Analysis of prescription patterns of antipsychotics agents in psychiatry

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Introduction. Wed describe the different diseases in which conventional and second generation antipsychotic (APS) prescriptions are made.

Method. Observational, retrospective, multicenter study based on the review of 300 clinical records of public and private sites, hospital and out-patient clinics, located in Salamanca, Vigo, Bilbao, Barcelona, Valencia, Oviedo and Malaga.

Results. The mean age of the population studied was 42 ± 17 years; 56.6 % were men. Atypical drugs (67 %) were used basically versus classical ones (33 %). Classical APS are basically prescribed in bipolar disorder with/without psychotic symptoms (20.6 %), schizophrenia (18.3%) and delusional disorder (11.5 %). Atypical APS are fundamentally prescribed in schizophrenia (31.5 %), bipolar disorders with/without psychotic symptoms (12.5 %) and other psychotic disorders (8.9 %). When the psychotic disorders are considered by groups (schizophrenia, bipolar disorder with psychotic symptoms, delusional disorder and other psychotic disorders), classical APS are used in 47.4 % and atypical APS in 62.5 %. APS were used «outside the indication» (off-label) in 32.8 %, including resistant depressions, serious obsessive-compulsive disorder and borderline personality disorder, with similar percentages for both conventional and atypical ones. In dementia, atypical APS were used in 5.1 % versus 1.5 % of the conventional ones. The most frequent reasons for prescription of classical APS were control of psychotic symptoms (33.6 %), aggressiveness-agitation (31.3 %), severe insomnia (16 %), impulsivity (6.9 %) and severe anxiety (6.1 %). Atypical APS were preferably used in the control of psychotic symptoms (58.8 %) and aggressiveness-agitation (25.5 %).

Conclusions. The use of APS basically occurs within their authorized indications (67.2 %). The off-label use (32.8 %) occurs both for the classical as well as atypical APS and occurs in serious diseases in which there are no alternative treatments.

Key words:
Antipsychotic. Bipolar disorder. Schizphrenia. Psychotic disorder.

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Análisis de los patrones de prescripción de antisicóticos en psiquiatría

Introducción. Se describen las diferentes patologías en las que se realizan prescripciones de antipsicóticos (APS) convencionales y de segunda generación.

Método. Estudio observacional, retrospectivo, multicéntrico, basado en la revisión de 300 historias clínicas de centros públicos y privados, hospitalarios y ambulatorios, localizados en Salamanca, Vigo, Bilbao, Barcelona, Valencia, Oviedo y Málaga.

Resultados. La edad media de la población estudiada fue de 42 ± 17 años; el 56,6 % eran varones. Se emplearon fundamentalmente atípicos (67 %) frente a clásicos (33 %). Los APS clásicos se prescribieron fundamentalmente en el trastorno bipolar con/sin síntomas psicóticos (20,6 %), esquizofrenia (18,3 %) y el trastorno delirante (11,5 %). Los APS atípicos se prescribieron fundamentalmente en esquizofrenia (31,5 %), trastorno bipolar con/sin síntomas psicóticos (12,5 %) y otros trastornos psicóticos (8,9 %). Considerando los trastornos psicóticos agrupadamente (esquizofrenia, trastorno bipolar con síntomas psicóticos, trastorno delirante y otros trastornos psicóticos) se utilizaron APS clásicos en el 47,4 % y APS atípicos en el 62,5 %. Se utilizaron APS «fuera de indicación» en el 32.8 %, incluyendo depresiones resistentes, trastorno obsesivo compulsivo grave y trastorno límite de la personalidad, con porcentajes similares, tanto de los convencionales como de los atípicos. En demencia se emplearon APS atípicos en un 5,1 frente a 1,5 % de los convencionales. Los motivos de prescripción más frecuentes para los APS clásicos fueron el control de síntomas psicóticos (33,6 %), agresividad-agitación (31,3 %), insomnio severo (16 %), impulsividad (6,9 %) y ansiedad severa (6,1 %). Los APS atípicos se utilizaron preferente-

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mente en el control de síntomas psicóticos (58,8 %) y agresividad-agitación (25,5 %).

Conclusiones. La utilización de APS tiene lugar fundamentalmente dentro de las indicaciones para los que están autorizados (67,2%). El uso «fuera de indicación» (32,8 %) se da de forma similar tanto para los APS clásicos como para los APS atípicos y se produce en patologías graves en las que no se cuenta con tratamientos alternativos.

Palabras clave:
Antipsicóticos. Trastorno bipolar. Esquizofrenia. Trastornos psicóticos.

INTRODUCTION

On the contrary to the classical antipsychotics (APS) (haloperidol, chlorpromazine, etc.), second generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, amisulpride and aripiprazole) have been sold in our country with more restricted therapeutic indications: more recently, schizophrenia and bipolar disorder. In contrast to the first years in the 1950's, where the APS data sheets included indications for very diverse and therefore unspecific generic psychiatric pictures, the new APS have authorization for very specific psychiatric diseases since controlled clinical trials are necessary to obtain administrative approval in each one of the diseases in which they are approved.

However, the scope of the use of the new APS overlaps with that of the first generation. Because they have fewer adverse effects, and above all less severity (extrapyramidal symptoms, acute dystonias, tardive dyskinesis), their prescription by the clinicians exceeds the narrow limit of their registered indications. On the other hand, a certain incoherence is seen in the use authorizations between the conventional and second generation ones, even though they largely share action mechanisms and that the latter have shown an efficacy profile that can be extrapolated to the conventional ones, with a clear improvement in tolerability, safety and relief of negative symptoms parameters of schizophrenia[1,2].

In general, the APS prescription guidelines in the daily clinical practice are based more on the symptoms present in a specific patient than on the diagnosis itself since, on many occasions, it may occur after treatment initiation. On the other hand, the diagnoses in psychiatry are presently based more on phenomenological criteria than physiopathological ones, with the limitations that this entails.

It is equally relevant to state that the evidence generated from controlled clinical trials show solid arguments in favor of the efficacy, but not the effectiveness, of a treatment when this is assessed under conditions that have little to do with the real conditions of its use in the daily practice. Thus, the strict inclusion and exclusion criteria that are commonly required in clinical trials generally leave out a significant part of the patients who, *a priori,* would have been included only based on their clinical diagnosis[3]. Due to this, the data obtained from the trial cannot be completely extrapolated to the general population[4].

Due to the wide range of symptoms that appear in the psychiatric population and that have benefited from treatment with an APS for years (delusions, hallucinations, aggressiveness, impulsivity, psychomotor agitation, extreme suicidal ideation, movement disorders, intense obsessive ideation, etc.), it is not strange that the prescription patterns in the daily clinical setting exceed the administrative therapeutic indications included in the data sheet both in the hospital as well as community practice[5,6]. It is also not strange that the last generation APS have slowly substituted the classical ones due to their greater efficacy in the negative symptoms and their unquestionable better tolerability[7,8].

These data reflect the paradox that even though the second generation APS have obtained a more reduced number of «administrative» therapeutic indications, they are used in the daily practice for the same indications as the classical ones, whether these have been approved by the corresponding certifying agencies or not[9]. In fact, the efficacy that these drugs may have in other diseases besides those officially approved is stated in a recent systematic review of controlled clinical trials on the *off-label* indications for second generation APS[10]. Thus, the possible efficacy of risperidone in the treatment of refractory obsessive-compulsive disorders, of certain development disorders and in the pathological stuttering and Gilles de la Tourettee syndrome is pointed out. On the other hand, the utility of olanzapine in the treatment of refractory depression and in borderline personality disorder is suggested.

According to the above, and given that there still is not sufficient information on the APS prescription patterns in our country, a multicenter, observational, retrospective study based on the review of clinical records of all those patients who had received an APS that could supply that knowledge to us was done.

The purpose of the study is to describe the different diseases and indications in which conventional and second generation APS are prescribed in the clinical practice in a sample of both hospital and out-patient Spanish psychiatric services and the public as well as private practice.

METHODS

Design

Observational, retrospective study of the prescription of APS based on the review of 311 consecutive clinical histories and selecting the last episode of patients treated during the last 6 months in the period January-June 2004. The study aimed to obtain information from 7 psychiatric sites of the country (Mental Health Care Sites, Hospital Sites of acute and chronic

patients and private out-patient clinics) located in Salamanca, Vigo, Bilbao, Barcelona, Valencia, Oviedo and Malaga.

Study population

The study population is made up of all the patients for whom a clinical history was opened during the last 6 months in the participating hospital and out-patient clinic sites. All those histories corresponding to an individual patient who had a prescription of at least one APS, whether first or second generation, and that had been prescribed as principal or concomitant treatment, were included. The data were obtained using a clinical care report form designed for this.

Principal assessment endpoints and measurement instruments

The following data were collected retrospectively: *a)* sociodemographic data: age and gender; *b)* data of care type: out-patient, hospital or both; public or private; *c)* primary and secondary diagnoses, if they exist, according to the ICD-10 international classification; *d)* antipsychotic(s) prescribed, dose and reason for prescription; *e)* other medications received by the patient (antidepressants, BZD, lithium, anticonvulsants and others); *f)* evolution time of the mental disorder (according to the items: *1.* first episode; *2.* evolution less than 5 years, and *3.* evolution greater than 5 years), and finally *g)* severity according to the 7-item Clinical Global Impression Scale-Severity (CGI-S).

Statistical analyses

A descriptive analysis of the frequencies of the different types of APS prescribed has been conducted —intergroup-classical versus atypical (and intragroup) for each one of the APS drugs collected, also calculating the mean dose in each case—. In addition, a descriptive statistical analysis has been conducted on the number of APS prescribed per patient, mean evolution time of the disease and concomitant medication in each case. An analysis of the distribution of frequencies in relationship with the entities diagnosed for which APS was prescribed and for the reasons that motivated this prescription was done. Finally, a simple descriptive analysis of the sociodemographic endpoints was conducted.

RESULTS

Patients

A total of 311 patients, mean age of 42.58 (SD: 17.81) years, 56.6% men and 43.4% women was included. In regards to the type of psychiatric care, this was done in public sites in 67.8% and in private ones in 32.2%. The care setting was in hospital regimen in 55% versus 45% in out-patient regimen.

Antipsychotic prescription pattern

Diagnostic entities and reason for prescription

The diagnostic entity for which APS was most frequently prescribed was schizophrenia (22.8%), followed by bipolar disorder, delusional disorder and other psychotic disorders. The global sum for the psychotic disorders group was 54.6%. The rest of the diagnoses, considered *off-label*, were borderline personality disorder, recurrent depressive disorders, dementia and anxiety disorders (table 1).

Regarding the reason for prescription, the most frequent was control of psychotic symptoms (51%), followed by control of aggressiveness-agitation, severe insomnia and impulsivity. The total reasons for prescription and their frequency is shown in table 2.

Type of antipsychotic used

In relationship with the type of APS, overall the atypical ones were prescribed more frequently than the classical ones (67% vs. 33%). A total of 78.14% of the sample took only one APS (n = 243); 19.29% (n = 60) required two, 2.25% (n = 7) three and 0.32% (n = 1) four. We did not find any patient with more than four antipsychotics.

Type of antipsychotic by setting and type of prescription

By setting of prescription, it is observed that both hospitalized and out-patients mostly received second generation APS (65.4% and 65.5% respectively). In regards to type of care, the preponderance of atypical prescription over classical ones was maintained in both public and private sites (68.8% and 60.5% of atypical prescription, respectively). It seems to be affirmed that the classical APS prescription values versus the atypical ones hardly vary in relationship with the type of site and type of care endpoints.

Type of antipsychotic by diagnostic entity and reason for prescription

The diagnostic entity for which classical APS are most frequently prescribed is bipolar disorder (20.6%), followed by schizophrenia (18.3%), delusional disorder (11.5%) and borderline personality disorder (7.6%) (table 1).

In regards to atypical APS, schizophrenia is the diagnosis having the most frequent prescription (31.5%), followed from a distance by bipolar disorder (12.4%), other psychotic disorders (8.9%), and to a lesser degree, borderline personality disorder (6.2%) delusional disorder (5.8%) and schizoaffective disorder (5.1%). Adding up all the disorders that occur with psychotic symptoms, the atypical APS were used more frequently (62.5%) than the classical ones (47.4%) (table 1).

Table 1 Diagnosis of the main prescription

Diagnostic group	Diagnostic entity	% use of APS	% use of classical APS	% use of atypical APS
Psychotic disorders	Schizophrenia (F20)	22.8	18.3	31.5
	Schizoaffective disorder (F25)	3.9	3.8	5.1
	Delusional disorder (F22)	7.7	11.5	5.8
	Other psychotic disorders (F21, F23, F24, F28 and F29)	9.0	6.9	8.9
Affective disorders	Bipolar disorder (F31) (mania and bipolar depression without psychotic symptoms)	8.0	14.5	6.6
	Bipolar disorder with psychotic symptoms (F31) (mania and bipolar depression with psychotic symptoms congruent or not with the mood state)	6.4	6.1	5.8
	Major depressive disorder, first episode (F32)	1.9	3.1	1.9
	Major recurrent depressive disorder (F33)	4.8	4.6	3.5
	Depressive disorder with psychotic symptoms (F32.3 and F33.3)	4.8	0.8	5.4
Anxiety disorders	Dysthmia (F34)	1.0	1.5	0.4
	Phobic disorders (F40)	0.0	0.0	0.0
	Panic disorder (F41.0)	1.0	2.3	0.0
	Generalized anxiety disorder (F41.1)	0.0	0.0	0.0
	Mixed anxiety-depressive disorder (F41.2)	0.3	0.0	0.4
	Obsessive compulsive disorder (OCD) (F42)	3.5	2.3	3.1
Personality disorders	Borderline personality disorder (F60.31)	7.4	7.6	6.2
	Other PD (F21 and F60, except F60.3)	1.6	3.2	1.2
Dementias (F00-F03)		4.5	1.5	5.1
Psychoactive substance use disorders (F10-F19)		1.3	1.5	1.2
Others		10.1	10.5	7.9

In relationship with the reason for prescription, classical APS were most frequently administered in control of psychotic symptoms (33.6 %), followed by aggressiveness-agitation (31.3 %). Severe insomnia (16 %), impulsivity (6.9 %) and severe anxiety (6.1 %) were found with much less frequency. The rest of the reasons for prescription do not exceed 3% in any of the cases (table 2).

In the case of atypical APS, control of psychotic symptoms was the most frequent reason for prescription (58.8 %), clearly superior to the prescription of classical APS for this purpose ($p < 0.001$). The second reason in frequency of prescription of atypical APS was control of aggressiveness-agitation (25.5). None of the reasons for prescription of the remaining atypical APS exceed 3 % (table 2).

Concomitant medication

The most frequently prescribed concomitant medications were benzodiazepines (72.3 %) followed by antidepressants (37.3 %), other mood stabilizer agents (18.6 %) and finally lithium (13.5 %) (table 3). Only 8.7 % received other medications, the anticholinergic agents (biperidene) being the most frequent for the correction of extrapyramidal effects secondary to some APS, above all in patients who took classical APS and risperidone. Other concomitant treatments are anticholinesterasics in the diagnosis of Alzheimer type dementia and β-blockers (propanolol).

DISCUSSION

It is interesting to observe that 67.2 % of the APS prescriptions are made in the indications approved according to their data sheet. Among these, 48.2 % correspond with the primary diagnosis of a mental disorder that occurs with psychotic symptoms (schizophrenia, schizoaffective disorder, delusional disorder, psychotic depression and other psychotic disorders). Some of the prescriptions made have been approved in recent years and were not an initial indication in the APS data sheets[11,12], as is the case of bipolar disorder with or without psychotic symptoms (14.5 % of the global prescriptions) and dementia (4.5 %). As it seems logical, the pharmaceutical industry initiated clinical trials for the approval of their APS in new indications, based on clinical observations made by the psychiatrists themselves.

Table 2 Reason for principal prescription

Reason for prescripction	% use of APS	% use of classical APS	% use of atypical APS
Control of psychotic symptoms	51.4	33.6	58.8
Aggressiveness-agitation	28.9	31.3	26.5
Impulsivity	3.5	6.9	2.3
Behavior D. associated to dementia	1.9	0.8	1.9
Behavior D. associated to substance use	1.0	0.8	1.2
Borderline personality behavior D.	1.0	0.8	0.8
Behavior D. in mental retardation	0.3	—	0.4
Non-specified behavior D.	0.3	—	0.4
Control of withdrawal symptoms to substances	0.3	—	0.4
Control motor tics	0.3	0.8	—
Severe insomnia	1.9	16.0	0.4
Antiobsessive potentiation	2.3	—	2.7
Severe anxiety	3.2	6.1	1.6
Mutism	0.6	1.5	—
Hyperactivity	0.3	—	0.4
Pharmacological potentiation	1.0		1.2
Demonstrated clinical efficacy	0.3	—	0.4
Not specified	1.3	1.5	0.8
Total	100.0	100.0	100.0

The remaining 32.8 % of the APS prescriptions made can be considered *off-label* or outside the indication since there is no express approval by the regulatory agencies in the indication for which they were prescribed. However, most of the diagnoses for which the *off-label* prescriptions have been made have a common characteristic: at present, there is no «administratively approved» treatment for them, or what is the same, there are no drugs on the market with specific indication that can relieve these sufferings. Such is the case of diseases such as mental retardation with associated behavior disorder, borderline type personality disorder (where unpredictable impulsive acts, self-injury, and suicidal gestures, if not psychotic decompensations, are frequent) or severe OCD refractory to treatment. Multiple studies show that these diseases clearly benefit from the use of antipsychotics, even though this does not appear as a specifically approved indication in the data sheet of any APS[13].

Table 3 Concomitant treatments

Treaatment type	N	%
Antidepressants	116	37.3
BZD	225	72.3
Anticonvulsants	58	18.6
Lithium	42	13.5
Others	27	8.7

It seems clear that the physician faces multiple and complicated clinical challenges daily that cannot be solved by only applying the regulation on approved indications since, since, on the contrary, he/she would lack pharmacological therapeutic instruments that have demonstrated utility, although it is true that this is empiric, to treat their patients during years. From the beginning of psychiatry, the physician has used psychodrugs with the art of one who requires «non-specific» instruments to relieve serious diseases that are frequently devastating. The clinician has had to anticipate the indications achieved by the pharmaceutical industry for their products, sometime even several years in advance of the official approval[14]. Many complex cases that must be faced daily could not form a part of the clinical trials for the search of indication because of the severity of the disease and the danger that these patients would have when deprived of the use of psychodrugs of potential utility.

Inevitably, there are «orphan» diseases that have not obtained the indication for the APS as no specific trials have ever been conducted[15]. Diseases such as tardive dyskinesis have been studied empirically, stressing the utility of some atypical APS without having performed controlled trials up to now[16]. On the other hand, we see cases of suicide attempts due to severe impulsivity (that are generally seen with frequency in borderline personality disorders), repeated self-aggressions (also frequent in these) and behavior disorders with psychomotor agitation that generally accompany diseases such as dementias or mental retardation. A therapeutic option in these cases is that of benzodiazepines. However, the large capacity of creating dependence these have at high doses over prolonged periods made the use of major tranquilizers inevitable to avoid provoking them. There is much data on the effectiveness of the APS in these suppositions, even when they are not expressly indicated for it[17-19].

The incorporation of pharmacoeconomic criteria in the prescription of APS should be aimed at using truly effective drugs that do not entail an excessive cost for the national health system. Although there are no complete data on the cost of schizophrenia in Spain, it is estimated that the direct costs (drugs, medical care and hospitalization) range from 4,000 to 6,000 dollars/patient/year, this being higher in the areas where intermediate services (mental health units and day centers) are not well implemented[20]. It seems that the greater cost of the atypical APS could entail a limitation for their generalized use in psychiatric population, although the sample of psychiatrists analyzed in this study gave preference to the use of atypical ones in diseases within the indication, but this is not so in those considered *off-label* where there were no significant differences of prescription between the typical and atypical ones.

In regards to the number of APS prescribed, more than one antipsychotic agent had to be used in 21.86 % of the population studied. Although there is no clear consensus for the association of APS, the reality could indicate that there is a population group with severe symptoms that is difficult to approach in monotherapy and with only pharmacological measures and that could be considered refractory to the usual treatments[21]. In most of the studies on prescription pattern, it is observed that the association of APS is a frequently used practice in different countries. The ACE study in Spain with more than 2000 patients reflected an association of APS in more than 39 % of the cases in public care and 34 % of those in private care[22] with similar values in the SOHO study with more than 10,000 European patients[23,24].

On the other hand, some severe sufferings such as serious impulsivity, behavior disorders and agitation in dementia or symptoms associated to some personality disorders are sufficiently serious, or of limited frequency, to never be compatible with the conduction of clinical trials as they do not fulfill the ethical criteria necessary for their approval. Consequently, they could never obtain an «administrative» indication. On other occasions, the diseases are rare and do not represent a commercial interest for any pharmaceutical industry to achieve their indication due to the costs this would entail. Thus, it is inevitable for the clinician to use the *off-label* of the APS in some diseases in order to protect their patients and provide the necessary relief.

The use patterns can be different between men and women. There are data that the doses used in women tend to be less and that their pattern of adverse effects differs from that of men since the women have worse tolerance to the appearance of weight increase, hypotension and cognitive dysfunction (Seeman, 2004). However, instructions are rarely included in the data sheets in regards to these differences so that, once again, the use pattern generally accepted by the clinicians is the action standard in most of the cases[25].

CONCLUSIONS

The APS are mostly used (67.2 % of the cases studied) for the treatment of entities for which their indication has been approved: schizophrenia, schizoaffective disorder, delusional disorder, other psychotic disorders and bipolar disorder with and without psychotic symptoms.

The most frequent reason to prescribe APS is the control of psychotic symptoms (51 %) and the control of aggressiveness-agitation (29 %), followed at a distance by other reasons (none with a frequency greater than 5 %).

The use of APS off-label (32.8 %) occurs in diseases that have the lack of an adequate treatment for them in common due to the absence on the market of drugs with «administrative authorization» that can relieve these sufferings. Mental retardation with associated behavior disorder, borderline type personality (where unpredictable self-injury impulsive acts are frequent), psychomotor agitation associated or not to dementia, harmful consumption of substances and severe OCD are found among these as the most frequent reasons.

The *off-label* use of APS seems inevitable in some severe diseases in order to protect the patients who, due to the special characteristics of severity, could never obtain the «administrative» indication through clinical trials. This use occurs similarly both for the atypical as well as classical APS.

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