Antipsychotic treatment in elderly patients on polypharmacy with schizophrenia

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Purpose of review
Elderly patients with schizophrenia (SCH) are treated with antipsychotics and are often on different comedications, including polypharmacy (five or more medications). Evidence-based guidelines and randomized controlled trials do not include patients on polypharmacy, something that represents a 'gap' between evidence-based recommendations and clinical prescribing patterns. In this context, narrative reviews are needed to help clinicians in daily practice.

Recent findings
Antipsychotic treatment efficacies in meta-analyses are similar in the elderly with SCH compared with the general population (medium effect size). Long-term cohort studies show that antipsychotic treatment reduces overall mortality, hospitalizations, and cardiovascular death. These studies are limited because polypharmacy was not studied. The prevalence of antipsychotic use as potentially inappropriate medications was very high in nursing homes (25%). The prevalence of antipsychotic polypharmacy was 40%. Different strategies to manage these problems are available, including collaboration with clinical pharmacists, leading to reduced polypharmacy and better adherence to treatment guidelines.

Summary
Elderly patients with SCH on polypharmacy are less frequently studied, although they represent many patients with SCH. Different potentially inappropriate medication lists and collaboration with clinical pharmacists represent effective strategies for medication optimization. More studies are needed on this topic (e.g., prospective nonrandomized studies).

Keywords
antipsychotics, elderly patients, polypharmacy, schizophrenia

INTRODUCTION

Schizophrenia (SCH) is a frequent disorder in older adults, in whom lifetime prevalence is between 0.5 and 1%. SCH in older adults includes 'early-onset' SCH and 'late-onset' SCH, defined as the onset of symptoms after the age of 44.3 years and accounts for app. 15–20% of all cases of SCH [1,2]. SCH was related to higher all-cause mortality than controls in a Hungarian national study ($n = 65\,169$, risk ratio = 2.4; $P < 0.0001$) and comorbidity with SCH was the highest for cerebrovascular and cardiovascular diseases (53.7%) [3]. Study results on treatment adherence suggest that clinicians should consider this for both somatic medications and antipsychotics when treating patients with SCH, and adherence to antipsychotics is a predictor of medication adherence for different comorbidities (e.g., hypertension and diabetes) [4]. SCH is being treated with pharmacotherapy, where antipsychotics are a key medication group [5,6]. Elderly patients with SCH are frequently treated with several different medications (antipsychotics and comedications), including polypharmacy (five or more medications at the same time) [7▪]. Polypharmacy is especially prevalent in patients with mental disorders, where antipsychotics are often involved in significant drug–drug interactions (DDIs), potential inappropriate medications (PIMs) and irrational polypharmacy (e.g., no clear indication) [8]. Polypharmacy has been associated with higher

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KEY POINTS

- Antipsychotics in elderly patients with SCH are not widely studied and therefore new studies and reviews are needed.
- Elderly patients with polypharmacy are frequent in the real clinical settings but these patients are excluded from clinical guidelines.
- The current article represents a review of a 'gap' between evidence-based research and basic clinical pharmacology, which represents a useful tool for clinicians in daily practice.

cognitive decline, more deaths, and higher costs, and therefore, prudent strategies are needed to avoid irrational polypharmacy in this particular population [9▪,10]. Antipsychotics as part of the polypharmacy regimen have been used in 42% of elderly patients with dementia in nursing homes in the United States ($n = 1159\,968$) [11▪].

Evidence-based pharmacotherapy is based on well-designed meta-analyses and randomized controlled trials (RCTs) where long-term effects are often unavailable. In this context, patients with polypharmacy are also excluded, although there are very frequent in real clinical settings and represent the understudies population [9▪,10]. This means a gap between evidence-based recommendations and clinical practice.

From this point of view, the main aim of this article is present recent evidence on this topic. Using a narrative review design, antipsychotics treatment in elderly patients with SCH and polypharmacy will be discussed.

Different studies and reviews (e.g., RCTs, cross-sectional studies, prepost studies, cohort trials, meta-analysis, systematic, and nonsystematic reviews) and guidelines for elderly patients were searched in different databases (Medline/PubMed, Google Scholar, Cochrane Library). The last search was done on the 17 April 2022. Different keywords relating to elderly patients, SCH, antipsychotics, polypharmacy, excessive polypharmacy, and psychogeriatrics were used. Additional references from meta-analysis and reviews were retrieved. The article missed by the main search was also checked if necessary.

EVIDENCE-BASED DATA ON ANTIPSYCHOTIC TREATMENT IN ELDERLY PATIENTS WITH SCHIZOPHRENIA

Antipsychotics in elderly patients with SCH have not been studied in well-designed RCTs and meta-analyses (e.g., network meta-analysis – NMA) as in the general population [5,6]. Antipsychotic short-term treatment has been studied in a few RCTs, and a meta-analysis on this topic was published in 2018 [6]. A pairwise meta-analysis published by Krause *et al*. in 2018 included only RCTs ($n = 18$; 1225 participants; RCTs published until 2009). Authors compared different antipsychotics (aripiprazole, amisulpride, risperidone, haloperidol, olanzapine, quetiapine, paliperidone, clozapine, chlorpromazine) with placebo or another antipsychotic. The definition of 'elderly' was very heterogeneous across the studies (minimum age 46–65, mean age 57–73, mean 66.1 years). Only three out of 18 selected studies included patients with a minimum age of 65 years [6]. Antipsychotics differed substantially in side effects, and small but robust differences were seen in efficacy. In improving the overall symptoms, olanzapine was significantly superior to haloperidol ($N = 2$, SMD (standardized mean difference) 0.47, confidence interval = CI 0.10–0.84). The results were similar to those in adult patients with SCH (SMD = 0.14, 0.08–0.21) in the NMA [5,6]. Paliperidone showed no significant difference compared with placebo ($N = 1$, SMD −0.32, CI −0.71–0.08). Acceptability was checked with dropouts due to any reason. Regarding head-to-head comparisons between different antipsychotics, olanzapine was significantly better accepted than risperidone [$N = 3$, odds ratio (OR) 0.54, CI 0.31–0.93]. One placebo-controlled study showed a nonsignificant superiority for paliperidone ($N = 1$, OR 0.41, CI 0.16–1.02) [6]. This meta-analysis has many important limitations. Patients with polypharmacy were excluded (no data on comedications). The median trial duration was 10 weeks (3–72 weeks). In this context, most real clinical patients were excluded.

Antipsychotic long-term effects, including a few older adults with SCH, were studied in Finland [median age (interquartile range (IQR)), 45.6 years (34.6–57.9), $n = 62\,250$] [12]. Inpatient settings from 1972 to 2014 in Finland (cohort of all persons with SCH) were included. Hospitalizations were the primary outcome measures (endpoint). The median time of 14.1 years (IQR, 6.9–20.0 years) was measured in the prevalent cohort [12]. The hazard ratio for all-cause hospitalization was 0.91 (95% CI, 0.89–0.92; $P < 0.001$), and for death, 0.76 (95% CI, 0.73–0.79; $P < 0.001$). Hazard ratio of psychiatric rehospitalization was 7% lower during any antipsychotic polypharmacy (APP) than any monotherapy period (hazard ratio, 0.93; 95% CI, 0.91–0.95; $P < 0.001$). These results are significant because patients were followed for more than 10 years on average (closer to real clinical patients), which is much longer than in RCTs, but the study has many limitations: first,

selection bias (cohort study, no randomization/within the design); second, median age app. 46 years (few data on older adults); third, few data about comedications except antipsychotic combinations (APP); fourth, DDIs and the adverse events (older adults have more DDIs and comorbidities) and fifth, no comorbidity data; and sixth, statistics (Cox Regression). On the contrary, few older adults were included, and therefore this study is not well representative of older adults. In the newest long-term cohort study in Finland (median age 45.6 years, interquartile range, IQR = 34.6–57.9), antipsychotics were studied for an even longer period in patients with SCH and their impact on mortality [13▪▪]. Inpatient care was studied between 1972 and 2014 in Finland ($N = 62\,250$), with up to 20 years of follow-up (median: 14.1 years). The cumulative mortality rates during a maximum follow-up of 20 years were 46.2% for no antipsychotic use, 25.7% for any antipsychotic use, and 15.6% for clozapine use. Hazard ratios = 0.48 (95% CI: 0.46–0.51) for all-cause mortality (Clozapine, adjusted hazard ratio = 0.39, 95% CI: 0.36–0.43) were for 52% lower for antipsychotics than no-treatment [13▪▪]. These important results show that long-term antipsychotic treatment decreases mortality. Still, many limitations should be mentioned (e.g., few older adults, no data on polypharmacy and comorbidity, no data on DDIs, no RCT design).

The Amisulpride ATLAS study was not included in the meta-analysis by Krause *et al.* [6]. Amisulpride was studied in older adults with 'very late' onset SCH (aged ≥60 years) in the ATLAS study [101 participants and 92 participants took medication (91%)], which was a long-term antipsychotic RCT (36 weeks), where amisulpride was compared with placebo. The authors used low-dose amisulpride (100 mg daily) compared with placebo, and amisulpride was superior in reducing psychosis symptoms over 12 weeks, and the effect was maintained after 12 weeks. In stage 2, Brief Psychiatric Rating Scale scores improved by a mean of 1.1 points (1.6) from 12 weeks to the final assessment in those who continued but deteriorated by 5.2 points (2.0) in those who switched from amisulpride to placebo [difference of 6.3 points (95% CI 0.9–11.7), $P = 0.024$] [14]. The authors observed important adverse events more often in the amisulpride group than in the placebo group in stage 1 ($P = 0.057$) and stage 2 ($P = 0.19$). The most frequent adverse events were different infections and extrapyramidal side-effects (three patients in the amisulpride group, none in the placebo group) [14]. This RCT has significant limitations (e.g., no data on comedications).

Overall there are few trials, including older adults with SCH, and especially trials from real-clinical settings are missing. Participants with polypharmacy are not checked or even included. The highest evidence (e.g., SMD = 0.5–0.8) for SCH treatment is for olanzapine and amisulpride (medium-to-high effect sizes) [5,6].

POLYPHARMACY IN ELDERLY PATIENTS WITH SCHIZOPHRENIA

Polypharmacy is frequently defined as using five or more medications concomitantly, and excessive polypharmacy uses 10 or more medications concomitantly [8,15]. Maher *et al.* conducted a systematic review on polypharmacy in elderly patients, and they reported that approximately 50% of older adults (aged over 65 years) received at least one unnecessary medication. The prevalence was the highest in nursing homes, and antipsychotics were often included in different interventions [16]. The researchers found that polypharmacy is highly prevalent in all included institutions in observational studies (primary care in USA, $N = 2976$, 37.1% men and 36% women aged 75+ used at least five different medications; hospital setting in Italy, $N = 1332$, admission-51.9% on 5+ medications; discharge-67% on 5+ medications); nursing homes in Canada, $N = 64\,395$, 15.5% on 9+ medications) [17,18,19]. Polypharmacy is associated with several negative outcomes (e.g., higher hospitalization and inappropriate prescribing rates), as shown in a systematic review ($N = 230$ different trials) [9▪]. Polypharmacy was also associated with a high number of DDIs., where 12% of DDIs were expressed. Among elderly patients in primary care ($n = 91$), antipsychotics were the most frequent included in DDIs (>50% of DDIs), which means that careful DDIs checking is needed before prescribing (e.g., quetiapine in combinations expressed in QTc prolongation, followed by haloperidol and sulpiride/amisulpride in combinations expressed in QT prolongation) [8]. This study shows that APP can lead to more DDIs, which is understudied in RCTs. Excessive polypharmacy (e.g., 10 or more medications) is especially prevalent in nursing homes and was also associated with excessive death [adjusted OR 1.96 (1.42–2.71)] [9▪,10]. Excessive polypharmacy was also common at the hospital admission in elderly patients aged at least 75 from nursing homes settings (49.4%), and therefore deprescribing strategies are recommended [20▪]. Dementia incidence has been increased significantly with the increase in the number of prescribed drugs and polypharmacy (cohort study in South Korea, $n = 1025\,340$), which represents a serious risk for dementia (5–<10 drugs: 2.64, 95% CI: 2.32–3.05; ≥10 drugs: 3.35, 95% CI: 2.38–4.71; <1 drug used as reference) [21]. In a Belgian study, with a sample of 1226 long-term care facility residents

with a mean age of 83.9 years (SD = 8.5), the mean number of medications per person was 9.0 (SD 3.6, range 0–23, median 9.0). The psychotropic prevalence in Belgian nursing homes was exceedingly high (81%), with excessive duplicate use. Benzodiazepines were used by 54% and antipsychotics by 33% of all residents [22]. This means that polypharmacy is a frequent treatment approach, and careful psychopharmacological selection should be used because these patients are not covered by the existing treatment guidelines and RCTs [5,6,7▪].

Elderly patients with SCH on polypharmacy are less frequently studied because polypharmacy has not been reported and excluded [5,6,7▪]. These patients have been included in different studies covering nursing home, ambulatory, or hospital populations, although patients with SCH were mixed or separated from other patients [8,18,19]. APP has been studied in elderly patients published by Wu *et al.* in one psychiatric hospital in Taiwan. In a comparative retrospective study, prescribing trends in the elderly with SCH (69.9 years, SD = 4.8 years; $n = 229$) and dementia ($n = 183$) have been studied. In this study APP increased from 2007 to 2012 and was significantly more frequent in patients with dementia (OR: 3.49, 95% CI: 1.29–9.39, $P = 0.014$), and a higher-than-recommended dose of antipsychotic drugs (OR: 4.98, 95% CI: 2.75–9.02, $P < 0.001$). Second-generation antipsychotics were the most frequently used in both groups (quetiapine and risperidone) [23]. In the newest cross-sectional study on this topic in Asia (58.0 years, SD = 6.7 years; $n = 879$), 15 Asian countries/territories were included and prescribing patterns were compared. The rate of APP was 40.5%, but researchers included all participants with 50 years or more (an important limitation) [24]. APP lacks evidence of effectiveness in the SCH treatment and produces more risks; therefore, APP-reducing strategies are needed [12,25▪]. These results mean that APP is common among elderly patients with SCH, although there was no data on the total polypharmacy and APP in whole polypharmacy. Therefore, these results are not fully generalizable to the research population.

More studies, including elderly patients with SCH on polypharmacy, were conducted in nursing homes, although SCH was not the only target population (e.g., mixed elderly patients) [26▪,27,28▪]. These studies were focused on the PIMs in elderly patients using different PIM lists (e.g., Priscus, STOPP/START, Beers) [29,30,31]. PIMs are medications that should be avoided in the elderly, and safer alternatives are available. PIM lists can lead to less irrational polypharmacy and represent an essential medication management tool [29,30,31]. Antipsychotics are listed only for other indications, except SCH or bipolar disorders (e.g., behavioural problems in dementia) [29,30,31]. Antipsychotics should not be used for behavioural problems of dementia and delirium because they are associated with a greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia. However, for SCH, there is a clear benefit for antipsychotic continuation [31].

Different treatment strategies have been established for medication optimization in this population, including careful medication selection and other PIM lists using and collaborating with a clinical pharmacist [29,30,31,32▪,33,34▪]. The latest review on this topic proposed a collaborative approach to address polypharmacy and avoidance of high-risk therapy [34▪]. An interdisciplinary collaboration, including clinical pharmacists has been studied recently [32▪,33]. In a systematic review, including 64 different trials (also non-RCTs), other clinical pharmacist's interventions in psychiatry and neurology were reported. Although the newest trials were not included, the authors reported positive outcomes in some trials, including antipsychotic deprescribing and elderly patients (e.g., APP reduction) [35▪]. Stuhec and Lah conducted a retrospective prepost study in a real clinical setting in primary care in Slovenia ($n = 48$), including elderly patients with polypharmacy and mental disorders (79.4 years, SD = 8.13) [32▪]. The mean number of medications per patient before the medical review provided by a clinical pharmacist was 12.6 (MEDIAN = 11) and decreased to 10.5 at the end of the study period ($P < 0.001$). Psychotropics represented 91.8% of all PIMs (e.g., haloperidol more than 2 mg/day in five patients), and 39.3% of all PIMs were benzodiazepines. The clinical pharmacist interventions improved treatment guidelines adherence in patients with SCH ($P < 0.05$), and all accepted interventions also continued until the end of the study-6 months [32▪]. Although these results are significant, this study has limitations (i.e., no control group, no randomization, selection bias, no outcomes measuring, polypharmacy, heterogeneous population, small sample size). These results align with a similar study, where only patients with antipsychotics and excessive polypharmacy were included. Nine out of 21 different clinical pharmacist interventions (42.8%) were accepted in this study [33].

CONCLUSION

Long-term antipsychotic treatment in patients with SCH can lead to better overall survival. Although these positive results, few studies are available,

including older adults with polypharmacy; therefore, more studies are needed. Polypharmacy is often not reported or excluded. Prudent prescribing, different PIM lists and collaboration with the clinical pharmacist represent valuable tools in medication management in this population.

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Conflicts of interest

There are no conflicts of interest.

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