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## Polypharmacy in psychiatric practice in the Canary Islands

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### Abstract

**Background:** Polypharmacy with psychoactive drugs is an increasingly common and debatable contemporary practice in clinical psychiatry based more upon experience than evidence. The objective of this study was to evaluate the prevalence and conditioners of polypharmacy in psychiatric patients.

**Method:** A cross-sectional survey was carried out using the Canary Islands Health Service Clinical Records Database. A representative sample (n = 2,647) of patients with mental disorders receiving psychotropic medication was studied.

**Results:** The mean number of psychoactive drugs prescribed was  $1.63 \pm 0.93$  (range 1–7). The rate of polypharmacy was 41.9%, with 27.8% of patients receiving two drugs, 9.1% receiving three, 3.2% receiving four, and 1.8% of the patients receiving five or more psychotropic drugs. Multiple regression analysis shows that variables sex and diagnosis have a predictive value with regard to the number of psychotropic drug used, being men and schizophrenic patients the most predisposed. Benzodiazepines were the more prevalent drugs in monotherapy, while anticonvulsants and antipsychotics were the more used in combination with other treatment. A questionable very high degree of same-class polypharmacy was evidenced, while multi-class, adjunctive and augmentation polypharmacy seem to be more appropriate.

**Conclusions:** Almost half of the psychiatric patients are treated with several psychotropics. Polypharmacy is common and seems to be problematic, especially when same class of drugs are prescribed together. Some diagnoses, such as schizophrenia, are associated with an increase risk of Polypharmacy but there is a lack of evidence based indicators that allows for quality evaluation on this practice.

### Background

The etymology of the word polypharmacy derives from *poly*, from the Greek word *polus* (many, much) and *pharmacy*, from the Greek word *pharmakon* (drug, poison) and literally means many drugs [1]. According to Werder

and Preskorn [2] the word polypharmacy first appeared in the medical literature in 1959 in the *New England Journal of Medicine* [3] and in the psychiatric literature in 1969 in an article citing its incidence at a state mental hospital [4].

The concurrent use of multiple psychoactive medications in a single patient, i.e. polypharmacy, is increasingly common and debatable contemporary practice in clinical psychiatry. This concomitant use of psychiatric drugs is based more probably upon experience than evidence [5] and is still hampered by a lack of systematic research. The great diversity of medications now available for the treatment of patients with psychiatric disorders, along with the increased safety of many of the new agents and probably the pressures of pharmaceutical industry, have created new opportunities for the use of multiple medications for a single condition. However, the history of medicine includes many examples where limited knowledge has led to widespread acceptance of practices that were later found to be inappropriate [6]. At the present time there is a compelling need of further studies about psychiatric drug combination treatments before clinical recommendations can be made.

Concerns with polypharmacy include the possibility of cumulative toxicity [7] and increased vulnerability to adverse events [8], as well as adherence issues which emerge with increasing regimen complexity [9]. Another serious concern with polypharmacy is the lack of evidence-based strategies available today to guide this practice [6] and the problem of drug costs for polypharmacy patients and how much of our always limited public resources it is possible to allocate to this treatment strategy [10].

The objective of the present study was to analyse the prevalence of polypharmacy with psychiatric drugs among patients attended by both general practitioners and psychiatrists working for the Canary Islands Health Service and affected by mental disorders, identifying the possible predictors of polypharmacy in psychiatric clinical practice.

## Methods

The present study is based on a representative sample of the citizens living at Gran Canaria island (755.489 inhabitants, density of population, 484 inhabitants/km<sup>2</sup>, 42 basic zones of health and 429 General Practitioners) attended by the Canary Islands Health Service (CIHS) with a diagnosis of mental disorder and under psychopharmacological treatment.

Patients were randomly selected from Primary Health Care Centres that were using a comprehensive electronic database system for keeping medical records and writing prescriptions (OMI-AP Database Program) [11]. As the system is not yet completely implemented in the whole territory, a bias toward the population living in the main urban areas (80% of the population) is assumed. Most patients were diagnosed and prescribed by their general

practitioners, but approximately 1 in 5 were referred to the community mental health care units were psychiatrists diagnosed, and prescribed for the first time. In almost all cases the follow up of patients, and the repeated prescriptions, were made by the general practitioners of the primary care health centres.

The sample comprised 2,647 patients, with 66.3% female and 33.7% male. The mean age was  $50.1 \pm 16.8$  years (range 15–90). Women registered a higher mean age than men ( $51.7 \pm 16.8$  vs.  $48 \pm 16.2$ ). Other socio-demographic and clinical characteristics of the sample studied are shown in Table 1.

Prescription data were retrieved from a cross-sectional survey carried out using the CIHS OMI-AP Database [11]. OMI-AP Database includes an electronic case record of every patient attended at the Primary Care Centres that contains all the prescriptions for each patient, providing information about the drug prescribed, its dosage and duration, the diagnosis of the patient, and producing the print-out of the corresponding prescriptions. All active episodes of psychiatric conditions been diagnosed and treated at December 20<sup>th</sup> 2003 were selected for analysis. No follow-up of these patients were intended nor was it possible at the present time of the development of the program. Despite that the database also contains dosages, the system is not reliable for this data.

In this paper, polypharmacy will refer broadly to the concurrent use of two or more psychiatric medications in the same patient. Possible predictors of polypharmacy were analyzed by stepwise linear multiple regression.

The diagnoses were registered by the attending physician according to ICD-10 [12], using the OMI-AP database corresponding tool, and grouped into the main ICD-10 chapter V (mental and behavioural disorders) diagnostic categories, which include: organic including symptomatic mental disorders (F0); mental and behavioural disorders due to psychoactive substance abuse (F1); schizophrenia, schizotypal and delusional disorders (F2); mood (affective) disorders (F3); neurotic, stress-related and somatoform disorders (F4); behavioural syndromes associated with physiological disturbances and physical factors (F5); disorders of the adult personality and behaviour (F6); and mental retardation (F7). Insomnia was considered as a separate diagnostic category since a high number of patients received psychotropic drugs to treat this symptom exclusively.

For evaluation purposes the drugs were divided into the common groups of psychotropics: antipsychotics, antidepressants and tranquillisers (including hypnotics, whereby benzodiazepines were predominantly used). The

**Table 1: Sample distribution according sex, age, diagnosis and psychotropic drugs prescribed, and risks factors for polypharmacy**

	Number of cases	Mean ± SD	One Drug %	Two Drugs %	Three Drugs %	Four Drugs %	Five Drugs %	Six Drugs %	Seven Drugs %	P Value	Sd R β
<b>Age</b>											
<18 years	7	1.4 ± 0.8	71.4	14.3	14.3	x	x	x	x	N.S. 0.785	-0.005
18–25 years	93	1.5 ± 0.9	67.7	21.5	4.3	4.3	2.2	x	x		
25–45 years	966	1.7 ± 0.9	55.3	30.3	8.9	4.0	0.8	0.5	0.1		
45–65 years	926	1.7 ± 1.0	56.7	26.3	11.2	3.5	1.6	0.4	0.2		
>65 years	655	1.5 ± 0.8	62.9	27.2	7.0	1.7	0.9	0.2	0.2		
<b>Gender</b>											
Male	892	1.7 ± 1.0	55.8	27.2	9.8	4.8	1.5	0.7	0.2	0.012	-0.048
Female	1,755	1.6 ± 0.9	59.3	28.1	8.8	2.5	1.0	0.2	0.1		
<b>Diagnosis</b>											
F0	68	1.7 ± 1.0	55.9	25.0	11.8	5.9	1.5	x	x	<0.0005	-0.233
F1	167	1.8 ± 0.9	43.7	33.5	17.4	4.8	0.6	x	x		
F2	113	2.9 ± 1.6	22.1	25.7	14.2	20.4	10.6	5.3	1.8		
F3	659	1.9 ± 1.0	43.2	34.7	15.0	4.2	2.0	0.5	0.3		
F4	1,344	1.4 ± 0.7	65.4	26.5	6.4	1.6	x	0.1	x		
F5	6	1.5 ± 0.5	50	50	x	x	x	x	x		
F6	10	2.8 ± 1.8	40	10	10	10	30	x	x		
F7	10	2.0 ± 1.3	40	40	10	x	10	x	x		
Insomnia	268	1.2 ± 0.4	85.1	14.9	x	x	x	x	x		
<b>Total</b>	<b>2,647</b>	<b>1.6 ± 0.9</b>	<b>58.1</b>	<b>27.8</b>	<b>9.1</b>	<b>3.2</b>	<b>1.2</b>	<b>0.4</b>	<b>0.2</b>		

Sd R β :Standardized regression coefficient β

following drugs were also recorded separately: lithium preparations, the group of anticonvulsants that are increasingly being used for psychiatric indications and anti-parkinsonian drugs.

In order to describe the impact and appropriateness of polypharmacy in greater detail, we have divided polypharmacy in the five categories suggested by the National Association of State Mental Health Program Directors (NASMHPD) [6] that includes:

**Same-Class Polypharmacy**

The use of more than one medication from the same medication class (e.g. two selective serotonin reuptake inhibitors, such as fluoxetine plus paroxetine).

**Multi-Class Polypharmacy**

The use of full therapeutic doses of more than one medication from different medication classes for the same symptom cluster (e.g. the use of lithium along with an atypical antipsychotic, such as fluoxetine plus olanzapine for treatment of mania).

**Adjunctive Polypharmacy**

The use of one medication to treat the side effects or secondary symptoms of another medication from a different medication class (e.g. the use of trazadone along with bupropion for insomnia).

**Augmentation**

The use of one medication at a lower than normal dose along with another medication from a different medication class at its full therapeutic dose, for the same symptom cluster (e.g. the addition of a low dose of haloperidol in a patient with a partial response to risperidone) or the addition of a medication that would not be used alone for the same symptom cluster (e.g. the addition of lithium in a person with major depression who is currently taking an antidepressant).

**Total Polypharmacy**

The total count of medications used in a patient, or total drug load.

**Results**

Table 1 shows the sample distribution according to sex, age, diagnosis and psychotropic drugs prescribed. The mean number of psychotropic drug used by the patients

**Table 2: Medications prescribed in the total sample of 2647 valid cases.**

	% of patients using this drug	% Monotherapy
<b>Tranquillisers</b>	<b>87.3</b>	<b>51.1</b>
Benzodiazepines	84.4	54.0
No Benzodiazepines	2.9	34.5
<b>Antidepressants</b>	<b>37.5</b>	<b>23.2</b>
SSRIs	29.0	24.1
Tricyclic Antidepressants	4.2	23.8
Other Antidepressants	4.3	16.3
<b>Antipsychotic</b>	<b>10.9</b>	<b>18.3</b>
Conventional <sup>1</sup>	5.2	17.3
Atypical <sup>2</sup>	4.6	21.7
Depot	1.1	9.1
<b>Anticonvulsants</b>	<b>4.8</b>	<b>18.7</b>
<b>Anti-parkinsonian drugs</b>	<b>1.7</b>	<b>0</b>
<b>Lithium</b>	<b>0.5</b>	<b>20.0</b>

1 Conventional antipsychotic mainly include, among others: Haloperidol and Chlorpromazine. 2. Atypical antipsychotic mainly include, among others: Olanzapine and Risperidone. SSRIs: Selective Serotonin Reuptake Inhibitors

was 1.63 (S.D. 0.93, range 1–7). Half of the patients (58.1%) were under monotherapy treatments, while 27.8% received two drugs, 9.1% received three, and 5% received four or more drugs.

Polypharmacy with psychoactive drugs was more prevalent in men than in women, in those with aged between 25 and 45 years, and in patients with diagnosis included in the schizophrenia, schizotypal and delusional disorders ICD-10 category.

The multiple regression analysis includes the variables age, gender and diagnosis but only the variables sex and diagnosis have a predictive value with regard to the number of psychotropic drugs used. In particular, diagnoses was the most reliable predictor (table 1).

Considering the drugs used (table 2), tranquilisers were the most frequent medication, since they were used by 87.3% of the patients (84.4% benzodiazepines), followed by the Selective Serotonin Reuptake Inhibitors (SSRI) used by 29% of patients, conventional antipsychotics with 5.2% and anticonvulsants with 4.8%.

The medication more prevalent in monotherapy was the group of benzodiazepines since more than half of these drugs were used alone. On the other hand, anticonvulsants and antipsychotics were the drugs most used in combination with other psychoactive medications.

Multi-Class Polypharmacy was the most prevalent type of polypharmacy evidenced in the sample affecting 20.9% of patients. The association of an SSRI with a benzodi-

azepine was present in 13.7% of patients, while 1.2% of patients were treated with the association of a tricyclic antidepressant and a benzodiazepine.

Same-Class polypharmacy was demonstrated in 18.5% of patients mainly as a result of patients treated with several benzodiazepines (16.2%), up to five at the same time to the same patient. The association of two conventional antipsychotics or two anticonvulsants were evidenced in 0.6% of patients.

Adjunctive polypharmacy was present in 1.5% of patients and consists mainly in the association of a conventional antipsychotic with an anti-parkinsonian drug. Augmentation polypharmacy was present in only 1% of patients consisting basically in the association of lithium and antidepressants.

Table 3 shows the percentages of patients prescribed with the different psychotropic medications according to diagnoses either in monotherapy or polypharmacy. In patients with organic including symptomatic mental disorders (F0, table 3), benzodiazepines (BZDs) and atypical antipsychotics were the drugs most used both alone as well as in combination. SSRIs were used predominantly as monotherapy. The more prevalent prescriptions include: 14.7% of patients with one SSRI, 14.7% with one benzodiazepine, 13.2% with one atypical antipsychotic, 7.4% with one conventional antipsychotic, 7.4% with the association of an atypical antipsychotic and one benzodiazepine, and 4.4% with the combination of an atypical antipsychotic and two BZDs

**Table 3: Percentages of patients prescribed different psychotropic medications, either in monotherapy or polypharmacy, according to diagnoses.**

	F0	F1	F2	F3	F4
<b>Tranquillisers</b>					
Benzodiazepines	45.6	85.6	54.8	74.6	91.1
No Benzodiazepines	11.8	24.6	1.8	0.9	0.4
<b>Antidepressants</b>					
SSRIs	23.5	19.8	10.6	53.9	25.5
Tricyclic Antidepressants	2.9	5.4	7.1	8.6	2.8
Other Antidepressants	5.9	-	6.2	9.4	2.1
<b>Antipsychotic</b>					
Conventional <sup>1</sup>	26.4	5.4	38.9	3.5	2.6
Atypical <sup>2</sup>	30.9	6.0	43.4	2.4	1.4
Depot	-	-	22.1	0.5	-
<b>Anticonvulsants</b>	1.5	6.6	20.3	6.6	3.5
<b>Anti-parkinsonian drugs</b>	5.9	-	32.7	0.3	0.1
<b>Lithium</b>	-	-	-	1.4	0.1
<b>Average no. of psychotropics</b>	<b>1.7 ± 0.9</b>	<b>1.9 ± 0.9</b>	<b>2.9 ± 1.6</b>	<b>1.9 ± 1.0</b>	<b>1.4 ± 0.7</b>

1 Conventional antipsychotic mainly include, among others: Haloperidol and Chlorpromazine. 2. Atypical antipsychotic mainly include, among others: Olanzapine and Risperidone. SSRIs: Selective Serotonin Reuptake Inhibitors (F0): Organic including symptomatic mental disorders (F1): Mental and behavioural disorders due to psychoactive substance abuse (F2): Schizophrenia, schizotypal and delusional disorders (F3): Mood (affective) disorders (F4): Neurotic, stress-related and somatoform disorders

In patients with mental and behavioural disorders due to psychoactive substance abuse (F1, table 3), is interesting to note that almost the totality of them received tranquilisers, mainly BZDs. A very high proportion of the BZDs used were in combination or with another benzodiazepine or with other psychoactive drugs. It is remarkable the small proportion of patients treated with antipsychotics in this diagnostic category. The more prevalent prescriptions include: 32.9% of patients with one benzodiazepine, 12.6% with two benzodiazepines, 7.8% of patients received 2 BZDs and one no benzodiazepine-tranquilliser, 7.2% received one SSRI and one BZD while 4.2% received one SSRI plus two BZDs.

Patients affected by schizophrenia, schizotypal and delusional disorders (F2, table 3), were predominantly treated through polypharmacy, being atypical antipsychotics the most prevalent option used. The figures reached by depot neuroleptics show that these drugs have relevant role to play. The use of anti-parkinsonian drugs reflect the pattern of neuroleptics used. It is remarkable the high proportion of patients using anticonvulsants and that more than a half of the patients received benzodiazepines. The more prevalent prescriptions include; 9.8% of patients with one atypical antipsychotic, 7.1% of patients with one BZD, 5.3% receiving one atypical antipsychotic plus one BZD and 3.5% receiving one conventional antipsychotic.

In the patients with mood or affective disorders (F3, table 3), BZDs were the more prevalent drugs used, since two-thirds of patients received them, mainly in combination.

SSRIs were the most frequent prescribed antidepressants, mostly in combination with BZDs. However, tricyclic antidepressants are still prescribed to 8.6% of patients. Anticonvulsant were used only by 6.6% of the patients and lithium only was used by 1.4% of patients. The more prevalent prescriptions include: 22.8% of patients receiving one SSRI plus one BZD, 22.2% receiving only one BZD, 16% receiving one SSRI alone, and 7.4% of patients receiving one SSRI plus two BZDs.

Patients with neurotic, stress-related and somatoform disorders (F4, table 3) were treated mainly through monotherapy with benzodiazepines. The combination of a SSRI with a BZD was the most prevalent polypharmacy strategy. Antipsychotics were used by 4% of patients and anticonvulsants by 3.5% of them. The more prevalent prescriptions include: 57.8% of patients receiving one benzodiazepine, 14.7% receiving one SSRI plus one BZD, 7.5% receiving two BZDs and 4.6% of patients receiving one SSRI alone.

## Discussion

The study of the polypharmacy phenomenon in psychiatry is inherently complex. Most diagnostic categories in psychiatry have not been shown to be valid because they are not discrete entities with natural boundaries that separate them from other disorders [13]. Moreover, diagnostic systems such as DSM-IV [14] and ICD-10 [12] foster diagnosing of comorbid conditions. A person with three different diagnoses might need three different treatments [15].

In addition, there is some confusion referring to the classification of psychiatric drugs since no standard criteria exist for the assignment of a single psychiatric drug to a group of substances and medications are arbitrarily grouped into medication classes, which do not always reflect their degree of pharmacological similarity. The classification of a drug can depend on its pharmaceutical basic schedule, biochemical mechanism, produced effects or the administrator's subjective intention. Furthermore, some single medications are by itself "polypharmacy-in-a-pill" since their complex mechanism of action involves effects on multiple receptors [16]. In addition, nowadays, many single medications have been approved for multiple indications.

Moreover, there are more drugs available, being aggressive promoted [17,18] and new groups of drugs used as psychotropics (e.g. anticonvulsants,  $\beta$ -blockers).

To define what constitutes an adequate psychotropic drug prescription is a complex task since it implies the consideration of pharmacological, clinical, social and economic aspects. This complexity probably contributes to the great existing variation in the volume and type of drugs prescribed in different countries, within one country and even within a single institution between individual doctors [19,20]. Some authors consider that the concept of adequate prescription is almost as abstract as that of health [21].

Finally, another question that makes difficult any analysis is the fact that the psychiatric medication provides the doctor with an opportunity to "do something" and to prescribe a "rational treatment" for the non-specific psychological problems and for the various social problems from patients in a manner which complies with the expectations associated with the role of a doctor [22].

The closure of psychiatric hospitals, psychiatric beds steadily decreasing, and a community psychiatry that has struggled for years to treat the most seriously ill individuals within the constraints of severely limited resources probably promote the polypharmacy of the most severe patients [23].

The prescription database of OMI-AP program permitted us to estimate the prevalence of concurrently use of more than one psychotropic medication in the treatment of psychiatric disorders. Prescription databases have been demonstrated to be a reliable source of information to analyze polypharmacy in other studies [24,25]. Although the database contains information about the prescribed daily dose and duration of treatment, we consider at the present time that this information is not reliable enough to be analysed.

Research that examines the concurrent use of multiple psychotropic medications in outpatient populations is scanty. The existing data are confined to open-labelled or case studies that investigate the adding of new drugs to resistant cases. Nonetheless, more good information about polypharmacy is available at the inpatient care level [15,26].

The results obtained in our study about prescription of psychotropic medications are in accordance to those obtained in previous pharmacoepidemiological studies in the same area about psychotropic use [19,20,27,28]. We registered in the same population a high prevalence of benzodiazepines prescriptions but it seems necessary to comment that, as it was shown in that study, that most of the anxiolytic prescriptions were written for dosages well below the Defined Daily Dose (DDD) (77.1% of cases), and in only 10% of all anxiolytic prescriptions was the prescribed dose in agreement with the DDD. This is important information when making any inference from drug consumption statistics. It is also remarkable that apart from being used in low doses, anxiolytics were also frequently prescribed as a single daily dose 'at supper' or 'before going to bed' (48.6% of prescriptions).

In our study, males were more exposed than women to polypharmacy with psychotropic medications and gender was one of the variables that explained the difference in the logistic regression. Furthermore our results do not show a clear relationship between age and polypharmacy with psychotropic drugs, which is a frequent fact in other studies about general polypharmacy [29,30]. We have no explanation for these findings apart from the different diagnostic profiles in the comparative studies, and the different epidemiological distribution of psychiatric diagnoses in the population, especially regarding gender.

Prescription databases do not usually include information about the morbidity for which the drug was prescribed and only few studies have focused on health problems as predictors of polypharmacy, with none of them employing a sample of the general population as study base [31]. Our results shown that psychiatric diagnosis was the most reliable predictor for polypharmacy, being the patients affected by schizophrenia, schizotypal and delusional disorders the most predisposed to develop polypharmacy.

The high prevalence of polypharmacy in psychiatry evidenced in our study is not substantiated on research literature that documents its safety and effectiveness. Polypharmacy with psychiatric medications is a growing practice that is derived from clinical experience, small trials and case reports [11]. Drug combinations often represent 'uncontrolled experiments', with unknown potential for toxic effects.

Currently, there is no evidence to justify same-class polypharmacy; our study shows a high degree of this kind of inappropriate polypharmacy that should be avoided. However, there is growing evidence of a wide range of situations where multi-class polypharmacy, adjunctive polypharmacy and augmentation are safe and effective treatments. In the face of this evidence, however, total polypharmacy is a growing concern. In our study, multi-class polypharmacy was a prevalent issue that seems to be appropriate used. Nevertheless, adjunctive polypharmacy and augmentation were little evident in the patients studied.

At the present time, psychiatric clinical practice needs to develop indicators for an appropriate polypharmacy of mental disorders. However, it is necessary to consider that the current standard for evaluation of psychiatric drugs, based on randomized controlled clinical trials, although is adequate to compare single medications, it fails when trying to study every potential drug combination.

## Conclusions

Polypharmacy with psychotropic drugs is a prevalent prescription practice in patients with mental disorders in the Canary Islands. Men are more exposed to be treated with multiple psychotropic medications and the diagnosis of the patient is the most reliable predictor for polypharmacy with these drugs. Prescription databases can be used to estimate epidemiological measures of polypharmacy and to identify which patients are at risk for polypharmacy in order to develop proper interventions that minimize the risks associated with this treatment alternative.

## Competing interests

None declared.

## Authors contributions

CD conceived and carried out the design of the study and participated in the statistical analysis and manuscript elaboration. ES was responsible of coordination and participated in the statistical analysis and manuscript elaboration. Both authors read and approved the final manuscript

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