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Multimorbidity, polypharmacy, referrals, and adverse drug events:

are we doing things well?

Abstract

Background
The consequences of multimorbidity include polypharmacy and repeated referrals for specialised care, which may increase the risk of adverse drug events (ADEs).

Aim
The objective of this study was to analyse the influence of multimorbidity, polypharmacy, and multiple referrals on the frequency of ADEs, as an indicator of therapeutic safety, in the context of a national healthcare system.

Design and setting
This was a multicentre, retrospective, observational study of 79 089 adult patients treated during 2008 in primary care centres.

Method
The explanatory patient variables sex, age, level of multimorbidity, polypharmacy, number of primary care physician visits, and number of different specialties attended were analysed. The response variable was the occurrence of ADEs. Logistic regression models were used to identify associations among the analysed variables.

Results
The prevalence of individuals with at least one ADE was 0.88%. Multivariate analysis identified the following variables as risk factors for the occurrence of ADE in descending order of effect size: multimorbidity level (odds ratio [OR] Veryhigh/Low = 45.26; ORHigh/Low = 17.58; ORModerate/Low = 4.25), polypharmacy (OR = 1.34), female sex (OR = 1.31), number of different specialties (OR = 1.20), and number of primary care physician visits (OR = 1.01). Age, however, did not show statistical significance (OR = 1.00; 95% confidence interval = 0.996 to 1.005).

Conclusion
The results of this study demonstrate that multimorbidity is strongly related to the occurrence of ADEs, insofar as it requires the intervention of multiple specialties and the prescription of multiple medications. Further research should shed light on the causal pathway between multimorbidity and increased risk of adverse events.

Keywords
adverse drug event; healthcare system, national; multimorbidity, multiple; polypharmacy; referral, hospital.

INTRODUCTION

The presence of several chronic illnesses in a single individual, termed multimorbidity, is a common occurrence in the majority of developed countries,[1] including Spain.[2] Although it particularly affects the older population, this problem is also present at other stages of life, including childhood.[3]

Recent studies have revealed the existence of patterns of multimorbidity that consist of systematically associated clinical conditions.[2] Such patterns evolve and worsen over the course of a patient's life, and reflect clinical situations that cut across individual medical specialties established by healthcare systems.[2]

The consequences of this complex reality for a healthcare system in which the majority of illnesses are chronic and affect the older and frailer portion of the population include polypharmacy (that is, the simultaneous and prolonged prescription of multiple medications to a single individual),[4] and repeated referrals for specialised care.[5]

These 'natural' consequences may have associated risks that are often unanticipated and insufficiently analysed, and ultimately compromise the health of the patient. For example, it has been evidenced that polypharmacy significantly increases the risk of inappropriate prescription and adverse drug events (ADEs).[6] In addition, care of the same patient by different specialists has been shown to carry a risk of fragmented care, with frequent failures of the communication among professionals that is essential for evaluating and monitoring the patient's therapeutic regimen.[7,8]

Because of its high frequency and its consequences for patients in terms of therapeutic safety, this complex reality (patients with multimorbidity, polypharmacy, and under the care of different specialists) justifies new studies to improve understanding and awareness of this scenario. To the study's knowledge, none of the studies that have analysed this issue have taken place in a healthcare system where the family physician serves as the entry point to the system and provides continuous care for the patient.[9]

This study aims to analyse the influence of these factors (multimorbidity, polypharmacy, and multiple referrals) on the frequency of ADEs, as an indicator of therapeutic safety, in the context of a national healthcare system.

METHOD

This was a multicentre observational study of patients treated at seven urban primary care centres in Zaragoza, Spain. Selection of centres to participate in this study was conducted based on the following quality inclusion criteria: (a) centres with computerised records for all appointments

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How this fits in

Patients with multimorbidity and polypharmacy, and under the care of different specialties, are now the rule rather than the exception. These conditions make patients' management and treatment difficult and may threaten their therapeutic safety. The results of this study demonstrate that multimorbidity is strongly related to the occurrence of adverse drug events, insofar as it requires the intervention of multiple specialties and the prescription of multiple medications.

and with more than 2 years' experience using this system by all physicians and nurses; (b) those with less that 20% of uncoded episodes; (c) those with less than 15% of notes (for example, prescription) listed in uncoded episodes; (d) those with less than 10% of prescriptions linked to uncoded episodes; (e) those with an average number of diagnoses higher than 3.5; and (f) those with less than 10% of patients with no diagnostic information.

All patients from the selected centres aged ≥14 years were included in the study if they were seen at least once during 2008 by their family physician and were assigned to the same doctor on 31 December of the same year. Information was extracted from primary care electronic medical records and the Aragón pharmacy database. Written consent by patients was not needed, since the work is based on the analysis of anonymous data contained in previously existing databases.

For each of the patients included in the study, the following variables were extracted from the record: age, sex, diagnostic episodes coded according to the International Classification of Primary Care (ICPC),[10] visits to the family physician, and referrals to specialists made by the family physician during 2008. The variable 'number of different specialties' was generated by adding all different specialties to which the patient was referred by their family physician during the study year, excluding internal referrals within the primary care setting (paediatrics, nursing, physical therapy, social work, dentistry, and midwifery).

Among the tools commonly used to measure and characterise multimorbidity is the Adjusted Clinical Groups System® (ACG), which is used to classify patients into 106 homogeneous categories as a function of clinical (diagnostic), demographic (age and sex), and need-for-care (frailty) variables obtained from the electronic medical record.[11] To reduce the number of ACG categories to a more practical level for analysis, those categories that group patients with similar levels of multimorbidity are aggregated by the system into so-called resource utilisation bands (RUB 1 = healthy, RUB 2 = low morbidity, RUB 3 = moderate morbidity, RUB 4 = high morbidity, and RUB 5 = very high morbidity).[12] Consequently, the system also assigns a RUB category to each patient.

From the pharmacy database, detailed information was extracted about the medications dispensed to the study population from the pharmacy offices in Aragón, excluding those medications administered at the hospital (for example, antineoplastic drugs, antiretroviral drugs, blood coagulation factors, immunostimulating interferons). Specifically, information was extracted about the prescribed and dispensed active ingredients coded according to the Anatomical, Therapeutic, Chemical (ATC) Classification System, as well as the month and year of dispensation. This methodology allowed the variable 'patient with polypharmacy' to be constructed, defined in the present study as a person who received six or more medications with different active compounds in at least 1 month of the study year. For this variable, categories V (Various) and Y (Effects and Accessories) from the ATC classification were excluded because these categories group products outside the strict definition of medications.

The dependent variable 'patient with at least one ADE' was generated based on the presence of at least one episode coded with the ICPC code A85 (Adverse Drug Effect; Correct Dose) in the patient's electronic medical record.

A descriptive analysis of the study variables was performed based on frequency calculations. χ^2 tests were used to determine independence between the presence of ADEs and the rest of the variables. To this end, continuous variables were categorised as follows: age (14–17, 18–34, 35–44, 45–54, 55–64, 65–69, 70–74, 75–79, 80–84, and ≥85 years), number of different specialties (0, 1–3, 4–6, and >6), and number of visits to the family physician (0, 1–9, 10–20, 21–30, and >30). Bivariate and multivariate logistic regression models were used to quantify the associations obtained from the independence tests. In this case, the continuous variables were introduced into the models, to maximise the use of the available information. Statistical analysis was performed using the program STATA (version 11).

Table 1. Distribution of patients with at least one adverse drug event according to demographic variables, level of multimorbidity, and health services use

Variable	Population (*n* = 79 089)	Presence of at least one ADE (*n* = 692), *n* (%)	95% CI of percentage	*P*-value
Age, years				
14–17	2059	16 (0.78)	0.40 to 1.16	<0.001
18–34	19 600	87 (0.44)	0.35 to 0.54	
35–44	12 456	76 (0.61)	0.47 to 0.75	
45–54	12 188	92 (0.75)	0.60 to 0.91	
55–64	12 347	136 (1.1)	0.92 to 1.29	
65–69	5193	74 (1.42)	1.10 to 1.75	
70–74	4970	75 (1.51)	1.17 to 1.85	
75–79	4717	67 (1.42)	1.08 to 1.76	
80–84	3206	43 (1.34)	0.94 to 1.74	
≥85	2348	26 (1.11)	0.68 to 1.53	
Sex				
Male	34 487	224 (0.65)	0.56 to 0.73	<0.001
Female	44 602	468 (1.05)	0.95 to 1.14	
RUB				
Healthy	9552	0 (0)	0	<0.001
Low morbidity	22 542	43 (0.19)	0.13 to 0.24	
Moderate morbidity	43 768	460 (1.05)	0.96 to 1.15	
High morbidity	3008	158 (5.25)	4.46 to 6.05	
Very high morbidity	219	31 (14.16)	9.53 to 18.78	
Number of different specialties				
0	45 297	237 (0.52)	0.46 to 0.59	<0.001
1–3	32 966	429 (1.3)	1.18 to 1.42	
4–6	811	25 (3.08)	1.89 to 4.27	
>6	15	1 (6.67)	6.40 to 19.73	
Number of family physician visits				
0	2698	28 (1.04)	0.66 to 1.42	<0.001
1–9	61 137	352 (0.58)	0.52 to 0.64	
10–20	12 171	234 (1.92)	1.68 to 2.17	
21–30	2169	56 (2.58)	1.91 to 3.25	
>30	914	22 (2.41)	1.41 to 3.40	
Polypharmacy[a]				
Yes	19 666	350 (1.78)	1.59 to 1.96	<0.001
No	59 423	342 (0.58)	0.51 to 0.64	

RUB = resource utilisation band.[12] [a]Six or more different active compounds in at least 1 month.

Table 2. Bivariate analysis of the risk of adverse drug events

Factors	OR	*P*-value	95% CI
Age	1.020	<0.001	(1.016 to 1.024)
Sex: female/male	1.622	<0.001	(1.382 to 1.903)
RUB			
Healthy	—	—	—
Low morbidity	Reference		
Moderate morbidity	5.558	<0.001	(4.064 to 7.600)
High morbidity	29.007	<0.001	(20.660 to 40.728)
Very high morbidity	86.278	<0.001	(53.196 to 139.933)
Number of different specialties	1.623	<0.001	(1.528 to 1.722)
Number of visits to family physician	1.061	<0.001	(1.054 to 1.068)
Polypharmacy[a]: yes/no	3.130	<0.001	(2.694 to 3.636)

OR = odds ratio. RUB = resource utilisation band.[12] [a]Six or more different active compounds in at least 1 month.

RESULTS

Of the 79 089 patients studied, 692 had at least one ADE during the study period. As seen in Table 1, in which the distribution of patients with ≥1 ADE is described according to the different categories of the study variables, the majority of these patients were female, were aged 70–74 years old, and had a very high level of multimorbidity, polypharmacy, a high frequency of family physician visits (that is, 21–30 annual visits), and a high number of referrals to different specialties (that is, six or more specialties).

While the bivariate analysis demonstrated statistically significant associations between the risk of ADE and all the independent variables studied (Table 2), the multivariate analysis (Table 3) identified the following variables as risk factors in descending order of effect size: level of multimorbidity (odds ratio [OR]Veryhigh/Low = 45.26; ORHigh/Low = 17.58; ORModerate/Low = 4.25), polypharmacy (OR = 1.34), female sex (OR = 1.31), number of different specialties (OR = 1.20), and number of visits to the primary care physician (OR = 1.01). Age, however, did not show statistical significance (OR = 1.00; 95% confidence interval = 0.996 to 1.005).

DISCUSSION

Summary

This study demonstrates the existence of a latent problem in the context of a national healthcare system in which the primary care physician acts as the entry point into the system and has the assigned function of monitoring the overall health of the patient. As the clinical situation of the patient becomes more complex and requires the intervention of different specialists, the likelihood of a lack of coordination among professionals and potential interactions among prescribed medications could favour the occurrence of undesirable effects, such as ADEs. The results of this study indicate that for every new specialty that participates in the care process, the probability that a patient will suffer an ADE increases by 12–28%, even after adjusting for known ADE risk factors such as age, sex, polypharmacy, frequency of primary care physician visits, and the burden of morbidity itself. While some factors such as age, sex, and level of multimorbidity have a direct relationship with the disease severity and clinical situation of the patient,[13–15] the undesirable effects of other factors, such as polypharmacy, frequency of family physician visits, and referrals to specialists, can be minimised. This reduction can be accomplished through new models of

Table 3. Multivariate analysis of the risk of adverse drug events

Factors	OR	*P*-value	95% CI
Age	1.001	0.811	(0.96 to 1.005)
Sex: female/male	1.307	0.001	(1.110 to 1.538)
RUB			
Healthy	—	—	—
Low morbidity	Reference		
Moderate morbidity	4.246	<0.001	(3.079 to 5.855)
High morbidity	17.577	<0.001	(12.229 to 25.265)
Very high morbidity	45.264	<0.001	(26.977 to 75.948)
Number of different specialties	1.195	<0.001	(1.116 to 1.280)
Number of visits to family physician	1.013	0.008	(1.003 to 1.023)
Polypharmacy[a]: yes/no	1.344	0.003	(1.106 to 1.634)

OR = odds ratio. RUB = resource utilisation band.[12] [a]Six or more different active compounds in at least 1 month.

professional practice, increased availability of adequate informative tools, or other improvement interventions.[16,17] Results from this study suggest that the effect of age on the occurrence of ADEs might disappear when the variable level of multimorbidity is considered.

Limitations of the study

Various limitations warrant prudent interpretation of the results of this study. The first is related to the result variable selected. Although ADEs are a good indicator of the safety of care (among the 10 leading causes of mortality worldwide,[18] and, on occasion, surpassing the cost of treatment of the baseline illness[19]), other indicators related to care, communication, diagnosis, or health management should also be considered and may offer a wider view of deficiencies in the care provided to patients with multimorbidity. However, it should be noted that, according to the 2008 APEAS study of patient safety in primary care performed by the Spanish Ministry of Health,[20] 47.8% of the adverse events detected in the primary care environment are due to medications,

The information about the occurrence of ADEs used in this study comes from an active registry of ADEs by physicians. Despite currently constituting the principal source of information for identifying areas of improvement in medication-related patient safety, this registry only includes 5–10% of the actual aggregate incidence of ADEs.[21] However, it is known that recorded ADEs tend to be those that involve a greater threat to the health of the patient.[22]

Importantly, the number of different specialties is an approximation of the number of different physicians who eventually prescribed medication to a single patient during the study year; an aspect that underlies the occurrence of ADEs.[7,8,23] This variable does not include care received by professionals other than the family physician, either within the primary care setting or in other settings such as an emergency room or hospital. Neither does it include referrals among specialists or care at private centres.

It should also be noted that the polypharmacy variable does not include medications administered at a hospital or over-the-counter drugs.

Comparison with existing literature

The presence of various chronic illnesses in a single patient is currently the rule rather than the exception. However, clinical care continues to be structured and organised to treat a single health problem at a time or, worse yet, to treat the various illnesses that a single patient has as if they were independent of each other and also isolated from the individual who suffers from them.[24] In fact, in the Spanish healthcare system, a considerable proportion of pharmaceutical prescriptions originate at the level of specialised care,[25,26] where it could be argued that the concept of the chief complaint takes priority over the overall health of the patient. In a recent hospital-based study of patients with polypharmacy, a lack of consideration of the medications that the patient was taking at the time of admission was responsible for up to 52.7% of medication errors.[27]

Most likely, one of the principal structural factors that makes clinical and therapeutic follow-up of the patient difficult for the group of professionals who provide care is related to the availability and adequate use of responsive and uniform information systems for the different levels of care.[28,29] Therefore, using a single electronic medical record or reinforcing the training of professionals in the use of available information tools would be beneficial steps.

Moreover, strengthening the necessary fluid and constant dialogue among professionals at different levels of care requires that organisational elements facilitate such dialogue. There are reports in the literature of interventions that yielded greater reduction of ADEs, including endowing hospital professionals with the specific function of reconciling medications,[30] or having geriatrics specialists evaluate frail, older patients.[31] However, one of the most effective measures for decreasing ADEs, and therefore improving the safety of the

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Ethical approval

Written consent by patients was not needed since the work is based on analysis of anonymous data contained in previously existing databases. The study is framed within a project that was favourably evaluated by the Clinical Research Ethics Committee of Aragon (CEICA).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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care being given, consists of enhancing and strengthening the natural role of the primary care physician as a 'medication reconciler'.[32] Whenever feasible, the family physician is ideally placed to conduct an appropriate pharmacologic review of the patient, which can include asking for the removal of medications that are of little use, redundant, not indicated, or contraindicated.[33]

Finally, it should not be forgotten that a large gap currently exists, on the part of professionals, in the availability of clinical guidelines and protocols that guide the management of patients with multimorbidity.[34] Physicians frequently find themselves deciding whether to apply criteria that, while adequate for each illness that a patient has, are not appropriate when the diseases are considered together.[4] Finding solutions to this problem has become a critical priority.

Implications for research and practice

Further studies are required to shed light on the causal pathway between multimorbidity and increased risk of adverse events. For example, research should address whether the existence of gaps that disrupt the continuity of care has undesirable consequences related to patient safety.

Longitudinal studies following patients with multimorbidity over their life course would enable better capture of the incidence of ADEs, avoiding underestimation resulting from the potential time lag between contacting health services and the occurrence of an adverse event.

Other research lines following from this study include: examining ADEs in relation to different therapeutic groups such as analgesics, cardiovascular medications, or antidepressants; determining the influence of healthcare providers; and studying other possible adverse events such as major trauma, suicide, or falls.

The results of this study demonstrate that multimorbidity is strongly related to the occurrence of ADEs, insofar as it requires the intervention of multiple specialties and the prescription of multiple medications.

As indicated by Starfield *et al* a decade ago,[35] it is necessary, now more than ever, to design strategies that encourage a review of the individual's health problems in their totality, rather than examining each of the patient's illnesses individually. This approach is important, as a result of the following factors: (1) the presence of concomitant chronic illnesses, which is most common in older people but also present at other stages of life; (2) frequent interactions between illnesses and medications or among medications that should not be forgotten or ignored; and (3) the fact that the repercussions of not taking such an approach greatly impact the healthcare system and can be devastating for the health of the patient.

Although this problem is complex, it is not intractable, and the scientific community is beginning to offer sufficient knowledge to be able to develop a solution.

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