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ORIGINAL ARTICLE

Antipsychotic polypharmacy in a general hospital inpatient psychiatric unit

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KEYWORDS

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Abstract

Introduction: The association of antipsychotics is common in clinical practice despite the lack of scientific evidence to support this practice. There are few data on these patterns of use in hospitals in Spain. However, such data are required for the development of indicators of quality of care.

Aims: To collect information on prescription of antipsychotics in a psychiatric inpatient unit.

Methods: We performed a retrospective observational study of inpatients under treatment with antipsychotic drugs in 2006.

Results: We reviewed 136 patients with a mean age of 38 years and a mean length of stay of 22 days. Antipsychotics were used primarily in schizophrenic disorder (44.9%). At admission, atypical antipsychotics (second or third generation) were the most frequently used drugs in monotherapy (41.2%), a combination of two or more antipsychotics was used in 43% of the patients and the use of additional medication (not antipsychotics) was very high (84.6%). At discharge, the results were similar, but a notable finding was the increase in the combination of an atypical antipsychotic with extended-release drugs (from 2% to 11%).

Conclusions: The use of atypical antipsychotics as the first therapeutic option is becoming established, confirming the phenomenon of polypharmacy in the treatment of psychoses. The study design did not allow directional relations to be established but some trends, such as the possibility that polypharmacy is more common in patients with schizophrenia and is associated with the use of depot antipsychotics, were confirmed.

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PALABRAS CLAVE

Psicosis;
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 Neurolépticos;
 Antipsicóticos;
 Pacientes psicóticos
 ingresados

Politerapia antipsicótica en una unidad de hospitalización psiquiátrica**Resumen**

Introducción: La asociación de antipsicóticos es frecuente en la práctica clínica a pesar de no estar sustentada por la evidencia científica. Existen pocos datos sobre estos patrones de uso a nivel hospitalario en España, que consideramos necesarios en la elaboración de indicadores de calidad asistencial.

Objetivo: Recoger información sobre la prescripción de antipsicóticos en una unidad de hospitalización psiquiátrica.

Métodos: Se trata de un estudio observacional retrospectivo, en el que se incluyen los pacientes ingresados en tratamiento con fármacos antipsicóticos durante el año 2006.

Resultados: Se revisó a 136 pacientes con una edad media de 38 años y una estancia media de 22 días. Los antipsicóticos se emplearon fundamentalmente en el tratamiento esquizofrénico (44,9%). Al inicio del ingreso, los antipsicóticos atípicos (AA) (de 2.ª a 3.ª generación) fueron los más utilizados en monoterapia (41,2%), la combinación de dos o más antipsicóticos se utilizó en un 43% de los pacientes y el uso de medicación adicional (no antipsicóticos) fue muy elevada (84,6%). En el momento del alta, los resultados son similares, destacando el incremento en la combinación de un AA con fármacos de liberación prolongada (de un 2-11%).

Conclusiones: Los AA se consolidan como la primera opción terapéutica, confirmándose asimismo el fenómeno de la polifarmacia en el tratamiento de las psicosis. El diseño del estudio no permite establecer relaciones direccionales, pero sí algunas tendencias, como la posibilidad de que la polifarmacia sea más frecuente en pacientes esquizofrénicos y con los antipsicóticos de depósito.

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Introduction

Antipsychotic polytherapy is defined as the concomitant use of 2 or more drugs in a patient for the treatment of a disorder. The aim is to increase the efficacy of the treatment and minimise side effects. Clinical guidelines and manuals unanimously recommend antipsychotic monotherapy, and there are very few empirical data in favour of polytherapy.¹ This theoretical axiom is not easy to recognise in day-to-day practice, where combinations of drugs are common. Prevalence figures for polytherapy cited in different studies range between 10% and 73%,^{1,2} with variations depending on the patient population, the active principle, the year the study was conducted, the study method, place of treatment (outpatients, acute care unit, long-stay unit), and the duration of the study.^{3,4}

There are obvious risks of combining psychiatric drugs. Firstly, there is a greater likelihood of side effects, and increases in toxicity and the mean daily dose (defined daily dose).⁵⁻⁸ In a recent prospective study of 93 hospitalised patients, Ganesen et al found no significant differences between patients in polytherapy and monotherapy, using the UKU scale as the instrument to measure side effects. The authors admit the study has limitations, but the data suggest the need for an in-depth study of the tolerability, side effects, and risks of combining antipsychotics.⁹ Secondly, there is a masking of the response to treatment, limiting the doctor's ability to assess the patients' response to the new treatment.⁴ Thirdly, dosage becomes increasingly complex, with difficulties for adherence and compliance

with the treatment.^{3,4} Lastly, polytherapy increases the already significant cost of the treatment in a context of limited healthcare resources.^{4,8,10}

Not all antipsychotics have the same mechanism of action and there are noticeable and ever-growing pharmacodynamic differences, leading to different therapeutic and side-effect profiles.² All this, together with the complexity and variety of symptoms suffered by patients, are good reasons for monotherapy not being the only treatment option. This argument is supported by the fact that there are patients resistant to treatment. According to the CATIE study,¹¹ at least two thirds of schizophrenics who begin taking an antipsychotic will respond inadequately to treatment. If we consider that after 2 prior failures, changing to clozapine is the final monotherapy option, it is not surprising that doctors try reasonable means of potentiating treatment.

Studies looking into combinations of antipsychotics are scarce. Patrick et al¹ used the following selection criteria in their review: an assessment of the efficacy on a single patient of the active principles alone, and then in combination treatment (Preskon and Lacey criteria), together with the use of standardised scales. Only 3 studies met the criteria (an open study and 2 case series). Financial reasons, and others related to methodological complexities make it almost impossible to obtain data from controlled studies for all the types of combinations.²

At present, atypical antipsychotics (AA) (2nd and 3rd generation antipsychotics) are recommended by different committees of experts as first line treatments, having shown good efficacy and the best side-effect profile.¹² Some authors think that their improved tolerability has

contributed to polypharmacy and the increase in costs.^{8,13} However, typical antipsychotics (TA) (conventional) are still used, and some authors think they have a faster onset of action and act more strongly on certain positive symptoms, with a known side-effect profile which enables a reasonable margin of use.¹⁴

Polypharmacy in the treatment of psychosis is not limited to combinations of antipsychotic drugs, but includes other groups of psychiatric drugs. The greater diversity of drugs available for treating patients with psychiatric disorders, the alleged safety of new ones, and probably pressure from the pharmaceutical industry have created new opportunities for using more than one drug on the same patient.¹⁰

Fifty years on, we have third generation antipsychotics (aripiprazole, paliperidone) and considerable experience in how to use them. However, the debate goes on and the treatment guidelines followed by healthcare providers are based more on experience than on evidence.¹⁵ More studies in treatment combinations are necessary before clinical recommendations can be made.¹⁶

In this study we wanted to obtain data about the day-to-day use of antipsychotics in acute patients admitted to the psychiatric unit of a general hospital whose healthcare profile fulfils standard criteria (staff shift pattern, occupation, and morbidity and mortality). The aim is to know the pharmacological guidelines that it uses, and describe the uses and combinations of different types of medication. Our working hypothesis is that polypharmacy is a very common practice, both when combining antipsychotics, and combining antipsychotics with psychiatric drugs from other groups. We think that AAs have become established as the first treatment option.

Material and method

A transversal, retrospective, epidemiological study was conducted in a psychiatric inpatient unit (Boyo Villanova Hospital, Zaragoza, Spain). All the discharge reports in 2006 were reviewed (1 January until 31 December, 2006) to identify all the patients treated with antipsychotics (136 in total) and to access their medical records to compile the following data: personal, socio-demographic, age of onset of disorder, previous admissions, diagnosis, duration of current hospital stay, and medication used. The ICD-10¹⁷ criteria were used for the main diagnosis and the comorbid diagnosis, these being classified into categories for ease of statistical analysis. The prescriptions of psychoactive principles were analysed, collecting all the possible combinations on admission and then after discharge. Subsequently, the data were classified according to the main indication (antipsychotics, antidepressants, anxiolytics, anticholinergics, and euthymic agents). The antipsychotics were further classified into: typical (TA), conventional; atypical (AA), 2nd/3rd generation; and according to the galenic formulation which determines the duration of their pharmacological action (prolonged release or depot antipsychotics). Research was carried out into antipsychotic polytherapy, defined as the use of 2 or more medications of the same type to treat the same

symptoms or disease in a single patient.¹ Lastly, research was conducted on polypharmacy, which is the combination of different groups of psychoactive drugs, and the nature of these combinations.

A descriptive statistical analysis was performed with SPSS program, version 12.0. To test the hypothesis in the statistical analysis, the significance level chosen was $P < .05$. Parametric tests were used when possible, whenever there was normal sampling distribution. The characteristics and design of the study do not meet the statistical conditions for directional relationships between variables to be established, but some tendencies were shown that could be the focus of studies with a controlled design.

Results

The sample of patients was mainly male, single, unemployed, with a low educational level, and they lived with their families (table 1). Many had been admitted to

Table 1 Socio-demographic data

n: 136		
<i>Age (years)</i>	Mean: 38.39 n	Range: 18-82 %
<i>Sex</i>		
Women	47	34.6
Men	89	65.4
<i>Occupation</i>		
Employed	26	19.1
Unemployed	36	26.5
Pensioner	58	42.6
Participating in government work scheme	3	2.2
No information	13	9.6
<i>Residence</i>		
Family	92	67.6
Residential care home	17	12.5
Assisted-living home	2	1.5
Alone	23	16.9
Other	2	1.5
<i>Academic level</i>		
Primary (up to 6 years)	81	59.6
Secondary (6-12 years)	24	17.6
Higher (over 12 years)	9	6.6
No information	22	16.2
<i>Marital status</i>		
Married	28	20.6
Single	94	69.1
Separated	11	8.1
No information	3	2.2

hospital on other occasions. The mean hospital stay of the group of patients was longer than the mean for the unit for the same year (22.1 compared with 17.88 days). The most common main diagnosis found in the patient sample under antipsychotic treatment was schizophrenia (44.9%), followed by bipolar disorder (14.3%), and acute psychotic disorder (11%). thirty-two percent of the patients had a comorbid diagnosis, notably disorders due to the use of psychotropic substances (16%) (table 2).

There was a high number of treatment variations and combinations carried out with active principles with an antipsychotic action (43 variations on admission and 47 on discharge). Risperidone was the most commonly used drug in monotherapy, and haloperidol the most common in combinations, both at the time of admission and discharge (fig. 1). As a group, AAs were the most commonly used drugs in monotherapy, both on admission (41.2%) and at discharge (36.8%). Few changes occurred in the prescription strategy during admission, but a tendency was observed to increase the use of AAs, both alone and in combination, and reduce the use of TAs. It is also worth pointing out the increase in the combining a depot antipsychotic with an AA (table 3).

Two or more antipsychotics were prescribed to 44% of patients on admission, rising to 51% at the time of discharge (fig. 2). There was a significant correlation

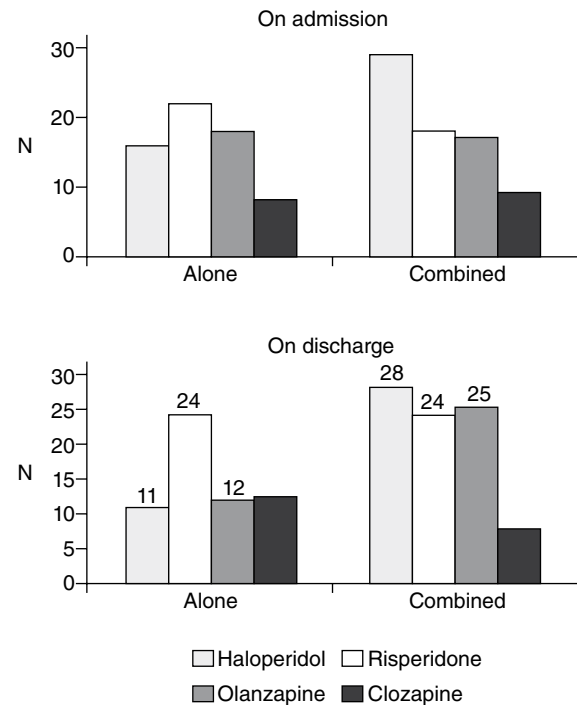


Figure 1 Main active principles used on admission and at discharge.

Table 2 Clinical variables

Age at onset (years)	Mean: 24.1 n	Range: 3-54 %
<i>Previous admissions</i>		
Yes	100 (mean: 2.7; mode: 2)	73.5
No	36	26.5
<i>Duration of disorder (years)</i>	Mean: 13.92	Range: 0-59
<i>Duration of current admission (days)</i>	Mean: 22.21	Range: 2-113
<i>Type of disorder</i>	n	%(of total)
Affective psychosis	22	16
Psychotic depression	3	2.2
Bipolar, depressive phase	6	4.4
Bipolar, manic phase	13	9.6
Schizophrenia	61	44.9
Schizoaffective	11	8.1
Acute psychosis	15	11
Other psychoses	27	19.8
Unspecified	12	8.8
Delirious disorder	6	4.4
Drug abuse	9	6.6
<i>Comorbid disorder</i>		
Psychoorganic syndrome	17	12.5
Personality disorder	3	2.2
Drug use disorder	22	16.2
Compulsive gambling	1	0.7
Mentally retarded	1	0.7

Table 3 Type of antipsychotic medication used (at onset and at time of admission)

Type of antipsychotic	Onset %	Discharge, %
Typical antipsychotic (1 st generation / conventional)	13.2	10.3
Atypical antipsychotic (2 nd and 3 rd generation)	41.2	36.8
Typical antipsychotic+typical antipsychotic	5.1	1.5
Typical antipsychotic+atypical antipsychotic	17.6	20.6
Atypical antipsychotic+atypical antipsychotic	8.8	8.1
Depot	0.7	0.7
Depot+typical antipsychotic	2.9	5.9
Depot+atypical antipsychotic	2.9	11
Depot+atypical antipsychotic+typical antipsychotic	3.7	4.4
None	3.7	0.7

($P=.03$) between the use of more than 1 antipsychotic and a diagnosis of schizophrenia (fig. 3). The use of depot antipsychotics was significantly correlated with: the use of more than 1 antipsychotic drug ($P<.001$); a longer hospital stay ($P=.031$); a diagnosis of schizophrenia ($P=.048$); and with taking psychoactive substances as a comorbid diagnosis ($P<.001$).

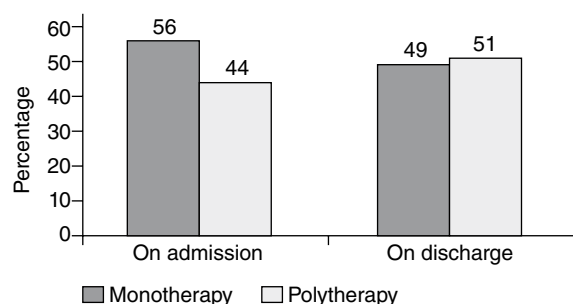


Figure 2 Antipsychotic polytherapy.

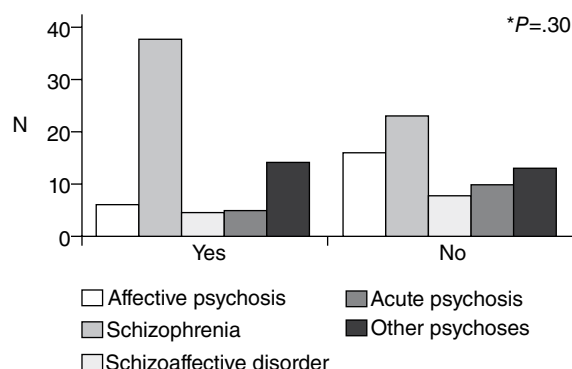


Figure 3 Antipsychotic polytherapy and main diagnosis.

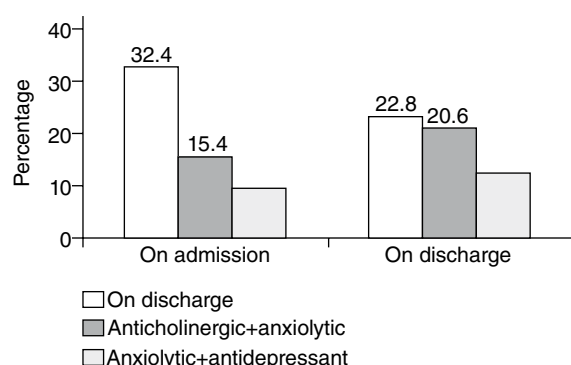


Figure 4 Type of additional psychotropic medication.

With many patients, other non-antipsychotic drugs were used simultaneously (polypharmacy), their use increasing during admission (from 84.6% to 87.5%). This group included different combinations of anxiolytics, antidepressants, anticholinergics, and euthymic agents. Anxiolytics were the most used drugs, and anticholinergics those that had the greatest increase in use during admission (fig. 4).

Discussion

Antipsychotic drugs are used in various diagnostic categories in which symptoms to be treated can appear. As expected,

they are most commonly used with schizophrenic patients, who have high comorbidity rates, mainly due to consuming drugs of abuse.

The prescriptions of active principles alone or in different combinations lead to a large number of treatment variations, both at the time of admission and on discharge. In our opinion, one of the determining factors of this practice is the difficulty in treating a set a complex, heterogeneous disorders which have the presence of psychotic symptoms in common, something which we can find in other medical specialities.¹⁰ Among active principles, risperidone is the most widely used in monotherapy, becoming one of the first choice drugs, together with olanzapine.⁵ The use of haloperidol is significant, above all in combination with other antipsychotics. In our opinion, its use profile makes it suitable for potentiating the antipsychotic action of other drugs. Its use is not such a preposterous idea in the light of the results of the 2 most important, non-commercial studies that compare first and second generation antipsychotics (CULASS and CATIE).¹⁸

With over 40 prescription variations in a sample of 136 patients, the information was difficult to manage, so the data was grouped into more workable categories. Second generation antipsychotics are the most used, both in monotherapy and in combinations, thus confirming that it is the main treatment option in our setting.¹⁶

In our opinion, another factor influencing the use of polytherapy is patient load and its repercussions on the length of stays in acute units. There are more combinations at the time of discharge, which we believe is an attempt to ensure clinical stability which can be fragile at times.²³ In most western countries during the last 40 years, we have witnessed policies designed to reduce hospital stays and the number of hospital beds, looking to return psychotic patients to the community quickly.²⁰ This has undoubtedly had beneficial effects; it has not only improved these patients' quality of life, but it has also reduced their dependency on medication, and lowered mortality.²¹ However, there are less positive data, including increases in suicide and criminal acts by psychotic patients, and an 80%-100% increase in admissions to acute wards.²²

During admission there is a tendency to increase the combinations of 2nd generation antipsychotics with TAs, and long-acting antipsychotics with AAs. We think the combination of an AA with a TA at the time of admission has the theoretical advantage of increasing the occupancy of dopamine D₂ receptors, and may have clinical benefits (greater potency and faster onset of action).¹⁴ There are 2 basic strategies in the acute phase: the use of a typical or conventional antipsychotic to "lead in" to the initiation of AA administration, or the isolated use of a TA to "top up" an AA.² In both cases, experts recommend a return to monotherapy as soon as the patient's condition is stable.¹⁹ Biancosino et al⁶ found that the strongest predictor of polytherapy at discharge is having started it on admission. If in addition a high percentage of patients receive polytherapy for long periods of time,^{3,16} we have to think that this is a deliberate choice of treatment, rather than a temporary practice.⁶

The data obtained confirm the null hypothesis that antipsychotic polytherapy is common practice, particularly

in schizophrenic patients, and is far from being the marginal situation that is claimed in most articles. The figures are similar to those found in the USA (50% Tapp et al, 2003²⁴), Europe (47% Rittmannsberger et al, 1999²⁵), and lower than those found in Spain (73% in Badajoz, Kivet et al, 1995²⁶); the figures always refer to hospitalised patients. The figures are lower in outpatients (15%⁴-27%⁶).

In our study, the figures for non-antipsychotic medication used in combination with antipsychotic drugs exceed comorbidity figures and, therefore, their use should be extended to the treatment of isolated symptoms or side effects. This is a complex reality to study. Most diagnostic categories in psychiatry do not have proven validity as they are not discrete entities with natural limits and it is common to find comorbidities that would justify the use of as many treatments as there are diseases in a patient.²⁷ Furthermore, there is a certain amount of confusion in the classification of psychiatric drugs, depending on the criteria used (chemical structure, clinical effects, pharmacodynamics). Due to their complex mechanism of action which targets several groups of receptors, some active principles could themselves be considered polypharmacy, as they are indicated for several disorders.²⁸

There are several limitations to this study. Firstly, the data were collected in one single healthcare unit, so differences may exist with others in terms of practice, protocols, and even the type of patients. Secondly, this is an observational retrospective study so this may have led to bias when assigning patients to groups and in their correlation with the variables investigated. Due to the specific conditions of the study, data could not be collected about the mean doses of antipsychotics, side effects, or the reasons for changes in drugs. Lastly, it was not possible to find standardised assessment scales. All of this limits the possibility to interpret and provide reasons for the results obtained, and to make generalisations based on them. However, we think the figures found for patients in polytherapy are very significant, and they coincide with those found in other studies.

The use of polytherapy should not be a first choice or generalised practice; on the contrary, it should be based on protocolised therapy, like that proposed by some authors (duration, type of combination, time of use, periodic checks, and reassessment of indications).² The importance of this problem has led to the development of specific strategies aimed at reducing polytherapy, and using it sensibly. Patrick et al²⁹ designed a programme aimed at reducing the use of polytherapy in a psychiatric hospital using a low-intensity individualised supervision of the prescriptions made up by the head of the department (without sanctions or positive reinforcement). They achieved a 10% reduction in polytherapy, higher than that of standard interventions (training and educational programmes about prescribing antipsychotics). Tucker³⁰ proposes systematising the use of antipsychotics using a computer program which makes it possible to quickly and easily find out the treatment records of his patients and those of his colleagues. This program, together with the application of a healthcare model for chronic diseases (including non-pharmacological strategies), obtained a reduction in polytherapy and economic costs.

In short, defining appropriate psychopharmacological prescribing is a complex task involving clinical, pharmacological, social, and economic considerations. Some people consider it to be a concept as complex as health itself.¹⁰

Conclusions

The null hypothesis was confirmed: polypharmacy is a common phenomenon, above all in schizophrenic patients and when depot antipsychotics are used. We believe it can be justified in therapy-resistant cases, provided it is used with sense and care. Second generation antipsychotics as a whole, have strengthened their position as the first therapeutic option with the significant use of haloperidol in combination.

Lastly, we would like to endorse Villagrán and Luque's proposal: "a sign of the quality of a department treating schizophrenic patients must be the degree to which combined treatment is used, and if it follows reasonable guidelines. This is the only way for evidence and eminence to achieve the desired balance when it comes to clinical decision-making".²

Conflict of interests

The authors affirm that they have no conflict of interests.

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