

ORIGINAL ARTICLE/ARTIGO ORIGINAL

Antipsychotic Polypharmacy and High Doses in a Rural Portuguese Community Mental Health Service

Polifarmácia e Sobredosagem Antipsicótica num Serviço Comunitário do Interior de Portugal

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Abstract

Introduction: Antipsychotic polypharmacy (APP) and high dose (APHD) remain a common practice in the treatment of severe mental illness, even though they are not supported by current international guidelines.

Methods: We aimed to establish the prescribing patterns of antipsychotics in a community mental health service in a rural setting, to determine the prevalence of APP and APHD treatment and to identify associated factors.

Results: We identified 284 patients. APP was present in 46.5% patients and was associated to younger age, single status, more previous psychiatric admissions, and anticholinergic prescription. Prescription of APHD was observed in 14.4% patients and was associated with previous inpatient admissions, being prescribed with a first generation long-acting injectable antipsychotic and anticholinergics. We also found that APP and APHD were mutually associated.

Conclusion: Despite current guidelines, we found prevalences of APP and APHD of 46.5% and 14.4%, respectively. Further studies are necessary to better evaluate the antipsychotic prescription patterns in Portugal.

Resumo

Introdução: A polifarmácia e a sobredosagem antipsicóticas permanecem uma prática comum no tratamento de doenças mentais graves, embora as normas mais atuais não o recomendem.

Métodos: Procurou-se identificar os padrões de prescrição antipsicótica num serviço comunitário com enquadramento rural, de forma a determinar a prevalência de polifarmácia e sobredosagem antipsicótica e fatores associados.

Resultados: Foram identificados 284 doentes. A polifarmácia antipsicótica foi observada em 46,5% dos doentes e associava-se a idades mais jovens, ser solteiro, internamentos psiquiátricos prévios e prescrição de anticolinérgicos. Por outro lado, a sobredosagem antipsicótica foi encontrada em 14,4% dos doentes e associava-se a internamentos psiquiátricos prévios, estar medicado com um antipsicótico injetável de primeira geração de longa duração de ação e com um anticolinérgico. Observou-se também que a sobredosagem e a polifarmácia estavam associadas.

Conclusão: Apesar das recomendações internacionais, identificaram-se prevalências de polifarmácia e sobredosagem antipsicótica de 46,5% e 14,4%, respetivamente. São necessários mais estudos para melhor caracterizar os padrões de prescrição antipsicótica em Portugal.

Keywords: Antipsychotic Agents; Community Mental Health Centers; Inappropriate Prescribing; Polypharmacy

Palavras-chave: Antipsicóticos; Centros Comunitários de Saúde Mental; Prescrição Inadequada; Polimedicação

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INTRODUCTION

Antipsychotics are an essential component of the pharmacologic arsenal of psychiatric treatment. Whilst designed for the treatment of psychotic disorders, their usage has expanded to functions such as impulse control, mood stabilization, sleep induction or potentiation of antidepressants.^{1,2} Long-acting injectable antipsychotic (LAIA) formulations are often used to ensure treatment adherence.³ Current guidelines recommend antipsychotic monotherapy as the standard care, considering polypharmacy (APP) solely as a last resort for refractory symptoms after multiple antipsychotic trials, including clozapine.^{4,5} Polypharmacy is defined as the concurrent use of two or more antipsychotics at a given time.^{6,7} Guidelines also discourage antipsychotic high-dose (APHD) prescribing, defined as a total daily dose of antipsychotic that exceeds the maximum recommended dose, whereas in monotherapy or in combination with other antipsychotics.⁸ Both practices are associated with several disadvantages, namely adverse effects, medication non-adherence and increased treatment^{7,9,10} costs though they remain common in clinical practice worldwide.¹¹⁻¹³ However, data regarding these practices in psychiatric community services is scarce. To the best of our knowledge, no prior studies have focused on the prevalence of APP and APHD in patients under the care of community mental health services in Portugal.

We aimed to characterize the antipsychotic prescriptions patterns of a Portuguese community mental health service (CMHS), determine the prevalence of APP and APHD prescribing and identify associated factors.

MATERIAL AND METHODS

a. Context

Data was collected from patients in a countryside CMHS, designed for individuals with serious mental illness requiring LAIA. Patients are referred to the CMHS by their assistant psychiatrist either from outpatient setting or directly from the inpatient service, upon patient agreement. The CMHS provides home visits for administration of LAIA by qualified nurses and regular monitorization by a psychiatrist and a social worker. The procedure enables proximity to the patient with serious mental illness and promotes treatment adherence.

b. Study design and sample

This was a retrospective and observational analysis of demographic and clinical data of patients receiving treatment in the CMHS in 2017. We included all patients receiving care for at least two months, accounting for at least one LAIA administration. We obtained a sample of 284 patients. Deidentified information was extracted from clinical files and treatment management plans. Data included basic demographic and clinical details (gender, age, marital status, psychiatric admissions, psychiatric diagnosis) as well as details on prescribed medication (oral AP, LAIA, anticholinergic prescription, AP total daily dose). Diagnoses were classified using the 10th edition of the International Statistical Classification of Diseases (ICD-10).¹⁴

For the purpose of analysis, chlorpromazine, flupenthixol, fluphenazine, haloperidol and zuclopenthixol were considered first generations antipsychotics (FGA), whereas the second-generation antipsychotics (SGA) included amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine and risperidone.

Antipsychotic polypharmacy was defined as the concomitant prescription of two or more antipsychotics. Cases where the same drug was prescribed in LAIA and oral formulations were considered as monotherapy.

Antipsychotic HD prescription was established when the single or combined daily dose of antipsychotic exceed the 100% of maximum dose recommended in international guidelines. In cases of polypharmacy, the dose for each antipsychotic was converted to a percentage of the maximum dose, which were then summed to obtain the combined daily dose.¹⁵

The study was approved by the Ethics Committee of the Local Mental Health Centre and the data was anonymized.

c. Statistical methods

IBM® SPSS®, version 25, was used to analyse the data obtained from this study.

The data were first tested to ensure they conformed to a normal distribution by using the Kolmogorov-Smirnov test or by considering the values of skewness and kurtosis (acceptable values for normality between -2 and +2). Descriptive statistics included the arithmetic mean (\bar{x}), standard deviation (SD), and standard error of the mean (SE), as well as the 95% confidence interval (95% CI). Where the data were not normally distributed, the median and the inter-quartile range (IQR) were noted.

In those situations where the data were normally distributed and the variances were constant, bivariate comparative analysis was made using the unpaired two-tailed Student's t test and bivariate association analysis involved the Point Biserial Correlation Coefficient Test (r_{pb}). Where the requirements for parametric statistical analysis were not met, bivariate comparative analysis was made using the Mann-Whitney (U) test and bivariate association analysis involved the Pearson Chi-Square (χ^2) test.

The minimum level of significance (α level) accepted throughout the development studies was 0.05 (*), considered to be moderately significant. Levels of 0.01 (**) were considered as significant and 0.001 (***) designated as highly significant.

RESULTS

The study included 284 patients from a community mental health service, receiving LAIA, of whom 69% were male. The average age of patients in the sample was 52.73 ± 14.36 . The most prevalent marital status was single (62%). The most frequent diagnosis, according to the ICD-10, was schizophrenia and other psychoses (56%), with most patients having a history of previous psychiatric hospitalizations (75%). Regarding antipsychotic treatment, 53.5% were on monotherapy (LAIA), more frequently with FGA (76.8%), with haloperidol being the most prescribed (50.4%) AP. A total of 46.5% of the patients were in APP (oral + LAIA),

with the most frequent association being the combination FGA + SGA (60.6%). A total of 51.4% of patients were medicated with anticholinergics, more frequently in patients in APP (35.6%) than in monotherapy patients (15.8%).

A percentage of 14.4% of patients were identified as APHD and belong to antipsychotic polypharmacy, with no case of APHD being identified in antipsychotic monotherapy.

Table 1. Sociodemographic and clinical characterization of the sample

Parameter	N (%)
Sex	- Male: 196 (69%); - Female: 88 (31%)
Age	- Average \pm Standard deviation: 52.73 \pm 14.355
Marital Status	- Single: 176 (62%); - Married/Civil Union: 45 (15.8%); - Divorced: 16 (5.6%); - Widowed: 2 (6.1%); - Not Specified: 41 (14.4%)
Previous Hospitalization	- Yes: 213 (75%); - No: 71 (25%)
Clinical Diagnosis (ICD-10)	- Schizophrenia and other psychoses: 159 (56%); - Bipolar affective disorder: 44 (15.5%); - Depressive disorder: 4 (1.4%); - Dementia: 4 (1.4%); - Mental or behavioral disorders secondary to the use of psychoactive substances: 4 (1.4%); - Others: 69 (24.3%)
AP Therapy	- AP monotherapy: 152 (53.5%) - Oral: 0 (0%) - LAIA: 152 (100.0%) - FGA: 116 (76.3%) - SGA: 36 (23.7%) - AP polypharmacy: 132 (46.5%) - Oral: 132 (100%) - LAIA: 132 (100%) - FGA: 102 (77.3%) - SGA: 30 (22.7%) - Associations: - FGA+SGA: 80 (60.6%) - SGA+SGA: 21 (15.9%) - FGA+FGA: 21 (15.9%) - Clozapine + FGA/SGA: 10 (7.6%)
APHD	- AP monotherapy: 0 (0%) - AP polypharmacy: - Oral: 41 (100%) - LAIA: 41 (100%) - FGA: 26 (63.4%) - SGA: 15 (36.6%) - Associations: - FGA+SGA: 25 (61%) - SGA+SGA: 10 (24.4%) - FGA+FGA: 2 (4.9%) - Clozapine + FGA/SGA: 4 (9.8%)

Parameter	N (%)
Anticholinergics	- in AP monotherapy: 24 of 152 (15.8%)
	- in AP polypharmacy: 47 of 132 (35.6%)
	- in APHD: 16 of 41 (39%)

a. Antipsychotic polypharmacy (APP)

As already depicted, 46.5% of the patients were in APP. APP has shown a significant statistical association with age ($p = 0.020$) and an extremely significant statistical association with previous hospitalization ($p = 0.006$) and prescription of anticholinergics ($p = 0.000$). APP showed an inverse proportional relationship with age ($r_{pb} = -0.138$), meaning that younger patients were more likely to be associated with APP than older patients. Patients with APP had a higher percentage of previous hospitalizations (82.6%) when compared with AP monotherapy (68.4%). APP was also associated with a higher percentage of anticholinergic prescription (35.6%) when compared to AP monotherapy (15.8%).

A significant statistical difference was found between AP monotherapy and APP with regard to marital status ($p = 0.001$) and clinical diagnosis (ICD-10) ($p = 0.023$). APP is predominant in single status (72.0%), whereas AP monotherapy is more common in single (53.3%), married/civil union (19.7%) and not specified status (19.1%). Regarding clinical diagnosis (ICD-10), APP is primarily concentrated in schizophrenia and other psychoses (62.9%), whereas AP monotherapy is distributed in a wider range of psychiatric disturbances such as schizophrenia and other psychoses (50.0%), bipolar affective disorder (15.8%) and non-specified disturbances (28.3%).

Table 2. Antipsychotic Polypharmacy (APP) and related factors

Pair of Variables	Inferential Test	p -value
APP vs Sex	Pearson Chi-Square (χ^2) Test (Association Test)	0.455 (No significant statistical association)
APP vs Age	Point Biserial Correlation Coefficient Test (r_{pb}) (Association Test)	0.020 (Significant statistical association)
APP vs Marital Status	Mann-Whitney (U) Test (Differences Test)	0.001 (Extremely significant statistical difference)
APP vs Previous Hospitalization	Pearson Chi-Square (χ^2) Test (Association Test)	0.006 (Extremely significant statistical association)
APP vs Clinical Diagnosis (ICD-10)	Mann-Whitney (U) Test (Differences Test)	0.023 (Significant statistical difference)
APP vs LAIA generation type	Pearson Chi-Square (χ^2) Test (Association Test)	0.849 (No significant statistical association)
APP vs Anticholinergic	Pearson Chi-Square (χ^2) Test (Association Test)	0.000 (Extremely significant statistical association)

The most frequent APP combination was the FGA + SGA combination (60.6%), with the most frequent LAIA APP being haloperidol/ fluphenazine decanoate (%). Regarding oral APs, the most commonly used were olanzapine (23.1%) and quetiapine (20.8%). Clozapine was used in 9 patients (6.8%).

b. Antipsychotic high doses (APHD)

As previously presented in Table 1, 14.4% of the patients had APHD. APHD has shown a significant statistical association with previous hospitalization ($p = 0.015$), LAIA generation type ($p = 0.029$) and prescription of anticholinergics ($p = 0.025$).

Patients with APHD had a higher percentage of previous hospitalizations (90.2%) when compared with recommended doses of APs (72.4%). APHD had a higher percentage of SGA (39.0%) than recommended doses of APs (21.0%). APHD was also associated with a higher percentage of anticholinergic prescription (39.0%).

Table 3. Antipsychotic High Doses (APHD) and related factors.

Pair of Variables	Inferential Test	<i>p</i> -value
APHD vs Sex	Pearson Chi-Square (χ^2) Test (Association Test)	0.534 (No significant statistical association)
APHD vs Age	Point Biserial Correlation Coefficient Test (r_{pb}) (Association Test)	0.386 (No significant statistical association)
APHD vs Marital Status	Mann-Whitney (U) Test (Differences Test)	0.733 (No significant statistical difference)
APHD vs Previous Hospitalization	Pearson Chi-Square (χ^2) Test (Association Test)	0.015 (Significant statistical association)
APHD vs Clinical Diagnosis (ICD-10)	Mann-Whitney (U) Test (Differences Test)	0.057 (No significant statistical difference)
APHD vs LAIA generation type	Pearson Chi-Square (χ^2) Test (Association Test)	0.029 (Significant statistical association)
APHD vs Anticholinergic	Pearson Chi-Square (χ^2) Test (Association Test)	0.025 (Significant statistical association)

All 41 patients with APHD had simultaneously APP and no case of AP monotherapy has been registered with APHD. Thus, it is no surprise that an extremely significant statistical association between APP and APHD has been found (Pearson Chi-Square (χ^2) Test, $p = 0.000$), with that association being of positive nature: higher levels of APP lead to higher prevalence of APHD. The most frequent LAIA administered in APHD is haloperidol decanoate (48.8%), accounting for almost half of the high dosage cases.

DISCUSSION

This study casts a light into the prescription patterns of antipsychotic agents in a Portuguese sample from a mental health community service in a rural setting. To the best of our knowledge, this is the first published study analysing APP and APHD on Portuguese patients in community mental health services.

APP was determined to be 46.5% in the study sample. The scarcity of studies in this population did not allow for a more straightforward comparison. However, APP studies on other populations found much lower rates. A nationwide study on Denmark's schizophrenia patients found that the highest rate of APP dated back to 1996 (30.8%), showing a decrease in the following years.¹⁶ In 2012, their APP rate was 24.6%.¹⁶ Cotes *et al*¹⁷ found an APP rate of 19% on Medicaid recipients prescribed with AP. In addition, a meta-analysis¹² found a global median of 19.5% of patients on APP. Galego *et al*¹² also analysed APP rates throughout the decades, and our rate is most similar to the medium APP rates of Asia, North America and Europe of the 80's and 90's.

Comparing to other Portuguese samples, we observed a similar APP rate in a study of AP prescription patterns in acute psychiatric wards (41.6%).⁸ On the other hand,

Martinho *et al*¹⁸ studied the prevalence of APP on compulsorily admitted patients and found that 70.1% were discharged with an APP prescription.

We verified that olanzapine and quetiapine were the most prescribed antipsychotics in the patients on APP of our sample. Both drugs may have been used not for their antipsychotic properties, but for their action as sleep inductors. We did not collect data on dosage, which would have been helpful to discern the therapeutic rationale for the prescription of quetiapine and olanzapine in these patients.

APP showed a significant statistical association with age, previous psychiatric admissions, and prescription of anticholinergics. On the other hand, a significant statistical difference between different marital status and different clinical diagnosis (ICD-10) with regard to APP prevalence was identified. No significant statistical association was found between APP and sex.

Our findings were congruent with the literature.^{8,16,20-23} We did not observe an association between FGA LAIA and APP, contrary to a study on individuals receiving compulsory treatment in the community.²⁴

Multiple reasons may be responsible for the high rate of APP in our study. In Portugal, there is a paucity of hospital beds in acute psychiatric wards,²⁵ which may pressure clinicians to reduce the number of admissions and its duration. It has been proposed that clinicians may use APP to obtain quicker clinical responses in either inpatient²⁶ or outpatient settings.¹⁶ Furthermore, APP may be continued in the outpatient setting, instead of changed to monotherapy, to avoid relapses.¹⁶ The shortage of resources in psychosocial support and community-based rehabilitation programs for people with serious mental illness may also contribute to the observed prescription pattern.

Last but not the least, psychiatric resources are asymmetrically distributed in Portugal, with the countryside facing greater challenges than the metropolitan areas.²⁷ The literature also

reports that rural settings are more associated with long-term APP, which may have also had contributed to our APP rate.²¹ APP is not recommended unless other trials in monotherapy, including clozapine, fail to demonstrate efficacy. In our sample, there was a clear discrepancy between the number of patients with schizophrenia and other psychosis and the number of patients prescribed with clozapine. It may be possible that, if more patients were prescribed with clozapine, there would be a lower rate of APP; however, our population contained, by definition, patients on LAIA, which means that patients on clozapine and LAIA would necessarily qualify as APP.

We observed a rate of 14.4% of APHD in the study sample, similar to other studies in Portuguese populations.⁸ Higher rates were found on populations receiving compulsory treatment, as shown in an Australian study,²⁴ which found 27% of APHD, and a Portuguese one,¹⁸ which obtained a rate of 51.4%. On the other hand, inpatient and community studies on UK,²⁶ Scotland²⁸ and Hong-Kong²⁹ found lower rates of APHD, 10%, 2% and 9.2%, respectively.

APHD showed a significant statistical association with previous hospitalization and prescription of anticholinergics. No significant statistical association has been found between APHD and sex or age. Additionally, no significant statistical difference has been found between different marital status and different clinical diagnosis (ICD-10) with regard to APHD.

The association between APHD and the use of anticholinergics was also found in past studies.¹⁸ APHD was associated with APP, as reported in other studies.^{8,24,26} It has been hypothesized that it becomes increasingly difficult for clinicians to calculate total AP dosages in patients prescribed with more than one AP.⁸

a. Strengths and limitations

To the best of our knowledge, this is the first study reporting on APP and APHD prescription patterns in patients on a community mental health service in Portugal.

However, it presents several limitations. Firstly, its retrospective design may have compromised the quality of the data and introduced errors, as we could only acquire data present in clinical records. Secondly, as a cross-sectional study, we did not possess data on evolution of AP prescription, so we remained blind to possible ongoing AP cross-titration switches or short-term oral AP prescriptions. We were also unaware of the previous AP trials of each patient, so we are unable to address whether APP was a last resource following multiple monotherapy trials, including clozapine. Lastly, we report specifically on patients on a rural community mental health service receiving LAIA, so our results may not be generalized to other settings and populations. However, our specificity fills a gap on the literature, particularly when it comes to Portuguese populations.

CONCLUSION

The present study reveals the prescription patterns on a rural Portuguese community mental health service user population. High prevalences of APP and APHD have been identified, as well as some sociodemographic and clinic factors that are statistically meaningful to the observed patterns. Given the scarcity of studies about APP and APHD in Portugal, further studies are required to better evaluate and optimize the antipsychotic prescription pattern, in order to meet international guidelines and standards.

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

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