Management of schizophrenia

Schizophrenia in older people is often a challenge to clinicians. Most research on treatment excludes people over 60 years of age, which has led to a lack of evidence for this age group. Attempts to differentiate schizophrenia in older and younger adults have produced equivocal results. Here, we give an overview of the classifications of this disorder, risk factors for and management of schizophrenia in older adults.

Dr Ashok Krishnamoorthy Consultant Psychiatrist, Maelor Hospital, Wrexham LL13 7TD
Dr Ashley Baldwin Consultant Psychiatrist, Sherdley Unit, Whiston Hospital, Prescot, L35 5DR
***Email** ashokpriya@gmail.com

Psychosis is characterised by a loss of contact with reality, manifesting as perceptual disturbances (hallucinations), impaired interpretation of the environment, false beliefs (delusions), and disorganised speech and behaviour. In older people, psychotic symptoms present in a wide range of conditions.

Research on schizophrenia has largely focused on the working age population; around 90% of published papers have excluded older patients.[1] Elderly people with schizophrenia are classified into those with early onset disease who grow older with the condition (graduates) and those with onset after age 65 years. As the percentage of people over 65 years old in the general population is predicted to increase, the proportion of "graduates" will also rise.

Psychotic symptoms are not uncommon in the elderly, ranging from 0.2 to 4.7%.[2] The prevalence of psychotic symptoms in a population based sample of individuals over 85 years of age without dementia has been reported as being 7.1–13.7%.[3] A range of factors are known to contribute to late-onset psychosis (box 1).

The prevalence of schizophrenia in people over 65 years of age is believed to be 1%[4] of which 25% have late onset illness and the rest are graduates. The features of schizophrenia appear to differ by age of onset (table 1). Women tend to be over-represented in the elderly population with schizophrenia.[5]

Classification

Late-onset schizophrenia has been given various terms, including paraphrenia, late paraphrenia, paranoia, and involutional paranoid disorder. It has also been classified as affecting a range of ages.

Late paraphrenia refers to all delusional disorders occurring after age 60 years; these are often associated with a discernible organic substrate.[6] The Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM IIIR)[7] included a separate category for patients whose schizophrenia emerged after age 45 years. In 1998, representatives from 17 countries met at the International Late-Onset Schizophrenia Group Consensus Conference and agreed two concepts regarding the classification of the disorder:

- Late-onset schizophrenia with onset after age 40 years
- Very late-onset schizophrenia-like-psychosis (VLSLP) with onset after age 60 years.

However, VLSLP can be seen as a phenotypic variant of early onset schizophrenia; an onset specifier such as "very late onset" would be more helpful than considering this as a separate entity. The current international classification system —International Classification of Diseases 10 (ICD-10) and DSM IVR—has no distinct place for late-onset schizophrenia. An arbitrary cut-off age of 65 years is used to separate general adult services and older people's services in the UK.

Biological correlates

Postmortem studies of dopamine receptors have shown a reduction in D2 receptors with age in normal ageing, and there is evidence that baseline numbers of dopamine receptors are increased both in early- and late-onset schizophrenia patients.[8,9] The ventricular–brain ratio is also increased in late

Table 1: Variation in the clinical features of schizophrenia with age of onset[18]

	Early onset schizophrenia (<40 years)	Late onset schizophrenia (40–65 years)	Very late onset schizophrenia-like-psychosis (>65 years)
Predominant gender	Male	Female	Female
Paranoid subtype	Marked	Very common	Common
Negative symptoms	Present	Present	Absent
Thought disorder	Present	Present	Absent
Brain structure abnormalities (eg strokes, tumours)	Absent	Absent	Marked
Neuropsychological impairment: learning and retention	Marked, absent	Present, absent	Both present, probably marked
Progressive cognitive deterioration	Absent	Absent	Marked
Family history of schizophrenia	Present	Present	Absent
Risk of tardive dyskinesia	Present	Present	Marked

onset schizophrenia compared with age- and sex-matched controls. These changes appear to be intermediate between those of healthy controls and patients with Alzheimer's disease.[10]

Women tend to predominate in patients with VLSLP, an observation that is supported by robust findings.[11–14] Neuroimaging has shown that such women have more extensive reductions in the parietal lobe and hippocampus than women with schizophrenia of earlier onset. One paper suggested that the antidopaminergic action of oestrogen has a protective function before the menopause.[15] Another hypothesis suggests that a single event in later life such as the development of microvascular disease or primary dementia could precipitate the illness.

People with late-onset schizophrenia did not have increased infarcts or white matter hyperintensities (WMH) compared with people with early-onset schizophrenia or with normal control when measured by MRI.[15–17] Though, overall, WMHs were no different, Miller et al[10] found some significant increase in WMHs in the frontal, temporal and occipital regions in the late onset group. The equivocal results in this area could be due to small sample sizes and difficulty in more precisely quantifying white matter lesions. The equivocal results in this area could be due to small sample sizes and difficulty quantifying white matter lesions.

The incidence of cognitive impairment appears to be similar in patients whose schizophrenia develops after age of 60 years and those with early onset.[17] But it is quantitatively different from that in dementia patients as learning capacity is preserved. Whether late-onset schizophrenia leads to dementia is currently inconclusive.

Management

People with early onset schizophrenia who grow older have additional problems, compared with younger patients, that can be a challenge to manage. These include early onset negative symptoms and cognitive deficits; lack of critical social support (as they are less likely to be married and have had children); comorbid substance abuse; and side effects of long-term antipsychotic treatment.

The graduates especially between the ages of 60 and 74 years have a high risk of developing

Box 1: Factors that contribute to elderly onset psychosis

- Age-related deterioration of frontal and temporal cortices
- Neurochemical changes associated with ageing
- Social isolation
- Sensory deficits
- Cognitive deficits
- Age-related pharmacokinetic and pharmacodynamic changes
- Polypharmacy

Box 2: Positive and negative effects of antipsychotics in elderly patients[8]

- Incidence of EPSE is more common in elderly patients with the use of conventional antipsychotics, and dosage needs to be titrated slowly
- Atypical antipsychotics appear to be the first choice agents given the reduced risk of EPSE
- Weight gain and glycaemic control need to be monitored with the use of atypical antipsychotics
- Risperidone and olanzapine are widely studied in elderly schizophrenia patients
- ECG monitoring is not routinely needed unless significant risk factors for QTc prolongation are present
- Choice of drug is based on individual risk–benefit profile
- Increased stroke risk with atypical antipsychotics is found in patients with dementia, but risk in schizophrenia has not been systematically studied.

physical problems, such as diabetes mellitus and heart disease when on antipsychotics, which after 75 years of age reaches a plateau.[19]

Antipsychotics are the mainstay of therapy for managing schizophrenia in the elderly. Legitimate concerns about their use include variable responsiveness, increased sensitivity to adverse effects (box 2), and decreased ability to report them. The impact of changes with age in the absorption and distribution of the drug should also be considered.

Conventional antipsychotics

Conventional antipsychotics have been used across all age groups for many years, but few studies have looked at their use in elderly people with schizophrenia. Significant improvement in psychotic symptoms was reported with haloperidol and trifluoperazine in the 1960s.[20,21] Depot conventional antipsychotics can be useful in patients with adherence problems.

The risks of developing extrapyramidal side effects (EPSE), urinary incontinence, and falls need to be considered before using conventional antipsychotics.[22,23] The use of anticholinergics to prevent EPSE leads to its own adverse effects, including confusion, delirium, tachycardia, and falls. There is also some evidence to suggest that antipsychotic treatment is associated with impaired cognition in elderly patients.[24,25]

Dosage requirements tend to be higher in schizophrenia patients than those with Alzheimer's-related psychosis. Start at a low dose and titrate slowly to minimise side effects.

Atypical antipsychotics

Atypical antipsychotics are considered first-line treatment for older patients with schizophrenia because of their better tolerability and side effect profile compared with conventional agents.[26] Suggested daily doses of atypical antipsychotics may be varied depending upon the patient profile.

Risperidone (Risperdal) has been extensively studied in the elderly, and 1.5–6mgs per day appears to be the favoured dosage.[27] Olanzapine (Zyprexa) appears to give patients a superior quality of life without significantly affecting body weight.

The CATIE trial found that olanzapine and risperidone were the most effective atypical antipsychotics in terms of discontinuation rates.[28] The efficacy of second generation antipsychotics was similar to that of conventional antipsychotics, but the study did not include patients over 65 years. Other major adverse effects of atypical antipsychotics include weight gain, dyslipidaemia, and type-2 diabetes.

In March 2004, the UK Medicines and Healthcare

products Regulatory Agency (MHRA) concluded that use of olanzapine and risperidone for treatment of the behavioural and psychological symptoms of dementia (BPSD) was associated with increased risk of stroke and should not be used.[29] The number needed to harm was calculated to be around 58.8 patients with dementia to cause one additional stroke event over a 6–12 week period.[30] Though mainly for use in dementia, this guidance has restricted use of olanzapine in people with schizophrenia because of the need to use the drugs long term. Antipsychotic use in the elderly with schizophrenia is licensed without restriction towards olanzapine or risperidone.

Quetiapine (Seroquel) is better tolerated by the elderly than conventional antipsychotics; it is not associated with significant weight gain at the dosages used in this age group. Common side effects, including postural hypotension, dizziness, and agitation, can be avoided with gradual titration from 25mg.

Dosages of up to 750mg/day in divided doses have been reported as safe in a multicentre, open label trial,[31] but this has not been consistently replicated by other studies. Commonly used maximum dosages are 300mg/day.[32]

Aripiprazole (Abilify) is less likely than other atypicals to cause extrapyramidal side-effects, sedation, weight gain, and cardiovascular side effects.[33] It holds promise in older people with schizophrenia, especially for maintenance treatment. Small studies have supported its use for treatment of positive and negative symptoms.[34] Amisulpride (Solian) is also used in the elderly population although well designed randomised controlled trials (RCT) are lacking in this age group. A recent open label study shows that it is effective in the dose range 50–200mg/day with minimal side effects.[35]

The value of clozapine in treatment-resistant schizophrenia is well established in early onset cases. The few studies of the older population have reported sedation, lethargy and hypotension, even at lower doses.[36] It is not as a first-line agent in elderly patients because of the associated weight gain, toxicity, and the need for blood monitoring. Therefore, its use is reserved for treatment resistant cases and in severe tardive dyskinesia.

Non-pharmacological management

Evidence for non-pharmacological management in elderly schizophrenia patients is very limited. Very few studies have assessed the use of cognitive behavioural therapy (CBT) to help elderly patients gain insight into the illness and provide them with coping strategies.[37] Mcquaid et al[38] developed an intervention for older people called *integrated cognitive behavioural therapy and social skills training,* which improved their ability to cope with stress and adhere to other forms of treatment. After remission of the psychotic episode, however, patients showed poor adherence to treatment due to limited social support. Other psychosocial interventions need to target social and independence skills.[39]

Conclusion

The outcome of schizophrenia in older adults has not been studied in great depth because of the difficulties conducting long-term follow-up.

Negative symptoms are less common in patients with late onset, compared with early onset, and individual episodes show limited response to antipsychotics. Deficits in cognitive functions tend to remain stable, and other symptoms are considered non-progressive.

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