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# Prescribing and deprescribing of atypical antipsychotics in older multimorbid patients

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## Abstract

**Background** In hospital practice, atypical antipsychotics are often used to manage delirium, sleep problems, agitation, or behavioural and psychological symptoms of dementia, while evidence remains uncertain regarding effectiveness and safety for those off-label indications. While guidelines to reduce inappropriate prescribing have been published, prescribing patterns in older multimorbid patients are not well understood. We thus aimed to investigate the patterns of prescribing and deprescribing of atypical antipsychotics over one year following an acute hospitalisation, as well as the appropriateness of prescriptions.

**Methods** We conducted a longitudinal analysis using data from the OPERAM trial, a European multicentre study assessing hospital pharmacotherapy optimisation in multimorbid older patients aged 70 years or older in Switzerland, Ireland, Belgium and the Netherlands between 2016 and 2019. Data were collected at different time points: admission, discharge, two months post-discharge and one year post-discharge. Atypical antipsychotic prescriptions were classified as appropriate, off-label but accepted, or potentially inappropriate. Outcomes included the prevalence of atypical antipsychotic use at the different time points, deprescribing rates for appropriate and inappropriate prescriptions, and the incidence of new atypical antipsychotic prescriptions among patients not previously treated.

**Results** The number of patients prescribed atypical antipsychotics increased from 88/2005 (4.4%) at admission to 116/1980 (5.9%) at discharge. At admission, 62.5% of these prescriptions were classified as potentially inappropriate. During hospitalisation, 20/53 (37.7%) patients with potentially inappropriate prescriptions either had the medication discontinued or were assigned a new diagnosis that justified the use under an off-label but accepted or otherwise appropriate indication. Additionally, 47 (2.5%) of the 1917 antipsychotic-naïve patients received a new prescription during index admission, with one third (36.2%) lacking a clear indication. Among those newly prescribed atypical antipsychotics without an appropriate indication during hospitalisation, only 58.3% had the medication discontinued within one year of follow-up.

**Conclusions** This study highlights the substantial prevalence of potentially inappropriate atypical antipsychotic prescribing in older multimorbid patients, with no clearly documented indication in almost half of the prescriptions initiated during hospitalisation and slow deprescribing efforts leading to long-term medication risks. Improving prescribing practices through education, protocol-driven deprescribing, and post-discharge follow-up is essential to reduce inappropriate use, and ultimately enhance patient safety.

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**Keywords** Atypical antipsychotics, Older multimorbid patients, Prescribing, Deprescribing, Off-label use, Medication safety

## Background

Atypical antipsychotics, also referred to as second-generation antipsychotics, have been widely approved by regulatory agencies, such as the Food and Drug Administration, Swissmedic and the European Medicines Agency, for treating neuropsychiatric disorders, including schizophrenia and bipolar disorder [1–4]. However, in recent years, there has been an increase in off-label use of those medications for their sedative and hypnotic effects, despite limited and inconclusive evidence supporting their efficacy for these indications [5, 6]. In hospital practice, atypical antipsychotics are commonly used to manage delirium, sleep problems, agitation, or behavioural and psychological symptoms of dementia (BPSD) [7–10]. Nevertheless, they can have several important short-term and long-term adverse effects, such as increased falls risk, somnolence, extrapyramidal symptoms, anticholinergic effects, cognitive decline, pneumonia, cerebrovascular events, metabolic complications and death [1, 11, 12]. Furthermore, stopping atypical antipsychotic drugs abruptly after prolonged use can lead to withdrawal symptoms [13]. Therefore, it is clinically important to minimise the prescribing of atypical antipsychotics at discharge when initiated during hospitalisation for off-label or potentially inappropriate indications such as hospital-acquired agitation, behavioural disturbances, delirium, or insomnia.

In response to concerns about adverse effects and withdrawal symptoms, guidelines have been developed aimed at decreasing inappropriate prescribing of atypical antipsychotics in older people [14, 15]. However, guidelines alone may not be sufficient to reduce inappropriate prescribing of these drugs, such that there is a strong case for specific deprescribing interventions to be developed [16–18]. Before deploying such interventions, it is important to analyse the prescribing patterns of atypical antipsychotics in older multimorbid patients. While previous studies have reported the prevalence of atypical antipsychotic use at specific time points such as admission and hospital discharge, there remains a notable lack of longitudinal data that capture the evolution of prescribing and deprescribing patterns over longer periods of time [19]. Moreover, most previous studies did not systematically assess the clinical appropriateness of atypical antipsychotic prescriptions.

We thus aimed to investigate the patterns of prescribing and deprescribing of atypical antipsychotics in older multimorbid patients during an acute hospitalisation and the following year, as well as the clinical appropriateness of those prescriptions.

## Methods

### Study design and setting

We analysed longitudinal data from the Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM) trial, a European multicentre, cluster-randomised controlled trial that evaluated the impact of an in-hospital medication review intervention led by a clinical pharmacologist using the STOPP/START criteria, with the aim of reducing avoidable hospital admissions in multimorbid older patients [20–22]. The study included data collection at hospital admission, at discharge, at two months post-discharge and at one year post-discharge. The results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

### Study population

The study population comprised all participants of the OPERAM trial. Inclusion criteria were patients aged 70 years or older with at least three chronic conditions and taking five or more long-term medications, defined as medications prescribed for at least the last 30 days. All patients were admitted to one of the participating hospitals in Switzerland, Ireland, Belgium, and the Netherlands between December 2016 and December 2019.

### Data collection and variable definition

Demographic data, including age, sex, and Charlson Comorbidity Index (CCI), were collected at admission. "Medications at admission" were defined as medications prescribed in the community before admission. Medications were coded using the Anatomical Therapeutic Chemical (ATC) Classification System [23]. Atypical antipsychotics included the following codes (substances): N05AE03 (Sertindole), N05AE04 (Ziprasidone), N05AE05 (Lurasidone), N05AH02 (Clozapine), N05AH03 (Olanzapine), N05AH04 (Quetiapine), N05AH05 (Asenapine), N05AH06 (Clotiapine), N05AL01 (Sulpiride), N05AL03 (Tiapride), N05AL05 (Amisulpride), N05AX08 (Risperidone), N05AX12 (Aripiprazole), N05AX13 (Paliperidone), N05AX15 (Cariprazine), N05AX16 (Brexpiprazole). Medications prescribed on an as-needed (PRN) basis were included in the total medication count.

Diagnoses were defined using ICD-10 codes and applied to define atypical antipsychotic prescriptions into three groups based on the appropriateness of their indications according to the current approvals of the drug regulatory authorities, including Swissmedic, and the

European Medicines Agency (EMA), as well as the indications accepted as off-label: [1, 3–5]

1. Appropriate indications: These included schizophrenia and schizoaffective disorders (acute psychosis and maintenance therapy, ICD F20.X, F25.X), acute mania (F30.X), major depressive disorder with psychotic features (F32.3), acute severe agitation (R45.1), borderline personality disorder (60.31), agitation symptoms in substance-induced psychotic disorders (F10.X-F14.X, each X.0, X.8, X.9), and psychosis in Parkinson's disease (F06.2 in combination with G20).
2. Special indications for selected medications are: Acute manic episodes associated with bipolar disorder (F31.1, F31.2, F31.6; Aripiprazole, Asenapine, Quetiapine, Olanzapine); acute treatment of depressive episodes in bipolar disorder (F31.3; F31.4, F31.5, F31.6; Quetiapine); prevention of recurrence of mania in bipolar disorder in patients whose manic episode has responded (F31.7; Aripiprazole, Asenapine, Quetiapine and Olanzapine); adjunctive treatment of major depressive episodes in patients who have had an inadequate response to antidepressant therapy (F32.2, F32.3; Quetiapine).
3. Off-label but accepted indications defined as indications that are mentioned in national or international guidelines (e.g., guidelines from the German Association of the Scientific Medical Societies or from the UK National Institute for Health and Care Excellence [NICE]), but not approved by the official regulatory bodies [24–31]. These included: acute delirium (F05.X), short-term (6–12 weeks) treatment of behavioural and psychological symptoms of dementia or BPSD (F63, U63.X), HIV-related dementia (F02.4-F02.8), substance-induced severe psychosis (F10.X-F19.X), autism spectrum disorder (F84.X), and second-line treatment for obsessive-compulsive disorder (F42.X), nausea and vomiting (R11).
4. Potentially inappropriate prescriptions: These were identified when no diagnosis matched the appropriate or off-label indications as defined above. These cases were assessed for the presence of an ICD-10 diagnosis that can lead to inappropriate prescribing of atypical antipsychotics, such as depression or anxiety disorders.

Follow-up data were collected at 2 months and 1 year after enrolment via structured telephone interviews with the participants or their proxies, conducted by a blinded member of the OPERAM team. Information collected included current medication use, newly initiated or discontinued medicines, medication adherence, hospital admissions, other healthcare utilisation, falls, quality of life, pain, basic activities of daily living, and mortality. Furthermore, medication was confirmed with the general practitioner and/or a pharmacist.

All data were verified for accuracy by trained clinical staff, ensuring consistency and reliability across the four study sites.

### Outcomes

The primary outcome of the OPERAM trial was the first drug-related readmission. In the present study, we assessed the following outcomes based on the initial (index) hospital admission: (1) prevalence of atypical antipsychotic use at key time points (admission, discharge, two months, and one year); (2) deprescribing rates among patients with appropriate, off-label and potentially inappropriate atypical antipsychotic prescriptions; (3) incidence of new atypical antipsychotic prescriptions among patients who were not on these medications at admission.

Deprescribing was defined as either a reduction in the prescribed daily dose or a complete discontinuation of the atypical antipsychotic. This definition was applied consistently across all time points and included as-needed (PRN) medications, for which the maximum possible total dose was considered. Potentially associated variables such as age, number of medications, comorbidity burden (Charlson Comorbidity Index), ward type and if the patient received an intervention to reduce inappropriate medication have also been considered in the analysis of prescribing and deprescribing patterns.

### Statistical analysis

Continuous variables were expressed as means with standard deviations and categorical variables as numbers with percentages. Comparisons between groups were conducted using chi-square tests for categorical data and Student's t-tests for continuous data.

The proportion of patients prescribed atypical antipsychotics at admission, categorised into appropriate, off-label, and potentially inappropriate indications was calculated. Additionally, for patients without atypical antipsychotic prescriptions at admission, the incidence of new prescriptions at discharge was analysed, distinguishing between appropriate, off-label, and potentially inappropriate indications. Similar analyses were conducted for patients without atypical antipsychotic prescriptions at discharge, focusing on new prescriptions at two months and at one year.

For patients already on atypical antipsychotics at admission, deprescribing rates were assessed at discharge

and two months after discharge, stratified by prescription indication type (appropriate, off-label, or potentially inappropriate). Among patients who were newly prescribed atypical antipsychotics at discharge, deprescribing rates were similarly analysed at two months and at one year. The number of patients on atypical antipsychotics was assessed via a follow-up phone call *and confirmed with patient pharmacist or physician.*

Subgroup analyses were conducted at each time point (admission, discharge, two months, and one year) to explore variations in prescribing practices based on intervention group, age (≥ 80 years vs. <80 years), specialty unit, number of medications (< 10 vs. ≥10), presence of dementia and survival at one year. These outcomes were chosen to provide a comprehensive description of the prescribing and deprescribing dynamics of atypical antipsychotics in older multimorbid patients. In addition to the overall analyses, subgroup comparisons were performed to explore differences in prescribing and deprescribing patterns based on intervention group allocation. These analyses focused on patients who were already receiving atypical antipsychotics prior to hospital admission, as well as those who were newly initiated on such medication during hospitalisation. For both groups, prescribing patterns were categorised according to indication appropriateness (appropriate, off-label, or potentially inappropriate), and subsequent deprescribing was assessed at discharge, two months, and one year. Chi-square tests were used to compare proportions between the intervention and control groups.

As missing data were to be expected in this population at follow-up time points due to withdrawal of informed consent, loss to follow-up, or death, we calculated the prevalence at each respective time point based on the participants still available. This complete case approach provides a pragmatic estimate of prevalence; however, we acknowledge that informative missingness may have introduced bias into the estimates.

**Table 1** Baseline patient characteristics at admission

| Characteristics | Not on Atypical Antipsychotics (*N* = 1917) | On Atypical Antipsychotics (*N* = 88) | *p*-value |
|---|---|---|---|
| Age [mean years (range)] | 79.4 (70.0–99.0) | 79.3 (70.0–99.0) | 0.849 |
| Female sex | 852 (44.4%) | 44 (50.0%) | 0.305 |
| Nursing home resident | 170 (8.9%) | 22 (25%) | < 0.001 |
| Days of hospitalisation | 8.0 (5.0–13.0) | 9.0 (5.0–14.0) | 0.989 |
| Site of enrolment | | | |
| Bern | 771 (40.2%) | 51 (58.6%) | < 0.001 |
| Cork | 326 (17.0%) | 20 (23.0%) | |
| Louvain | 374 (19.5%) | 12 (13.6%) | |
| Utrecht | 446 (23.3%) | 5 (5.7%) | |
| Comorbidities | | | |
| Number of coded diagnosis | 11.0 (8.0–16.0) | 12.0 (9.0–18.0) | 0.028 |
| Charlson Comorbidity Index | 2.0 (1.0–4.0) | 2.0 (1.0–4.0) | 0.998 |
| Number of long-term (> 3 months) medications | 10.0 (7.0–13.0) | 13.0 (9.0–16.0) | < 0.001 |
| Schizophrenia | 3 (0.2%) | 2 (2.3%) | < 0.001 |
| Acute mania | 0 (0.0%) | 1 (1.1%) | < 0.001 |
| Major depression | 105 (5.5%) | 14 (16.1%) | < 0.001 |
| Bipolar disorder | 7 (0.4%) | 6 (6.9%) | < 0.001 |
| Dementia | 84 (4.4%) | 27 (30.7%) | < 0.001 |
| Agitation in Delirium or Dementia | 34 (1.8%) | 5 (5.7%) | 0.009 |
| Acute Delirium | 79 (4.1%) | 11 (12.5%) | < 0.001 |
| Substance induced Psychosis | 143 (7.5%) | 11 (12.5%) | 0.076 |
| HIV-related dementia | 0 (0.0%) | 1 (1.1%) | < 0.001 |
| Insomnia | 197 (10.3%) | 13 (14.8%) | 0.164 |
| Nausea | 5 (0.5%) | 0 (0.0%) | 0.500 |
| Atypical Antipsychotic on admission | | | |
| Appropriate indication | | 4 (4.6%) | |
| Off-label indication | | 21 (24.1%) | |
| Without indication | | 63 (71.6%) | |

Summarised patient characteristics at baseline. Categorical variables are presented as number with percentages [n (%)], continuous variables are expressed as median with IQR [median (IQR)], age is expressed as mean with age range [mean (range)]

*Abbreviations*: *IQR* interquartile range, *n* number

## Results

### Baseline characteristics

The study population comprised 2008 patients at admission. Following the withdrawal of three patients, 2005 patients were included in the analysis. Among them, 88 (4.4%) were prescribed atypical antipsychotics at admission. The mean age of included patients was 79.4 years (range 70.0–99.0 years), with 896 patients (44.7%) being female. Median Charlson Comorbidity Index (CCI) was 2.0 (IQR 1.0–4.0), median length of hospitalisation was 9.0 days (IQR 5.0–13.0). Patients prescribed atypical antipsychotics had a median number of 12.0 medications (IQR 9.0–18.0) compared to 11.0 (IQR 8.0–16.0) for those not prescribed atypical antipsychotics (Table 1).

### Prevalence for atypical antipsychotics at admission, discharge, two months, and one year

At admission, 2005 patients were examined, at discharge 1980 patients, at two months 1726 patients, and at one year 1493 patients. All other patients had withdrawn their informed consent, were lost to follow-up, or had died (Supplementary Fig. 1). The proportion of patients on atypical antipsychotics was similar at admission ($N = 88/2005$, 4.4%), at discharge ($N = 116/1980$, 5.9%), at two months ($N = 103/1726$, 6.0%) and at one year ($N = 88/1493$, 5.9%). However, due to new prescriptions and deprescribing, these numbers do not necessarily represent the same patients at each time point.

### Indications for atypical antipsychotics at admission

Fifty-five of 88 (62.5%) patients taking atypical antipsychotics on admission did not have an appropriate indication recorded. Fourteen (15.9%) of these 88 patients on atypical antipsychotics met the criteria for appropriate use of atypical antipsychotics, while 19/88 (21.6%) had an off-label but accepted indication (Fig. 1).

Among the 14 cases with an appropriate indication, seven had depression, six had bipolar disorder, two patients had schizoaffective disorder, one had severe depression with psychotic symptoms, and one had a previous manic episode. Of the 21 cases prescribed atypical antipsychotics for off-label indications, 11 (52.4%) had delirium, 10 (47.6%) substance-induced mental and behavioural disorders (alcohol, tobacco, sedatives, or others), and one patient had Parkinson's dementia. In 55 patients without a documented appropriate or off-label indication, the following potential reasons for prescription of atypical antipsychotics were identified: dementia in 20/55 cases (36.4%), depression in 11/55 cases (20.0%), insomnia in 8/55 cases (14.5%), anxiety disorder in 5/55 cases (9.1%), and sleep disorder in 5/55 cases (9.1%). In 15/55 cases (27.3%), no documented diagnoses or indications were found to justify therapy with atypical antipsychotics (Supplementary Table 1).

### Change in atypical antipsychotic prescribing during hospitalisation

The number of patients prescribed atypical antipsychotics increased from 88/2005 (4.4%) at admission to 116/1980 (5.9%) at discharge. New prescribing of atypical antipsychotics during hospitalisation occurred in 47 (2.5%) of 1894 patients who were discharged. Among these, 26 prescriptions (55.3%) were for off-label but accepted indications, while 17 prescriptions (36.2%) did not have any coded indication. Deprescribing was observed in 35/87 (40.2%) patients with an atypical antipsychotic at admission who were followed up at discharge (Fig. 2).

The most frequently coded indication for an atypical antipsychotic prescription during hospital stay was delirium in 22 cases (84.6%), followed by psychiatric behavioural disturbances due to substance use in five cases (19.2%; some patients had multiple indications simultaneously). The most frequently identified potential reasons for atypical antipsychotic prescription in the 17 patients without appropriate or off-label indication were insomnia ($N = 7$, 33.3%), cerebral infarction ($N = 4$, 19%), dementia ($N = 4$, 19%), and other sensory perception disorders ($N = 2$, 9.5%).

### Change in atypical antipsychotic prescribing within two months and one year post-discharge

During the index hospital stay, 47 of the 1893 patients (2.5%) who were not receiving atypical antipsychotics at admission but remained under follow-up at discharge were newly prescribed an atypical antipsychotic. Of these 47 patients, 26 (55.3%) received the medication for an off-label indication, 17 (36.2%) for a potentially inappropriate indication.

At two months post-discharge, 21 of the 26 patients (80.8%) with an off-label indication were still in follow-up. Of these, 2 patients (9.5%) had their antipsychotic treatment deprescribed. After one year, 14 of the 15 patients (93.3%).who remained in follow-up had been deprescribed.

Among the 17 of 47 patients (36.2%) with a potentially inappropriate indication for antipsychotic use at discharge, 13 were available for follow-up at two months and 12 at one year. In this subgroup, antipsychotics were deprescribed in 2 of 13 cases (15.4%) within two months, and in 7 of 12 cases (58.3%) within one year.

At the time of discharge, 1863 of the 1980 (94.1%) assessed patients were not on atypical antipsychotic therapy. Of these, there were 1846 patients who had not received atypical antipsychotics at admission and 17 patients whose atypical antipsychotic treatment was discontinued during hospitalisation. Among those 1863 patients who were not prescribed antipsychotics at discharge, 16/1630 patients (1.0%) had been newly commenced on atypical antipsychotics within two months, and 38/1411 patients (2.7%) within one year post-discharge (Fig. 1).

#### *Association of patient and clinical factors with atypical antipsychotic use*

Table 2 summarises the proportion of participants on atypical antipsychotics at different time points, categorised by intervention group, age, ward type, medication burden, dementia diagnosis, and survival status at one year. No statistically significant differences were observed between the intervention and control groups at any time point ($p > 0.05$).

Age also showed no significant interaction with atypical antipsychotics use, although participants aged ≥ 80 years had higher use at each time point compared to younger participants. The type of hospital unit at admission had a significant effect on atypical antipsychotic use at one year, with internal medicine units having a higher proportion (6.8%) of patients still prescribed atypical antipsychotics compared to patients who had been admitted to surgical units (2.4%, $p < 0.01$).

Patients with a higher chronic medication burden (≥ 10 long-term daily medications) consistently showed increased atypical antipsychotic use compared to those

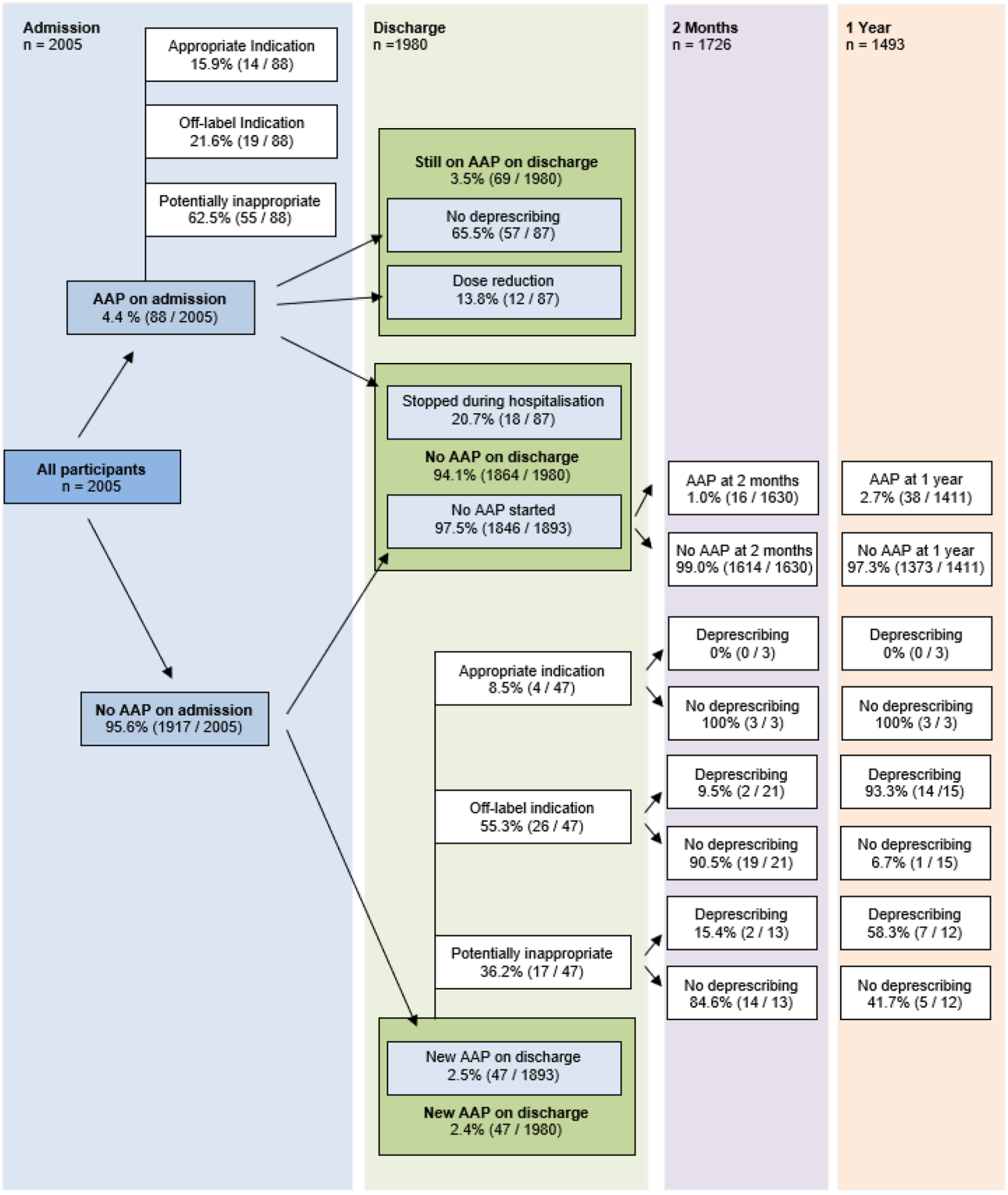


**Fig. 1** Longitudinal patterns of atypical antipsychotics (AAP) deprescribing in the OPERAM trial. The numerators of column one become denominators of column two, etc. However, the total number of patients change at each follow-up, given lost-to-follow-up across time ($N = 2005$ at admission, $N = 1980$ at discharge, $N = 1726$ at two months, $N = 1493$ at one year), explaining that the numbers are not exactly the same across columns. For example, of the 88 patients who were on an atypical antipsychotic at admission (numerator in column 1), 87 (denominator in column two) were still in the study follow-up at discharge. Of the 1917 (numerator in column one) patients without an atypical antipsychotic at admission, 1893 (denominator in column two) remained in the follow-up at discharge. The same logic applies to the follow-ups at two months and one year

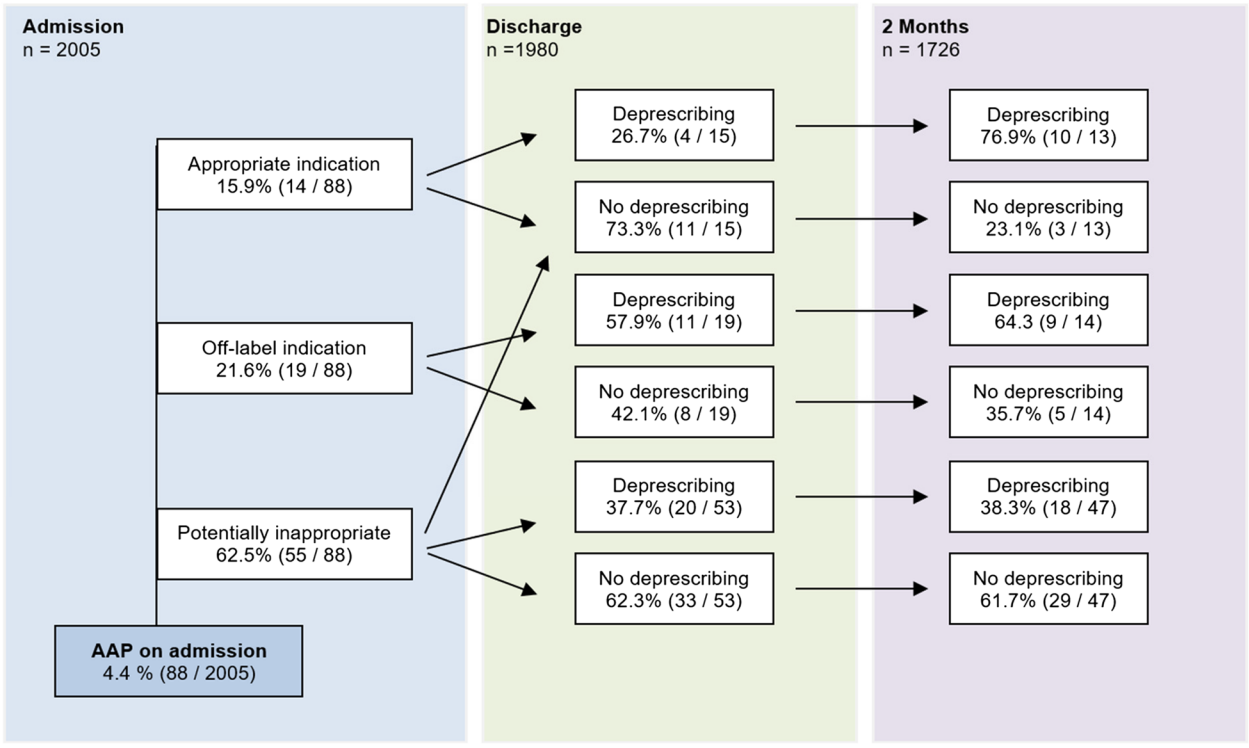


**Fig. 2** Pattern of atypical antipsychotics (AAP) deprescribing in the OPERAM trial during hospitalisation. Deprescribing means either reducing the dose or stopping the medication. One patient with potentially inappropriate indication at admission was diagnosed with a new condition during the hospital stay that justified treatment with an AAP. The numerators of column one become denominators of column two, etc. However, the total number of patients change at each follow-up, given lost-to-follow-up across time ($N = 2005$ at admission, $N = 1980$ at discharge, $N = 1726$ at two months, $N = 1493$ at one year), explaining that the numbers are not exactly the same across columns. For example, of the 88 patients who were on an atypical antipsychotic at admission (numerator in column one), 87 (denominator in column two) were still in the study follow-up at discharge. The same logic applies to the follow-ups at two months

with fewer daily medications i.e. < 10 long-term daily medications, with significant differences persisting at two months ($p = 0.03$) and one year ($p = 0.02$) post-discharge.

Dementia was strongly associated with higher atypical antipsychotic use at all time points ($p < 0.001$). Finally, among participants who died within one year, atypical antipsychotics use at discharge was significantly higher (8.6%) compared to those who survived to one year post-discharge from the index admission (5.1%, $p = 0.01$).

Additional subgroup analyses were conducted to compare prescribing and deprescribing patterns between intervention and control groups. No statistically significant differences were observed in indication appropriateness or deprescribing rates among patients already receiving atypical antipsychotics prior to admission (Supplementary Table 2) or among those newly initiated on such treatment during hospitalisation (Supplementary Table 3).

## Discussion

### Key results

This study of older adults with multimorbidity and polypharmacy across four European countries highlights the significant challenges in optimising atypical antipsychotic prescribing during hospitalisation. At hospital admission, 4.4% of patients were prescribed atypical antipsychotics but the majority (62.5%) of these prescriptions were classified as potentially inappropriate. One-third of patients with potentially inappropriate prescriptions had deprescribing at discharge and almost 60.0% at one year, emphasising that deprescribing of atypical antipsychotics is a long-term process.

During hospitalisation, 47 (2.5%) of the 1893 antipsychotic-naive patients at admission who were followed up at discharge were newly prescribed an atypical antipsychotic, and in more than one-third (36.2%) of these cases, no clear indication was documented. Among those without a clear indication, deprescribing of the atypical antipsychotic occurred infrequently in the early post-discharge period, with only 15.4% of these cases having the medication discontinued within two months of discharge. However, within one year of discharge, 58.3% of patients newly started on atypical antipsychotics during hospitalisation, without a clear indication, had the medication deprescribed. New prescriptions continued to occur after discharge, but at a low level with 1.0% of

**Table 2** Atypical antipsychotics prescription – interaction with patient variables

| | Baseline | Discharge | 2 Months | 1 Year |
|---|---|---|---|---|
| Intervention group | | | | |
| Intervention | 4.9% (47/961) | 6.1% (58/947) | 6.2% (52/833) | 6.6% (48/726) |
| Control | 3.9% (41/1044) | 5.6% (58/1033) | 5.7% (51/893) | 5.2% (40/767) |
| | $p=0.345$ | $p=0.629$ | $p=0.641$ | $p=0.252$ |
| Age (years) | | | | |
| < 80 | 4.3% (46/1078) | 5.2% (55/1065) | 5.0% (47/946) | 5.3% (45/843) |
| >= 80 | 4.5% (42/927) | 6.7% (61/915) | 7.2% (56/780) | 6.6% (43/650) |
| | $p=0.696$ | $p=0.156$ | $p=0.054$ | $p=0.299$ |
| Ward | | | | |
| Medicine | 4.7% (77/1624) | 5.9% (95/1602) | 6.0% (84/1390) | 6.8% (81/1198) |
| Surgery | 2.9% (11/381) | 5.6% (21/378) | 5.7% (19/336) | 2.4% (7/295) |
| | $p=0.122$ | $p=0.799$ | $p=0.787$ | $p=0.004$ |
| Number of long-term medications | | | | |
| < 10 | 2.5% (24/976) | 4.9% (47/963) | 4.7% (40/855) | 4.4% (34/765) |
| >= 10 | 6.2% (64/1029) | 6.8% (69/1017) | 7.2% (63/871) | 7.4% (54/728) |
| | $p<0.001$ | $p=0.071$ | $p=0.025$ | $p=0.015$ |
| Dementia status | | | | |
| No Dementia | 3.2% (61/1894) | 4.5% (85/1869) | 4.8% (78/1630) | 4.5% (63/1413) |
| Dementia | 24.3% (27/111) | 27.9% (31/111) | 26.0% (25/96) | 31.3% (25/80) |
| | $p<0.001$ | $p<0.001$ | $p<0.001$ | $p<0.001$ |
| Survival status at 1 year | | | | |
| Alive | 4.3% (70/1632) | 5.2% (84/1607) | 5.8% (88/1521) | NA |
| Death | 4.8% (18/373) | 8.6% (32/373) | 7.3% (15/205) | NA |
| | $p=0.609$ | $p=0.010$ | $p=0.385$ | NA |

Percentage of participants on atypical antipsychotic at different time points grouped by potential reasons for interaction

follow-up patients receiving an atypical antipsychotic within two months and 2.7% within one year. These findings suggest that atypical antipsychotics are often prescribed to older hospitalised patients in a manner that does not align with best practice guidelines. This pattern of repeat prescription issue and delayed deprescribing exposes this vulnerable population to the avoidable risks of atypical antipsychotics including falls, cognitive impairment and metabolic complications [1, 14, 15].

## Interpretation

### *Prescribing patterns at admission*

The overall prevalence of atypical antipsychotic use at admission was (4.4%) somewhat lower than reported in a previous study of similar hospitalised older people (7.2%) [19]. However, the high rate of potentially inappropriate prescriptions (62.5%) indicates that inappropriate antipsychotic prescribing remains a significant problem, even before hospitalisation. This aligns with findings from Kalisch Ellett et al., who reported similar concerns in older hospitalised patients in Australia [32]. Atypical antipsychotics were more frequently prescribed to patients with dementia and those taking ≥ 10 daily medications, with both groups being highly susceptible to adverse drug effects and adverse drug interactions, emphasising the need for particular caution when prescribing in these patient groups. However, our data do not allow us to determine the direction of this association [33, 34]. The strong link between dementia and antipsychotic use follows a well-established pattern: in patients with dementia, behavioural and psychological symptoms frequently lead to atypical antipsychotic prescribing, despite clear guideline advice against their use whenever possible [35]. This is particularly problematic because the persistence of antipsychotic medications prescribed during hospitalisation in patients with dementia can remain as high as 81% even one year after discharge [36]. This practice persists despite numerous safety warnings, including the EMA warning in 2004 highlighting increased mortality risk in older patients with dementia following exposure to atypical antipsychotics [37, 38]. EMA reported an almost twofold increased risk of all-cause mortality and a threefold increase in cerebrovascular events in patients living with dementia treated with risperidone and olanzapine [39]. Initially limited to these two atypical antipsychotics, safety warnings by international and national agencies were later extended to all atypical antipsychotics in 2009 [40].

In our study, no clear diagnosis justifying the prescription could be found for a quarter of patients prescribed atypical antipsychotics without appropriate or off-label indication at admission. This raises concerns that incomplete or no documentation in their medical records may have contributed to some cases of seemingly inappropriate prescribing of atypical antipsychotics. This issue has been noted in earlier research on atypical antipsychotic use, with some studies reporting up to 60% of medical records were missing key information, including the primary diagnosis (17.5%), additional diagnoses (28%) and presenting symptoms (20%) [32, 41].

### *New prescriptions during hospitalisation and at discharge*

The 2.5% initiation rate for atypical antipsychotics during hospitalisation, with 36.2% of these new prescriptions lacking clear indications, reflects similar concerns from previous studies about frequent and often inappropriate prescribing of antipsychotics in acute hospital settings [42, 43]. In our study, the most common reason for new atypical antipsychotic prescriptions was delirium,

a condition often managed with antipsychotics despite guidelines recommending caution [19, 42]. Research suggests that stress and uncertainty among resident physicians, along with pressure from other healthcare professionals, contribute to potentially inappropriate prescribing of atypical antipsychotics in older hospitalised patients [44, 45]. Additionally, cost pressure and the systematic stress within healthcare may further exacerbate this issue. In our study, medications on PRN basis were also included in the analysis. However, as these medications may not have actually been administered or taken by the patient, we cannot exclude an overestimation of the true number of medications and the extent of drug exposure.

These findings highlight the challenge of balancing acute symptom management (e.g., agitation in delirium) with long-term medication safety, as the lack of deprescribing plans at discharge can result in unnecessary continuation and chronic inappropriate antipsychotic use.

#### *Deprescribing patterns over time*

The deprescribing rates observed in this study are noteworthy. Of the 88 patients who were receiving atypical antipsychotics at admission, 35 (40.2%) had the medication deprescribed by discharge. Among those with potentially inappropriate prescriptions, 37.7% were either deprescribed or had a suitable indication documented at discharge. This implies that in nearly one-third of cases, clinicians either identified the lack of a valid indication and chose to stop the medication or were able to justify continued use, reflecting clinical awareness and judgement. The fact that we did not find any differences between the intervention group, which received a systematic medication review and the control group regarding the proportion of patients discharged with atypical antipsychotics further suggests that hospital physicians may already engage in medication reviews as part of routine clinical practice, enabling them to distinguish between appropriate and inappropriate prescription indications. To further explore this, we compared prescribing and deprescribing patterns by indication appropriateness. No significant differences were found between groups in terms of antipsychotic prescriptions (Supplementary Tables 2 and 3).

However, among patients newly started on atypical antipsychotics during hospitalisation, there was a non-significant trend suggesting more cautious prescribing in the intervention group. No clear trends were observed for deprescribing. Overall, the structured medication review had little effect on prescribing rates but may have influenced decisions about starting antipsychotics.

The effectiveness of the intervention might thus have been limited not due to a lack of awareness, but potentially because of other barriers to deprescribing. Several barriers to reducing inappropriate prescribing have been identified, ranging from intrinsic factors (such as physicians' beliefs, attitudes, and knowledge) to extrinsic factors (including patient expectations, work environment, healthcare system constraints, and cultural influences) [46]. However, the OPERAM study demonstrated that structured medication reviews alone have a limited impact on deprescribing, likely due to systemic obstacles such as fragmented care transitions, prescribing inertia, and prescriber uncertainty [21].

In the early post-discharge period, deprescribing of atypical antipsychotics remained uncommon, with only 15.4% of patients who had been newly initiated on these medications during hospitalisation for a potentially inappropriate indication having the drug discontinued within two months of discharge. However, over the course of a year's follow-up, the deprescribing rate increased, with 58.3% of these patients having the atypical antipsychotic medication withdrawn. This pattern is consistent with previous work showing that once antipsychotics are prescribed in older adults, they tend to be continued, even when initially started for transient symptoms [32, 43]. In the present study, the majority (84.6%) of off-label atypical antipsychotic prescriptions during hospitalisation were likely issued for symptoms of delirium and substance-induced mental and behavioural disorder. We may have underestimated the prevalence of BPSD, as these were likely coded under the general diagnosis of delirium. At the time of data collection, BPSD was not consistently or systematically recorded as a distinct clinical entity, and no specific ICD-10 code existed for this syndrome. As a result, patients presenting with agitation, psychosis, or other neuropsychiatric symptoms related to dementia may have been categorised under delirium, potentially obscuring more precise characterisation of symptom patterns and related prescribing practices. Nevertheless, in a comparable population, 31.3% of patients developed delirium during hospitalisation, yet only 5% of those affected experienced complete resolution of symptoms at the time of discharge. An additional 20% showed symptom resolution at three months post-discharge [47]. This may explain the relatively low deprescribing rate after two months and even after one year in the present study. Despite possible off-label indications for use in patients with delirium, recent reviews have found that only low-quality evidence supports the use of atypical antipsychotics, although a potential benefit may exist in patients experiencing acute distress or severe agitation [48–50]. Furthermore, these reviews concluded that antipsychotics do not reduce the severity or duration of delirium, do not improve cognitive function, do not resolve symptoms, and have no effect on mortality or length of hospital stay [48, 49].

Among the patients who were newly commenced on atypical antipsychotics during hospitalisation without an appropriate indication, only 58.3% had the medication deprescribed within one year. Given that the OPERAM study does not provide a detailed direct linkage between specific diagnoses and prescribed medications, the rationale for initiating atypical antipsychotics remains largely speculative. A considerable proportion of prescriptions were issued in patients with a previous cerebral infarction (19%) or in patients with dementia (19%). The chronic nature of these underlying conditions may contribute to the continued use of atypical antipsychotics. Another potential explanation is the older age and multimorbidity of the OPERAM participants, for which deprescribing might not be always the first priority, notably due to lack of time among healthcare professionals. However, this high proportion of patients without deprescribing of atypical antipsychotics newly started at discharge at one year and the fact that most of those patients missed an appropriate prescribing indication underscore the importance of carefully evaluating any new prescription during hospitalisation and continuation at discharge. This might help avoid long-term potentially inappropriate prescriptions, given some inertia in deprescribing.

The subgroup analysis showed that patients with dementia were significantly more likely to be prescribed atypical antipsychotics, an unsurprising finding. At admission, 31% of patients in the atypical antipsychotic group had dementia, compared to a dementia prevalence of 4.4% in the group that did not receive atypical antipsychotics. This confirms results of previous studies showing that patients with dementia frequently receive atypical antipsychotics, despite the increased risk of adverse events [33, 36, 51]. This trend persisted throughout the index hospital stay, with a strong association still present at discharge. Patients with dementia often receive atypical antipsychotics to manage behavioural symptoms, despite the substantial risks associated with this practice i.e. increased risk of stroke, venous thromboembolism, myocardial infarctions, and other severe adverse events [34].

### *Clinical implications*

Future research should not only focus on identifying inappropriate prescriptions in older patients in hospitals, but also on developing effective strategies to support hospital physicians in deprescribing – ideally by initiating discontinuation planning for atypical antipsychotics before discharge – in close collaboration with both patients and general practitioners. Integrating structured medication review with appropriate deprescribing into discharge planning could further reduce the use of atypical antipsychotics after hospitalisation. However, such efforts face several challenges, including patient expectations, prescribing habits, fear of adverse outcomes due to medication withdrawal, and systemic barriers [52]. Engaging patients, families, and caregivers—guided by evidence-based deprescribing recommendations—is essential [53]. In previous qualitative studies, physicians also emphasise the need for structural changes, such as dedicated funding for medication reviews, improved communication systems, access to non-pharmacological alternatives, updated deprescribing guidelines, and better tools to strengthen patient involvement in medication decisions [52, 53].

### Limitations

This study has some limitations. First, the observational design precludes definitive causal conclusions regarding prescribing practices and patient outcomes. Second, potential documentation inaccuracies may have led to underestimation or misclassification of appropriate prescribing indications. In a quarter of all atypical antipsychotic-medicated patients without an appropriate or off-label indication at admission, a clear diagnosis linked to the atypical antipsychotic therapy could not be determined. Moreover, our dataset did not include detailed clinical documentation of neuropsychiatric symptoms that might have led to the prescription of antipsychotics. This limits the ability to explore the relationship between specific symptom profiles—particularly in patients with dementia—and the persistence of antipsychotic prescribing. Third, in this study we considered, in line with EMA approvals, the acute treatment of a manic or depressive episode in the context of bipolar disorder with certain atypical antipsychotics, as well as the add-on treatment of major depression with inadequate response to conventional antidepressants, to be appropriate indications. We identified seven patients with bipolar disorder who were treated with olanzapine or quetiapine, and six patients with depression who received quetiapine. However, in both groups, there was no documented evidence that an acute manic or depressive episode, or an acute major depressive episode, was actually present. A coding or documentation error cannot be entirely ruled out in these cases. However, since we cannot definitively determine whether these patients received atypical antipsychotics without an appropriate indication, and in order to remain cautious with respect to statements regarding potentially inappropriate pharmacotherapy, we classified all patients with bipolar disorder (ICD-10: F31) as well as those with a depressive episode (ICD-10: F32) who received an appropriate atypical antipsychotic (e.g., quetiapine) as having received treatment with an adequate indication. Fourth, while we examined antipsychotic deprescribing following hospitalisation, we did not assess possible unintended consequences of deprescribing, such as the substitution with other psychotropic medications.

Prior studies have suggested that deprescribing antipsychotics in patients with dementia may lead to increased use of therapeutic alternatives, including antidepressants and anxiolytics [54, 55]. This may be an important area for future research. Fifth, we conducted multiple comparisons across several subgroups and time points as shown in Table 2. While unadjusted p-values are reported, we acknowledge the increased risk of type I error due to multiple testing. These results should therefore be interpreted with some caution, particularly for marginally significant findings. Sixth, the data are from 2016 to 2019 and might be somewhat outdated. Finally, a limitation of our study is that we did not directly assess clinical outcomes or adverse events related to the continued inappropriate use of atypical antipsychotics. Although a previous analysis of the OPERAM cohort found no overall association between antipsychotic prescribing and drug-related readmissions, individual cases of harm such as falls and delirium were still observed [56]. Consequently, without a direct outcome assessment in our specific analysis, we cannot exclude the possibility of relevant patient risks.

## Conclusion

This study highlights the widespread issue of potentially inappropriate antipsychotic prescribing in older multimorbid patients following acute hospitalisation. Many new prescriptions initiated during the hospital stay were potentially inappropriate, and deprescribing efforts were slow and insufficient, exposing patients to unnecessary long-term risks from atypical antipsychotic therapy. Dementia and polypharmacy were key predictors of inappropriate atypical antipsychotic use. To enhance patient safety, we urgently need to improve prescribing practices for atypical antipsychotics in older hospitalised patients. By prioritising education, protocol-driven deprescribing, and post-discharge follow-up, healthcare systems will be better placed to reduce inappropriate atypical antipsychotic use and associated risks in this vulnerable population.

### Abbreviations

| | |
|---|---|
| AAP | Atypical Antipsychotics |
| ATC | Anatomical Therapeutic Chemical Classification System |
| BPSD | Behavioural and psychological symptoms of dementia |
| CCI | Charlson Comorbidity Index |
| EMA | European Medicines Agency |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, 10th Revision |
| IQR | Interquartile range |
| NA | Not available |
| OPERAM | OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly |
| SNSF | Swiss National Science Foundation |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| WHO | World Health Organization |

## Supplementary Information

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Supplementary Material 1.

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### Authors' contributions

All authors meet criteria for authorship as stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Study concept and design: CA. Acquisition of data: OPERAM trial, and CS. Analysis and interpretation of data: All authors. Drafting of the manuscript: CS and CA. Critical revision of the manuscript for important intellectual content: All authors. The author(s) read and approved the final manuscript.

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### Data availability

The datasets analysed during the current study will be made available on reasonable request. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by the OPERAM publication committee.

## Declarations

### Ethic approval and consent to participate

This study was approved by the independent research ethics committees at each site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland, ID 2016–01200; Medical Research Ethics Committee Utrecht, Netherlands, ID 15–522/D; Comité d'Ethique Hospitalo-Facultaire Saint-Luc-UCL: 2016/20JUL/347–Belgian registration No: B403201629175; Cork University Teaching Hospitals Clinical Ethics Committee, Cork, Republic of Ireland; ID ECM 4 (o) 07/02/17), and Swissmedic as responsible regulatory authority. Written informed consent was obtained from the patients or their legal representatives before enrolment. This study adhered to the Declaration of Helsinki.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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## References

1. Chokhawala K, Stevens L. StatPearls. Antipsychotic Medications; 2024.
2. Christian R, Saavedra L, Gaynes BN, Sheitman B, Wines RCM, Jonas DE, et al. Future Research Needs for First- and Second-Generation Antipsychotics for Children and Young Adults. AHRQ Future Research Needs Papers; 2012. Rockville (MD).
3. Swissmedic. Swissmedicinfo Cited 2024. Available from: https://www.swissmedicinfo.ch/
4. European Medical Agency (EMA). European Public Assessment Reports. 2024. Available from: https://www.ema.europa.eu/en/medicines. Accessed Sept 10 2025.
5. Hojlund M, Andersen JH, Andersen K, Correll CU, Hallas J. Use of antipsychotics in Denmark 1997–2018: a nation-wide drug utilisation study with focus on off-label use and associated diagnoses. Epidemiol Psychiatr Sci. 2021;30:e28.
6. Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. J Manag Care Pharm. 2012;18(5 Suppl B):S1–20.
7. Alexopoulos GS, Jeste DV, Chung H, Carpenter D, Ross R, Docherty JP. The expert consensus guideline series. Treatment of dementia and its behavioral disturbances. Introduction: methods, commentary, and summary. Postgrad Med. 2005;Spec No:6–22.
8. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005;294(15):1934–43.
9. Gareri P, Segura-Garcia C, Manfredi VG, Bruni A, Ciambrone P, Cerminara G, et al. Use of atypical antipsychotics in the elderly: a clinical review. Clin Interv Aging. 2014;9:1363–73.
10. Markowitz JD, Narasimhan M. Delirium and antipsychotics: a systematic review of epidemiology and somatic treatment options. Psychiatry (Edgmont). 2008;5(10):29–36.
11. Stogios N, Smith E, Bowden S, Tran V, Asgariroozbehani R, McIntyre WB, et al. Metabolic adverse effects of off-label use of second-generation antipsychotics in the adult population: a systematic review and meta-analysis. Neuropsychopharmacology. 2022;47(3):664–72.
12. Mok PLH, Carr MJ, Guthrie B, Morales DR, Sheikh A, Elliott RA, et al. Multiple adverse outcomes associated with antipsychotic use in people with dementia: population based matched cohort study. BMJ. 2024;385:e076268.
13. Cerovecki A, Musil R, Klimke A, Seemuller F, Haen E, Schennach R, et al. Withdrawal symptoms and rebound syndromes associated with switching and discontinuing atypical antipsychotics: theoretical background and practical recommendations. CNS Drugs. 2013;27(7):545–72.
14. Farrell B, Richardson L, Raman-Wilms L, de Launay D, Alsabbagh MW, Conklin J. Self-efficacy for deprescribing: A survey for health care professionals using evidence-based deprescribing guidelines. Res Social Adm Pharm. 2018;14(1):18–25.
15. Smartermedicine CWS. Top-5-Listen - Stationäre Allgemeine Innere Medizin (2023) 2023 [Available from: https://www.smartermedicine.ch/de/top-5-listen/stationaere-allgemeine-innere-medizin-2023
16. Rosenberg A, Agiro A, Gottlieb M, Barron J, Brady P, Liu Y, et al. Early trends among seven recommendations from the choosing wisely campaign. JAMA Intern Med. 2015;175(12):1913–20.
17. Cliff BQ, Avancena ALV, Hirth RA, Lee SD. The impact of choosing wisely interventions on Low-Value medical services: A systematic review. Milbank Q. 2021;99(4):1024–58.
18. Goto NA, van Heel DAM, Dautzenberg L, Sibille FX, Jennings E, Bauer DC, et al. Impact of discontinuation of Fall-Risk-Increasing drugs on falls in multimorbid older patients with polypharmacy. J Am Geriatr Soc. 2025;73(2):123–32.
19. Herzig SJ, Rothberg MB, Guess JR, Stevens JP, Marshall J, Gurwitz JH, et al. Antipsychotic use in hospitalized adults: Rates, Indications, and predictors. J Am Geriatr Soc. 2016;64(2):299–305.
20. Adam L, Moutzouri E, Baumgartner C, Loewe AL, Feller M, M'Rabet-Bensalah K, et al. Rationale and design of optimising therapy to prevent avoidable hospital admissions in multimorbid older people (OPERAM): a cluster randomised controlled trial. BMJ Open. 2019;9(6):e026769.
21. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M, et al. Optimizing therapy to prevent avoidable hospital admissions in multimorbid older adults (OPERAM): cluster randomised controlled trial. BMJ. 2021;374:n1585.
22. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.
23. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2024 2024 [Available from: https://atcddd.fhi.no/atc_ddd_index/
24. Maglione M, Maher AR, Hu J, Wang Z, Shanman R, Shekelle PG, et al. Off-label use of atypical Antipsychotics: an update. AHRQ Comparative Effectiveness Reviews. Rockville (MD): 2011.
25. Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA. 2011;306(12):1359–69.
26. National Institute for Health and Care Excellence (NICE) Guideline [NG97]. Dementia: Assessment, management and support for people living with dementia and their carers. London. 2018. Available from: https://www.nice.org.uk/guidance/ng97. Accessed on Sept 10 2025.
27. Jessen F, Bohr L, Kruse C, Dodel R. [The German S3 guidelines on dementia]. Nervenarzt. 2023;94(7):609–13.
28. Braune S, Gurlit S. [Management of delirium in the intensive care Unit]. Dtsch Med Wochenschr. 2017;142(24):1820–4.
29. National Institute for Health and Care Excellence (NICE). Guidelines. Autism spectrum disorder in under 19s: support and management. National Institute for Health and Care Excellence: Clinical Guidelines. London2021.
30. National Institute for Health and Care Excellence (NICE). Guidelines. Obsessive-Compulsive Disorder: Core Interventions in the Treatment of Obsessive-Compulsive Disorder and Body Dysmorphic Disorder. National Institute for Health and Care Excellence: Guidelines; Leicester (UK)2006.
31. Kennedy SKF, Goodall S, Lee SF, DeAngelis C, Jocko A, Charbonneau F et al. 2020 ASCO, 2023 NCCN, 2023 MASCC/ESMO, and 2019 CCO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Support Care Cancer. 2024;32(5):280.
32. Kalisch Ellett LM, Pratt NL, Apajee J, Roughead EE. Initiation and continuation of antipsychotic medicines in older people following non-psychiatric hospital admission. Int J Clin Pharm. 2019;41(5):1341–7.
33. Steinberg M, Lyketsos CG. Atypical antipsychotic use in patients with dementia: managing safety concerns. Am J Psychiatry. 2012;169(9):900–6.
34. Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007;146(11):775–86.
35. Reus VI, Fochtmann LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, et al. The American psychiatric association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry. 2016;173(5):543–6.
36. Zhang AD, Zepel L, Woolson S, Miller KEM, Schleiden LJ, Shepherd-Banigan M, et al. Initiation and persistence of antipsychotic medications at hospital discharge among Community-Dwelling veterans with dementia. Am J Geriatr Psychiatry. 2025;33(5):500–11.
37. Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. Arch Intern Med. 2010;170(1):96–103.
38. Medicines and Healthcare Products Regulatory Agency (MHRA). Message to healthcare professionals: ATYPICAL ANTIPSYCHOTIC DRUGS AND STROKE. 2004.
39. European Medicines Agency (EMA) Science Medicines Health. European public assessment report (EPAR) for Zyprexa Velotab - olanzapine. London: EMA. 2013. Available from https://www.ema.europa.eu/en/medicines/human/EPAR/zyprexa-velotab. Accessed on September 10 2025.

40. Sultana J, Fontana A, Giorgianni F, Pasqua A, Cricelli C, Spina E, et al. The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the united Kingdom and italy: A Population-Based study. CNS Drugs. 2016;30(11):1097–109.
41. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. JAMA. 2007;297(8):831–41.
42. Phan SV, Lugin Y, Morgan K. Rates of new antipsychotic prescriptions and continuation at discharge from a medical unit in a community teaching hospital serving rural counties. Ment Health Clin. 2019;9(2):88–92.
43. Loh KP, Ramdass S, Garb JL, Brennan MJ, Lindenauer PK, Lagu T. From hospital to community: use of antipsychotics in hospitalized elders. J Hosp Med. 2014;9(12):802–4.
44. Lauffenburger JC, Coll MD, Kim E, Robertson T, Oran R, Haff N, et al. Prescribing decision making by medical residents on night shifts: A qualitative study. Med Educ. 2022;56(10):1032–41.
45. Brennan N, Corrigan O, Allard J, Archer J, Barnes R, Bleakley A, et al. The transition from medical student to junior doctor: today's experiences of tomorrow's Doctors. Med Educ. 2010;44(5):449–58.
46. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. BMJ Open. 2014;4(12):e006544.
47. Levkoff SE, Evans DA, Liptzin B, Cleary PD, Lipsitz LA, Wetle TT, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med. 1992;152(2):334–40.
48. Burry L, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, et al. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev. 2018;6(6):CD005594.
49. Nikooie R, Neufeld KJ, Oh ES, Wilson LM, Zhang A, Robinson KA, et al. Antipsychotics for treating delirium in hospitalized adults: A systematic review. Ann Intern Med. 2019;171(7):485–95.
50. National Institute for Health and Care Excellence (NICE). Delirium in adults: Quality standard [QS63]. London: NICE. 2014. Available from: https://www.nice.org.uk/guidance/qs63/chapter/quality-statement-3-use-of-antipsychotic-medication-for-people-who-are-distressed. Accessed on September 10 2025.
51. Martinez C, Jones RW, Rietbrock S. Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease and other dementias including those treated with antidementia drugs in the community in the UK: a cohort study. BMJ Open. 2013;3(1):e002080.
52. Wallis KA, Andrews A, Henderson M. Swimming against the tide: primary care physicians' views on deprescribing in everyday practice. Ann Fam Med. 2017;15(4):341–6.
53. Bjerre LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Can Fam Physician. 2018;64(1):17–27.
54. Olivieri-Mui BL, Devlin JW, Ochoa A, Schenck D, Briesacher B. Perceptions vs. evidence: therapeutic substitutes for antipsychotics in patients with dementia in long-term care. Aging Ment Health. 2018;22(4):544–9.
55. Harris DA, Maclagan LC, Iaboni A, Austin PC, Rosella LC, Maxwell CJ, et al. Potential unintended consequences of antipsychotic reduction in Ontario nursing homes. J Am Med Dir Assoc. 2022;23(6):1066–72. e7.
56. Bienfait A, Lagreula J, Blum MR, Rodondi N, Sallevelt B, Knol W, et al. Antipsychotic prescribing and drug-related readmissions in multimorbid older inpatients: a post-hoc analysis of the OPERAM population. Int J Clin Pharm. 2024;46(3):656–64.


## Publisher's Note