C. de las Cuevas[1]
E. J. Sanz[2]
J. A. de la Fuente[3]
M. Cueto[4]

Polypharmacy in psychiatric patients as an alternative to limited mental health resources

[1] Service of Psychiatry
University of La Laguna
[2] Service of Pharmacology
University of La Laguna.
[3] Psychiatry Service
University Hospital Nuestra Señora de la Candelaria
[4] Service of Primary Health Care
Canary Island Service of Health
Tenerife (Spain)

Introduction. Polypharmacy with psychoactive drugs is an increasingly common and debatable contemporary practice in clinical psychiatry more probably based on experience than evidence. The objective of this study was to evaluate the prevalence and estimators of polypharmacy in psychiatric patients living in an area with very limited mental health resources.

Method. All patients (n = 352) with mental disorders receiving psychotropic medication living in La Gomera were studied through an audit of case records and a second phase confirmation strategy through personal interviews.

Results. The mean number of psychoactive drugs prescribed was 2.22 ± 0.70 (range: 1-6). The rate of polypharmacy was 67 %, with 34.1 % of patients receiving two drugs, 20.5 % receiving three drugs and 12.5 % of the patients receiving four or more psychotropic drugs at the same time. Multiple regression analysis shows that none of the variables considered (age, sex, marital status, educational level, work activity and diagnosis) had predictive value in regards to the number of psychotropic drug used. Benzodiazepines were the most prevalent drugs in single drug therapy, while antidepressants and antipsychotics were the most used in combination with other treatment. A questionably very high degree of same-class polypharmacy was observed, while multiclass, adjunctive and augmentation polypharmacy seems to be more appropriate.

Conclusion. The psychiatric clinical practice needs to develop indicators for an appropriate polypharmacy of mental disorders. More research is still needed to identify patients at risk of polypharmacy in order to develop interventions that minimize the risks associated to this treatment alternative.

Key words:
Polypharmacy. Psychotropic drugs. Psychiatric patients. Single drug therapy.

Actas Esp Psiquiatr 2005;33(2):81-86

Correspondence:
Carlos de las Cuevas
Urbanización Las Cañas, 33
38208 La Laguna (Santa Cruz de Tenerife) (Spain)
E-mail: cuevas@ull.es

La polimedicación de los pacientes psiquiátricos como alternativa a la escasez de recursos asistenciales

Introducción. La polimedicación con fármacos psicoactivos es una polémica práctica habitual en psiquiatría que hasta el momento presente está más basada en la experiencia que en la evidencia. El objetivo del presente estudio es valorar la prevalencia y los posibles determinantes de la polimedicación de los pacientes psiquiátricos residentes en un área sanitaria con importantes carencias asistenciales.

Método. La totalidad (n = 352) de los pacientes psiquiátricos bajo tratamiento psicofarmacológico residentes en la isla de La Gomera fueron evaluados a través de una auditoría de historias clínicas y de una segunda fase que incluyó una entrevista personal con cada paciente confirmadora del consumo de los fármacos prescritos.

Resultados. El número medio de fármacos psicoactivos consumidos por paciente fue de 2,22 ± 0,7 (rango: 1-6). La tasa de polimedicación registrada fue del 67 %, con un 34,1 % de los pacientes consumidores de dos fármacos, un 20,5 % consumidores de tres y un 12,5 % consumidores de cuatro o más fármacos psicoactivos al mismo tiempo. El análisis de regresión múltiple realizado puso de manifiesto que ninguna de las variables consideradas (edad, sexo, estado civil, nivel cultural, actividad laboral y diagnóstico) resultó ser un predictor fiable o factor de riesgo para el desarrollo de polimedicación. Las benzodiazepinas fueron el fármaco más prevalerte en monoterapia, mientras que los antidepresivos y los antipsicóticos fueron los más empleados en combinación. Una cuestionable alta polimedicación con fármacos de la misma clase farmacológica fue puesta de manifiesto, mientras que la polimedicación con fármacos de distinta clase o la auxiliar demostraron ser más adecuadas.

Conclusión. La práctica clínica psiquiátrica necesita desarrollar indicadores que permitan una polimedicación adecuada de los trastornos mentales. Todavía se necesita más investigación que permita identificar a los pacientes

en riesgo de polimedicación para poder minimizar los riesgos asociados a esta extendida práctica asistencial.

Palabras clave:
Polimedicación. Fármacos psicoactivos. Pacientes psiquiátricos. Monoterapia.

INTRODUCTION

Although most of the scientific psychiatric texts advocate psychopharmacological single drug therapy in the treatment of mental disorders[1-3], the use of psychoactive drug combinations is a common practical controversy in psychiatry[4], which, up to now, lacks neurobiological grounds to support it[5,6]. Traditionally, polymedication or polypharmacy has had negative connotations, up to the point that several authors consider it an indicator of poor psychiatric practice[7]. However, the use of different psychoactive drugs in one patient may sometimes constitute an effective clinical intervention to be considered. There are favorable experiences in the resolution of resistant clinical pictures, in the elimination of residual symptoms, to increase speed of action or to avoid or counteract adverse effects of some medication.

There are different types of risks associated to polymedication of psychiatric disorders. In the first place, polypharmacy is associated with an increased risk of adverse effects and undesired interactions[8]. In addition, this therapeutic alternative entails more difficult treatment regimes that hinder their compliance[9,10]. The fact that when multiple drugs are used, the effects of one may be confused with those of others exists. This makes it difficult for the prescriber to be able to distinguish which medications help the patient and which harm him/her. On the other hand, polymedication makes it necessary to use more medication to treat the drugs' side effects, which contributes to the problem. Finally, the new psychiatric drugs are very expensive and the public health care systems have scarce and limited economic resources that must be handled as efficiently as possible[11].

The presently available data on the polymedication use frequency in psychiatry, that is, concomitant use in the same patient of several psychoactive drugs in the treat-ment of his/her psychiatric disorder, are scarce and not very reliable and the opinions on its usefulness and safety vary[12,13]. For Stahl[14], the concomitant use of psychodrugs in the treatment of mental disease is based more on experience than on evidence and still requires systematic investigation.

This present study aims to establish the prevalence of polymedication with psychoactive drugs, as well as their determinants, in the treatment of patients with psychiatric disorders in a remote health care area, with very limited health care resources in mental health material, where treatment with psychodrugs is the main, if not only, treatment alternative.

MATERIAL AND METHOD

In the present study, we will consider polymedication as that drug treatment that involves the use of two or more psychotropic drugs in the psychiatry treatment of an individual patient. In order to evaluate the impact and adequacy of polymedication of psychiatric disorders in greater detail, we have divided this treatment modality into the five categories suggested by the National Association of State Mental Health Program Directors (NASMHPD)[13]. They include:

- *Same-class polymedication.* The use of more than one medication of the same pharmacological class (e.g., two selective serotonin reuptake inhibitors, such as fluoxetine plus paroxetine, in the same patient).
- *Multi-class polymedication.* 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 olanzapine for treatment of mania).
- *Adjunctive polymedication.* 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 buproprion for insomnia).
- *Augmentation polymedication.* 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. Total polypharmacy should include prescription medications, over-the counter medications, and even alternative medical therapies.

The patients were diagnosed according to the ICD-10 chapter V criteria[15] and grouped according to the main categories of this classification.

In order to facilitate the evaluation, the drugs prescribed were categorized in common psychodrug groups: antipsychotics, antidepressants, tranquilizers (including hypnotics, the benzodiazepinic drugs being those used most). Lithium, the different anticonvulsants, beta blockers and anti-parkinsonian drugs were recorded independently.

La Gomera is one of the seven islands that make up the Canary Islands archipelago and constitutes a health care area of the Canary Island Health Service. La Gomera is a small island of 378 km^2, with a maximum length of 26 km and width of 17 km, and its present population is 18,285 inhabitants distributed into six districts. The health care resources of La

Gomera are made up by one 33 bed hospital (11 medical, 15 surgical, 3 pediatric and 4 obstetrics) and four primary health care centers. The health care staff that works on the island includes 17 professionals from different specialities and 11 primary health care physicians who live on the island. The mental health problems of the citizens living in La Gomera are treated by one psychiatrist and one psychologist who travel once a week to attend to the programmed visits (12 patients day, relationship 1st time/successive 33 %, 30 minutes for 1st time and 20 minutes for successive ones). There is no other resource on the island for the care of patients with mental care problems. The patients who require psychiatric hospitalization are transferred to a Short Hospitalization Unit of the Hospital Nuestra Señora de la Candelaria in the island of Tenerife.

The study sample was made up by all (n = 352) the patients with psychiatric diagnosis who were receiving psychopharmacological treatment and who were residents in the health care area of La Gomera on November 2003. The prescription and psychoactive drug consumption data were obtained through an auditing of the clinical records and ratified by personal interview with each patient.

RESULTS

Table 1 shows the distribution of the sample based on gender, age, diagnosis and drugs prescribed to the patients. The mean number of psychoactive drugs prescribed and consumed per patient was 2.2 (standard desviation [SD]: 0.7; range: 1-6). Only 33 % of the patients were treated with single drug therapy, while 34.1 % were treated with 2 drugs, 20.5 % received three psychodrugs and 12.5 % were prescribed and consumed 4 or more psychodrugs simultaneously.

Polymedication with psychoactive drugs showed a similar prevalence in both genders, and was slightly overrepresented in patients whose ages ranged from 18 to 25 years and in those whose diagnoses were included in the ICD-10 category corresponding to schizophrenia, schizotypal disorders and delusional disorders. However, the logistic regression analysis carried out manifested that none of the variables considered (gender, age, civil status, educational level, occupation activity and diagnosis) was a reliable predictor or a risk factor to be considered for the development of polymedication.

Benzodiazepine tranquilizers were the most prescribed drugs, being consumed by more than 60 % of the patients (table 2), followed by selective serotonin reupta-ke inhibitors (SSRI) that were prescribed and consumed in 37.5 % of the patients.

The most prevalent drug in the single drug regime was benzodiazepines that registered a 10.8 % value, followed by different antidepressants of the SSRI and antidepressants

Table 1 Distribution of the sample according to gender, age, diagnoses, pshychoactive drugs prescribed and polymedication risk factors

	% of cases	Mean ± SD	1 drug	2 drug	3 drug	4 drug	5 drug	6 drug	P value	Standard regression β coefficient
Gender									0,629	–0,037
Male	29.5	2.2 ± 1.2	34.6 %	30.8 %	17.3 %	15.4 %	X	1.9 %		
Female	70.5	2.1 ± 1.0	32.3 %	35.5 %	21.8 %	8.9 %	1.6 %	X		
Age									0.190	–0.100
18-25 years	5.1	2.2 ± 1.6	44.4 %	22.2 %	22.2 %	X	X	11.1 %		
25-45 years	37.5	2.4 ± 1.2	28.8 %	27.3 %	25.8 %	15.2 %	3.0 %	X		
45-65 years	32.4	1.9 ± 0.9	40.4 %	31.6 %	19.3 %	8.8 %	X	X		
> 65 years	25.0	2.1 ± 1.1	27.3 %	50.0 %	13.6 %	9.1 %	X	X		
Diagnosis									0.136	–0.114
F1	2.3	1.7 ± 0.5	25 %	75 %	X	X	X	X		
F2	20.5	2.5 ± 1.1	25 %	19.4 %	33.3 %	22.2 %	X	X		
F3	36.4	2.3 ± 1.0	23.4 %	43.8 %	17.2 %	12.5 %	3.1 %	X		
F4	35.8	1.8 ± 0.9	42.9 %	34.9 %	19 %	3.2 %	X	X		
F5	1.1	1.0	100 %	X	X	X	X	X		
F6	2.8	1.4 ± 0.9	80 %	10 %	10 %	X	X	X		
F7	1.1	5 ± 1.4	X	X	X	50 %	X	50 %		
Global	352	2.2 ± 0.7	33 %	34.1 %	20.5 %	10.8 %	1.1 %	0.6 %		

Table 2 Treatments prescribed in the global sample

	N	% of responses	% of patients	% single drug therapy
Tranquilizers	120	36.0	68.2	11.4 %
Benzodiacepines	116	33.8	65.9	10.8 %
Non benzodiacepines	4	1.2	2.3	0.6 %
Antidepressants	138	40.2	78.6	16.5 %
SSRI	66	19.2	37.5	6.3 %
Tricyclic antidepressants	24	7.0	13.6	3.4 %
Other antidepressants	48	14.0	27.3	6.8 %
Antisychotics	56	16.4	40.9	5.1 %
Conventional	11	3.2	6.3	0 %
Atypical	43	12.6	23.5	5.1 %
Depot	2	0.6	11.1	0 %
Anticonvulsants	2	0.6	1.1	0 %
Anti-parkinsonians	11	3.2	6.3	0 %
Lithium	10	2.9	5.7	0 %
Total responses		100.0	194.9	
Mean psychodrugs		2.2 ± 0.7 (min, 1; max, 6)		

Table 3 Treatments prescribed in patients according to their diagnosis

	F2	F3	F4
Tranquilizers	46.3	67.2	81.0
Benzodiazepines	43.5	67.2	77.8
Non-benzodiazepines	2.8	–	3.2
Antidepressants	50	94.5	80.3
SSRI	33.3	46.9	31.7
Tricyclic antidepressants	5.6	12.5	21.6
Other antidepressants	11.1	35.1	27.0
Antipsychotics	114.0	16.0	–
Conventional	25.0	1.6	–
Atypical	86.2	14.0	–
Depot	2.8	–	–
Anticonvulsants	8.3	15.6	–
Anti-parkinsonians	25	3.1	
Lithium	–	6.3	–
Meann psychodrugs	2.5 ± 1.1	2.3 ± 1.0	1.8 ± 0.9

that reached 6.8 % of the prescriptions in the single drug therapy regime.

The most frequent association of drugs was the combination of a non-SSRI or non-tricyclic antidepressants (mainly venlafaxine) and a benzodiazepine that accounted for 11.9 % of the prescriptions. The combination of a SSRI with one benzodiazepine was present in 11.4 % of the cases, while the association of a SSRI with two benzodiazepines occurred in 4.5 % of the prescriptions.

Multi-class polymedication, that is, with two full therapeutic doses of more than one medications of different pharmacological classes, was the most frequent in the sample studied. It affected 42.6 % of the patients, while the same-class polymedication occurred in 19.3 % of the cases, the association of several benzodiazepines being the most frequent combination of this category. The adjuvant polymedication was present in 5.1 % of the cases and was a reflection of the association of both atypical as well as conventional antipsychotic drugs and anticholinergic drugs. In the sample studied, no augmenting polymedication strategy was manifested.

Among the patients suffering schizophrenia, schizotypal disorders and delusions disorders (F2, table 3), the prescription of an atypical antipsychotic exclusively was the most prevalent prescription recorded in 25 % of the cases. The combination of an atypical antipsychotic, one benzodiazepine and selective serotonin reuptake inhibitor was present in 11.1 % of the patients, while the association of a SSRI together with an atypical antipsychotic was observed in 5.6 % of the sample.

Among the patients with diagnoses included in the affective or mood disorders category (F3 table 3), the association of a SSRI antidepressant and a benzodiazepine was present in 20.3 % of the patients, this being the most frequent option, followed by a non-SSRI or non-tricyclic antidepressant and a benzodiazepine which accounted for 15.6 % of the prescriptions. The third most frequent option in this category was the prescription of a SSRI antidepressant exclusively, which occurred in 10.9 % of the prescriptions.

The patients with diagnoses included in neurotic disorders category, related with stress and somatoforms (F4, table 3), received a benzodiazepine drug exclusively as the most frequent prescription in 23.8 % of the cases, followed by the prescription of Venlafaxine associated to benzodiazepine in 15.9 % and a SSRI antidepressant and benzodiazepine in 11.1 %.

DISCUSSION

The etymological origin of the word polypharmacy, equivalent to polymedication, is derived from the Greek words polus (much) and pharmakon (drug or poison) and literally means many drugs or, alternatively, much poison[16]. According to Wender and Preskom (2003)[17], the first appearance of the world polypharmacy in the medical literature goes

back to 1959 in the New England Journal of Medicine[18] and in the psychiatric literature to 1969 in an article that mentioned its incidence in a state psychiatric hospital[19].

Since then, the large diversity of the drugs available in the treatment of mental diseases as well as its greater safety and probably the important pressures from the pharmaceutical industry in the promotion of their prescription have created new opportunities for the use of multiple drugs in the treatment of an individual patient. However, the history of medicine is full of examples in which limited knowledge led to a wide acceptance of practices which were later considered inappropriate[13]. At present, studies on the combination of psychoactive drugs are still necessary before clinical recommendations can be made in this regards.

The study of polymedication in the psychiatric clinical practice is inherently complex. Among other reasons, the fact that most of the categories diagnosed in psychiatry have not been shown to be valid since they do not constitute discreet entities with natural limits that separate them from other disorders stands out[20]. Furthermore, the present diagnostic classifications in use, the DSM-IV-TR[21] and the ICD-10[15] promote the diagnosis of comorbid disorders, so that it could be thought that a person with three different diagnoses could need three different treatments[22]. On the other hand, the classification of the psychoactive drugs could depend on their basic pharmacological structure, on their biochemical action mechanism, on the effects produced or on the subjective intention of the prescriber[13]. To complicate the outlook even more, some simple drugs constitute «polymedications in one pill» by themselves[23] since their action mechanisms are complex and involve multiple receptors. Furthermore, at present, many drugs have been approved in multiple indications. In addition, there is increasingly greater availability every day of psychoactive drugs that are aggressively promoted by the pharmaceutical industry, and the psychiatric clinical practice is incorporating new groups of drugs from other specialities that are used as psychotropic agents (for example, different types of anticonvulsants or the β-blockers).

Closing of psychiatric hospitals, less effective availability of acute patient beds and a community psychiatry with limited resources probably also influence the development of polymedication, above all, of the most serious patients. In our study, these factors seem to be relevant, since the nonexistence of any health care alternative other than weekly out-patient visits seems to head towards inevitable polymedication of the mental disorders present, as is manifested by the fact that the amounts of polymedication recorded are significantly greater than those obtained in another health care area of the Canary Islands, such as Gran Canaria, which has an adequate development of community resources for attention to mental health problems[24].

Defining what an adequate prescription is with psychoactive drugs is a really complex task since it involves the consideration of pharmacological, clinical, social and economic aspects. This complexity probably contributes to the great variability observed in the volume and type of drugs prescribed among different countries, within a same nation, and even among the different physicians of one institution[11,25]. Some authors have reached the conclusion that the concept of adequate prescription is almost as abstract as that of health[26].

Much of the great frequency of polymedication observed in our study does not have a scientific foundation that supports its effectiveness and safety. Polymedication with psychoactive drugs is a practice derived from clinical experience and which frequently represents «uncontrolled experiments» with an unknown toxic potential. At present, there is no scientific evidence that justifies the practice of polymedication with drugs of the same class and the high percentage recorded in our study should be corrected. However, the scientific literature offers us, day after day, new evidence on a wide number of situations in which polymedication with psychoactive drugs of different classes, adjuvant polymedication and augmentation or potentiation strategies seem to be indicated. However, potentiation and adjuvant strategies were uncommon in our study.

At present, the psychiatric clinical practice needs the development of indicators that permit adequate polymedication of mental disorders. However, it must be considered that the present strategies for the evaluation of psychoactive drugs, based on randomized controlled clinical trials, although they are adequate to compare individual drugs, fail when trying to study each potential drug combination, since this type of design tries to avoid the confusion that occurs with the use of additional agents. Meanwhile, research is needed on what patients are at risk of polymedication with psychoactive drugs to be able to develop adequate interventions that make it possible to minimize the risks associated to this extended health care practice.

REFERENCES

1. Andreasen, NC, Black DW. Introductory textbook of psychiatry. Washington: American Psychiatric Press, 1991.
2. Schazberg AF, Nemeroff CB. The American Psychiatric Textbook of Psychopharmacology. Washington: American Psychiatric Press, 1995.
3. Gelder M, Gath D, Mayou R, Cowen, P. Oxford textbook of psychiatry. Third edition. Oxford: Oxford University Press, 1996.
4. Welch R, Snaterse M. Combination therapy: is clinical practice leading the way. Clin Psychiatry, 2003;64(1):94.
5. Preskozn SH. Polypharmacy: when is it rational? J Pract Psychiatry Behav Health 1995;1:92-8.
6. Lewis L. Reduce polypharmacy and boost appropriate drug use. J Am Med Dir Assoc 2001;2(4):36-7.
7. Mason AS. Basic principles in the use of antipsychotic agents. Hosp Community Psychiatry 1973;24:825-9.

8. Tanaka E, Hisawa S. Clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system. J Clin Pharm Ther 1999;24:7-16.
9. Muir AJ, Sanders LL, Wilkinson WE, Schmader K. Reducing medication regimen complexity: a controlled trial. J Gen Intern Med 2001;16:77-82.
10. Murray MD, Kroenke K. Polypharmacy and medication adherence. Small Steps on a Long Road. J Gen Intern Med, 2001;16(2): 137-9.
11. De las Cuevas C, Sanz E, de la Fuente, JA. Variations in antidepressant prescribing practice. ¿Clinical need or market influences? Pharmacoepidemiol Drug Saf 2002;11:515-22.
12. Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. Eur J Clin Pharmacol 1997;53(1):7-11.
13. NASMHPD Medical Directors. Technical report on psychiatric polypharmacy. National Association of State Mental Health Program Directors. Alexandria, Virginia, 2001.
14. Stahl, SM. Antipsychotic polypharmacy: evidence based or eminence based? Acta Psychiatr Scand 2002:106;321-2.
15. World Health Organization. International Statistical Classification of diseases and related health problems, tenth revision. Vol 1. Geneva: WHO, 1992.
16. Berube MS, Neely DJ, DeVinne, PB. American Heritage Dictionary. 2nd College ed. Boston: Houghton Mifflin Co, 1982.
17. Werder, SF, Preskorn, SH. Managing polypharmacy: walking the fine line between help and harm. Current Psychiatry Online 2003;2(2)
18. Friend DG. Polypharmacy: multiple-ingredient and shotgun prescriptions. N Engl J Med 1959;260(20):1015-8.
19. Sheppard C, Collins L, Fiorentino D, Fracchia J, Merlis S. Polypharmacy in psychiatric treatment. I. Incidence at a state hospital. Curr Ther Res Clin Exp 1969;(12):765-74.
20. Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. Am J Psychiatry 2003;160(1):4-12.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders IV-TR. (Fourth edition, text revision.) Washington: American Psychiatric Association, 2000.
22. Rittmannsberger H. The use of drug monotherapy in psychiatric inpatinte treatment. Progress in neuro-psycho-pharmacology and biological psychiatry 2002;26:547-51.
23. Kapur S. Polypharmacy-in-a-Pill: a scientific advance or are we making a virtue of our necessities? Med Gen Med 2001;3(2).
25. De las Cuevas C, Sanz EJ. Polypharmacy in psychiatric practice in the Canary Islands. BMC Psychiatry 2004;4:18.
25. De las Cuevas C, Sanz EJ. Do therapeutic indications of antidepressants change from one year to another? Published Online: Pharmacoepidemiol Drug Saf, 2003.
26. Harris CM, Heywood PL, Clayden AD. The Analysis of prescribing in general practice: a guide to audit and research. London: HSMO, 1990.