Original

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Clinical and therapeutic characterization of a portuguese sample of patients with schizophrenia

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Introduction. The development of Mental Health policies for psychiatric disorders should be driven by a correct knowledge of the socio-demographic, clinical and therapeutic realities of the disease. There is paucity of detailed studies in the Portuguese population that does not allow a direct comparison with other European countries. The objective of the present study is to characterize the sociodemograhic and clinical characteristics of schizophrenia patients in Portugal and the therapeutic patterns.

Methods. This multicentric, cross sectional, non interventional study was designed to describe the demographic and clinical data of patients with schizophrenia (n=474), and also the demographic and professional characteristics of their treating psychiatrists.

Results. The most frequent diagnosis found was paranoid schizophrenia (54%), with comorbid psychiatric conditions in 39,7% and somatic diseases in 28.4% of the patients. About half the patients were on second generation antipsychotics (SGS) as principal therapy, although haloperidol has been the most frequent drug prescribed as so (35.9 %). 59.51 % of the patients were on antipsychotic monotherapy, and 45% on a depot formulation. Antipsychotic dose vary widely, and they are quite often prescribed on off label doses.

Discussion. Our sample is similar to others found in naturalistic studies, however slightly different from clinical trials. In general, patients with schizophrenia tend to be treated with SGA, although have a higher chance to be on a long-term formulation and to be on polytherapy than in other studies. Somatic diseases are maybe under diagnosed and are undertreated.

Caracterización clínica y terapéutica de un muestreo portugués de pacientes con esquizofrenia

Introducción. El desarrollo de las políticas de salud mental sobre trastornos psiquiátricos graves debe llevarse a cabo con un conocimiento adecuado de las realidades socio-demográficas, y clínicas de los padrones de prescripción. En Portugal, los estudios epidemiológicos no tienen un nivel de detalle que haga posible una comprensión profunda de este fenómeno. En la población portuguesa que sufre esquizofrenia hay una carencia de estudios en profundidad que limitan su comparación con otros países europeos. Este estudio ha sido diseñado con el objetivo principal de conocer la práctica clínica habitual y las características de la esquizofrenia en Portugal.

Método. Se trata de un estudio observacional, descriptivo, transversal y multicéntrico, con datos recogidos en la práctica clínica corriente. Se han analizado un total de 474 pacientes.

Resultados. El diagnóstico más frecuente la esquizofrenia paranoide (54%), de severidad moderada, con frecuentes complicaciones psiquiátricas (39,7%) y somáticas (28,4%). El 48,6% de los pacientes presentaban consumo de drogas. Aproximadamente la mitad de los pacientes tomaban antipsicóticos atípicos como tratamiento principal, aunque el haloperidol fue el medicamento prescrito con más frecuencia (35,9%). El 59,51% de los pacientes estaban siendo tratados en monoterapia antipsicótica y el 45% con una formulación de larga duración inyectable.

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Las dosis de los antipsicóticos eran muy variables y con frecuencia fuera de la indicación autorizada. El 37,9% de los pacientes tenían terapia concomitante no farmacológica.

Conclusiones. Los pacientes presentan características sociodemográficas similares a las de otros ensayos clínicos naturalistas, pero diferentes de los ensayos clínicos con fármacos. En general, los pacientes se tratan con antipsicóticos atípicos, aunque un gran porcentaje prosigue con formulaciones de liberación lenta en terapia de combinación con dos o más antipsicóticos, en cifras mayores que en otros estudios similares. Las enfermedades somáticas quizás se infradiagnostican o se tratan de manera insuficiente.

Palabras clave:
Esquizofrenia, Portugal, demografía, tratamiento, epidemiología.

INTRODUCTION

Mental Health policies regarding schizophrenia and its allocation of resources have been a matter of debate in recent times, as direct and indirect costs are enormous. These policies must be developed based on a correct knowledge of the reality. The Portuguese Censo Psiquiátrico 2001[1] (Portuguese Psychiatric Census 2001) is a solid and rigorous epidemiological work. However, the data generated are mainly epidemiogical, and do not have an optimal level of detail. Although many studies have been published in the literature regarding the socio-demographic and clinical characteristics of patients suffering from schizophrenia, we were not able to find any such study published in Portugal.

Furthermore, having knowledge of the therapeutic patterns can also be quite important in order to develop Mental Health policies. Indeed, the management of this disorder has changed since the introduction, in recent years, of second-generation antipsychotics (SGA). These drugs have clearly improved the therapeutic approach to this disorder.[2] In fact, when the SGAs are compared to first-generation antipsychotics (FGA), a lower probability of inducing extra pyramidal-symptoms (EPS) is clearly found and it also seems to have other advantages in regards to hyperprolactinemia and beneficial mood effects. Although numerous trials have favored SGA as a first-line drug therapy in patients with schizophrenia, and these findings have been translated into guidelines by many important agencies, controversies and discrepancies on its advantages still exist.[3, 4]

These controversies may also be caused by the difficulties found when translating these very well-designed trials into the clinical practice. The increasing number of the so-called "naturalist studies" in psychiatry may also reflect these difficulties. Although we were not able to find direct comparative studies in the literature on how psychiatrists translate these guidelines into the clinical practice and on their perception of the pattern of adherence, they are probably country specific.

Even though some of these issues have been addressed in other populations, we have not found any similar studies in the literature within the Portuguese population. Furthermore, it seems that in addition to the cultural and social differences, the Portuguese population has some particularities, in regards to social and genetic aspects of schizophrenia.[5] No studies were found on the literature on how Portuguese psychiatrists treat patients with schizophrenia.

The objective of the present study has been to characterize the therapeutic patterns and the sociodemograhic and clinical characteristics of schizophrenia patients in Portugal.

Such a detailed characterization is clearly an unmet need. It would provide data for developing evidence-based Mental Health policies and for further studies in this field.

MATERIAL AND METHODS

This multicentric, cross-sectional, non-interventional study was designed to describe the frequency and characteristics of the pharmacological prescription of patients with schizophrenia. This study was performed between August 2004 and August 2005.

Eligible patients, aged 18-years and older, were required to fill out the Diagnostic and Statistic Manual IV (DSM-IV) criteria for schizophrenia. Patients who had been prescribed pharmacological treatment in the last 6 months were selected from the private or public outpatient clinics. Written consent was obtained before their enrolment in the study. The Ethics Committees were notified and a submission process was conducted when required and the necessary approvals obtained.

The primary study objective was the description and comparative descriptions of the main antipsychotic therapy in regards to the distributions, doses and administration route. A description of other concomitant antipsychotics, other psychotropic medications, duration, discontinuation and adherence to the main antipsychotic drugs, adverse events and non-pharmacologic therapy was also made.

Secondary objectives were the comparison and descriptions of patients with schizophrenia (demographic

Table 1	Past and current substance consumption							
	Alcohol	Tobacco	Cannabis	Opioids	Cocaine	Hallucinogens	Amphetamines	Other
Current substance consumption	16.8% (80)	41.8% (199)	1.8% (20)	0.4% (2)	0% (0)	0.2% (1)	0% (0)	1.7% (8)
Past substance consumption	39.1% (194)	47.7% (227)	31.6 (93)	6.1% (29)	4.6% (22)	2.7% (13)	3.4% (10)	2.7% (13)

Table 2	Socidemographic and clinical characteristics of the sample, indicated as % of the total sample				
Age of diagnosis	24.9±7.33 (10-65)				
Duration of illness	<1 year 3.0% (14)		1-5 years 13.2% (61)		<5 years 83.7% (386)
Number of previous admissions	1.2±0.5 (1-3)				
Time from last admission	69.0±93.73 (0-612) months				
Schizophrenia familiy history	Yes 23.2% (100)				
Adverse events	EPS and TD 23% (107)	Fatigue and somnolence 15% (73)	Weight gain 23.3% (111)	Dry mouth 15% (72)	Sexual dysfunction 8% (38)	Other (n=145)
Psychiatric comorbidities	Depression 15.8% (75)	Anxiety* 14.7% (70)	Cognitive deficits 34.0% (162)	Sleep disturbances 11.8% (56)	Personality disorders 4.0% (19)
Somatic comorbidities	Hypertension 6.9% (33)	Hypercholesterolemia 9.0% (43)	Hypertriglyceridemia 6.3% (30)	Diabetes 4.2% (20)	Other 9.9% (47)
Other psychiatric medications	Benzodizepines (incl. Zolpidem) 63.7%	Anticholinergics 45.8% (218)	Antidepressants 20.6% (98)	Antiseizures 8.8% (42)	Other 1.9% (9)
Treatment Adherence	Good 85% (395)		Regular 12%		Bad 2.2% (22)
Other medications	Anti-hypertensive 1.9% (9)	Antidyslipidemia 1.5% (7)	Antidiabetics 1.9% (2)	Antiulcer 1.7% (9)	Other 2.1% (10)
Non pharmacological treatment	Occupational therapy 18.5% (88)	Individual psycotherapy 12.0% (57)	Rehabilitation 8.4% (40)	Community support 8.2% (39)	Psychopedology 2.9% (14)	Other psychotherapy (group and familiy) 1.9% (9)

Legend: Indif Indifferenciated, TD tardive dyskinesia, EPS extrapyramidal symptoms, NA not applicable, because it is the sum of several events that can be present in more than one individual, *Anxiety includes anxiety (symptom), all types of phobia and obsessions.

and clinical data) and of their attending psychiatrists (demographic and professional characteristics).

All the statistical analyses were performed using the SAS version 9.1, according to Altman methodology. A descriptive approach was used for a general description of the data. In the comparative analysis of the principal pharmacological therapies, either a chi-square (for categorical variables) or a Kruskal-Wallis test (for numeric variables) was performed. The Kruskall-Wallis test was performed after confirming deviations to the normality and homogeneity of variances.

Table 3	The sociodemograhic characteristics of the Psychiatrists			
Sex	Male 53.3% (16)		Female 46.7% (14)	
Age	44.57±9.1 years old			
Region	Alentejo 6.7% (2)	Algarve 3.3% (1)	Center 16.7% (5)	Lisbon and Taje Valley 26.7% (8)	North 46.7% (14)
Working status	Public practice 72.4% (21)		Private practice 27.6% (8)	
Years of experience	9.0±6.1 (1-26) after becoming a specialist			

Table 4	Frequencies and doses of antipsychotic therapy

Drug	Patients using drug as principal therapy		Doses of antipsychotic therapy (mg/day), or equivalent		
	%	n	n	Mean±sd	Max–min
Haloperidol	35.9	171			
Haloperidol (oral)			95	14.55±18	1–150
Haloperidol (depot)			156	27.43±13.9	2.5–75
Risperidone	17.4	83			
Risperidone (oral)			126	4.72±2.36	1–14
Risperidone (depot)			6	17.71±4.7	12.5–25
Olanzapine	16.2	77	113	13.66±6.52	5–30
Clozapine	6.1	29	44	177.95±139.94	10–650
Phluphenzaine	6.1	29	44	13.31±12.2	0.25–66.7
Quetiapine	4.4	21	30	533±248	100–1000
Amisulpride	3.6	17	37	358.16±208.91	2–900
Zuclopenthixol	3.2	15			
Zuclopenthixol (oral)			5	129±97.4	15–200
Zuclopenthixol (depot)			16	68.75±24.81	33.33–133.33
Ziprasidone	1.9	9	15	119±46	40–180
Aripiprazole	1.1	5	6	17±7	10–30
Flupentixol	1.1	5			
Flupentixol (oral)			2	4.5±2.12	3–6
Flupentixol (depot)			6	18.61±11.85	4–33.33
Other FGA	1.8	9			
Other SGA	0.2	1			
Combinations	1	5			
FGA total	48.1	229			
SGA total	50.8	242			
Undefinied	1.1	5			

SAMPLE DESCRIPTION

A total of 478 patients were enrolled. However, the principal therapy could not be identified in 2 of them so that all the data presented refer to 476 patients. The majority of the patients were male (72.5%) with a mean age of 43 years. Most of the patients were single (73.5%), living with their father and/or mother (30% and 40%, respectively), were retired (57.4%), and belonged to a low social-economic class (Graffar III- IV 43.3%). Mean education years found was 7.5; 22.5% of patients lived permanently in Psychiatric Hospitals.

Clinically, the most frequent diagnosis found was paranoid schizophrenia (54%), of moderate severity (39.7%), lasting for 5 or more years in 87% of the patients. The mean age of diagnosis was 24.9 years and for first admission 28.4 years. Mean number of admissions was 1.29, and the severity of illness, ranging from 1 (less severe) to 5 (most severe) has been classified as 3.03 (mean). No family history for schizophrenia was found on 76.8% of the patients.

Almost half of the individuals reported substance consumption (48.6%), mainly tobacco (41.8%), alcohol (16.81%), and cannabis (1.8%). In the past, however, these figures were higher, as more than 60% of patients reported substance consumption, mainly tobacco (47.7%), alcohol (39.1%), cannabis (19.5%), and others (Table 1).

More than two thirds of the patients had psychiatric comorbidities, especially cognitive deficits (34.0%), depression (15.8%), anxiety and anxiety disorders (19.7%) and sleep changes (11.8%). Somatic diseases were described in 28.4% of the patients, mostly (26.5%) cardiovascular risk factors (hypertension, diabetes, hypertrygliceridemia, and hypercholesterolemia). A detailed description can be seen in Table 2.

PSYCHIATRIST'S CHARACTERIZATION

Thirty psychiatrists participated in the study. Their demographic characteristics are detailed on Table 3.

THERAPY DESCRIPTION

59.51 % of the patients were taking antipsychotic monotherapy and the rest were taking two or more of these drugs concomitantly. About 50% of the patients were prescribed an SGA as principal therapy, although haloperidol was the most frequent drug prescribed as such (35.9 %), followed by risperidone (17.4 %) and olanzapine (16.2 %). However, haloperidol is mostly prescribed as a *depot* formulation (32.8% of all patients). Almost 45% of patients were taking a *depot* formulation.

Antipsychotic doses vary widely and they are very often prescribed as off label doses. It is noteworthy that clozapine and ziprasidone were the only SGAs prescribed within the officially approved range, with clozapine clearly under the maximum allowed dose. A detailed prescription can be seen in Table 4.

Benzodiazepines were the most common psychotropic medication prescribed as cotherapy (68.7%), followed by antidepressants (29.5%). A total of 34.3% of the patients were medicated with anticholinergics. Only one patient was taking lithium and none were receiving electroconvulsive therapy.

A total of 37.9% of patients were receiving non-pharmacological therapy, mostly occupational therapy (46.4%), individual psychotherapy (31.23%), rehabilitation (31.3%), and others.

The most common adverse events (AE) considered were weight gain (42.7% of all AE), extrapyramidal symptoms (38.7%), dry mouth (27.7%), and blurred vision (8.8%).

In the inferential analysis, some statistical positive and negative associations have been found between the principal therapy and some demographic and clinical data.

Typical antipsychotics were positively associated with an older age.

Some clinical features were found to be statistically associated to the principal therapy, namely schizophrenia subtype, illness duration, number of previous admissions and the time from previous admission. A positive correlation was also found between the presence of extrapyramidal symptoms (and the probability of being treated with anticholinergic dugs), weight gain and the principal therapy.

Fewer years of education, the presence of cognitive deficits, a higher percentage of insight regarding the disease, and longer time from last admission have all also been associated with the principal therapy.

DISCUSSION

We report herein the description of the therapy in a naturalistic setting of a large sample of patients suffering from schizophrenia.

Due to the large amount of information obtained, it is difficult to make a comparison regarding all the data published in the literature. The data from the present study will be compared with very similar observational studies and with large and important studies.

This study sample, consisting of consecutive patients suffering from schizophrenia and receiving treatment for that condition is clearly non-restrictive when compared to the clinical trials population. The sociodemographic characteristics of the sample under study do not greatly differ from other descriptive studies from Spain[3] and France.[6] The typical patient is a man, with average age 40 years, single, not working, and living within a family setting. These characteristics are also similar to the results of the Censo Psiquiátrico 2001[1]. These results probably mean that the non-restrictive inclusion and exclusion criteria yielded a group of patients quite similar to real life.

Clinically paranoid, undifferentiated, and residual schizophrenia accounts for almost 90% of the cases. These values are similar to the data published in similar studies.[3]

Substance consumption is a well-known occurrence in patients suffering from schizophrenia. Theses results probably tend to underestimate the real consumption, although they are quite high and are within the range published in the literature: 21-45%.[7, 8] Unfortunately, we have not been able to distinguish between consumption, abuse and dependence.

The clinical and demographic characteristics of the present sample are not very different from a large clinical trials sample, such as CATIE study.[9] In CATIE study, the most common patient is male (70%), mean age 41±11 years old, mean education years 12±2.1, single 59%, 85% unemployed, and presenting other diseases in the last 5 years: depression (28%), alcohol abuse/dependence (25%), drug abuse/dependence (29%), and anxiety disorders (except obsessive-compulsive disorder) (14%).

The reported prevalence of somatic comorbidities is much lower than the one found in other studies. CATIE study[9] found a prevalence of diabetes, hyperlipidemia and hypertension of 11%, 14%, and 20%, respectively. However, extensive reviews found much higher values: high glucose prevalence of 17 or 29% (depending on the method), low HDL-cholesterol 58.6% and of high fasting triglycerides 41.4%.[10, 11] These values clearly need to be studied in greater depth as they could mean that, for some reason, the Portuguese population with schizophrenia is more resistant to cardiovascular disorders and to diabetes. On the other hand, the Portuguese Health Services may possibly be underdiagnosing these diseases in this specific patient population. Furthermore, apparently only 12 to 30% of the patients presenting these disorders are actually being treated for these serious conditions. Physical comorbidities account for 60% of premature deaths in schizophrenia.[12] The reasons for these discrepancies have been studied and they may be related both to health care providers (e.g., lack of adequate follow-up for these patients by non psychiatric doctors) and to the patient/disease (e.g., low recognition of physical symptoms by patients).[12] In any event, immediate actions are warranted to understand and solve these discrepancies.

The perception of treatment adherence is clearly high, as most psychiatrists think their patients are compliant with the treatment. Although several reports state that more two thirds of the patients with schizophrenia are non-compliant and that the psychiatrists do not acknowledge this reality,[13-14] the majority of the current sample was receiving long- term formulations. Thus, this perception of high treatment adherence probably relies on the high number of patients on intramuscular long-term formulations.

About 60% of the patients were on monotherapy, revealing that many patients cannot be appropriately treated with a single-dose regimen. When compared with other similar studies, schizophrenia patients in Portugal tended to show slightly lower rates of antipsychotic monotherapy. French, Spanish, and IC-SOHO studies yielded monotherapy rates of 65%,[3] 64%,[6] and 76%,[15] respectively. Antipsychotic monotherapy is a common guideline,[16] and has clear advantages over polytherapy. However, these cross-country high rates of antipsychotic polytherapy commonly found on clinical practice make it necessary to reflect on the real effectiveness of antipsychotic monotherapy for schizophrenia.

Interestingly, the majority of the patients have also been prescribed an SGA as principal therapy, indicating a concordance between the prescription pattern and the majority of the guidelines In the Spanish study, 82% of the patients were treated with SGA, although it was not indicated if this was considered the principal therapy.[3] Much lower data were found in France as only 40% of patients with schizophrenia were treated with a SGA.[6]

Obviously, no relationship can be concluded between the utility or validity of the guidelines and this prescription pattern. This is a descriptive study so that it is not possible to obtain causality relationships.

As stated before, the dose range for prescription of antipsychotics varies greatly and sometimes clearly exceeds the recommended range. This probably means that some patients need higher doses than those recommended for a therapeutic effect. Curiously, clozapine has been one of the exemptions as it has never been used above 650 mg. Clozapine is indicated in refractory schizophrenia, a subgroup of patients that usually require high doses. This issue seems to be country-specific as clozapine is clearly prescribed in higher doses in England and in France: mean dose 427 mg[17] and 422 mg (100-900 mg),[18] respectively and in IC-SHO study it is lower: mean between 150 and 230 mg.[15]

When other psychiatric diseases are compared with the drugs prescribed, it seems that benzodiazepines and antidepressants are prescribed for other indications than anxiety/

insomnia and depression, respectively. Antidepressants may be used for negative symptoms. However, it is not clear why benzodiazepines are so commonly prescribed, as anxiety and sleep related problems only account for 37% of all psychiatric co morbidities. The use of anticholinergics probably reflects the use of typical antipsychotics. Antiepileptic drugs are probably used for mood or impulse control, although the current study cannot distinguish between them. It is surprising that lithium and electroconvulsive therapy are hardly, if not at all, used.

Only 38% of patients are submitted to non-pharmacological therapy, something that is clearly beyond that of other countries and this will probably change in the next few years.

In regards to the statistical correlations found, no cause-effect relation can be obtained. As stated before, this has been an observational study, and the relationship can be inverse or there may be other reasons for the association (e.g. typical antipsychotics are mostly observed as prescriptions in residual schizophrenia). It cannot be concluded that FGA causes residual schizophrenia or that residual should be treated with these agents. This relationship is probably complex, involving historical reasons: old, residual patients have probably been taking these FGA for a long time and negative symptoms parallel the natural course of the disease and the prescription of these agents.

To our knowledge, this is the first detailed observational study published involving a large number of Portuguese patients suffering from schizophrenia. Although simple, the design was strong and the study was generally well conducted. Important limitations were the observational design, that prevented the establishment of cause-effect relations, and the generation of data by report, that tends to be less reliable than a direct confirmation. A selection bias can be argued, as only motivated psychiatrists participated in the study. However, our results are not different from the epidemiological studies performed in Portugal.

In conclusion, the present study characterized the demographic, clinical and therapeutic pattern of patients with schizophrenia in Portugal. We consider that the most important finding is that our sample is similar to others found in naturalistic studies but different from clinical trials. In general, patients with schizophrenia tend to be treated with SGA, although they have a greater likelihood of being treated with a long-term formulation and to receiving polytherapy (antipsychotics and other). Somatic diseases may be underdiagnosed and undertreated.

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