MATTI ISOHANNI, ERIKA JÄÄSKELÄINEN,
HANNU KOPONEN, BRIAN J. MILLER, ESA LEINONEN, TIINA TALASLAHTI

ANTIPSYCHOTICS IN LATE-LIFE SCHIZOPHRENIA – A NARRATIVE REVIEW

ABSTRACT

The number of people with late-life schizophrenia is increasing, but few prospective longitudinal studies have analysed antipsychotic use in this group. The aim of this narrative review is to present key points of current knowledge regarding the use of antipsychotics in late-life schizophrenia. In general, antipsychotic medications have had a major impact on symptom relief in schizophrenia. If used with caution, they are relatively safe and effective in older patients. Given the significant somatic comorbidity and excess mortality in late-life schizophrenia, treatment approaches should include a combination of judicious use of antipsychotics with non-pharmacological treatments. Antipsychotics should be used cautiously with the goal of optimizing outcomes with regular monitoring of adverse effects and using lowest effective doses. Cessation of antipsychotic treatment may be possible for some patients.

KEY WORDS: AGEING, GERIATRIC, LATE LIFE, SCHIZOPHRENIA, ANTIPSYCHOTIC AGENT

INTRODUCTION

An increasing number of people with schizophrenia will survive into advanced age following illness onset in early adulthood or midlife (1-4). Concordantly, the importance of geriatric psychopharmacology will increase. Scientific research on patients with schizophrenia largely focuses on patients diagnosed in early adulthood (EOS, early-onset schizophrenia), but patients with late onset (LOS, diagnosed at age 40-60) or very late onset (VLOS, diagnosed after age 60 or more) of illness are also studied (5-6). In this review, individuals with late-life schizophrenia (over age 55-65) (1) are discussed regardless of the age of onset of illness.

In late-life schizophrenia, as summarized by Cowling et al. 2012 (1), less frequent episodes of symptom exacerbation and increased sensitivity to medications are observed. Positive symptoms are less severe, negative ones may increase, substance abuse is less common and mental health functioning may improve. Hospitalizations are more likely to be due to physical problems rather than psychotic relapses. However, less is known about the real-world prescribing practices of psychiatrists for patients with late-life schizophrenia. Older age is a risk factor for antipsychotic side effects, including metabolic syndrome and movement disorders.

Data on the trajectory of schizophrenia in late life is essential for the planning of treatment and service provision. Due to changes in psychopathology and neuropathology, social functioning and physical health across the lifespan, we cannot assume that findings in younger patients apply to individuals with late-life schizophrenia.

Antipsychotics are efficacious during the acute and early maintenance phase of schizophrenia following acute illness episodes (7-11). Evidence on the efficacy of antipsychotics is less clear from a longitudinal or even lifespan perspective (9,12). Antipsychotics remain the mainstay of treatment for late-life schizophrenia. The effectiveness of both typical and atypical antipsychotics has been demonstrated, commonly favouring atypical antipsychotics (6). However, most of the evidence is not based on rigorously conducted trials. Effective non-pharmacological treatments have also yet to be developed.

We present here a narrative review of current knowledge of antipsychotic medication in late-life schizophrenia, particularly the clinical challenges, treatment algorithms and recommendations, medication management (7) and the efficacy of available antipsychotics. We also draw attention to the associated methodological challenges and important areas for further research.

METHODS

SEARCH STRATEGY

In October 2019 we conducted a literature search in PubMed, Scopus, Web of Science and Cochrane Library using the following search terms (including MeSH): (aging OR ageing OR late life) AND schizophren* AND antipsychotic*. All identified studies were screened based on the title and abstract. Articles focusing on antipsychotic drug selection, dosing, discontinuation, adverse effects, risk-benefit ratio and clinical recommendations among patients with late-life schizophrenia were included. Articles and books were also searched manually. The reference lists of both review and original research articles were examined to identify additional references that would be applicable to the goals of this paper. We considered a broad range of eligible approaches and study designs: observational studies (cross-sectional, case-control, cohort or longitudinal, surveys, case studies, systematic reviews and meta-analyses) and also intervention studies.

NARRATIVE REVIEW

Narrative reviews highlight new and unanswered topics that are difficult to analyse in systematic reviews and tend to focus on author-selected studies (13). Our aim in this narrative review was, first of all, to analyse the existing literature on the key clinical questions of antipsychotics in late-life schizophrenia, primarily drug selection, dosing, discontinuation, adverse effects and the risk-benefit ratio. Finally, based on the literature and the authors' own experiences, we present clinical recommendations for "real-world" antipsychotic use in the *Table*.

3. RESULTS

SEARCH RESULTS AND SELECTED REVIEW TYPE

The search strategy identified potentially relevant articles in PubMed (n=220), Scopus (n=428), Web of Science (n=192) and Cochrane Library (n=38). After the removal of duplicates and non-relevant articles, 437 articles were selected for comprehensive evaluation. A total of 53 articles (listed in references) from the search and other sources were included in this narrative review.

Only a few epidemiologically sound and representative studies and samples were found, as well as only a few systematic and updated treatment algorithms and recommendations. No randomized placebo-controlled trials were available to guide antipsychotic treatment in late-life

schizophrenia. Many experts stressed that no guidelines can address the complexities of an individual patient at advanced age and sound clinical judgment based on clinical experience should be used.

Existing data are difficult to analyse in a systematic quantitative review, and definitive treatment recommendations limited. Therefore, we performed a narrative review focusing on studies based on author selection (13).

DRUG USE AND DOSING

Among patients with late-life schizophrenia, the use of first-generation antipsychotics (FGAs) decreased, and the use of second-generation antipsychotics (SGAs) as well as combined and SGA use increased during 1998-2003 in Finland (6). Almost 40% of aged outpatients did not buy any antipsychotics (6).

Age effects on dosing of antipsychotics in schizophrenia have not been well understood. Age appears to have a biphasic, inverted U-shaped association with antipsychotic dose (14,15). The dose increases with age through the third decade, subsequently plateaus, and decreases after the fifth decade. Age-related decline in prescribed dose is likely associated with the natural history of schizophrenia and physiological ageing, suggesting that increased antipsychotic sensitivity with ageing comes from age-related functional decline in the dopaminergic system. This age-related antipsychotic sensitivity highlights the importance of finding the lowest possible effective dose of antipsychotics. In a study of 1,418 patients across 30 sites in Tokyo, LOS and VLOS patients were treated with 1/2 and 1/3, respectively, of the dose for EOS (15).

Lowest effective doses of antipsychotics are likely influenced by several clinical and demographic characteristics of patients, age being the most important. However, dosing and tolerability of antipsychotics have been studied primarily in younger patients, and very limited data are available for age-specific dosing. Due to the age-related physiologic changes as well as increased inter-individual variation in pharmacokinetics and pharmacodynamics, individualized dosing with regard to age will be important for safer drug treatment. Therefore, cautious psychopharmacologic interventions could include simple medication regimens avoiding polypharmacy, awareness of patients' sensitivity to drugs, and gradual dose titration and regular monitoring.

Long-term antipsychotic medication, especially in high doses, has been repeatedly questioned (9). Current evidence-based guidelines are undifferentiated (especially in mid- and long-term illness duration) in regard to optimal doses, dose tapering or low-dose maintenance therapy. Guidelines recommend low doses, but do not suggest how to go about tapering (i.e. at what point in the clinical course of illness, over what time period, etc.), as data on the safety of tapering is still limited, particularly for patients with late-life schizophrenia. Some studies have questioned whether patients with schizophrenia need to be on antipsychotics throughout their lives. Indeed, some adverse effects such as risk of tardive dyskinesia clearly associate with a total lifetime exposure to antipsychotics, especially FGAs.

Strategies for personalized antipsychotic dosing and dose tapering may benefit a subgroup of patients (16), but may also be associated with incremental risk of relapse or excess mortality. When aiming for an optimal risk-benefit ratio and balancing symptomatic, functional and somatic outcomes, lower ranges of effective dosing are the primary goals. But what do the principles "lowest effective dose" or "according to individual patient needs" mean in clinical practice? Uchida et al. (17) found no differences between moderate antipsychotic dose (50-100% of the defined daily dose, DDD) and standard dose, with respect to overall treatment failure or hospitalization. Low dose (<50% of the DDD) were associated with greater risk of hospitalization and relapse. The current literature does not support the safe reduction of guideline-concordant antipsychotic dosing by 50% or more in stabilized individuals receiving originally moderate or high doses (9). Antipsychotic dose reduction is feasible in patients with stable disease, thus decreasing adverse effects (18).

Discontinuing antipsychotics. No guideline-concordant prescribing consensus exists on the optimal duration of antipsychotic treatment, especially among older patients, rather a tendency towards recommending continuous treatment in symptomatic patients (9). In studies with a long duration of follow-up, having first-episode psychosis (19) or midlife schizophrenia (20) about 30% and 20%, respectively, achieved remission with no use of antipsychotics.

This literature search failed to find any studies in which antipsychotics were discontinued exclusively in patients with late-life schizophrenia and underscored a paucity of data. Discontinuation of antipsychotic treatment might be realistic in some patients with late-life schizophrenia, although more systematic studies are needed (21-23). Of course, many older patients with schizophrenia (almost 40% (6)) may self-discontinue medication.

ADVERSE EFFECTS AND CHALLENGES RELATED TO ANTIPSYCHOTICS IN LATE-LIFE SCHIZOPHRENIA

Clinical heterogeneity and wide inter-individual variations are hallmark features of late-life schizophrenia, with the course ranging from mild impairment to severe disability (1,24), also related to outcomes and side effects of antipsychotics. The varied course seen in younger patients with schizophrenia continues into later life, but remission and clinical and functional recovery are realistic goals for some individuals (1).

A wide range of adverse effects related to antipsychotics are common and sometimes serious. There is little evidence of better efficacy of doses above the therapeutic range (25), and the general harm reduction strategy is to reduce to the lowest effective dose (26). Anticholinergics, benzodiazepines, antipsychotics and opioids all have significant adverse effects in the elderly population. In clinical practice, the most common side effects of antipsychotics include anticholinergic (such as urinary retention, constipation and confusion), neurologic (extrapyramidal symptoms, drug-induced parkinsonism and dyskinesia, tardive dyskinesia), altered thermoregulation, reduced bone density, metabolic syndrome, weight gain, increased visceral adiposity, (orthostatic) hypotension, poor dentition, excessive sedation and cardiac conduction disturbances. Both typical and atypical antipsychotics have been linked with an increased risk of falls and fractures in older patients (27).

Polypharmacy, defined as being prescribed five or more medications, has been shown to be associated with a decline in mental and physical functioning in the elderly (28). Given the potential risks, careful monitoring of adverse effects and managing drug interactions are essential.

Antipsychotics and cognition. A high anticholinergic burden contributes to specific cognitive deficits. Older patients with schizophrenia experience relatively greater decline in cognitive functioning than other individuals (29) even though cognitive trajectories are heterogeneous. This has implications regarding their ability to function independently, and also regarding medication practices. High doses of antipsychotics may worsen cognition and reducing the dose may improve cognitive function (30).

Poor medication adherence is common in schizophrenia: about or over 50% in most studies. Antipsychotic non-adherence (failing to initially fill or refill a prescription, discontinuing a medication before completing the therapy, taking more or less or other of a medication than prescribed) is an important risk factor for poor response and relapse (31). Many older patients have difficulty in remembering and understanding medication precepts of swallowing their tablets and capsules. Partial adherence to antipsychotic medication is a rule rather than exception in every age group with schizophrenia.

Older people may be poor, socially isolated and suspicious or uncomfortable about medical interventions, and therefore actively avoid medications. Cognitive deficits may also hinder medication compliance, which, in turn, may lead to unintentional non-adherence. Illness denial and comorbid substance use may be important predictors of intentional non-adherence (32). Side effects (e.g. sexual dysfunction, inability to drive) may lead to stopping the medication. Antipsychotic non-adherence is often underestimated by the treatment team and non-disclosure is common, as is also peer, relative and kinship support.

Despite decades of focused research, unified approaches and practices that significantly increase adherence rates have not been identified (31). Improving adherence includes simplifying medication regimens, psychoeducation, engaging family support, (32) medication use of robots and other electronic interventions (33).

ANTIPSYCHOTICS AND SOMATIC COMORBIDITY

With ageing, positive symptoms of schizophrenia tend to become less severe and substance use less common, and mental health functioning may improve (1). Physical comorbidity is a rule, however, and older age is a risk factor for most side effects of antipsychotics, including metabolic syndrome and neurologic adverse effects (34).

Medical comorbidity is common throughout the life course of schizophrenia, but is particularly pertinent to older patients, given the increase in age-related disorders. The comorbid illnesses associated with premature death are often related to lifestyle factors such as smoking, diet and lack of exercise. These illnesses may also be exacerbated by certain treatments for schizophrenia. Antipsychotic medications have been responsible for a significant reduction in symptoms and mortality in a population-based patient sample with schizophrenia (35), but they can also cause negative effects, including impact on cardiovascular and metabolic function, diabetes and lipid levels.

COMORBID DEPRESSION

Clinically significant depressive symptoms are common in older persons with schizophrenia (3) and can have a significant impact on quality of life, functioning, psychopathology and comorbid medical conditions. Most studies do not have

longitudinal data, therefore identification of the course of depression and the causal direction of associated variables is difficult to ascertain. It is important to systematically assess these individuals for symptoms of depression and actively utilize psychological and pharmacological treatments aimed at alleviating depressive symptoms.

The treatment of depressive symptoms in elderly patients with schizophrenia includes first reassessing the diagnosis to make sure that symptoms are not due to a comorbid condition, metabolic problems, substance abuse or medication. Augmentation with antidepressant medication can be helpful, and antidepressants in combination with psychosocial interventions are important treatments for older patients with schizophrenia and depressive symptoms (36). Some second-generation antipsychotics may also relieve symptoms of depression (37).

ANTIPSYCHOTICS AND MORTALITY

Reduced life expectancy (an average of 15-20 years) is a reality in schizophrenia (38). A register-based study by Talaslahti et al. 2012 (5) concluded that all-cause mortality of older patients with schizophrenia was almost three times that of the general population. Mortality from unnatural causes, such as suicides and accidents, was found to be eleven times higher than in the general population. Excess mortality may be the result of both lifestyle factors and lack of adequate medical care.

Prevention of excess mortality is an area of major concern in schizophrenia, regardless of age. Improving lifestyle, early diagnostics of medical comorbidity, adequate somatic and psychiatric care and suicide prevention are key targets in reducing mortality throughout the lifespan. Antipsychotic treatment may decrease all-cause mortality (35,39), but more studies are still needed in this age group.

MEDICATION MANAGEMENT IN OLD AGE SCHIZOPHRENIA

Medication management is an ongoing process to organize and monitor the recommended use of antipsychotics, aiming at the facilitation of their cost-effective, adherent, and acceptable use. Medication management is implemented by an optimal organizational environment, teamwork and therapeutic alliance (7). The age-related antipsychotic sensitivity and common somatic comorbidities highlight the importance of low doses to minimize side effects. Medication management may include multiple models and practices. For instance, Integrated Care Pathways (ICPs) are designed to manage specific conditions using standardized assessments and measurement-based interventions. Older patients with schizophrenia treated with antipsychotics within an ICP experienced higher rates of monitoring and less psychotropic polypharmacy than older patients treated with antipsychotics under treatment in usual conditions (40).

Skilled prescription practices or combining antipsychotics with psychosocial therapies and good medication management may improve their risk-benefit ratio. Key elements in medication management of patients with late-life schizophrenia are presented in the *Table*. These recommendations are based on the literature reviewed and clinical experiences of the authors.

Table: Key principles and practices in antipsychotic pharmacotherapy for elderly individuals with schizophrenia

Patient perspectives

- Documenting illness and medication histories, clinical responses, informed consent for antipsychotics, efficacies, tolerance profile, safety, harms and side effects and their acceptability, adherence
- Proper diagnosing of psychiatric and somatic disorders using medical examinations and routine laboratory studies
- Assessing ageing pathways, cognitive function, insight into illness, drug experiences and attitudes, beliefs about antipsychotics and medication self-management skills
- To maximize benefits and minimize harms favours simple regimens, avoidance of polypharmacy, awareness of patient sensitivity to drugs, gradual dose titration and finding the lowest effective dose
- When antipsychotics are started, titrated, switched (e.g. to clozapine or long-acting injectable antipsychotics), tapered or discontinued, a 1 to 3-month test period may help in weighing the risks and benefits
- Patient and family inclusion and home care in planning, decisions and adherence strategies

Prescriber and treatment team perspectives

- Orientation to guidelines, reviews and meta-analyses aimed at appropriate prescribing patterns, drug choice and dose
- Organizing optimal visit frequency and content
- Timely and thorough assessment of therapeutic response and side effects, risk-benefit ratio, duration, remission, recovery, cognitive capacities, somatic illness, non-adherence and treatment resistance
- Monitoring for side effects and adverse effects in clinical and laboratory follow-up: most importantly sedation, tardive dyskinesia, extrapyramidal symptoms, metabolic disturbances, fall risk and cognitive impairment
- Recognizing and correcting inappropriate drug choices, doses and polypharmacy
- Team work useful especially in critical situations: early warning signs, relapse, antipsychotic treatment resistance, non-adherence, worsening tardive dyskinesia, somatic comorbidities, negative drug attitude, multiple prescribers and staff turnover or holidays

In summary

- In late-life schizophrenia the pharmacotherapy requirements change with ageing, comorbidities, symptom burden and illness phase
- Guideline-concordant algorithms are vague. No guidelines can address the complexities of an individual patient but personalized, tailored antipsychotic medication is needed
- The critical aim rests on identifying the lowest effective dose of antipsychotics and optimizing benefits and harms
- Successful medication management rests on a participatory relationship, shared decision making, overcoming fragmentation, and having a general consensus between patients, relatives, other caregivers, clinicians and the treatment team
- Combination of antipsychotics, psychoeducation, psychosocial interventions and somatic care should be offered to all individuals with late-life schizophrenia

CURRENT TREATMENT RECOMMENDATIONS AND CLINICAL GUIDELINES FOR THE USE OF ANTIPSYCHOTICS IN LATE-LIFE SCHIZOPHRENIA

Treatment guidelines for older adults with schizophrenia consider the effects of age on the response to antipsychotics. Although atypical antipsychotics are used to treat very late-onset schizophrenia-like psychosis, their benefits and risks have not been properly evaluated. No randomized placebo-controlled trial data are available to guide antipsychotic treatment in late-life schizophrenia. Few clinical trials and case series in older adults (41) have demonstrated that the efficacy of antipsychotic medications may continue across the lifespan, rather that sensitivity to side effects in older age, with poorer tolerability may mitigate the benefits of treatment.

Although antipsychotics play a key role in the treatment of older patients with schizophrenia, there has been a dearth of comparative data to guide selection of agents. Data on geriatric patients with schizophrenia are generally scarce, particularly for treatment-resistant subpopulations, underscoring the need for more research in this important area (42). Even in the most recent meta-analysis, the mean age of patients was 37 years, and despite the massive number of trials and patients (402 RCTs, 53 463 participants) more data on the elderly patients are urgently needed (43).

The ageing process has a substantial influence on the pharmacokinetics and pharmacodynamics of these treatments. Elderly patients are more sensitive to adverse effects and interactions, largely due to age-related changes in the central nervous system and the reduction of body's capacity to metabolize antipsychotics and other drugs. As a result, recommended doses of many drugs (e.g. antipsychotics) are lower in the elderly. Starting doses of antipsychotic drugs in older patients should be in the range of 25-50% of that recommended for younger patients. Other challenging factors in this patient population include high rates of somatic comorbidity, drug interactions and age-related adverse effects to brain structure and functioning.

A 2012 Cochrane systematic review (44) of the use of antipsychotic medication for elderly people with schizophrenia was critical of the lack of robust data available to guide clinicians regarding the optimal administration of antipsychotics. The review states that there is no trial-based evidence upon which to base guidelines for the treatment of late-life schizophrenia. There is a need for high quality randomized controlled clinical trials. Until they are undertaken, people with late-life schizophrenia will be treated by doctors using clinical judgement and habit to guide prescribing.

Among current first line options, SGAs have a better side effect profile and are more suitable for elderly people. Among SGAs, which are primarily used as long-term medication, the choice of medication should be guided by their clinical indications and adverse effect profile, with use of lower initial and target doses (compared to younger and midlife adults) and periodic reviews of whether or not their continued use is warranted (see Table). Based on one expert consensus (45), risperidone was recommended for use in first line treatment, with quetiapine, olanzapine and aripiprazole as second line agents.

In treatment-resistant schizophrenia the gold standard is clozapine (24). Concerns about serious side effects have resulted in some avoidance of clozapine prescription for older patients. Common adverse effects include hypotension, weight gain, hypersalivation, constipation, sedation and myoclonus/seizure. Clozapine use is also associated with potentially fatal agranulocytosis (with modestly increased risk in elderly women) and myocarditis/cardiomyopathy. This perhaps also partly explains why almost all studies of clozapine to date have usually excluded older patients (46). Nevertheless, the benefits of clozapine use seen in seemingly intractable cases of schizophrenia in younger populations has encouraged researchers to re-examine its use in the elderly, particularly in cases where distressing psychotic symptoms are unresponsive to high doses of other antipsychotic medications. One study suggested that clozapine would be effective in reducing symptoms of schizophrenia in older patients (47). Where clozapine is used, dosing should be more cautious and regular monitoring (including therapeutic drug monitoring, at least when titrating clozapine dose) is required to ensure safety (48).

Depot, i.e. long-acting injections (LAI), should be considered in older patients who have difficulties in taking medication because of their cognitive, psychological or physical impairments. The use of LAIs can help improve adherence to treatment (10,49).

5. DISCUSSION

MAIN RESULTS

In this narrative review, we present current knowledge of the clinical challenges, treatment practices and recommendations of antipsychotics in late-life schizophrenia. Treatment approaches should include a combination of judicious use of

antipsychotic medications with psychosocial treatments and medication management. Antipsychotic medications should be used at the lowest effective doses, and outcomes should be optimized by regular monitoring of both efficacy and adverse effects.

Few and methodically limited trials and observational studies in older individuals with schizophrenia have demonstrated that the efficacy of antipsychotics continues across the lifespan, rather that sensitivity to adverse effects increases in old age, which may mitigate their benefits. Antipsychotic drugs with a wider therapeutic spectrum and fewer side effects are urgently needed especially for older patients with schizophrenia.

UNANSWERED QUESTIONS AND DIRECTIONS FOR FUTURE RESEARCH

This narrative review revealed a paucity of literature or minimally studied topics related to antipsychotic medication in elderly patients with schizophrenia. The minimal availability of psychotherapy research in the area of late-life schizophrenia is similarly troubling. Most results and recommendations (e.g. dosing) for schizophrenia are primarily based on younger patients with early or midlife onset of illness and thus may not apply to older adults.

Randomized controlled trials (RCTs) with long-term follow-up studies are difficult to conduct and tend to be rather reductionistic when analysing the complex, even lifespan interactions between the brain, environment and antipsychotics (12).

Observational, naturalistic, non-experimental settings may be the only realistic option when investigating the long-term effects of antipsychotics. However, in these studies the patients are not treated randomly which may cause residual confounding. Only a few studies present cumulative, long-term or lifetime medication data.

Specific antipsychotic-related challenges among older individuals with schizophrenia are minimally studied, for instance, interactions between normal ageing, schizophrenia and antipsychotics, age-related changes in pharmacokinetics and pharmacodynamics and in the blood-brain barrier. Dose-finding studies in elderly patients are rare even though mostly older patients are prescribed lower antipsychotic doses. The paucity of all these data makes optimal dosing challenging and highlights the importance of evaluation of adverse effects in elderly patients. Somatic comorbidities increase the number of prescribers and medications. The fragmentation in treatment increases the risk of suboptimal medication management (7).

Ethical and legal issues provide guidance for medication management, especially the Hippocratic Oath: *primum non nocere* (first, do no harm): minimize or avoid the iatrogenic burden of antipsychotics (harmful adverse effects). The risk of long-term harms is the most important reason to minimize antipsychotic doses. In Finnish legislation on patient rights, the patient must accept their treatment (Finnish Act on the Status and Rights of Patients 1992), which in principle is especially pronounced in the treatment of schizophrenia.

Modern technology. Future challenges are to increase mHealth (i.e. mobile health) applications or electronic health and mobile devices, mainly wearable devices like mobile phones, to provide objective long-term data to monitor compliance, medication effects, symptoms or treatment progress. Information may range from skin conductance and temperature to the number of exchanged short message service (SMS) text messages to number of incoming and outgoing calls and electronic reminders. The variety of personal data, easily acquirable, offers a unique opportunity to study lifestyle and behaviour at the physical, cognitive and environmental level (50,51). These data may initiate a new trend in healthcare provision characterized by tailored interventions. It is still uncertain how older patients with schizophrenia and limited cognitive, economic and educational skills are able to adopt and use such modern technology and how these innovations effect the costs of care.

CONCLUSIONS

An increasing number of people with schizophrenia survive into old age. The number of people with late-life schizophrenia spectrum disorders will increase in the coming years. There is still a paucity of scientific data regarding the developmental trajectory from illness onset in adolescence or early-mid adulthood into older age, even though interesting models (e.g. pathological accelerated ageing profile or even paradoxical ageing finding creative ways to age (52) well) are presented. However, longitudinal studies continue to defy the Kraepelinian notion of an inevitable deteriorating course of illness (53). Many older patients continue to have active disease, somatic comorbidity and high mortality, but some achieve sustained remission or recovery, and require minimal or no psychiatric care or medication. In contrast to early-onset schizophrenia, later onset of illness may also indicate enhanced social capital, longer occupational history and existing family and other social networks.

Schizophrenia remains a serious and debilitating disease for many older people, but studies continue to produce positive findings about our ability to alleviate symptoms, improve social and cognitive functioning and quality of life in this population. Antipsychotic medications have had a major impact on symptomatic relief and, if used with caution and skill, are relatively safe and effective in older patients. Recent studies support the need to develop rehabilitative interventions that enhance independent living skills, health and overall quality of life. Social integration, mood, cognition and physical health have critical roles in achieving successful ageing in schizophrenia.

Still, many elderly patients with schizophrenia may have social disabilities making them vulnerable to poverty, isolation and poor quality of life, and therefore experiencing double stigmatization: one caused by schizophrenia itself, another by general ageism, perhaps as a reflection of ageist attitudes in wider society. Both are potential sources of prejudice and discriminatory practices. An improved understanding of the course of schizophrenia over the lifespan can advance our understanding when choosing the most appropriate antipsychotic medication in this complex disorder.

Conflict of Interest

Matti Isohanni: nothing to declare
Erika Jääskeläinen: nothing to declare
Hannu Koponen nothing to declare
Brian Miller: nothing to declare
Esa Leinonen: nothing to declare
Tiina Talaslahti: nothing to declare

Authors:

Matti Isohanni, Professor of Psychiatry (emeritus). Center for Life Course Health Research, University of Oulu, P.O. Box 5000, 90014 Oulu, Finland

Erika Jääskeläinen, MD, PhD, Adjunct Professor, Center for Life Course Health Research, University of Oulu, Oulu, Finland; Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland; Department of Psychiatry, Oulu University Hospital, Oulu, Finland

Hannu Koponen, Professor of Old Age Psychiatry, Helsinki University and Helsinki University Hospital, psychiatry, Helsinki, Finland

Brian J. Miller, MD, PhD, MPH, Department of Psychiatry, Augusta University, 997 St. Sebastian Way, Augusta, GA 30912.

Esa Leinonen, Professor of Psychiatry (emeritus), Faculty of Medicine and Health Technology, Tampere University, Department of Psychiatry, Pitkäniemi Hospital, Tampere University Hospital

Tiina Talaslahti, MD, PhD, Psychiatry, University of Helsinki and Helsinki University Hospital; Helsinki, Finland

References:

1. Cowling D, Miettunen J, Jääskeläinen E et al. *Ageing in schizophrenia: a review*. Psychiatria Fennica 2012;43:39–68

2. Tampi RR, Young J, Hoq R, Resnick K, Tampi DJ. *Psychotic disorders in late life: a narrative review*. Ther Adv Psychopharmacol 2019;9:2045125319882798.
doi: 10.1177/2045125319882798

3. Cohen CI, Meesters PD, Zhao J. *New perspectives on schizophrenia in later life: implications for treatment, policy, and research*. Lancet Psychiatry 2015;2:340-50.
doi 10.1016/S2215-0366(15)00003-6

4. Miettunen J, Immonen J, McGrath J, Isohanni M, Jääskeläinen E. *The age of onset of schizophrenia spectrum disorders*. In: de Girolamo G, McGorry P, Sartorius N eds. *The age of onset of mental disorders. Ethiopathogenetic and treatment implications*. Springer 2019; 55–73. doi:10.1007/978-3-319-72619-9_4

5. Talaslahti T, Alanen HM, Hakko H, Isohanni M, Häkkinen U, Leinonen E. *Mortality and causes of death in older patients with schizophrenia. Int J Ger Psychiatry 2012:27:1131-37*

6. Talaslahti T, Alanen HM, Hakko H, Isohanni M, Häkkinen U, Leinonen E *Change in antipsychotic usage pattern and risk of relapse in older patients with schizophrenia*, Int J Ger Psychiatry 2013:28:1305-11

7. Isohanni M, Miettunen, Jääskeläinen E, et al. *Under-utilized opportunities to optimize medication management in long-term treatment of schizophrenia*. World Psychiatry 2018:17:172-3

8. De Hert M, Sermon J, Geerts P, Vansteeland K, Peuskens J, Detraux J. *The use of continuous treatment versus placebo or intermittent treatment strategies in stabilized patients with schizophrenia: a systematic review and meta-analysis of randomized controlled trials with first- and second-generation antipsychotics*. CNS Drugs 2015;29: 637–58. doi 10.1007/s40263-015-0269-4

9. Correll CU, Rubio CM, Kane JM. *What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia?* World Psychiatry 2018;17:149-60

10. Kishimoto T, Hagi K, Nitta M et al. *Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies*. Schizophr Bull 2018; 44:603-19. doi 10.1093/schbul/sbx090

11. Tiihonen J, Tanskanen A, Taipale H. *20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia*. Am J Psychiatry 2018;175:765-73. doi 10.1176/appi.ajp.2018.17091001

12. Isohanni M, Miettunen J, Penttilä M. *Life span development of schizophrenia: symptoms, clinical course and outcomes. In: Dimensions of Psychotic Disorders: Comprehensive Conceptualization and Treatments*. Tamminga CA, Ivleva EI, Reininghaus U, van Os J eds. Oxford University Press (in press)

13. Uman LS. *Systematic reviews and meta-analyses*. J Can Acad Child Adolesc Psychiatry 2011; 20: 57–9

14. Uchida H, Mamo DC. *Dosing of antipsychotics in schizophrenia across the life-spectrum*. Prog Neuropsychopharmacol Biol Psychiatry 2009:31:917-20

15. Uchida H, Suzuki T, Mamo DC et al. *Effects of age and age of onset on prescribed antipsychotic dose in schizophrenia spectrum disorders: a survey of 1,418 patients in Japan*. Am J Geriatr Psychiatry 2008:16:584-93

16. Wunderink L, Nieboer RM, Wiersma D et al. *Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial.* JAMA Psychiatry 2013;70:913–20

17. Uchida H, Suzuki T, Takeuchi H et al. *Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis*. Schizophr Bull 2011;37:788-99

18, Graff-Guerrero A, Rajji TK, Mulsant BH et al. *Evaluation of antipsychotic dose reduction in late-life schizophrenia: A prospective dopamine D2/3 receptor occupancy study*. JAMA Psychiatry 2015;72:927-34. doi 10.1001/jamapsychiatry.2015.0891

19. Wils RS, Gotfredsen DR, Hjorthøj C et al. *Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis*. Schizophr Res 2017:182:42-8

20. Moilanen J, Haapea M, Miettunen J et al. *Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication - A 10-year follow-up of the Northern Finland 1966 Birth Cohort study*. Eur Psychiatry 2013;28:53-8

21. Takeuchi H, Suzuki T, Uchida H, Watanabe K, Mimura M. *Antipsychotic treatment for schizophrenia in the maintenance phase: a systematic review of the guidelines and algorithms.* Schizophr Res 2012;134:219–25

22. Zipursky RB, Menezes NM, Streinen DL. *Risks of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review.*Schizophr Res 2014:152:408-14

23. Tani H, Suzuki, T, Fleischhacker W, Tomita, M, Mimura, M, Uchida, H. *Clinical characteristics of patients with schizophrenia who successfully discontinued antipsychotics: a literature review*. J Clin Psychopharmacology 2018:38:582-589

24. Molins C, Roldán A, Corripio I et al. *Response to antipsychotic drugs in treatment-resistant schizophrenia: conclusions based on systematic review.* Schizophr Res 2016;178:64-7. doi 10.1016/j.schres.2016.09.016

25. Smith RC, Leucht S, Davis JM. *Maximizing response to first-line antipsychotics in schizophrenia: a review focused on finding from meta-analysis*. Psychopharmacology 2019: 236:545–59. https://doi.org/10.1007/s00213-018-5133-z

26. Zhou Y, Li G, Li D, Cui H, Ning Y. *Dose reduction of risperidone and olanzapine can improve cognitive function and negative symptoms in stable schizophrenic patients: A single-blinded, 52-week, randomized controlled study*. J Psychopharmacol 2018;32:524-32. doi 10.1177/0269881118756062

27. Hien LT, Cumming RG, Cameron ID et al. *Atypical antipsychotic medications and risk of falls in residents of aged care facilities*. J Am Geriatr Soc 2005;53:1290–95

28. Williams S, Miller G, Khoury R, Grossberg GT. *Rational deprescribing in the elderly*. Annals Clin Psychiatry 2019:31:144-52

29. Loewenstein DA, Czaja SJ, Bowie CR, Harvey PD. *Age-associated differences in cognitive performance in older patients with schizophrenia: a comparison with healthy older adults*. Am J Geriatric Psychiatry 2012;20:29–40

30. Rajji TK, Ismail Z, Mulsant BH. *Age at onset and cognition in schizophrenia: meta-analysis*. Br J Psychiatry 2009:195:286–93. doi 10.1192/bjp.bp.108.060723

31. Dufort A, Zipursky RB. *Understanding and managing treatment adherence in schizophrenia*. Clin Schizophr Relat Psychoses 2019 Jan 3. doi 10.3371/CSRP.ADRZ.121218

32. Wilk JE, West JC, Marcus SC, Countis L, Regier DA, Olfson M. *Family contact and the management of medication non-adherence in schizophrenia*. Community Ment Health J 2008;44:377–80. doi 10.1007/s10597-008-9139-6

33. Velligan D, Mintz J, Maples N et al. *A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia*. Schizophr Bull 2013;39:999–1007

34. Jeste DV, Maglione JE *Treating older adults with schizophrenia: challenges and opportunities*. Schizophr Bull 2013:39:966-8

35. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. *11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study)*. Lancet 2009; 374:620-7.
doi: 10.1016/S0140-6736(09)60742-X.

36. Gregory A, Mallikarjun P, Upthegrove R. *Treatment of depression in schizophrenia: systematic review and meta-analysis*. Br J Psychiatry 2017; 211:198-204

37. Felmet K, Zisook S, Kasckow JW. *Elderly patients with schizophrenia and depression: diagnosis and treatment*. Clin Schizophr Relat Psychoses 2011;4:239-50.

38. Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. *Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders*. Br J Psychiatry 2011;199:453-8

39. Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J. *20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20)*. World Psychiatry 2020;19:61-68

40. Abdool PS, Supasitthumrong T, Patel K, Mulsant BH, Rajji TK. *Using an integrated care pathway for late-life schizophrenia improves monitoring of adverse effects of antipsychotics and reduces antipsychotic polypharmacy*. Am J Ger Psychiatry 2019:27:84-90

41. Howard R, Cort E, Bradley R et al. *Antipsychotic treatment of very late-onset schizophrenia-like psychosis (ATLAS): a randomised, controlled, double-blind trial*. Lancet Psychiatry 2018;5:553-63. doi 10.1016/S2215-0366(18)30141-X

42. Suzuki T, Remington G, Uchida H, Rajji TK, Graff-Guerrero A, Mamo DC. *Management of schizophrenia in late life with antipsychotic medications: A qualitative review*. Drugs and Aging
2011:28:961-80

43. Huhn M, Nikolakopoulou A, Sneider-Toma J et.al. *Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis*. Lancet 2019;394:939-51

44. Cochrane Systematic Review: *Antipsychotic drug treatment for elderly people with late-onset schizophrenia*. Intervention Version published: 15 February 2012.
https://doi.org/10.1002/14651858.CD004162.pub2

45. Alexopoulos GS, Streim JE, Carpenter D. *Commentary: expert consensus guidelines for using antipsychotic agents in older patients*. J Clin Psychiatry 2004;65:100–2

46. Suzuki T, Remington G, Uchida H, Rajji TK, Graff-Guerrero A, Mamo DC. *Management of schizophrenia in late life with antipsychotic medications: a qualitative review*. Drugs Aging 2011;28:961-80

47. Snowdon J, Halliday G. *A study of the use of clozapine in old age psychiatry*. Int Clin Psychopharmacol 2011;26:232-5

48. Bowskill S, Couchman L, MacCabe, JH, Flanagan RJ. *Plasma clozapine and norclozapine in relation to prescribed dose and other factors in patients aged 65 years and over: data from a therapeutic drug monitoring service, 1996–2010*. Hum. Psychopharmacol Clin Exp 2012; 27:277-83. doi 10.1002/hup.2223

49. Kane JM, Schooler NR, Marcy P, Achtyes ED, Correll CU, Robinson DG. *Patients with early-phase schizophrenia will accept treatment with sustained-release medication (Long-Acting Injectable antipsychotics): results from the recruitment phase of the PRELAPSE Trial*. J Clin Psychiatr 2019;23:80:18m12546. doi 10.4088/JCP.18m12546

50. Kreyenbuhl J, Record EJ, Himelhoch S et al. *Development and feasibility testing of a smartphone intervention to improve adherence to antipsychotic medications*. Clin Schizophr Rel Psychosis 2019:12:152-167

51. Seppälä J, De Vita I, Jämsä T et al. *Smartphone and wearable sensors-based m-Health approach for psychiatric disorders and symptoms: a systematic review and link to m-RESIST project*. MIR Ment Health 2019;20;6:e9819. doi 10.2196/mental.9819

52. Mushkin P, Band-Winterstain P. Avieli H. *Like every normal person?! The paradoxical effect of aging with schizophrenia*. Qualitative Health Research 2018. doi 10,1177/1049732316764389

53. Jääskeläinen E, Juola P, Hirvonen N et al. *Systematic review and meta-analysis of recovery in schizophrenia*. Schizophr Bull 2013;39:1296-306.