

## PRESCRIPTION PATTERNS AT DISCHARGE FROM HOSPITALISATION IN OLDER ADULTS WITH SEVERE MENTAL ILLNESS

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### Abstract

**Objective:** We analyzed prescription patterns of psychotropic medication in older patients with severe mental disorder in comparison with the adult population under 65 years old.

**Method:** All inpatient admissions between 2008 and 2013 at the Department of Psychiatry and Mental Health Inpatient Unit, Vila Nova de Gaia/Espinho Healthcare Center, Portugal, were analyzed. Prescription patterns at discharge among older ( $\geq 65$  years) and younger patients ( $< 65$  years) were compared concerning total number of psychoactive drugs and antipsychotics, antipsychotic dose, antipsychotic polytherapy, benzodiazepines, antidepressants and mood stabilizers.

**Results:** 1229 admissions with a diagnosis of schizophrenia and related psychotic disorders and bipolar disorder were included. 77 patients were  $> 65$  years old. The number of psychoactive drugs prescribed at discharge was lower in older patients as well as the number and dose of antipsychotics. Polytherapy with antipsychotics was less frequent in this group as well as the use of anticholinergics. 68% of elders were medicated with at least one benzodiazepine. Top prescribed drugs in older patients were: Lorazepam (52%), Risperidone (47%), Sertraline (22%), Quetiapine (15%), Mirtazapine (14%) and Olanzapine (12%).

**Conclusions:** Our findings were in accordance with recommendations of lower use of antipsychotic medication and polytherapy in older patients. However, the high frequency of benzodiazepines' prescription and the proportion of patients still receiving anticholinergics and typical antipsychotics warrant the implementation of strategies to improve psychopharmacological management in this specific population.

**Key words:** prescription, psychotropic medication, older patients, antipsychotic polytherapy, benzodiazepines, antidepressants, mood stabilizers, schizophrenia, psychotic disorders, bipolar disorder

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**Declaration of interest:** we declare that we have no competing interests

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### Introduction

Aging is characterized by an intricate progression of physiological changes. Medication for older adults is often perceived as complex and problematic and efforts should be made to improve drug therapy in this age group (Beers and Ouslander 1998). Psychopharmacological treatment in older adults should take into account several specificities. Reports of increased susceptibility of older adults to side effects of psychotropic medication are common in the literature; therapeutic efficacy is often observed with lower dosages; side effects may interact with factors associated with aging, worsening it. For example, anticholinergics may worsen cognitive decline associated with age; psychoactive drugs may worsen pre-existing comorbidities. In this age group it is expected to find multiple medical comorbidities beyond psychiatric disorders (Jenike 1996).

These differences between older and younger adults are due to pharmacodynamic and pharmacokinetic differences and are often difficult to determine with accuracy for a specific individual (Jenike 1996). The

use of multiple prescription drugs by older individuals may contribute to reduced effectiveness and increased toxicity through many interacting mechanisms and may also decrease compliance as polypharmacy reduces the likelihood that any of the medications will be taken as prescribed (Rambhade et al. 2012).

Pharmacological management of severe mental disorders usually involves the prescription of antipsychotics and mood stabilizers, associated with major side effects, and many times it is needed to add other drug classes, such as benzodiazepines and anticholinergics.

Taken this into account, older adults with severe mental disorder represent a challenge to safe psychopharmacological treatment and one would expect to find differences in prescription patterns in this age group, reflecting risk minimization while maintaining efficacy. Several studies have found that psychotropic agents constitute a large portion of the potentially inappropriate prescriptions for the elderly in various settings (Mort and Aparasu 2000).

The aim of this study was to analyze prescription

patterns of psychotropic medication in older patients with severe mental disorder and compare it with the adult population below 65 years old, focusing in specific key differences one would expect to find between this age groups.

## Material and methods

We retrospectively analyzed all inpatient admissions from 2008 to 2013 at the Department of Psychiatry and Mental Health Inpatient Unit, Vila Nova de Gaia/Espinho Healthcare Center, in Vila Nova de Gaia - Portugal, covering a catchment area of 340000 people, mostly urban and located in the northwest of the country. In the present study we compared prescription patterns at discharge between older adults ( $\geq 65$  years) and younger patients (18 years - 65 years).

The following sociodemographic variables were extracted: sex, age, education and cohabitation. Education was categorized according to established grades in the Portuguese education system: 1st-4th years (Elementary School), 5th-9th years (Mid-School), 10th-12th years (High School),  $>12$ th years (University). If patients were living with at least one other person (relative or friend) it was categorized as Cohabitation. Length of stay was defined as time elapsed between admission and discharge. Number of admissions was the number of times the same patient was previously admitted in our inpatient unit. We defined year of admission in 3 categories, collapsing 2 years in each of them (2008-2009, 2010-2011, 2012-2013).

Total number of psychoactive drugs was calculated as the arithmetic sum of all drugs normally used to modulate psychological or brain function. Total number of antipsychotics was the sum of all antipsychotics prescribed at discharge. The dose of antipsychotics was calculated as the sum of equivalent doses of all antipsychotics prescribed. Polytherapy with antipsychotics was defined as the co-prescription of at least two antipsychotics at the same time.

Equivalent doses resulted from conversion of original doses to haloperidol equivalents, based on equivalence doses proposed by Andreasen et al. (2010). Drugs not mentioned in the previously cited article were searched in the literature regarding the respective equivalence dose to chlorpromazine and then further converted to haloperidol equivalents (Suzuki 2014) (Leucht 2014). Many studies use chlorpromazine equivalents, however, chlorpromazine is barely used in Portugal as a main antipsychotic. Therefore it would make more sense to convert doses to a drug regularly used in our practice, such as haloperidol, and for which there is some data on conversion dosages. Additionally, as proposed by Andreasen et al. (2010), chlorpromazine is not routinely used in many centers so that its role as a comparator should be updated. Haloperidol equivalents conversion was as follows: Haloperidol 2mg = Aripiprazol 6.8mgs, Clozapine 115.6mgs, Olanzapine 5.1mgs, Quetiapine 152.0mgs, Risperidone 1.4mgs, Ziprasidone 53.1mg, Zotepine 50.0mgs, Fluphenazine 1.9mgs, Zuclopentixol 21.0mgs, Pimozide 2.0mgs, Amissulpride 108.0mgs, Perphenazine 7.4mgs, Chlorpromazine 108.0mgs, Levomepromazine 108.0mgs. Following the literature, we also created a variable coding for the presence of antipsychotics in high dose, i.e. prescribed in doses higher than 18,5mg haloperidol equivalents ( $>1000$ mg of chlorpromazine).

The dose of benzodiazepines was calculated as the sum of all benzodiazepines prescribed, converted to the equivalent diazepam dose, in accordance with published

studies (Ashton 2002) (British National Formulary) (Sostmann et al. 1989). Diazepam equivalents conversion was as follows: Diazepam 10mg = Alprazolam 0.5mg, Lorazepam 1mg, Oxazepam 20mg, Clonazepam 0.5mg, Flurazepam 22.5mg, Midazolam 13mg, Ethyl loflazepate 2mg, Cloxazolam 1.5mg, Chlorazepate 15mg, Estazolam 1.5mg, Clobazam 20mg, Mexazolam 2mg, Halazepam 20mg, Bromazepam 6mg.

We further calculated equivalence doses for antidepressants and mood stabilizers. Such equivalency is much more controversial and there are no established rules regarding recommended procedures. Nevertheless we based on fluoxetine equivalent doses proposed by Karlsson et al. (2000) and Hayasaka et al. (2015) for antidepressants and lithium equivalent doses as proposed by Centorrino et al. (2006). Fluoxetine equivalents conversion was as follows: Fluoxetine 20mg = Bupropion 150mg, Duloxetine 30mg, Venlafaxine 75mg, Citalopram 20mg, Escitalopram 10mg, Fluvoxamine 100mg, Paroxetine 20mg, Sertraline 50mg, Clomipramine 100mg, Amitriptyline 100mg, Maprotiline 75mg, Mianserine 30mg, Mirtazapine 15mg, Moclobemide 300mg. Lithium equivalents conversion was as follows: Lithium 1mg = Valproic acid 0.70mg and Carbamazepine 1.17mg. Only approved mood stabilizers were included in the analysis of mood stabilizers prescription patterns. When patients were prescribed the same drug but via different routes of administration, e.g., intramuscular plus oral, we counted that as only one antipsychotic.

Data was extracted to an Excel database specifically designed for the study. For data analysis we used SPSS v21.0.

## Results

We analyzed 1229 admissions of patients with a diagnosis of schizophrenia and related psychotic disorders and bipolar disorder. The older patients group ( $\geq 65$  years) was composed of 77 individual and 1152 patients were less than 65 years old. **Table 1** shows several sociodemographic and administrative variables. In the older group mean age was 72,3 years old and in patients  $<65$  years mean age was 40,9 years old. There were more females among older patients (61% vs 46%;  $p=0,008$ ) and education level was lower (above 4th grade: 38% vs 79%,  $p<0,001$ ). Living alone was also more frequent among older patients (31% vs 18%;  $p=0,012$ ). Mean length of stay was similar between groups (23,6 days vs 24,0 days;  $p>0,05$ ). The mean number of recorded previous admissions was lower for older patients (1,3 vs 2,6;  $p<0,001$ ) and approximately two thirds of patients had a diagnosis of Schizophrenia or related psychotic disorders and one third a diagnosis of Bipolar disorder. Medical comorbidity was present in 53% of older patients and 21% of younger patients ( $p<0,001$ ). Most common medical comorbidities in older patients were cardiovascular (22%), endocrine (22%), respiratory (14%), genitourinary (10%) and hematological (5%) disorders.

**Table 2** summarizes prescription patterns after psychiatric hospitalization by age group (older vs younger adults). The mean number of psychoactive drugs prescribed at discharge was lower in older patients (2,8 vs 3,3;  $p<0,001$ ) as well as the number of antipsychotics (0,9 vs 1,2;  $p<0,001$ ) and the equivalent antipsychotic dose (5,3mg vs 9,5mg;  $p<0,001$ ). The proportion of patients receiving high dose of antipsychotics didn't reach significance between groups, probably due to small number of patients. Only a small

**Table 1.** Admissions between 2008-2013 in patients with severe mental illness

	<65 years	>65 years	p value
<b>Sex, n/N (%)</b>			
Female	525/1152 (46)	47/77 (61)	<b>0,008*</b>
<b>Age, mean (SD)</b>	40,9 (11,8)	72,3 (5,8)	
<b>Education level, n/N (%)</b>			
1st-4th grade or lower	182/865 (21)	21/34 (62)	<b>&lt;0,001*</b>
>4th grade	683/865 (79)	13/34 (38)	
<b>Cohabitation, n/N (%)</b>			
Living alone	190/1060 (18)	18/58 (31)	0,012
<b>Year of admission, n/N (%)</b>			
2008-2009	367/1149 (32)	24/77 (31)	
2010-2011	368/1149 (32)	24/77 (31)	>0,05
2012-2013	414/1149 (36)	29/77 (38)	
<b>Length of stay, mean (SD)</b>	24,0 (19,4)	23,6 (29,7)	>0,05
<b>Number of Admissions, mean (SD)</b>	2,6 (2,9)	1,3 (1,5)	<b>&lt;0,001**</b>
<b>Diagnosis, n/N (%)</b>			
Schizophrenia and other related psychosis	842/1150 (73)	53/76 (70)	>0,05
Bipolar disorder	308/1150 (27)	23/76 (30)	
<b>Medical Comorbidities, n/N (%)</b>			
Yes	242/1152 (21)	34/77 (53)	<b>&lt;0,001**</b>
Cardiovascular Disorders	104/1152 (9)	17/77 (22)	
Endocrine Disorders	138/1152 (12)	17/77 (22)	
Respiratory Disorders	35/1152 (3)	11/77 (14)	
Genitourinary Disorders	46/1152 (5)	8/77 (10)	
Hematological Disorders	23/1152 (2)	4/77 (5)	

proportion of patients had no antipsychotic (8% vs 5%;  $p>0,05$ ) and the use of typical antipsychotics was less frequent among older patients (25% vs 37%;  $p=0,031$ ). Polytherapy with antipsychotics was less frequent in older patients (8% vs 25%;  $p<0,001$ ) and the use of long-acting antipsychotics was lower in this group of patients (18% vs 44%;  $p<0,001$ ). Additionally, the use of anticholinergics was 21% in younger patients and 12% in older patients ( $p<0,048$ ). 88% of younger patients and 68% of older patients were medicated with at least one benzodiazepine ( $p<0,001$ ) and the mean dose of diazepam equivalents was also lower in older patients (30mg vs 42mg;  $p<0,001$ ). The frequency of use of antidepressants and mood stabilizers was not significantly different between groups, however the mean fluoxetine equivalents administered was higher in older patients (33mg vs 23 mg;  $p<0,001$ ) and lithium equivalents for mood stabilizers was lower in the group of older patients (586mg vs 769mg;  $p<0,001$ ). Top prescribed drugs in older patients were: Lorazepam (52%), Risperidone (47%), Sertraline (22%), Quetiapine (15%), Mirtazapine (14%), Olanzapine (12%), Bromazepam (8%), Biperiden (4%).

## Discussion

The use of psychotropic medication in the elderly is typically complex, mainly because of its side effects. Potentially inappropriate medication (PIM) is a concept

developed by Beers who established several criteria, later reviewed by the American Geriatrics Society (Fick et al. 2015). According to these criteria some medications should be avoided and, if necessary, the dose should be adjusted to reduce the likelihood of side effects.

In our study we found several differences in prescription patterns between older and younger adults with severe mental disorder. The mean number of psychoactive drugs prescribed at discharge was lower in older patients (3.1 vs 3.7;  $p<0,05$ ), as well as the number of antipsychotics (1.3 vs 1.6;  $p<0,05$ ) and its equivalent haloperidol doses (5,8 vs 9,9mg;  $p<0,05$ ). These observations are in line with other studies, emphasizing avoidance of polypharmacy and adjustment of medication doses in the elderly (Alexopoulos et al. 2004, Fick et al. 2015, O'Mahony 2015).

Only 8% of older patients were not medicated with any antipsychotic, as expected, due to the fact that our analysis included only people with severe mental disorders. As generally recommended (O'Mahony 2015), the majority of those medicated with antipsychotic medication were taking an atypical antipsychotic (60%). The prescription of a typical AP was less frequent in older adults (25%), which is also in line with recommendations, based on the higher risk of extrapyramidal and anticholinergic side effects (Ndukwe et al. 2014, Nishtala et al. 2010, Snowdon et al. 2006, Rapoport 2005). On the other hand, 8% of the older patients were polymedicated with antipsychotics,

**Table 2.** Psychoactive Drugs at Discharge by Age Group

	<65 years	>65 years	p value
<b>Total Psychoactive Drugs</b>			
Number, mean	3,7 (1,3)	3,1 (1,2)	<0,001*
<b>Total Antipsychotics</b>			
Number, mean (SD)	1,6 (0,7)	1,3 (0,5)	<0,001*
Dose, mg, mean (SD) <sup>#</sup>	9,9 (6,3)	5,8 (4,6)	<0,001*
High Dosage, n (%) <sup>##</sup>	110 (10)	3 (4)	>0,05**
<b>Total AP's, by class</b>			
No Antipsychotics, n(%)	59 (5)	6 (8)	>0,05**
Typical AP's, n(%)	425 (37)	19 (25)	<b>0,031**</b>
Atypical AP's, n(%)	766 (67)	46 (60)	>0,05**
<b>Polytherapy with Antipsychotics***</b>			
Yes, n(%)	287 (25)	6 (8)	<0,001**
<b>Long-Acting AP's</b>			
Yes, n(%)	505 (44)	14 (18)	<0,001**
<b>Anticholinergics</b>			
Yes, n(%)	243 (21)	9 (12)	<b>0,048**</b>
<b>Benzodiazepines</b>			
≥1 Benzodiazepines, n(%)	1008 (88)	52 (68)	<0,001**
Dose, mg, mean (SD)	42 (27)	30 (20)	<b>0,008*</b>
<b>Antidepressants</b>			
Yes, n(%)	327 (28)	27 (35)	>0,05**
Dose, mg, mean (SD)	23 (12)	33 (17)	<0,001*
<b>Mood Stabilizers</b>			
Yes, n(%)	373 (32)	20 (26)	>0,05**
Dose, mg, mean (SD)	746 (250)	596 (216)	<b>0,005*</b>
<b>8 Most Prescribed Psychoactive Drugs<sup>+</sup></b>			
	Lorazepam (67)	Lorazepam (52)	
	Risperidone (39)	Risperidone (47)	
	Olanzapine (17)	Sertraline (22)	
	Sertraline (15)	Quetiapine (15)	
	Quetiapine (15)	Mirtazapine (14)	
	Biperiden (12)	Olanzapine (12)	
	Bromazepam (10)	Bromazepam (8)	
	Mirtazapine (2)	Biperiden (4)	

significantly lower compared to younger patients. This results show that prescription patterns regarding number of psychoactive drugs, antipsychotic polymedication and dose, are lower in older adults, as recommended (Desai 2003). However, despite these differences one should question the real need of 25% of older adults being prescribed a typical antipsychotic and 8% having polytherapy with antipsychotics.

In addition, only 18% of the elder population received long-acting antipsychotics, in contrast with almost half of the younger adults. There are few studies regarding the use of depot antipsychotics in elderly patients (Masand and Gupta 2003). The literature states that long-acting antipsychotic medication should be considered in older individuals for whom long-term treatment is indicated (Singh and Connor 2009). Our findings could be associated with less experience using these medications in this age group, the difficulty in

subtle dose adjustments and concerns about managing side-effects.

The two most prescribed psychoactive medications in both groups were lorazepam and risperidone (67% vs 52% and 39% vs 49%, respectively). On the other hand, olanzapine, which is related with a higher risk of cardiovascular and metabolic side effects (Stephenson and Pilowsky 1999), was prescribed only in a minority of older patients (12%). The high dispensing of atypical antipsychotics is of concern due to multiple warnings concerning cerebrovascular events and death associated with these agents (Fick et al. 2015). Nevertheless, if their specific efficacy is considered and if rationally used, they can effectively control symptoms and ameliorate functioning (Gareri 2014). The high prescription of risperidone found in the present study could be related with behavioral control in patients with dementia, which is more common in this age group.

We intended also to examine the use of other potentially harmful substances, such as benzodiazepines (BDZ), mood stabilizers and anticholinergics. Benzodiazepines (BDZ) are related with worse cognition, higher incidence of falls, fractures and subsequent hospital admissions (Fick et al. 2015, O'Mahony et al. 2015, Holbrook et al. 2000). Elderly patients are more sensitive to BDZ's specific adverse effects, especially long-acting ones (Fick et al. 2015). In our study approximately 70% of older patients were prescribed benzodiazepines. Lorazepam was the most prescribed BDZ, a trend observed in other countries (Ndukwe et al. 2014) and the use of long-acting benzodiazepines was low. Although BDZ's were prescribed less frequently and at lower mean dosages in older patients compared to younger patients, the magnitude of BDZ use frequency (68%) and dose (30mg diazepam equivalents; SD=20mg) observed in older patients is nevertheless far from the existent orientations that advocate avoidance of these drugs (O'Mahony et al. 2015, Hovstadius et al. 2014). Even if we take into account the fact that our study focused on inpatients, there seems to be room for improvement, implementing non-pharmacological strategies for behavioral management.

Another recommendation in elderly patients is to reduce the use of antiepileptic or mood stabilizers, particularly valproate, as it has been associated with significant toxicity, accelerated brain volume loss, greater cognitive impairment and an increased risk of mortality (Fleisher et al. 2011). The ongoing use of such agents should be therefore of concern. In this study 26% of the older patients were medicated with a mood stabilizer, even though the mean dosage was substantially lower when compared with the control group ( $p=0,005$ ).

Despite the significant lower frequency of anticholinergic prescription in older patients ( $p=0,048$ ), there was still a non-negligible minority of patients for whom anticholinergics were prescribed anticholinergics (9%). In contrast, a recent Swedish survey reported the use of this drugs in 1,5% of the older population (Hovstadius et al. 2014). Our practice conflicts with several guidelines, which recommend its avoidance (Fick et al. 2015, O'Mahony et al. 2015). This finding could be related to the fact that 25% of older adults were prescribed a typical antipsychotic. Anticholinergics are mainly prescribed to reduced extrapyramidal side effects associated with typical antipsychotics (and atypical antipsychotics to a less degree) but themselves with a significant side effect profile ranging from dry mouth, constipation, visual impairment, confusion, delirium and severe cognitive decline (Tune, 2001)

Prescription patterns vary between countries and regions, an issue associated with economic factors, prescribing habits and differences in populations, among others (Zullino et al. 2005). This study brings light to the prescribing practice in the elderly in a Portuguese healthcare center, comparing it with international observations and recommendations, thus aiming to improve future practice. The literature available on psychotropic use in the elderly focuses primarily on data concerning the general population or patients with dementia. The current study aimed to focus on a more specific and understudied group - inpatients with severe mental disorder.

The present study highlights the importance of auditing prescription patterns as a way of identifying current practices and propose specific ways of improving it. In addition, it provides data for comparison in future studies.

One limitation of this study was the small number of older patients, precluding a better profiling of this age

group. More specifically, it restricted the comparison between groups and the inclusion of prescription patterns across time. Moreover, there were significant sociodemographic differences between groups that may have confounded our results. In addition, adjusting for possible confounding was not performed due to sample size. Finally, the study focused on the whole population of patients with severe mental disorder admitted in a single inpatient psychiatric unit in a general hospital, between 2008-2013, which limits the generalization of our findings.

## Conclusion

The present study analyzed prescription patterns among older patients with severe mental disorder during acute hospitalization, in comparison with younger patients. Overall, in the older patients' group, we found, in accordance with recommendations, a lower frequency of antipsychotic prescription and polytherapy, as well as the use of lower antipsychotic dose, antidepressants, mood stabilizers and anticholinergics. In addition, there was a low use of long-action benzodiazepines. However, the frequency of benzodiazepine use approximated 70% and a non-negligible proportion of older patients received anticholinergics (12%) and typical antipsychotics (25%), which warrants the implementation of strategies to improve it.

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