalence rates of LOS in a Dutch catchment area of 25,600 adults aged 60 years and older was 0.14%, compared to EOS (0.35%) and VLOS (0.05%) (Meesters et al., 2012).

There is evidence that incidence rates are higher for women, and women:men ratios vary from 1.7:1 to as high as 45:2 (Bleuler, 1943; Herbert and Jacobson, 1967; Howard et al., 2000; Meesters et al., 2012). Whether gender ratios represent real differences in incidence rates based

on true risk factors or whether they are impacted by research bias or cohort effects remains subject to debate.

In a 1997 study conducted in the UK, African-Caribbean people were underrepresented among very late-onset (first symptoms after 60 years) compared to very early-onset cases that were diagnosed before age 25 years (4% and 40%, respectively), but older adults from this ethnic background had higher incidence rates of broad schizophrenia (diagnosed 30–64 years of age) and VLOSP compared to Caucasians (Bhugra et al., 1997; Castle et al., 1997; Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2003; Reeves et al., 2001; Reeves et al., 2002).

Risk factors and correlates

As with epidemiology, the literature on LOS is limited by lack of standardization in outcomes criteria, populations, and evaluation tools, as underscored in a systematic review by Brunelle and colleagues (2011). Longitudinal studies assessing predictors of LOS are few and current knowledge relies primarily on cross-sectional data (Köhler et al., 2007).

Genetic risk

A significant family history of psychotic disorders has not been reported with LOS, although this probably reflects a lower familial burden in LOS compared to EOS rather than a complete lack of association. A wide variation can be noted in the reported prevalence rates of schizophrenia in relatives of both EOS and LOS subjects, which can be attributed to the different age cutoffs and/or diagnostic criteria used. To our knowledge, only Köhler et al. (2007) have prospectively studied the risk imparted by a positive family psychiatric history. Neither depressive nor psychotic disorders appeared to increase risk, consistent with cross-sectional evidence. Jeste and colleagues (1995) found no difference in family prevalence of depression in persons with LOS or EOS, or unaffected controls.

More recently, data from linkage-analyses seem to suggest that the age of onset is, at least in part, dependent on genetic predisposition, and that genes also have an effect on the phenotype (Hamshere et al., 2011). This may partly explain differences in clinical presentation of LOS and EOS. Several genetic risk factors have been proposed for LOS. The *DRD2* gene and specifically one of its polymorphisms, *rs2734839*, was strongly associated with older age of onset, although the number of subjects above age 40 was insufficient to draw any firm conclusions (Voisey et al., 2011). A link between the CCR5 32-bp deletion allele and LOS has also been suggested (Rasmussen et al., 2006). Dopa-decarboxylase seems to affect the age at first presentation, with certain genotypes containing the 1-bp deletion potentially increasing the likelihood of LOS in men (Borglum et al., 2001). These findings point toward a genetic susceptibility to psychosis even in late-onset cases, which could be both specific to LOS

and shared with EOS, though the genetic susceptibility seems lower for LOS than for EOS.

Gender

The higher incidence rate of LOS in women does not necessarily imply causality. While it may indicate higher risk, other factors like access to care, proportion of individuals at risk, or even diagnostic bias may underlie this higher rate. It has been hypothesized that differences in life-expectancy between genders could also contribute to the increased incidence found in older women compared to men (Howard et al., 1994). As the gap in longevity between men and women has narrowed between 1970 and the twenty-first century, and might continue to do so over the next decades, it would be interesting to see if this is accompanied by a corresponding trend of the incidence rates for LOS to even out between both genders (Pinkhasov et al., 2010). Surprisingly, no difference in incidence rates of late-onset psychosis was found in a systematic review of longitudinal risk factors, possibly because higher incidence in women does not translate into a higher risk ratio in prospective studies (Brunelle et al., 2011). Huang and Zhang (2009) studied Taiwanese individuals older than age 60 admitted with a diagnosis of schizophrenia and reported that the difference in gender proportions was not significant between the early- and late-onset groups, women representing 44.8% and 34.7% of all cases, respectively.

Interestingly, as the familial burden of schizophrenia increases, the effect of gender on age of onset appears to lessen. Several authors have reported comparable men-to-women ratios in patients with a positive family history, even in late-onset cases (Abel et al., 2010; Leboyer et al., 1992; Rasanen et al., 2000) The observed gender differences in prevalence rates for LOS have led to the so-called oestrogen hypothesis of schizophrenia—the onset of symptoms in older women due to the loss of the previous protection conferred by the oestrogenic influence (Häfner et al., 1998; Seeman and Lang, 1990). Oestrogen modulates several neurotransmitter systems, including the dopaminergic, serotonergic, GABA-ergic, noradrenergic, and cholinergic pathways, all of which have been implicated in psychotic disorders (Behl et al., 1995; Brann et al., 2007; Kölsch and Rao, 2002; Lee and McEwen, 2001). However, attempts to identify specific polymorphisms of the oestrogen receptors responsible for schizophrenia or LOS have been mostly inconclusive, and there are currently no data supporting the hypothesis that a genetic variant would have a specific influence on age of onset other than through the general mechanisms (Ouyang et al., 2001). Using first admissions data for VLOSLP, Reeves and colleagues (2002) found that male patients were significantly more likely to be lost at follow-up, which points to differences in help-seeking behaviours between genders.

In summary, the question of whether female gender is itself a significant risk factor for the development of LOS is not fully understood yet, but women constitute a higher proportion of the clinical population. However,

gender does not seem to exert any direct effect outside its association with age at onset (Häfner, 2003; Häfner et al., 1998; Leboyer et al., 1992).

Sensory loss/medical comorbidity

Sensory loss has been consistently implicated in the development of late-life psychosis since an association with hearing loss was reported for the first time by Kay and Roth (Kay and Roth, 1961; Roth, 1955). Symptoms of paranoia following experimentally induced deafness have been described and the literature suggests that adjustments to hearing aids can lead to the resolution of symptoms (Eastwood et al., 1981; Khan et al., 1988; Zimbardo et al., 1981). Authors have reported that hearing loss in those cases is more often conductive and usually severe, bilateral, and appearing early in life (Cooper, 1976; Cooper and Curry, 1976; Cooper et al., 1974; Prager and Jeste, 1993). The association between schizophrenia and hearing impairment appears stronger for VLOSLP than for LOS, but these associations have not been confirmed in longitudinal studies. Less convincing evidence exists for an association with visual deficits (Howard et al., 2000), though prospective studies have demonstrated that people with visual deficits are at significantly increased risk of psychosis, although it has not been demonstrated specifically for LOS (Blazer et al., 1996; Forsell, 2000; Köhler et al., 2007).

Although the existing evidence suggests a correlation, specific aetiological pathways linking sensory deficit and psychosis have been disputed. Proposed theories include sensory loss, reinforcing premorbid tendencies toward isolation (Corbin and Eastwood, 1986), or that persons with sensory loss would simply be less likely to seek treatment. Comparing patients with early- vs very-late-onset, Rodriguez-Ferrera and colleagues (2004) obtained a higher than expected prevalence of hearing loss in their very-late-onset group (54%), with only 15% in the younger onset group including cases of EOS and LOS, with a mean age of onset of 36 years (SD = 11.3). Almeida and colleagues (1992) reported very similar rates of 41% and 6.6% for LOS and EOS, respectively. Reported prevalence rates of hearing deficits in the literature in the general older population range between 25% and 80% (Newman and Sandridge, 2004). A recent review suggested that hearing deficits severe enough to impair conversation affect approximately 10% of the general population and as many as 40% of adults over age 65, with 80% of all cases of hearing loss occurring in older people (Huang and Tang, 2010). In light of these numbers, the high frequency of hearing impairments in patients with VLOSLP and to a lesser extent LOS is hardly surprising.

There is very limited literature on medical comorbidity in people with LOS, especially considering the significant burden of medical issues in the older population in general and in the psychiatric population in particular. Indeed, some ‘geriatric syndromes’ are specific to this group, which is also at higher risk of accumulating concurrent medical illnesses, with resulting adverse effect on functional and cognitive status. At least 20–30% of people over 65 years of age are believed to suffer from chronic

diseases (De Luca d'Alessandro et al., 2011). Moreover, medical issues are often overlooked in this population. Data from a chart review of 79 consecutive geriatric psychiatry hospital admissions (University of California, San Diego, Senior Behavioral Health Unit) indicate that 34% of the patients had unrecognized medical conditions (Woo et al., 2003).

An association between occlusive carotid and vertebral arteries disease and late-onset of psychiatric disorders has been reported and cardiovascular risk factors seem to be increased in subjects with LOS, but also late-onset affective disorders (van der Heijden et al., 2010). Barak and colleagues (2002) indicated that medical comorbidities were frequent in both groups of older people with either VLOSLP or chronic schizophrenia (71.4% vs 57.1%, respectively, although it was not significant), with hypertension being the most frequent medical condition, followed by ischaemic heart disease and diabetes. The rates of medical comorbidities seem to be higher in late-onset delusional disorder than schizophrenia, with also more neurological conditions in the first group (Riecher-Rössler et al., 2003). Evidence for potential medical risk factors from longitudinal studies is limited. Henderson and colleagues (1998) found that current physical symptoms increased the risk of delusions and hallucinations, although causality was not established for past physical illnesses. There is a dearth of data about the topic of a history of obstetric or perinatal complications in LOS patients. To our knowledge, only one longitudinal study has been published discussing the rates of perinatal complications in LOS, retrospectively looking at a small sample of 12 LOS patients and concluding against any predisposing effect (Castle et al., 1997; Reulbach et al., 2007).

Cognitive patterns and psychopathology

Cognitive patterns and psychological mechanisms have been discussed extensively in the general literature on LOS. 'Theory of mind', 'mentalization', and 'social cognition' are related concepts that describe the processes used by human beings to make sense of their environment and interact with others. It has been proposed that decreased social exploration is an expected phenomenon with normal ageing and that its interaction with cognitive impairment could increase the susceptibility to psychotic symptoms in people with otherwise healthy development and mentalization patterns. Similar to what has been reported for EOS patients, those with LOS have been found to make significantly more mentalizing errors on testing than older controls, but they did not demonstrate the impaired performance in probabilistic reasoning and exaggeration in self-attribution bias typical of the early-onset individuals (Moore et al., 2006). The literature on social cognition has been burgeoning over the last years in the field of schizophrenia in general, and the extent of the deficits appears to mirror those in neurocognition; whether this will prove relevant in the LOS population remains to be determined (Hofer et al., 2010). Fromholt and colleagues (1999) described the psychological characteristics of 20 individuals with late paraphrenia and found that the subjects' emotional reactions and coping

mechanisms appeared congruent to their subjective views of the problem. That is, their reactions would have been deemed rational or logical if the patients' perceptions corresponded to the reality. This was replicated in a later study by Quin and colleagues (2009). Fromholt and colleagues (1999) also noted that in all but one patient the delusional ideas were plausible, i.e. they 'did not violate physical laws or include references to any supernatural phenomena'. One study found that EOS patients had significantly lower scores on the Hinting Task, a measure of Theory of Mind abilities, compared to age-comparable LOS patients and controls, after adjusting for educational achievement (Smeets-Janssen et al., 2013). The authors proposed that better Theory of Mind functioning might be protective and delay the age of onset of schizophrenia.

In the historical literature on social tendencies and LOS, there are contradictions. While the late paraphrenia described by Roth has been thought to occur mostly in older women with a lifelong tendency toward solitariness and suspiciousness, Janzarik's 'Kontaktmangelparanoid' was described in women with a previously high level of vitality and poor tolerance to solitude who found themselves newly isolated by factors inherent to the ageing process (Janzarik, 1957, 1973; Kojo, 2010; Roth, 1955). In most cases, a progressive deterioration in social networks often prefigured the onset of psychosis and initiated a process of 'life-review' in which subjects reminisced over hostile relationships with some family members, expressed regrets for past actions, and described well-established patterns of solitary coping styles that could be related to the perception of having always been different or 'outsiders' as described by most patients (Quin et al., 2009). Whether they might be the origin or a consequence of LOS remains unclear. Comparing older people with late-onset of depression or schizophrenia and unaffected age-matched controls, Giblin and colleagues (2004) demonstrated that LOS patients had significantly higher scores in the following domains on the Schema Questionnaire: 'rejection and disconnection', 'impaired autonomy and performance', 'other-directedness', and 'over vigilance and inhibition'. They were also more likely to have a low morale about the ageing process, even compared to those with major depression. However, they had the highest severity of current depressive symptoms, which could have introduced a significant recall bias (Schmidt et al., 1995). Contrary to these findings, there is evidence pointing toward a lack of aetiological association between depressive schemas and LOS. Indeed, McCulloch and colleagues (2006) found that not only was there no indication of depressive cognition or self-conception in individuals with late-onset psychosis, but also there was nothing to suggest changes over time; hence the possible contribution of depression to the onset of symptoms was limited.

Unfortunately, to our knowledge only two groups have assessed this topic longitudinally. Köhler and colleagues (2007) found that lifetime depressive symptoms at baseline were not associated with the onset of psychosis (not restricted to schizophrenia) in individuals over age 50,

despite a significant effect in younger cohorts. Interestingly, although there was a trend toward lower influence with older age of onset, ‘neuroticism’ retained its significance as a contributive factor in late-onset psychosis. This is congruent with the analysis from Bogren and colleagues (2010b) of premorbid behavioural and personality-related signs and symptoms predictive of psychosis, with only the two clusters ‘nervous-tense’ and ‘abnormal-antisocial’ reaching significance for schizophrenia. The description of the latter cluster indicates what would now be more suggestive of cluster A personality disorders.

Abnormal premorbid personality traits have often been implicated. Fuchs (1999b) found high rates of personality pathology in a sample of 38 late paraphrenia patients and indicated that 39% had met the criteria for paranoid or schizoid personality disorders prior to the psychosis, and the frequency of characteristic traits has been reported to be as high as 70% in older literature. Subjects affected by late-onset psychotic disorders have been described by early British authors as ‘suspicious’, ‘quarrelsome’, ‘hostile’, ‘sensitive’, ‘unsociable’, ‘reticent’, ‘odd’, ‘eccentric’, ‘histrionic’, ‘pretentious’, and exhibiting a long-standing difficulty to establish or maintain intimate relationships (Giblin et al., 2004; Herbert and Jacobson, 1967; Howard et al., 1994; Kay and Roth, 1961; Post, 1966). In LOS specifically, Pearlson and colleagues (1989) noted patterns of having been ‘reclusive and introverted’, with ‘few friends, poor interpersonal relationships and peculiar religious beliefs’. Brodaty and colleagues (1999) described persons with LOS as ‘odd and eccentric’, ‘suspicious and detached’ compared to normal controls, and similar to previously described traits in late paraphrenia. Longitudinally, no premorbid condition has been clearly associated with the onset of psychotic symptoms; anxious manifestations may potentially be predisposing and a prior diagnosis of post-traumatic stress disorder had been given to several LOS patients with significant childhood trauma (Reulbach et al., 2007; Sachdev et al., 2000; Tien and Eaton, 1992). Although substance-related disorders are more common in older people with schizophrenia than without, LOS specifically has not been well studied (Jeste et al., 1996; Mulsant et al., 1993). Reviews of the longitudinal studies were inconclusive (Brunelle et al., 2011; Köhler et al., 2007; Tien and Eaton, 1992; Wiles et al., 2006).

Pathophysiologic processes

Sociodemographic factors

Some sociodemographic characteristics of the subjects affected by LOS are likely not predisposing factors and reflect the direct consequences of later age of onset. However, they are important to the understanding of the pathogenesis of schizophrenia in late life, and are mentioned here.

Studies consistently show that subjects with LOS may have similar marriage rates as normal controls (especially for VLOSLP) and are much more likely to be, currently or formerly, married than their earlier-onset

counterparts (Barak et al., 2002; Girard and Simard, 2008; Hassett, 2002). It has also been suggested that they might have higher rates of divorce (or initiating the divorce) and widowhood (Almeida et al., 1992; Rees, 1971; Fuchs, 1999b; Girard and Simard, 2008; Herbert and Jacobson, 1967; Howard et al., 1994; Jeste et al., 1995; Kay and Roth, 1961). One exception emerged from a comparison of EOS and LOS in chronically hospitalized patients in Taiwan, with high rates of marriage in both groups, possibly corresponding to a cultural phenomenon (Huang and Zhang, 2009). Compared to those with early-onset, patients with LOS might have fewer friends and fewer children than normal controls (Barak et al., 2002; Brodaty et al., 1999; Gurian et al., 1992; McCulloch et al., 2006; Rodriguez-Ferrera et al., 2004; Romero-Rubiales et al., 2004; Semple et al., 1997).

While an association with academic achievement remains unclear, better work performance and employment history reflected a much better level of premorbid adjustment for schizophrenia patients diagnosed later in life (Barak et al., 2002; Castle et al., 1997; Fuchs, 1999b; Girard and Simard, 2008; Girard et al., 2011; Jeste et al., 1995; Vahia et al., 2010). These findings, however, have not been replicated in longitudinal studies (Brunelle et al., 2011). Functional limitations have not been studied in relation to schizophrenia and there is inconsistent evidence as to whether they increase the risk of psychosis in older people directly (Blazer et al., 1996; Forsell, 2000). Although there are very limited data on this topic, it is possible that an urban status at birth might predispose to LOS, as has been suggested already for EOS (Marcelis et al., 1998).

Adverse life events

Negative experiences early in life can affect developmental tasks and thereby increase susceptibility to psychosis when they occur early in life, but psychosocial stressors may exert a larger impact on the psychotic episode’s development. Both have been described in relation to LOS, although the specificity and wide range of adverse events described in the literature likely impairs generalization. Results from a systematic review of longitudinal studies on LOS indicated that both the number and intensity of negative life events can contribute to the onset of psychotic symptoms later in life, and exposure to the Holocaust has been implicated for schizophrenia specifically (Brunelle et al., 2011; Reulbach et al., 2007). Childhood traumas and experiences perceived as discriminating, humiliating, or threatening have been frequently identified in subjects with LOS (Fuchs, 1994, 1999a,b; Gurian et al., 1992; Rockwell et al., 1994). For those with EOS, early life events have not been associated with the persistence of psychotic symptoms in older age, but the accumulation of stressors throughout the lifetime has been implicated (Cohen et al., 2011). Psychosocial adversity can play a role during adulthood as well, and certain ethnic groups such as African-Americans have been diagnosed more frequently. While diagnostic bias, perceived discrimination, and stress related to the migration have been implicated for these associations, none has emerged as a significant predisposing

factor in longitudinal evidence (Blazer et al., 1996; Brunelle et al., 2011; Forsell, 2000; Forsell and Henderson, 1998; Mitter et al., 2005; Mitter et al., 2004; Reeves et al., 2003; Reeves et al., 2001). In a recent article on LOS from Japan, psychosocial stresses were deemed causally related in 65.8% of the cases, and in 36% of those the subjects reported a sense of loss. Similar associations with acute stresses or losses have been reported in other studies (Rees, 1971; Fromholt et al., 1999; Janzarik, 1973; Kay and Roth, 1961; Yasuda and Kato, 2009). This is compatible with the view of LOS and EOS as unique single disorders, with LOS manifesting later in more resilient individuals (Schmid et al., 2011).

Neuropathology

Neuropathological mechanisms remain central to contemporary conceptualizations of schizophrenia, including: i) dysfunction of the neurotransmitter pathways in the central nervous system, primarily implicating dopamine, glutamate, and serotonin; ii) neurodevelopmental alterations, suggested by regional brain abnormalities on both structural and functional imaging; and iii) modifications at the cellular level, with a postulated reduction in oligodendrocytes and/or aberrant neuronal cytoarchitecture (Pickard, 2011). However, the extent to which these processes contribute specifically to illness manifestation in late life and the role of alternative mechanisms is not well understood.

The first brain imaging study of the late-onset population was published by Haug (1962) involving seven patients with a first episode of ‘psychosis’ after the age of 45 years. Using the technique of pneumoencephalography, he reported evidence of cerebral atrophy and dilated ventricles. It took almost a twenty-five years for the next study reporting on brain imaging in patients with LOS, when Miller and colleagues (1986) reported computer tomography (CT) results on a small sample of five women with late paraphrenia, and noted that three had cortical or subcortical changes and another showed signs of normal pressure hydrocephalus. Several subsequent studies all determined that ventricle-to-brain ratios (VBRs) were larger in the patients than the normal controls group (Naguib and Levy, 1987; Pearlson and Rabins, 1988; Rabins et al., 1987). More recent investigations have mostly used magnetic resonance imaging (MRI) techniques, in an attempt to assess periventricular and deep white matter changes better. The first two studies (Breitner et al., 1990; Miller et al., 1989) described the MRIs of subjects with a broader diagnosis of ‘late-life psychosis’ or ‘late-onset paranoid illness’. In the first study, 20% of them had evidence of ‘silent vascular disease’ and tumours were discovered in another 12%. The second group reported vascular lesions in the pons or medulla of seven out of eight subjects, but none in normal controls. Miller and colleagues (1991) later wrote that white matter lesions affected 42% of subjects, presenting with first onset of ‘psychosis’ after age 45, as opposed to only 8% of the age-matched healthy comparison subjects, predominantly in the

temporal and frontal lobes. However, no definite pattern of white matter lesions has been established.

A literature review published in 2010 suggested that extracranial arterial pathology also contributed to the development of LOS. A significantly higher burden of premorbid cardiovascular risk factors was described in those with late-onset psychiatric disorders, including schizophrenia (van der Heijden et al., 2010). It is possible that this finding reflects a distinction between LOS and VLOSLP.

Volumetric studies have failed to pinpoint any abnormality specific to late-onset patients and findings are mostly concordant to those with EOS. The only notable difference was the larger thalamic volumes found in patients with LOS compared to their early-onset counterparts (Barta et al., 1997; Corey-Bloom et al., 1995; Rabins et al., 2000; Sachdev and Brodaty, 1999b; Sachdev et al., 2000; Sachdev et al., 1999; Sachdev and Brodaty, 1999a; Symonds et al., 1997). One recent study showed larger gray matter volumes in the left precuneus of LOS patients compared to EOS patients and non-psychiatric controls (Egashira et al., 2014). However, there have been no demonstrated alterations in the size of the frontal lobes, hippocampus, parahippocampus, thalamus, or basal ganglia structures in patients with LOS compared to older controls (Howard et al., 1995). Sachdev and colleagues (2000) later confirmed that the hippocampus and amygdala volumes in older people with LOS and EOS were comparable and were not significantly associated with their cognitive performances.

Diffusion tensor imaging (DTI) results have confirmed the integrity of frontal lobes and frontal cortical tracts, which had already been suggested by volumetric studies (Jones et al., 2005). However, studies using single photon emission tomography (SPECT) have suggested that up to 83% of LOS patients suffered from frontal or temporal hypoperfusion. In one study, the regional cerebral blood flow of patients with LOS showed a different pattern of alteration than that of subjects with EOS. Reduced blood flow was observed bilaterally in the postcentral gyrus for LOS patients, while the precentral and inferior frontal gyri were more affected in the EOS group. It was postulated that these changes were more likely attributable to the age of onset rather than the chronological age of the subjects (Wake et al., 2011; Wake et al., 2016). One case study found resolution of differential blood flow in the striatum and thalamus compared to the left frontal and temporal cortex after successful treatment for VLOS with catatonia (Tsujino et al., 2011).

Lohr and colleagues (1997) reported a significant difference in the frequency of minor physical anomalies in those two sets of patients. While the subjects with Alzheimer’s dementia did not differ from normal controls, older people with LOS or EOS, as well as those with unipolar depression, all had more anomalies. Pathological examinations have been rarely reported, but the absence of Alzheimer’s disease as defined by extensive neurofibrillary tangles seems to be consistent (Bozikas et al.,

2002; Casanova et al., 2002). Although the proportion of tangles was not abnormal, other neuritic changes have been observed. On the basis of their studies, Casanova and colleagues have proposed the concept of a ‘restricted limbic tauopathy’ that affects LOS and, to some extent, EOS patients (Casanova et al., 2002; Casanova and Lindzen, 2003). In patients with schizophrenia, the familial loading for Alzheimer’s, vascular, or Lewy body dementias has not been found to be higher in those with a later compared to an earlier onset of symptoms (Brodaty et al., 1999; Howard et al., 1997). From a systematic review of the longitudinal studies on the risk factors for late-onset psychosis, cognitive impairment not reaching the threshold for dementia emerged as a probable predictor for psychotic symptoms at follow-up, but not for schizophrenia per se (Brunelle et al., 2011; Forsell, 2000; Henderson et al., 1998; Tien and Eaton, 1992). The Weschler Adult Intelligence Scale-Revised (WAIS-R) similarities subtest and the California Verbal Learning Test (short- and long-delay free recall) may be the two most sensitive neuropsychological measures discriminating between LOS and Alzheimer’s disease in patients already diagnosed with LOS or VLOSLP (Girard et al., 2011; Zakzanis et al., 2003). However, neuropsychological testing in individuals without psychosis was not shown to have any predictive value regarding the likelihood of subsequently exhibiting schizophrenia manifestations (Blazer et al., 1996; Henderson et al., 1998).

In summary, LOS does not appear to be related to Alzheimer’s disease or other dementia pathology. However, it is still unclear whether a neurodegenerative process is at play in this condition, mainly because of the lack of distinction in the literature between cases of LOS and VLOSLP and the pooling of various psychotic disorders together in studies. Current evidence indicates that VLOSLP might be more associated with a neurodegenerative disease, while LOS is more aetiologically similar to EOS, although this is not completely clear.

Inflammation

A number of studies have reported elevated levels of inflammatory markers and oxidative stress markers in schizophrenia, though few studies have examined inflammatory markers specifically in LOS (Joseph et al., 2015; Lee et al., 2016a,b). In 2014, Wium-Andersen and colleagues (2014) reported that elevated levels of C-reactive protein (CRP), a biomarker of systemic inflammation, were associated with a six- to 11-fold increased risk for LOS and VLOS based on a 20-year longitudinal Danish cohort study of over 78,000 individuals. Mean CRP levels were higher for persons with schizophrenia (EOS and LOS subtypes) compared to those without schizophrenia, even when adjusting for age and gender. This was the first study examining a large cohort for LOS and VLOS in regards to inflammatory markers.

Clinical features

Positive and negative symptoms

The conclusions of the International Consensus on Late-Onset Schizophrenia Group pointed toward greater similarities than differences in the clinical presentation of schizophrenia arising in early and late life, especially regarding the positive symptomatology and between ages 40 and 60 years. However, in clinical samples, cases with very late onset were associated with a low prevalence of formal thought disorder and affective blunting and a higher prevalence of visual hallucinations (Grahame, 1984; Howard et al., 1993; Howard et al., 2000; Jeste et al., 1995; Jeste et al., 1997; Kay and Roth, 1961; Pearlson et al., 1989; Post, 1966).

Whether LOS patients experience more severe positive symptoms overall compared to those with early-onset is not fully clear. Yasuda and Kato (2009) found that the paranoid subtype applied to over one-half of their LOS sample and was significantly higher than in the older group with earlier onset. Mason and colleagues (2013) reported similar findings of increased paranoia in the LOS group, however the differences dissipated when the analysis matched for age (Mason et al., 2013). On the other hand, Vahia and colleagues (2010) suggested similar rates for the early- and late-onset groups, although positive symptoms were less severe overall among those with LOS. The absence of significant difference in positive symptomatology has been replicated in other studies (Hanssen et al., 2015; Huang and Zhang, 2009; Jeste et al., 1995; Pearlson et al., 1989; Rodriguez-Ferrera et al., 2004). Some specific features do appear to be more common in the LOS population, such as persecutory, elaborate, and systematized delusions. Delusions and hallucinations may become more prevalent with older age rather than with older age of onset, but delusions of partition or ‘the belief that people, objects or radiation can pass through what would normally constitute a barrier to such passage’ are especially frequent in those with LOS and much rarer in older and young EOS patients (Howard, 2006; Howard et al., 1992). Individuals with a later onset are also more susceptible to experience visual, olfactory, or tactile hallucinations and in several sensory modalities simultaneously (Alici-Evcimen et al., 2003; Castle et al., 1997; Girard and Simard, 2008; Howard et al., 1993; Pearlson et al., 1989; Sato et al., 2004; Wynn Owen and Castle, 1999).

It has been increasingly recognized that a later onset might not be as protective as originally assumed, with recent evidence suggesting comparable severities of negative symptoms in EOS and LOS and even in VLOSLP (Girard and Simard, 2008; Jeste et al., 1995; Vahia et al., 2010). Indeed, VLOSLP seems to be characterized by prominent positive symptoms but not less negative symptomatology than LOS, although it is rarely specifically assessed on its own. The level of psychomotor activity appears to distinguish the two conditions, with LOS patients presenting with more apathy and abnormal psychomotor activity (Barak et al., 2002; Girard and Simard, 2008).

Cognition

Cognitive changes are among the cardinal features of schizophrenia, regardless of age of onset, and had been under consideration for inclusion as a distinct dimension in the DSM-5 section on schizophrenia—though ultimately they were not included (Bora et al., 2010; Keefe and Fenton, 2007; Laughren, 2011).

Consistent with the overall literature on schizophrenia, late-onset patients were found to have lower cognitive performance than normal controls. Ting and colleagues (2010) reported that LOS patients were more impaired than age-matched controls on most cognitive tests, with the exception of those for the recall of newly learned verbal information (using the California Verbal Learning Test: Woods et al., 2006). However, those with LOS outperformed patients with Alzheimer's disease on every measure, including retrieval, the only notable exception being a nonsignificant difference in learning new verbal material. These more recent findings are very similar to the first neuropsychological descriptions of LOS patients, attributed to Hopkins and Roth in 1953. Comparing older subjects belonging to several different diagnostic categories, they reported that those with late paraphrenia had a much better performance on all tests than those with dementia. The severity of impairments was similar in late paraphrenia and affective patients, but the two groups showed distinct patterns on neuropsychological assessment (Hopkins and Roth, 1953). One longitudinal study found no difference in risk of developing dementia between patients with LOS and late-life depression (Rabins and Lavrisha, 2003).

Rajji and colleagues (2009) conducted a meta-analysis on cognitive deficits found in subjects with a first-episode in adult life, youth-onset, or LOS. From the nine studies selected, the authors concluded that LOS patients have an overall better cognitive performance than those with youth-onset or first-episode schizophrenia, though the patterns of cognitive deficits differ in each group. The LOS patients had more impairment on measures of attention, fluency, global cognition, IQ, and visuospatial construction than the other two subgroups, while arithmetic, digit symbol coding, and vocabulary were mostly preserved. Similarly, a study of LOS patients, EOS patients matched for duration of illness, and age-matched controls showed that LOS patients had intermediate memory performance—better than the EOS patients but worse than the controls (Brichant-Petitjean et al., 2013). This challenges the assumption of minimal differences in the cognitive functioning of patients with EOS and LOS (Heaton et al., 1994; Jeste et al., 1995; Sachdev et al., 1999). It is possible that this design allowed for the detection of results that did not reach significance in isolated studies because of small sample sizes; but it might also reflect the patient groups in the analysed studies. Unfortunately, in most studies, older adults with LOS are compared to older adults with EOS. It has been suggested that the younger the age of onset, the greater the severity of cognitive and functional impairments; however, while chronicity contributes significantly to the cognition

scores, it has not been shown to alter the effect of age of onset on specific measures. LOS subjects most consistently perform better on measures of abstraction/flexibility, semantic/verbal memory, and learning. These findings have been replicated by other authors, although some also noted lesser impairment in processing speed for the late-onset group (Girard et al., 2011; Jeste et al., 1997; Tuulio-Henriksson et al., 2004; Vahia et al., 2010).

Comparisons of executive functions in LOS and EOS are inconsistent and the current consensus is that impairments are manifest regardless of age of onset (Rajji and Mulsant, 2008). A positive correlation exists between family history of schizophrenia, younger age of onset, and poorer cognitive performance, although familial loading might not have such a significant effect in late-onset cases. How this contributes to the neurocognitive features in LOS has, however, not been well studied (Goldberg et al., 2011; Tuulio-Henriksson et al., 2004). One 2015 study found no significant neuropsychological differences between LOS and VLOSLP, when controlling for age (Hanssen et al., 2015).

Mood

Compared to normal controls, patients with LOS appear to endorse a higher level of depressive symptoms (Jeste et al., 1995; Moore et al., 2006). However, there was no evidence of depression in the LOS group in a study by McCulloch and colleagues (2006) comparing LOS patients to depression patients and healthy controls; both LOS and normal subjects exhibited a better self-esteem than the depressed individuals. When comparing with older EOS patients, Jeste and colleagues (1995) found no significant between-group differences, and a study by Rodriguez-Ferrera and colleagues (2004) showed a trend toward higher depression levels in EOS, though significance was not reported.

Differential diagnoses of psychotic symptoms in older people

Several conditions can present with psychotic symptoms in older patients. A detailed discussion of all possible causes is beyond the scope of this section, but we summarize the major differential diagnoses.

Early-onset schizophrenia

Table 43.1 provides a summary of the differences between EOS and LOS. Recent studies suggest that LOS is likely a distinct subtype of schizophrenia due to psychopathological and mechanistic differences from EOS (Maglione et al., 2014).

Table 43.1 Characteristics of various types of late-life psychosis.

	EOS	LOS	VLOSLP	PoD
Family history of schizophrenia	+	+	–	–
Female preponderance	–	+	++	–
Minor physical anomalies	+	+	–	–
Specific brain abnormalities (MRI)	–	–	+	+/–
Dementia-like cognitive decline	–	–	+	++
Magnitude of cognitive impairment	+	+	++	+++
Paranoid subtype	+	++	++?	N/A
Visual vs auditory hallucinations	+/–	+	+?	++
Complex vs simple delusions	++	+	+?	+/–

Thought disorder	+/++	+	–	–
Negative symptoms	++	+	–	–
Required neuroleptic dose	++	+	+	+/–

EOS, early-onset schizophrenia; LOS, late-onset schizophrenia; MRI, magnetic resonance imaging; N/A, not applicable; PoD, psychosis of dementia; VLOSLP, very-late-onset schizophrenia-like psychosis; +, moderately present; ++, strongly present; +++ very strongly present; –, not likely to be present; ?, only partially supported by the literature.

Delusional disorder and other primary psychoses

Significant overlap exists between LOS, delusional disorder (DD), and late paraphrenia, to the extent that authors have challenged the validity of any diagnostic division (Howard et al., 1994; Jørgensen and Munk-Jørgensen, 1985). Riecher-Rössler and colleagues (2003) proposed that ‘since clear and aetiologically meaningful differentiation between these diagnostic categories is not possible, they should not be separated by artificial diagnostic criteria for research purposes’. However, other authors have reported some evidence to support the clinical distinction of DD from schizophrenia with onset after age 40 (Evans et al., 1996). A diagnosis of DD is more often seen in older patients and is not an uncommon expression of psychosis in this population. For example, Alici-Evcimen and colleagues (2003) described 27 cases of late-onset psychosis in the 420 inpatients admitted to the sole geriatric psychiatry unit of a Turkish hospital between 1993 and 2002. From those 27 patients, five had EOS. Eight were diagnosed as having LOS, six with VLOS, and eight had DD. In a study of older people with schizophrenia, it was found that 27% of those diagnosed after age 60 met the criteria for DD, as opposed to none in the early-onset group (Rodriguez-Ferrera et al., 2004). In fact, diagnostic classification seems to rely heavily on age. Results from another group suggest that age accounted for 22% of the variation in the two diagnoses of schizophrenia and DD (Riecher-Rössler et al., 2003).

Schizophreniform disorder resembles schizophrenia, but lasts less than six months. Older patients with this disorder often demonstrated good premorbid adaptation, and the sudden onset of florid psychotic symptoms generally leaves them perplexed and confused. The episode might end as abruptly as it had begun, often with a return to the premorbid level of functioning (Jørgensen et al., 1997).

Schizoaffective illness in older patients has not been well described, probably because it is often included with cases of LOS. Among 27 very-late-onset psychosis cases described by Rodriguez-Ferrera and colleagues (2004), two received a diagnosis of schizoaffective disorder. Holden (1987) did describe a schizoaffective subtype of late paraphrenia associated with a high prevalence of auditory hallucinations but almost no visual manifestations. Affected patients had low rates of psychiatric antecedents and sensory deficits and were most likely to be alive at ten years compared to the other subgroups.

Isolated hallucinations can be found in visually impaired individuals (Schadlu et al., 2009). They have been described as a commonly occurring phenomenon in persons who have experienced widowhood, described in approximately 4% of widowers (Rees, 1971; Khouzam et al., 2005).

Delusions of misidentification, e.g. the Capgras syndrome, might occur in people with primary psychotic disorders but should herald the possibility of an underlying organic condition. They are relatively common in

Alzheimer`s dementia and other neurological or medical conditions (Khouzam et al., 2005). Paranoid personality can increase the risk of late-life psychosis, but premorbid suspiciousness can also worsen with age (Manford and Andermann, 1998; Paulsen et al., 2000).

Affective disorders

Psychosis is an especially frequent accompanying feature to depressive episodes in later life. Delusions or hallucinations are mood-congruent in the majority of the cases and somatic manifestations are especially common (Jørgensen et al., 1997; Khouzam et al., 2005).

Grandiose delusions commonly appear during manic episodes. Although mania tends to emerge as an early feature in the course of bipolar disorder, it can occur for the first time in late life or can reappear as a consequence of medication changes. Mania in older people should be differentiated from frontotemporal dementia (Almeida et al., 1992; Sajatovic and Chen, 2011).

Delirium and substance-induced psychotic disorders

While substance use disorders are comparatively less common in the older population, they are still observed with some frequency. Also, older adults are at risk for withdrawal due to sudden lack of access because of financial, mobility-related, or medical conditions. Alcohol and benzodiazepines are associated with especially high risk of psychotic phenomena during both intoxication and withdrawal and their use is not uncommon (American Psychiatric Association, 2000; Blazer and Wu, 2011; Khouzam et al., 2005). Delirium from any cause should also be suspected in first onset of psychosis and behavioural disturbances in late life (Reeves and Brister, 2008).

Dementia

Psychotic manifestations, especially visual hallucinations, can present in virtually every type of dementia and occur in up to 50% of patients at some point over the course of the illness. They are a characteristic feature of Lewy body dementia. Certain gene mutations such as progranulin (*PGRN*) and *C9ORF72* have been associated with hallucinations and psychosis in patients with frontotemporal dementia (Le Ber et al., 2008; Snowden et al., 2012). Also, people with dementia are especially vulnerable to anticholinergic side effects of medications and the resulting delirium. Psychosis can be a poor prognostic marker in this population, where antipsychotic treatment is associated with an increased mortality rate (American Psychiatric Association, 2000; Hardy, 2003; Kales et al., 2007; Paulsen et al., 2000).

Management

Clinical evaluation

The evaluation of older people presenting with schizophrenia manifestations requires assessment similar to that for any psychiatric illness in late life. Extra focus should be given to collateral information, owing to the high risk of guardedness and poor insight due to psychosis and cognitive impairment. It is also important to assess the impact of the disease on the social network. Assessment of safety includes ruling out the risk of violence toward others, even though this is reportedly more common in younger rather than older adults (Martínez-Martín et al., 2011).

The pharmacological history should focus on potentially contributing medications, including over-the-counter, herbal remedies, interactions, recent changes, and medication adherence (e.g. anticholinergic medications are often implicated as a cause of psychotic symptoms in older adults). Sexual and substance use histories should be gathered considering the risk of intoxication, withdrawal, neoplastic lesions, and sexually transmitted diseases. A complete review of personal and familial antecedents, both medical and psychiatric, with a specific focus on psychotic and neurodegenerative disorders, is mandated and should include a discussion of the premorbid level of functioning. Information should be obtained on the current pattern of impairment, course of symptoms, and accompanying physical or psychological manifestations. During physical examination, the clinician should look for evidence of neglect, abuse, decreased hygiene, incontinence, or cachexia, as well as for any sign of delirium or any indication of its aetiology. Neurological assessment should rule out increased intracranial pressure, localizing lesions, or neurodegenerative conditions like Huntington’s and Parkinson’s disease or Lewy body dementia, lesions of the basal ganglia or cerebellum, or seizures. A basic cognitive evaluation is mandated in all patients and should be repeated over time to rule out fluctuations in the context of delirium.

A basic work-up should consist of a complete blood count, blood chemistry profile (glucose, electrolytes with calcium and magnesium, blood urea nitrogen, creatinine, and liver function tests), urinalysis (and urine culture, if indicated), thyroid function studies, toxicology screening, vitamin B_{12} and folate levels, and serological tests for syphilis. Brain imaging is recommended, especially for cases with acute deterioration, altered consciousness, or abnormalities on neurological examination. Some authors also present evidence for electrocardiography and routine chest radiography (Boyce, 2008; Howard et al., 2000; Reeves and Brister, 2008). It may be useful to obtain a baseline lipid panel, weight, height, and waist circumference before an antipsychotic trial, in order to monitor metabolic side effects.

Ancillary investigations should focus on ruling out other suspected aetiology based on the history and physical examination. The decision to

perform comprehensive neuropsychological evaluation should be guided by clinical judgment, especially in settings with limited resources.

Pharmacology

Antipsychotics

No pharmacologic treatment guidelines for LOS have been established to date, mostly due to the limited evidence in this specific population. The bulk of the literature in this regard pertains to older patients with chronic schizophrenia; moreover, studies on the late-onset population usually failed to distinguish between LOS and VLOSLP. Arunpongpaisal and colleagues (2003) published a Cochrane systematic review on antipsychotic drugs use in older people with LOS, and revised it in 2012. While the 2003 search found no randomized controlled trials meeting their inclusion criteria and upon which to base any guidelines, the 2012 review identified a single randomized controlled trial of risperidone and olanzapine that was of acceptable quality (Essali and Ali, 2012). Due to the paucity of published trials, clinicians must for now use ‘clinical judgment and habit to guide prescribing’ (Arunpongpaisal et al., 2003; Essali and Ali, 2012). However, a more recently published study by Jin and colleagues (2013), which specifically studied older adults on antipsychotic medications, found that quetiapine may have the highest incidence of adverse events. The study also noted that older adults on antipsychotics had high discontinuation rates, limited improvement in psychotic symptoms and a 36% incidence of metabolic syndrome (Jin et al., 2013).

Atypical antipsychotics are now favoured, mainly because of the propensity of first-generation neuroleptics to induce extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), to which older individuals are more prone. Benefits have been observed in older patients initially treated with risperidone or olanzapine after the switch from a typical antipsychotic (Jeste et al., 1999a,b; Ritchie et al., 2003; Ritchie et al., 2006). In older people, as many as 2–30% of patients per year may develop TD with typical antipsychotics and they are also less likely to experience remission compared to younger individuals. Newer agents have a safer side-effect profile but are not risk-free; TD still emerges in approximately 5% of treated older patients each year, in keeping with the young to old risk ratio of 1:5 observed with first-generation medications (Correll et al., 2004). Older people are also more sensitive to EPS, even with second-generation antipsychotics like risperidone, and this risk may be higher for those with EOS (Jeste et al., 1995; Lemmens et al., 1999). Other related side effects include orthostatic hypotension, cardiac conduction abnormalities, agranulocytosis, and neuroleptic malignant syndrome (NMS). Hyperprolactinaemia from dopamine blockade is associated with osteoporosis, increasing the risk of hip fractures (Boyce, 2008; Reeves and Brister, 2008; Sachdev and Brodaty, 1999a). Both classes of antipsychotics have been implicated in increasing cardiovascular and all-cause mortality (Isaac and Koch, 2010; Kales et al.,

2007; Kelly et al., 2010; Schneider et al., 2005). Age-related changes in liver and kidney function, decreased lean body mass, and polypharmacy may additionally impact the pharmacokinetics and pharmacodynamics of antipsychotics (Sable and Jeste, 2002; Tsuboi et al., 2011).

The International Consensus suggested that one-half to one-quarter the doses of that used in younger patients could be used in LOS patients and as low as one-tenth in VLOSLP. The initiation of therapy should be made at a very low dosage, with cautious increments up to the lowest effective dose (Howard et al., 2000). For example, risperidone should be introduced at 0.25–0.50 mg/day and titrated by no more than 0.50 mg/day to a target range of 1.25–3.50 mg/day. Starting and target dose-ranges of olanzapine should be 1–2.5 mg/day titrated up to 5–15 mg/day. With quetiapine these should be 12.5–25 mg/day titrated to 100–300 mg/day (Alexopoulos et al., 2004; Jeste et al., 1996; Reeves and Brister, 2008). Recent data suggest the efficacy of aripiprazole with doses as high as 15–30 mg/day, but some recommend the more modest target of 10–15 mg/day, introduced at 2 mg/day (Coley et al., 2009; Kohen et al., 2010; Madhusoodanan et al., 2004; Rado and Janicak, 2010). Lower dosing strategies have been suggested for late-life psychosis in the context of delusional disorder or dementia (Tsuboi et al., 2011). Amisulpride has also been demonstrated to be comparable to risperidone in older patients and doses of 200–400 mg/day have been used, introduced at 50 or 100 mg/day (Psarros et al., 2009). More recently, the ATLAS trial (Howard et al., 2018) reported that a daily dose of 100 mg of amisulpride was effective and well tolerated. Depot medications may have a more continuous delivery and are often used in nonadherent patients, minimizing the plasma level fluctuations that can be especially problematic in older people (Lasser et al., 2004). Long-acting risperidone at doses starting at 25 mg every two weeks was shown to be safe in older patients followed for one year. Some patients received and tolerated doses as high as 75 mg every two weeks (Kissling et al., 2007; Lasser et al., 2004; Singh and O’Connor, 2009). As in the younger population, depot formulations have not been found to be more effective than oral antipsychotics if adherence is good (Reeves et al., 2002). Paliperidone extended-release (ER) consists of the active metabolite 9-hydroxyrisperidone in a tablet using patented extended-release technology to provide continual and consistent delivery over 24 hours. It has theoretical advantages in older people, like a once-daily schedule, minimal hepatic metabolism, potentially fewer side effects, and limited plasma fluctuations in cases of missed doses (Turkoz et al., 2011). In a 30-week trial involving patients around age 70 with EOS and LOS, paliperidone ER was found to be safe and well tolerated, with an age-related increase in somnolence and tachycardia. Age of onset did not impact these findings. Paliperidone also seemed to be effective at reducing symptoms, but the study was not powered to assess this outcome. Dose range was 3–12 mg/day and started at 6 mg/day (Tzimos et al., 2008).

According to a survey of expert clinicians in the US, risperidone should be the drug of choice in late-life schizophrenia, and quetiapine, olanzapine, and aripiprazole are good second-line options (Alexopoulos et al., 2004). There is more limited evidence regarding the use of ziprasidone and clozapine and none for LOS specifically. Clozapine especially should be used with caution considering its side-effect profile and important anticholinergic activity, and polypharmacy using more than one antipsychotic should be avoided.

Adjunctive medications

Although younger age is correlated with a more frequent use of adjunctive mood stabilizers for schizophrenia, recent data support their use in older people as well. Adjunct ER valproate (mean dose 587.50 mg/day) was effective and well tolerated in an open-label study on 20 older chronically ill patients, and was associated with symptomatic improvement, better global function, and lower depression scores (Sajatovic et al., 2008; Sim et al., 2011). The resolution of comorbid depressive symptoms with adjunctive phytoestrogens in a woman with LOS was discussed in a case report (Rakesh et al., 2011). Cholinergic neurotransmission has been implicated in psychosis and visual hallucinations, but there is currently no evidence regarding the use of cholinesterase inhibitors for this purpose, although there seem to be a role for them in management of associated cognitive deficits (Patel et al., 2010; Ribeiz et al., 2010). There is also a theoretical rationale for the use of memantine and reports of a positive impact in cases of catatonic schizophrenia (Zdanys and Tampi, 2008). To our knowledge, there are no data supporting the addition of these agents in older adults, particularly those with LOS.

Addition of SSRIs, specifically citalopram, has been shown to be effective in treating subsyndromal depressive symptoms in older persons with schizophrenia. More importantly, such treatment may reduce risk of suicide.

There is supporting evidence regarding electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) for refractory symptoms in younger patients with schizophrenia (Matheson et al., 2010). To date, there are no publications reporting LOS treatment with ECT, but rTMS in LOS has been the focus of a case report, describing one individual with auditory hallucinations successfully treated with both acute and maintenance rTMS (Poulet et al., 2008).

A few recent studies have suggested efficacy of oestrogen therapies for schizophrenia, although the overall evidence is weak. Several open label and randomized controlled trials of estradiol derivatives and conjugated oestrogen in premenopausal women have demonstrated improvements in positive symptoms (Akhondzadeh et al., 2003; Ghafari et al., 2013; Kulkarni et al., 1996; Kulkarni et al., 2015; Kulkarni et al., 2001, 2002) and cognition (Ko et al., 2006). However, two studies did not report any

significant symptom improvement with oestrogen treatments—one using a combined estradiol-progestin therapy and the other studying a conjugated oestrogen therapy (Bergemann et al., 2005; Louza et al., 2004). Two studies of raloxifene, a selective oestrogen receptor modulator (SERM), have reported improvements in cognition (Weickert and Weickert, 2017) and brain activation (Ji et al., 2016; Kindler et al., 2015) in premenopausal women. The raloxifene studies in postmenopausal women generally include only EOS patients and have shown some improvements in positive and negative symptoms (Kianimehr et al., 2014; Kulkarni et al., 2010; Usall et al., 2011; Usall et al., 2016). In men, one study showed that two-week estradiol treatment rapidly improved psychopathological symptoms (Kulkarni et al., 2011) and that eight-week raloxifene treatment led to greater improvements in negative symptoms and general psychopathology (Khodaie-Ardakani et al., 2015). One case report described improvement in psychotic symptoms with hormone replacement therapy alone in a perimenopausal woman with LOS (Bergemann et al., 2007). Notably, the largest published study of raloxifene plus antipsychotics versus placebo plus antipsychotics in 200 severely ill decompensated postmenopausal women with schizophrenia or schizoaffective disorder was a 16-week double-blind randomized controlled trial. It reported that individuals in the active treatment arm had *worse* outcome than those in the placebo arm. The authors concluded that their data do not support the use of raloxifene in severely decompensated patients with schizophrenia or schizoaffective disorder.

To date, no published trials have examined the therapeutic use of oestrogens or SERMs in LOS patients of either gender.

A recent open-label trial of yokukansan, an herbal remedy with serotonergic, dopaminergic and glutamatergic actions that has been studied in treatment-resistant schizophrenia and dementia patients with agitation (Matsuda et al., 2013), found significant improvement in psychotic symptoms in patients with VLOSLP compared to placebo (Miyaoka et al., 2013).

Valbenazine, a selective vesicular monoamine transporter 2 (VMAT2) inhibitor was approved by the FDA in April 2017 as the first and only approved treatment for tardive dyskinesia in adults. Unlike tetrabenazine, a VMAT2 inhibitor that is approved for Huntington’s chorea, valbenazine is dosed once daily and had few side effects related to monoamine depletion (Huntington Study, 2006). The once-daily dosed medication was shown to significantly improve movement systems as rated by the Abnormal Involuntary Movement Scale and Clinical Global Impression of Change—Tardive Dyskinesia over a six-week trial and was well-tolerated in the participants (Hauser et al., 2017; O’Brien et al., 2015). These trials were conducted in patients aged 18–85 years old, with average age 55 to 57 years. More than half of the participants were diagnosed with schizophrenia or schizoaffective disorder, though a number of participants with mood disorders and gastrointestinal disorders were also included. It is unclear what proportion of these participants had LOS

compared to EOS. Further studies on the effects of this new tardive dyskinesia treatment in LOS are warranted to finetune its use in older persons.

Psychosocial treatments

Most trials of psychosocial interventions for older persons with schizophrenia have targeted patients with EOS. Keeping in mind the significant differences in premorbid psychosocial functioning between those with EOS and those with LOS, there is a need for studies comparing results of psychosocial interventions in early-and late-onset patients. Psychosocial interventions can have significant benefits other than immediate symptomatic relief. For example, a socially stimulating group intervention targeting lonely older individuals with schizophrenia has been associated with better cognitive functioning, improvements in wellbeing, and lower mortality (Pitkala et al., 2011; Routasalo, 2009). This is particularly relevant to the LOS population impacted by high prevalence of social isolation, which has also been found to increase the risk of dementia (Wilson et al., 2007). Three nonpharmacological treatments have been designed specifically for the older population with schizophrenia and they are all group based.

Functional Adaptation Skills Training (FAST) and its modified version for older Latinos—Programa de Entrenamiento de Aptitudes para Latinos (PEDAL)—are manualized therapies implemented in the group format. Both have been found to improve social and everyday functional skills and to decrease the short-term use of emergency medical services (Mausbach et al., 2008; Patterson et al., 2006; Patterson et al., 2003).

Cognitive-behavioural social skills training (CBSST) is another group intervention designed for older people with schizophrenia. It combines two modalities with efficacy in younger patients. CBSST is based on the concept of challenging the common beliefs that interfere with treatment in this population and by providing repetitive practice of behaviours to improve retention and skill development. It has been associated with learning of new coping skills and better social functioning after treatment and also at one-year follow-up. However, gains in cognitive insight following CBSST appear to not be maintained at follow-up. This suggests that improvements in function are not necessarily an outcome of better insight (Granholm et al., 2005; Granholm et al., 2007; McQuaid et al., 2000).

Enhanced skills training (ST) and healthcare management (HM) combine skills training for daily living and medication management plus preventive nursing visits to address medical comorbidities in older adults with severe mental illnesses (SMI). ST + HM has been associated with improved social functioning and independent living skills, whereas functioning remained constant or declined for the HM-only group. The two groups receiving HM demonstrated increased use of preventive health services and identification of previously undetected medical

disorders (Bartels et al., 2004). A derivative, Helping Older People Experience Success (HOPES), is an integrated model of psychosocial rehabilitation and healthcare management and appears helpful in improving community living skills (Pratt et al., 2008).

The potential benefits of employment are numerous and older adults with SMI often manifest a desire to work despite low rates of paid jobs (Auslander and Jeste, 2002; Twamley et al., 2005). Ageing with schizophrenia can be associated with challenges in the workplace (Jeste and Nasrallah, 2003; Kurtz, 2005). However, competitive employment and, specifically, supported employment (SE) has been associated with better outcomes compared to conventional vocational rehabilitation (CVR). The goal of SE is rapid and individualized placement in competitive work with on-site training if required, following the 'place-then-train' philosophy. CVR reflects the 'train-then-place' approach with prevocational training and volunteering and gradual contact with competitive work (Twamley et al., 2005; Twamley et al., 2008).

Treatment adherence and service utilization

No study has assessed treatment adherence in patients with LOS specifically, but both psychosis and ageing have been linked to adherence problems. Partial adherence to treatment is observed in at least 20–50% of patients in the general population, but these rates approach 70–80% in persons with psychotic disorders. In older patients taking antipsychotics and medications for hypertension, diabetes, or hyperlipidaemia, researchers have reported similar adherence for psychiatric and nonpsychiatric medications. These rates ranged from 52–64%. Several factors related to old age may result in poor adherence, including sensory impairments, cognitive deficits, osteoarthritis, restricted mobility, lack of transportation, social isolation, financial insecurity, polypharmacy, and increased sensitivity to side effects. Poor adherence is associated with recurrence of symptoms and readmission, and with significant personal and societal costs (Masand and Gupta, 2003).

Studies have shown that among the population with chronic psychotic disorders, older age is associated with a lower use of all mental health services, with the exception of case management. This is in keeping with the observed decline in mental health expenditures in older people and the fact that the higher costs of case management and inpatient/crisis residential services among older persons are attributed largely to the population with schizophrenia. A significant drop in the use of outpatient services has been noted with age; this might explain the more frequent use of psychiatric emergency response teams and psychiatric emergency unit admissions (Gilmer et al., 2006; Jin et al., 2003).

These findings are consistent with those of McNulty and colleagues (2003) describing the high level of unmet care needs in a community sample of older people with schizophrenia or related disorders in Scotland, 59% of them with onset of symptoms after age 45. Reeves and

colleagues (2002) also observed that only 59% of older people previously diagnosed with VLOSLP were still in contact with psychiatric services after three years. A 2016 UK study reported low antipsychotic treatment rates (48% at three months, 27% at 12 months) in patients with VLOSLP (Sin Fai Lam et al., 2016).

It is also critical to assess capacity for healthcare and financial decisions. There is considerable heterogeneity in the level of decisional capacity among patients with schizophrenia, and age itself has not been found to strongly predict the lack of capacity to consent. Negative and cognitive symptoms have a more significant impact on the decision-making capacity than psychosis per se, and capacity should be assessed when appropriate, by using instruments such as the MacArthur Competence Assessment Tool for Treatment (MacCAT-T) (Grisso et al., 1997). Advanced care directives should be reviewed in any patient, but even more so in older adults, and should minimally include a discussion on living will and proxy decision-making.

Prognosis

Course of symptoms and functioning

Considerable reductions in schizophrenia symptoms have been observed in persons with LOS treated with antipsychotics. Open studies of typical antipsychotics have reported full remission in 48–61% of patients and higher proportions of at least partial response (Howard et al., 2000; Sable and Jeste, 2002). Better results have been noted with second-generation antipsychotics, even in the VLOSLP population, with substantial improvements noted in up to 77% of patients, with a more favourable response in those from outpatient vs inpatient settings. In older people treated with atypical neuroleptics, a more positive outcome could be seen in those with LOS as opposed to EOS (Barak et al., 2002; Scott et al., 2010).

Mazeh and colleagues (2005) followed 21 inpatients fulfilling criteria for schizophrenia with first onset at age 70 or later for a mean duration of 30 months. They compared this group to 21 older inpatients with onset of schizophrenia before age 40. Worsening of symptoms was reported in only one VLOSLP subject. Most had a single episode with full or partial remission, while almost one-half of the EOS patients experienced a relapse. The choice of the control group might have biased the findings, as the literature suggests that ageing is associated with an overall improvement in psychosocial function and psychopathology in older adults with EOS, although most remain impaired (Auslander and Jeste, 2004; Jeste and Nasrallah, 2003; Jeste et al., 2011). The findings in LOS patients are in keeping with results for the VLOSLP population reported by Reeves and colleagues (2002), with 52% having a single admission. Similarly, Brodaty and colleagues (2003) followed individuals with first onset of schizophrenia at 50 years or older, and observed a considerable decrease in symptomatology over time; 68.4% of them fulfilled DSM-IV

criteria one year after the diagnosis, and only 16.7% met criteria at five-year follow-up.

However, the broader literature tends to suggest partial, rather than complete, symptomatic improvement over time in LOS and VLOSLP, which mirrors the literature on late paraphrenia from the 1960s (Kay and Roth, 1961). Jeste and colleagues (1995) reported that most of the LOS patients in their sample had a chronic course with illness duration longer than two years, with an average of 5.7 years SD ± 5.5. Copeland and colleagues (1998) described residual symptoms and no case with complete recovery in subjects who had developed schizophrenia after age 65, although worsening was not seen either. Meesters and colleagues (2011) observed no significant difference in rates of symptomatic remission among those patients with early, late, or very late onset. Literature on psychotic disorders in late life seems to indicate that female gender, good treatment adherence, and schizoaffective illness are predictors of a favourable outcome. Findings are more inconsistent regarding the impact of cognition, sensory deficits, and ethnicity on the course of illness and psychotic symptoms specifically, although cognitive impairment has been associated with worse functional status (Auslander and Jeste, 2004; Granholm et al., 2008; Harvey, 2001; Palmer et al., 2002). People diagnosed with LOS and delusional disorder do not seem to differ in terms of outcomes. A dose-related effect was shown regarding antipsychotic use. Contact with a community psychiatric nurse also appears to lead to a more favourable course in LOS and late paraphrenia (Hassett, 2002; Holden, 1987; Howard and Levy, 1992; Meesters et al., 2011; Reeves et al., 2002; Riecher-Rössler et al., 2003).

Partial improvement in symptomatology can be achieved in most patients, though this does not necessarily translate into functional recovery (Patterson et al., 2003). Brodaty and colleagues (2003) demonstrated that even though the majority of LOS patients did not meet DSM-IV criteria for schizophrenia at follow-up, they were still functionally impaired, with GAF scores still below 50. Nineteen of the 21 patients included in a follow-up study by Mazeh and colleagues (2005) were able to stay at home for 30 months following discharge. Mild difficulties in the activities of daily living (ADLs), still within the normal range, characterized the 13 subjects with LOS described by Laks and colleagues (2006), with no significant deterioration in the functional scores at the one-year reassessment. These results underscore the heterogeneity in clinical and functional outcomes in the LOS and VLOSLP populations.

Course of cognition

Although there is no indication of an increased risk of Alzheimer’s disease in patients with LOS, some data support a general neurodegenerative pathophysiology. In follow-up studies on LOS or psychosis, significant cognitive deficits have been described in up to 50% of patients, especially

in very-late-onset cases (Brodaty et al., 2003; Korner et al., 2008; Korner et al., 2009a, 2009b).

Yet, most of the evidence points towards relative stability in the cognitive abilities of patients with LOS. Palmer and colleagues (2003) found no evidence of cognitive decline for schizophrenia patients in both late- and early-onset groups compared to normal controls, while two Alzheimer's disease comparison groups (persons with very mild deficits and persons with psychotic symptoms at baseline) manifested progressive impairments. The absence of significant change in neuropsychological performance over time in individuals with LOS has been replicated. Although people with LOS do not experience a greater worsening of their cognition compared to age-matched controls, they do not show the same level of improvement following intervention (Granholm et al., 2010). This could have treatment implications, as it suggests a ceiling effect in response to interventions that have a cognitive remediation component.

Quality of life

In older patients with schizophrenia, symptomatic remission has been associated with a higher reported quality of life (QoL), intermediate between that of younger patients and healthy comparison subjects (Auslander and Jeste, 2004; Bankole et al., 2008). A study by Folsom and colleagues (2009) suggested that older age may, in fact, be associated with greater mental health-related QoL in this population. On the other hand, Meesters and colleagues (2011) could not demonstrate any correlation between symptomatic remission and QoL in older people with schizophrenia, although the remission rates in their sample were lower than those reported from convenience samples. This is consistent with studies indicating significantly greater improvement in psychological and health-related QoL in patients treated with olanzapine rather than risperidone (Ritchie et al., 2003; Ritchie et al., 2006). In light of the significant interplay between cognitive status and social situation with regard to overall function and QoL, the failure to include measures of QoL in most outcome studies on LOS or VLOSLP as well as the exclusion of late-onset patients from some papers on QoL area is a drawback (Meesters et al., 2010).

A similar effect to medications has not been as clearly established with psychosocial interventions. No impact on QoL was demonstrated following participation in FAST (Patterson et al., 2006; Patterson et al., 2003). Improvement in QoL resulting from better functioning following CBSST was postulated by the authors, but as QoL was not part of the outcomes measured, this remains hypothetical (Emmerson et al., 2009). We did not find any mention of QoL in relation to ST + HM (Bartels et al., 2004). However, vocational rehabilitation, particularly supported employment, does appear to lead to better QoL (Bartels and Pratt, 2009; Twamley et al., 2005; Twamley et al., 2008). This could indicate that better functioning seems to be associated with greater wellbeing; other avenues also need to be considered. The importance of positive social

support and interactions cannot be minimized, as married middle-aged and older adults with schizophrenia reported better QoL, despite the presence of depressive symptoms in both groups (Nyer et al., 2010).

Mortality

While increased morbidity and mortality rates have been noted in schizophrenia for decades, recent studies have reported a growing mortality gap between individuals with schizophrenia and the general population (Laursen and Nordentoft, 2011; Lee et al., 2017; Saha et al., 2007). Whether late-onset cases herald a specifically higher mortality risk is not clear. Most outcome studies reporting deceased subjects did not include a control group. The onset of psychotic symptoms in late life was associated with double the risk of mortality at follow-up by Henderson and Kay (1997), while Östling and colleagues (2007) found no such association. A 2015 Finnish registry study reported that VLOSLP had higher mortality risk compared to EOS patients, mostly attributable to physical comorbidities and accidents (Talaslahti et al., 2015). Although the risk of suicide might be somewhat lower in older patients with schizophrenia by approximately 5% compared to younger affected individuals, they are still at risk of suicidal behaviours, and age of onset was not found to mitigate this risk one way or another (Barak, 2004).

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