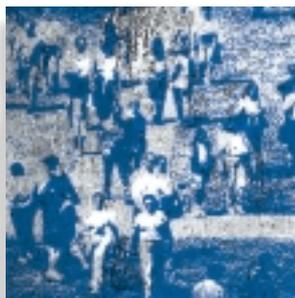# Clinical research

Schizophrenia in late life: emerging issues

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Schizophrenia in late life is emerging as a major public health concern worldwide. We discuss several areas of research and clinical care that are particularly pertinent to older persons with schizophrenia, including the public health challenge and the cost of care. We then discuss clinical issues relevant to late-life schizophrenia (course of illness and cognition), medical care and comorbidity in older psychiatric patients (general and illness-related), and treatment concerns related to the use of atypical antipsychotics in older persons with psychosis (efficacy and side effects). Clinical care for this ever-increasing segment of our population requires special consideration of the unique characteristics of older persons with schizophrenia.

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As the population in the USA and other developed nations ages, the number of older persons with a major psychiatric disorder is expected to increase. It has been estimated that by the year 2030, the number of persons over age 65 with a major psychiatric disorder will be roughly equal to the number of people aged 30 to 44 with a similar disorder.[1] This demographic trend has major implications for both the costs and logistics of caring for this growing group of older persons with major psychiatric disorders. This article will discuss several emerging areas of research and clinical care that are particularly pertinent to older persons with schizophrenia. These topics will include the public health challenge and the cost of care for older patients with schizophrenia. We will also discuss the course of schizophrenia in late life, including clinical differences between early-and late-onset schizophrenia, with respect to neurocognitive decline and remission, and the nature and importance of comorbid medical conditions and medical care for older persons with schizophrenia. Finally, we will report the results of the only randomized clinical trial that compared two atypical antipsychotics in older patients with schizophrenia, and discuss recent regulatory actions with respect to the side effects of atypical antipsychotics that may be of particular concern in late-life schizophrenia.

By convention, the geriatric population is considered to include those aged 65 and older. However, the terms "later life" or "late onset" have come to represent different age-groups when discussing schizophrenia. Late-life schizophrenia comprises two distinct groups: those individuals who were diagnosed with schizophrenia early in life (late adolescence or young adulthood) and who are now middle-aged; and those who are diagnosed when they are elderly (45 years or older). Those individuals who are diagnosed with schizophrenia at the age of 45 or older are classified as late-onset schizophrenia. Our center has included

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both middle-aged and elderly persons with schizophrenia, those with early or late onset. The average age of our cohort is around age 60 and we use no upper age cutoff.

The public health challenge

A recent report by Bartels and colleagues examined the annual health care costs for adults with schizophrenia, depression, dementia, or physical illnesses in one small US state (New Hampshire).[2] In general, except for dementia, costs of care increased with the age of patients, with those over 85 incurring the greatest per-capita expense. Among people aged 65 or over, annual per-person care for those with schizophrenia, $40 000 or more, was the most costly: (about 50% higher than for those with depression and about three times higher than for those receiving care for only physical illnesses). The patients with schizophrenia incurred higher annual costs in all age-groups compared with depression or medical conditions. The cost-by-age data were different for patients with dementia, where younger patients incurred higher costs. However, among patients over age 65, the cost of care was higher for the patients with schizophrenia compared with those with dementia.

This report also calculated the costs associated with the various treatment settings, such as outpatient clinics, inpatient hospitals, and nursing homes, where people with schizophrenia in each age cohort received their treatment. Among the younger patients (aged 19 to 44), outpatient mental health treatment consumed approximately 50% of the annual expenditures ($10 244 in outpatient costs, $20 066 in total costs). In contrast, in those patients aged 75 and older, only 5% of the annual expenditures were for outpatient care ($1755 of $34 320), and the vast majority of expenditures were for nursing home care ($28 395 or 83%). Even in old age, schizophrenia is expensive. The costs of treating schizophrenia increase with age, across the entire adult life span. The need for this level of care is a reflection of the degree of symptomatology and disability in these patients. As Bartels et al point out, interventions that optimize functioning and decrease use of nursing homes are particularly needed for older patients with schizophrenia.

Course of schizophrenia in late life

The clinical presentation of older persons with schizophrenia differs somewhat from that of younger persons, and the course of this disorder into old age sheds light on some unresolved cognitive and social issues. In this sec-

tion, we discuss the clinical differences between patients with early- versus late-onset schizophrenia, review the emerging research describing changes in symptoms and neuropsychological deficits over time, and consider a new perspective on remission from schizophrenia.

Age of onset of schizophrenia

Since the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R)*, "late-onset" schizophrenia has been defined as onset of symptoms after the age of 44,[3] and accounts for approximately 15% to 20% of all cases of schizophrenia.[4] Most patients with late-onset schizophrenia have onset of illness during middle age. Onset after age 65 usually signifies very-late-onset schizophrenia-like psychosis, which is typically secondary to general medical conditions, such as dementia or other neurodegenerative disorders.[5] Women are more likely to have late-onset schizophrenia than men. In addition, persons with late-onset schizophrenia tend to have better premorbid functioning, fewer negative symptoms, and less severe neurocognitive impairments. Although the conventional wisdom has been that the symptoms of schizophrenia progress with age, recent investigations have found that many symptoms of schizophrenia improve with age. Older patients typically have fewer and less severe positive symptoms than their younger counterparts[6]; negative symptoms, however, tend to persist into late life.[5] Finally, patients with late-onset schizophrenia typically require lower daily doses of antipsychotics compared with patients with an early onset of the disorder.[7,8]

Neuropsychological changes over time

Schizophrenia is commonly associated with mild-to-moderate neuropsychological deficits,[9] which, more than severity of psychopathology, are the most robust predictors of functional independence,[10] including functional independence among older patients with schizophrenia.[11-13] The Kraepelinian notion of schizophrenia as dementia praecox colored conventional thinking regarding the long-term course of this disorder for many years, in that it was generally assumed that there was a progressive deterioration in functioning as patients aged. However, with the exception of studies of chronically institutionalized "poor outcome" patients,[14,15] who represent a small minority of the contemporary population of older persons with schizophrenia,[16] the weight of empirical data on the longitudinal

course of neuropsychological deficits in schizophrenia in fact documents a remarkably stable pattern of neuropsychological functioning,[17,18] even among older patients with schizophrenia, as well as those whose symptoms first emerge in mid- to late life.[18,19] For instance, in a recent study from our research center, we annually administered a comprehensive neuropsychological test battery to 142 patients with *DSM-III-R* or *DSM-IV* diagnoses of schizophrenia (confirmed with a structured clinical interview), as well as 206 healthy comparison subjects. We found that patients' neuropsychological functioning remained stable over follow-up periods of up to 5 years or more, even among the subset whose positive or negative symptoms deteriorated or improved over the follow-up periods, and among those ages 65 or older, as well as those whose symptoms onset in mid- to late life. In short, while patients with schizophrenia as a group have worse neurocognitive functioning than the general population, there does not appear to be risk of greater than age-normal progressive decline, at least among noninstitutionalized patients. Moreover, given the importance of neuropsychological abilities to independent functioning, these findings of stability suggest a reason for optimism about the long-term prospects of maintaining a degree of functional independence as patients age.

Informed consent and decisional capacity

Patients with schizophrenia are routinely asked to provide informed consent for their antipsychotic medication treatment. However, because of the cognitive deficits, as well as insight deficits, which are sometimes present among those with schizophrenia,[9,20] some schizophrenia patients may lack the capacity to provide independent consent for treatment. On the other hand, empirical data document considerable heterogeneity among older as well as younger schizophrenia patients in terms of the level of decisional capacity,[21-23] and age is not itself a strong predictor of the level of decisional capacity among such patients.[23-25] Nonetheless, due to the increased likelihood of medical comorbidity and polypharmacy present in the older population,[26,27] together with the increased physical frailty of some elderly persons, and the still relatively limited empirical database on the safety and efficacy of antipsychotic medications for use with "real-world" elderly patients, the very nature of treatment decisions and consent may be particularly complex in the context of treating older patients with schizophrenia, and

thus consent issues are particularly salient. The strongest predictors of impaired decisional capacity tend to be level of cognitive deficits, and to a lesser degree, severity of negative symptoms.[23,25,28,29] Therefore, when recommending treatment for patients with notable cognitive deficits and/or substantial negative symptoms, clinicians should be particularly alert to the possible presence of impaired consent capacity. One instrument that can be helpful in further evaluating such patients is the MacArthur Competence Assessment Tool for Treatment (MacCAT-T).[22] The MacCAT-T involves a 15- to 20-minute semistructured interview, which assesses a range of consent-relevant topics, including the patient's ability to understand the nature of his or her condition and the proposed treatment, his or her ability to apply (appreciate the significance of) that information to his or her own situation, and to consider the risks and benefits of the proposed treatment relative to alternative choices, as well as to express a clear and consistent choice. (See Dunn et al,[30] in press, for a thorough review of this and other decisional capacity instruments.) Issues of "competency" are most commonly addressed when patients are refusing a recommended treatment, but given the considerations described above, there may be merit in considering decisional capacity even when patients are accepting recommended treatment, particularly when more than one viable alternative is present with varying risk-benefit considerations.

Remission

Despite the stability of cognitive functioning, the clinical presentation of schizophrenia may vary over the course of the illness. The symptoms and functioning in some persons with schizophrenia will worsen over time, and many will remain stable. Some, however, will improve. It should be no surprise that remission from schizophrenia has been found to range from 3% to 64% of patients[31]; however, these prior reports used a variety of criteria to define remission.
We developed a definition of remission that included the following criteria[32]: (i) previously meeting *DSM-III-R* or *DSM-IV* criteria for schizophrenia or schizoaffective disorder; (ii) receiving a course specifier of "in full remission"; (iii) living independently for the prior 2 years; iv) no psychiatric hospitalizations in the prior 5 years; (v) current psychosocial functioning reported to be within the "normal" range, confirmed by caregiver or other

informant; and (vi) currently not taking antipsychotic medications, or taking less than 50% of prior highest dose. We recognize that by including criteria other than symptomatology (function, hospitalization, and medication) that our criteria may be considered stringent (see, for example, Andreasen et al[33]).

In the database of patients enrolled in our center, there were a total of 155 patients over age 60 who were living independently. Of these, 12 met the above criteria for remission. Comparing the patients with remission with a cohort of patients with symptomatic schizophrenia and a second cohort of normal control patients, the patients whose schizophrenia had remitted were found to have psychopathology that was similar to the normal controls. On measures of cognition, health-related quality of life, and everyday functioning, the patients with remitted schizophrenia were intermediate between normal controls and patients with symptomatic schizophrenia. These findings suggest that patients were not achieving a normal state of functioning, but rather were returning to a premorbid state of suboptimal and somewhat impaired function.

An important remaining question is what factors contribute to remission, and what approaches to intervention can enhance the likelihood of remission. There is considerable promise in the expanded use of rehabilitation-oriented psychosocial interventions in this regard.[34-36] Initial results are promising with regard to improvement of function. The longer-term outcomes, including the achievement of remission, remain open issues.

Medical conditions in older persons with schizophrenia

Until recently, a topic that has arguably received inadequate attention is comorbid medical conditions in people with schizophrenia, including adequacy of medical care and the prevalence of comorbid conditions. Medical comorbidity is even more pertinent to older persons with schizophrenia, given the increase in age-related disorders. A series of articles by Druss and colleagues compared the care that patients with schizophrenia received after suffering a myocardial infarction (MI) with the care received by persons with no mental illness.[37,38] Using the proportion of patients who undergo cardiac catheterization post-MI as a measure of quality of care (a proxy measure that has been used in other investigations of health disparities[39]) they reported that, compared with patients with no mental illness, patients with schizophrenia were 60% less likely to undergo a cardiac catheterization after an MI.[37] A second report found that these same patients had a 30% greater 1-year mortality than non–mentally ill patients. Approximately half of this increased mortality was due to a lack of quality medical treatment after the MI.[38]

Work in our center[40] found that, in middle-aged and older homeless patients with mental illness, those patients with schizophrenia were less likely to receive primary and preventive care than patients with major depression. Similarly, Himmelhoch and colleagues have shown that the prevalence (22.6%) of chronic obstructive pulmonary disease (COPD) was substantial in people with serious mental illness and substantially higher than overall national norms in the USA: the prevalence of chronic bronchitis in the schizophrenia sample was 19.5% (compared with the national rate of 6.1%) and emphysema was 7.9% (compared with the national rate of 1.5%).[41] Conversely, we are aware of at least one report that indicates that patients with schizophrenia may be receiving quality medical care; this study found that patients with schizophrenia had slightly better diabetes control than a matched group of patients with no mental illness (using hemoglobin A_{1c} levels).[42]

Among persons with schizophrenia, the most common cause of death is heart disease (just like in the general population),[43] yet it has been estimated that persons with schizophrenia on average die 10 years earlier than the general population.[44] The growing concerns about the risk of diabetes, MI, and stroke in patients taking second-generation antipsychotics has also increased the awareness of the importance of comorbid medical conditions in patients with schizophrenia. An investigation of midlife adult patients with schizophrenia treated in a community mental health center (mean age 44) found that diabetes and lung disease were more common among persons with schizophrenia than in the general US population.[45] Future research should examine whether these disorders are also more prevalent among older persons with schizophrenia, or whether these disorders have an earlier age of onset among persons with schizophrenia.

Preventive health care is another area of major concern for all people with schizophrenia, especially the older patients. Work in our center,[46] for example, has shown that, compared with women with no known diagnosis, middle-aged and older women with schizophrenia were 25% less likely to have had a pelvic examination and Pap

smear in the past 3 years (96% versus 71%) and 30% less likely to have had a mammogram in the past 2 years (98% versus 68%). Considering that, at the time the study was completed, hormone replacement therapy (HRT) was much more widely recommended than it is today, the women with schizophrenia were 22% less likely to have ever had HRT (78% versus 56%).

Unrecognized or poorly managed comorbid medical illness is a significant source of excess disability and mortality in older persons with schizophrenia. The organization and delivery of care in a coordinated manner may be a challenge. All these are important directions for new research.

Antipsychotics in late-life schizophrenia

Use of conventional neuroleptic medications in older patients is highly problematic, with observed incidence rates of tardive dyskinesia in excess of 20% in the first year of treatment and growing to over 50% in 3 years of cumulative treatment.[47,48] Importantly, these findings emerged in the context of very low dosing of the medication. Therefore, safety and efficacy of the atypical antipsychotic medications in older patients with schizophrenia is an important consideration. The initial registration studies of the atypical antipsychotic medications contained few older patients. To date, the only two antipsychotic medications that have been specifically investigated in a randomized clinical trial in patients over age 60 are risperidone and olanzapine.[49] These medications were compared in an 8-week, double-blind study of elderly (age over 60) patients with schizophrenia. The dosing of both medications was flexible, with a range of 1 to 3 mg/day for risperidone and 5 to 20 mg/day for olanzapine. The primary outcome measures were the change on the Positive And Negative Syndrome Scale (PANSS) and rates of extrapyramidal symptoms (EPSs). This investigation found that patients in both groups showed significant improvement during the 8-week trial, and that this improvement was similar for both treatment groups. The rates of EPSs were also similar in both groups.

Side effects of atypical antipsychotics in elderly patients

The safety and adverse events profile of atypical antipsychotics in elderly patients treated is mixed. On the positive side, there is a significantly lower incidence of tardive dyskinesia among older patients taking atypical antipsychotics compared with the older typical antipsychotics. There is widespread concern regarding the effect of atypical antipsychotics on cardiovascular and metabolic function, diabetes, and lipid levels, with resultant warnings issued by various regulatory and professional organizations. It is beyond the scope of this paper to review the substantial body of literature in these areas.

Particular safety concerns have been raised regarding the use of atypical antipsychotics in older patients with dementia. Elevated mortality rates have been reported in placebo-controlled trials of atypical antipsychotics in demented patients taking active drugs compared with placebo. On the basis of the findings of a 1.6- to 1.7-fold increase in the risk of mortality in patients with behavioral disturbances due to dementia taking atypical antipsychotics compared with placebo, alerts and warnings have been issued in the USA, the UK, and Canada with respect to use of all atypical antipsychotics in demented patients. An increase in cerebrovascular adverse events was also observed in these studies. It should be noted that these studies were typically carried out in nursing home settings in very old patients with a variety of dementing disorders, and many of the patients had elevated vascular risk factors, including history of hypertension and stroke. Agitation and psychosis, the behavioral disturbances of Alzheimer's disease, and other dementing disorders present difficult and complex clinical management problems. Currently available treatments, both pharmacological and behavioral, are far from optimal, from both a safety and efficacy perspective. "No treatment" is clearly not an option for many patients. Therefore, great care must taken in use of any treatment, and close monitoring is essential.

It remains unclear whether these concerns are specific to older patients with dementias or whether they are generalizable to atypical antipsychotic use in all older patients. With funding from the National Institutes of Health, we have initiated a comprehensive prospective study of a large sample (n=450) of older persons in whom an atypical antipsychotic is identified as a treatment of choice. Patients are randomized to one of four medications (aripiprazole, olanzapine, quetiapine, and risperidone), and assessed every 3 months for at least 2 years. The protocol includes complete physical examinations, periodic questionnaires and standardized rating scales, and a variety of metabolic measures and markers of vascular inflammation and endothelial dysfunction. This

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study provides the opportunity to address the many questions that are emerging about the use of atypical antipsychotic medications in the older patient.

Conclusions

Schizophrenia in late life is a serious illness. It is profoundly disabling for most people with the disease, and care for these patients places great pressure on health care systems. We have provided an overview of several important issues in the field: the pressure created by schizophrenia in late life on the health care system; the epidemiology of the illness; the significance of age of onset to clinical course and outcome, especially remission; the special concerns at the medicine–psychiatry interface; and the efficacy and safety of antipsychotic medications. We have raised issues of safety with respect to use of atypical antipsychotics in older people with dementias, and questioned the generalizability of this concern to broader, nondemented clinical populations. Finally, it is important to note that the pharmacological treatments available for use in schizophrenia are far from ideal. The drugs are expensive; remission, though possible, is uncommon; and patients are often in the position of achieving some reduction in symptom severity but rarely to the level of wellness. As was shown in the recently completed Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial in the USA,[50] problems of tolerability and side effects interact such that few patients actually stay with the drug treatment they are prescribed, or, for that matter, with any treatment. Clearly, we need better drugs and better approaches to the discovery and development of drugs.[51] At the same time, we need to acknowledge the important statement of the National Institute for Clinical Excellence (NICE) in the UK: "… The management of schizophrenia involves a comprehensive package of care, […] drug therapy accounts for less than 5% of the total health care costs of schizophrenia."[52] Future directions in research and clinical care of older persons with schizophrenia should include psychosocial interventions aimed at improving functioning and illness management. ❏

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Esquizofrenia a edad avanzada: temas emergentes

La esquizofrenia a edad avanzada se está constituyendo en un gran problema de salud pública a nivel mundial. En este trabajo se discuten algunas áreas de investigación y cuidados clínicos que son particularmente pertinentes a las personas ancianas con esquizofrenia, incluyendo los desafíos de la salud pública y los costos de atención. Además se discuten temas clínicos relacionados con la esquizofrenia en la edad avanzada (curso de la enfermedad y aspectos cognitivos), los cuidados médicos y la comorbilidad en pacientes psiquiátricos ancianos (generales y en relación con la enfermedad), y tratamientos relacionados con el empleo de antipsicóticos atípicos en personas ancianas con psicosis (eficacia y efectos colaterales). El cuidado clínico para este segmento –siempre creciente– de nuestra población, requiere de una consideración especial por las características específicas que representan las personas ancianas con esquizofrenia.

Problèmes spécifiques de la schizophrénie en fin de vie

La schizophrénie dans la dernière partie de la vie est en train de devenir un problème majeur de santé publique dans le monde entier. Nous abordons plusieurs domaines de la recherche et discutons des soins cliniques particulièrement adaptés aux personnes âgées atteintes de schizophrénie, y compris du défi de santé publique que cela représente et des coûts des soins qui s'y rapportent. Nous traitons ensuite les questions cliniques relatives à la schizophrénie en fin de vie (évolution de la maladie, et cognition), les soins médicaux, et la comorbidité chez les patients psychiatriques âgés (en général et liée à la maladie), et les problèmes thérapeutiques liés à l'utilisation d'antipsychotiques atypiques chez les personnes âgées psychotiques (efficacité et effets indésirables). Les soins apportés à cette partie de la population toujours croissante requièrent spécialement notre attention en raison de la caractéristique spécifique que représente le sujet âgé schizophrène.

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