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Polypharmacy in Patients With Inflammatory Bowel Disease

Prevalence and Outcomes in a Single-center Series

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Background: Polypharmacy can complicate the course and management of chronic diseases, and has been little explored in patients with inflammatory bowel disease (IBD) to date.

Aim: The aim of this study was to determine the prevalence of polypharmacy in a series of IBD patients, describing associated factors and its correlation with poor disease outcomes.

Materials and Methods: Retrospective study of a single-center series. Polypharmacy was defined as the simultaneous use of 5 or more drugs. Disease outcomes, IBD treatment nonadherence and undertreatment were evaluated at 1 year.

Results: A total of 407 patients were included [56% males, median age: 48 y (interquartile range, 18 to 92 y)], of whom 60.2% had Crohn's disease; Chronic comorbidity and multiple comorbidities were present in 54% and 27% of patients, respectively. Median number of prescriptions per patient was 3 (range: 0 to 15). Polypharmacy was identified in 18.4% of cases, inappropriate medication in 10.5% and use of high-risk drugs in 6.1% (mainly opioids). In multivariate analysis, polypharmacy was associated with chronic comorbidity [odds ratio (OR) = 10.1, 95% confidence interval (CI): 2.14-47.56; $P<0.003$], multiple comorbidities (OR = 3.53, 95% CI: 1.46-8.51; $P=0.005$) and age above 62 years (OR = 3.54, 95% CI: 1.67-7.51; $P=0.001$). No association with poor disease outcomes was found at 12 months. However, polypharmacy was the only factor associated with IBD treatment nonadherence (OR = 2.24, 95% CI: 1.13-4.54, $P=0.02$).

Conclusions: Polypharmacy occurs in around 1 in 5 patients with IBD, mainly in older adults and those with comorbidity. This situation could interfere with adherence to IBD treatment and therapeutic success.

Key Words: polypharmacy, inflammatory bowel disease, comorbidity, outcomes

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The concept of polypharmacy (PP) is still under debate, and no universal definition has yet been adopted.[1] Although the simplest description is the use of multiple medicines, but there are >100 interpretations of PP in the literature. In the systematic review published by Masnoon et al,[2] the most common definition for PP was the use of 5 or more medications. PP is a global problem at present. In a nationally representative population of the United States that included individuals aged 57 to 85 years old, the prevalence of PP (defined as the use of at least 5 medications) was 29%, increasing to 37% in the older population.[3] Although these percentages were lower in several European series, with reported prevalence of PP ranging from 1.2% to 9%, an increase of up to 34% also found in older adults.[4,5] PP has a major impact on healthcare due to its high prevalence among older individuals and association with chronic diseases and multiple comorbidities, which are themselves frequently interrelated.[6]

Ageing of the world's population has been observed in recent decades, mainly due to increased life expectancy.[7–9] One of the consequences of ageing is the presence and increase of most chronic diseases and multimorbidity.[10–12] A cross-sectional survey performed in 2003, 2008, and 2013 in a Chinese population reported a continuous increase in chronic conditions among middle-aged and older adults.[13] It is interesting to note that associations have been found between several chronic diseases, such as respiratory, mental health, cardiometabolic, endocrinological, osteometabolic, and mechanical-pain disease and PP, with association patterns becoming more complex with age.[14]

Importantly, PP is also associated with poor outcomes such as drug interactions,[15] adverse events,[16] poor drug compliance,[17] undertreatment,[18] hospitalization,[19] and even mortality.[20]

Inflammatory bowel disease (IBD) is a chronic digestive condition affecting both young and older adults. At present, around 10% to 30% of patients are over 60 years old, some of whom were diagnosed at older ages.[21] The

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worldwide incidence rate of IBD is increasing across all age groups, and its overall prevalence among older individuals is expected to grow substantially.[22–25] Consequently, the occurrence of other chronic conditions associated with IBD is expected, especially in older patients. In a Swiss cohort of 4791 IBD patients, 78% had at least 1 comorbidity, with a median of 3, the most frequent being cardiovascular diseases, rheumatologic conditions, and acid-related disorders; comorbidities such as chronic pain, bone diseases, migraines, cancer, and iron-deficiency anemia were more frequent in non-IBD patients.[26] Other studies have associated IBD with different chronic conditions, such as psychiatric disorders[27] and other autoimmune diseases.[28] Despite the high prevalence of older IBD patients, and the fact that most of these patients will become even older over the coming years, there are few studies on their treatment and management beyond specific IBD treatments, and a considerable gap in knowledge surrounding PP remains. Given the scant literature evaluating the prevalence, characteristics and consequences of PP in the IBD population, the aim of this study was to explore these in a clinical series of IBD patients, identifying possible associated factors and their correlation with poor disease outcomes.

MATERIALS AND METHODS

Study Design and Endpoints

This was an observational, noninterventional, retrospective single-center study conducted in patients aged 18 years and above with IBD [Crohn's disease and ulcerative colitis according to the second European Crohn's Colitis Organization (ECCO) diagnostic criteria[29,30]] who visited our IBD Unit between September and October 2018. Data were extracted by reviewing clinical records and the electronic drug prescription program. Patients who were lost to follow-up from this visit up to 1 year later were not included.

We collected active drug prescriptions, demographic data, clinical features, adherence to IBD treatment and outcomes 12 months after the index visit.

The primary objective of this study was to evaluate the prevalence of PP and inappropriate and high-risk medication at the index visit. Secondary objectives were to identify factors associated with PP, and to evaluate outcomes associated with PP at 12 months [flares, hospitalizations, surgeries, and outcomes related with IBD treatment (nonadherence and undertreatment)].

Definitions

PP was defined as the simultaneous use of at least 5 drugs.[2] IBD-specific treatment taken per patient were included for this variable (except biological therapy). We did not consider supplements or over-the-counter drugs. Inappropriate medication use was defined according to STOPP criteria, a screening tool to quickly identify common errors regarding medication according to organs and systems.[31] High-risk drugs were defined as those with a high likelihood of causing harm if misused and which present a narrow therapeutic index. The acronym APINCH was developed by the Australian Commission on Safety and Quality in Health Care,[32] and defines high-risk medication: anti-infectives, potassium and other electrolytes, insulin, narcotics and other sedatives, chemotherapeutic agents, and heparin and other anticoagulants.

We identified patient comorbidities considered as chronic conditions and included in the *International Statistical Classification of Diseases and Related Health Problems, 11th Revision* (ICD-11).[33] Of these, we selected as significative neoplasms, metabolic diseases, diseases of the respiratory, cardiovascular and musculoskeletal system, and connective tissue diseases and mental-behavioral disorders. Multiple comorbidities was defined when any 3 comorbidities were present.

To describe outcomes at 12 months, we evaluated the presence of flare using clinical activity indices (Harvey Bradshaw Index score ≥ 5 for Crohn's disease and Simple Clinical Colitis Activity Index score ≥ 5 for ulcerative colitis)[34,35] and/or the need to add or switch IBD treatment (1 step). We also recorded hospitalization due to active IBD disease as well as related surgeries. Treatment adherence was evaluated by reviewing clinical records, in which patients are usually asked about drugs they have forgotten to take between visits. We considered a patient adherent when their medication adherence percentage (defined as the number of treatments absent in a given time period divided by the number of treatments prescribed in that same time period) was $>80\%$. Undertreatment was defined as inadequate patient management with specific IBD therapy, as suggested by evidence-based medicine or as recommended by IBD scientific societies.[36,37]

Statistical Analysis

In the descriptive analysis, categorical variables were expressed as absolute and relative frequencies. For quantitative variables, we calculated the mean and SD, or the median and interquartile range for variables without normal distribution. In the univariate analysis, categorical variables were compared using the χ^2 test and quantitative variables using the Student t test. Analysis of variance test were used to compare age with PP.

Univariate analysis was performed to identify poor outcomes associated with PP, stratifying by disease severity. Factors that were found to be significantly associated with undertreatment and treatment nonadherence (including PP) were further explored in a multivariate analysis using a logistic regression model. We used the odds ratio (OR) with a 95% confidence interval (CI). A P-value <0.05 was considered statistically significant.

Ethical Considerations

The design and methodology of this study was reviewed and approved by the Clinical Research Ethics Committee of the University Hospital Ramón y Cajal, Madrid, Spain. Written informed consent was obtained from all patients to participate in the study.

RESULTS

Baseline Patient Characteristics

Four hundred seven patients were recruited. Demographics and disease-related findings are shown in Table 1. Most patients were men (56%); median age was 48 years old (18 to 92 y). A total of 60.4% patients presented Crohn's disease and 38.8% had ulcerative colitis. Chronic comorbidity was present in 54% of cases, among which metabolic disease (29%), cardiovascular disease (25.5%), and mental-behavioral disorders (12.8%) were the most prevalent. One in every 4 comorbid patients (27%) presented multiple comorbidities (Table 2).

TABLE 1. Demographic and Disease-related Characteristics

Characteristics	N = 407 [n (%)]
Sex	
Male	228 (56)
Female	179 (44)
Age [mean (range)] (y)	48 (18-92)
IBD	
Crohn's disease	246 (60.4)
Ulcerative colitis	158 (38.8)
Unclassified	3 (0.7)
Tobacco use	
No	333 (81.8)
Yes	74 (18.2)
Previous surgery	
No	288 (70.8)
Yes	119 (29.2)
Activity	
Mild	151 (37.1)
Moderate	174 (42.8)
Severe	82 (20.1)
Crohn's disease behavior	
Luminal (B1)	118 (47.9)
Stricturing (B2)	84 (34.1)
Penetrating (B3)	48 (19.5)
IBD treatment (%)	
Biologic	29.2
Oral mesalamine	18.9
Thiopurines	17.2
No treatment	16.5
Combination therapy (biologic plus immunomodulator)	12.8
Methotrexate	2
Tofacitinib	2
Steroids	1.5
Extraintestinal manifestations	
No	356 (87.5)
Yes	51 (12.5)

IBD indicates inflammatory bowel disease.

Use of PP, Inappropriate Prescriptions, and High-risk Drugs

The median number of prescriptions was 3 (range: 0 to 15). Percentages of the number of drugs taken per patient are shown in Figure 1. The median number of IBD-specific treatment was 1 (interquartile range: 1). Major drug classes used were analgesics (27.3%), proton pump inhibitors (PPIs) (24.8%), antihypertensives (21.4%), psychoactive drugs (20%), and statins (14.5%) (Fig. 2). PP was identified in 18.4% of cases, inappropriate prescriptions in 10.5%, and high-risk drugs in 6.1% (mainly opioids). The most common inappropriate prescriptions were for benzodiazepines, neuroleptics, opioids and antihistaminics in fall-risk dependent patients and for opioids, tricyclic antidepressants, and/or nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with arterial hypertension. In the univariate analysis (Table 3), age over 61 years old, presence of any chronic disease, dependence, and multimorbidity were factors significantly associated with PP. In the multivariate analysis (Table 3), age over 62 years old (OR: 3.54, 95% CI: 1.67-7.51; $P = 0.001$), presence of concomitant chronic disease (OR: 10.1, 95% CI: 2.14-47.56; $P = 0.03$), specific presence of mental-behavioral disorders (OR: 2.3, 95% CI: 1.01-5.26, $P = 0.047$), and multimorbidity (OR: 3.53, 95% CI: 1.46-8.51; $P = 0.005$) were significantly associated with PP.

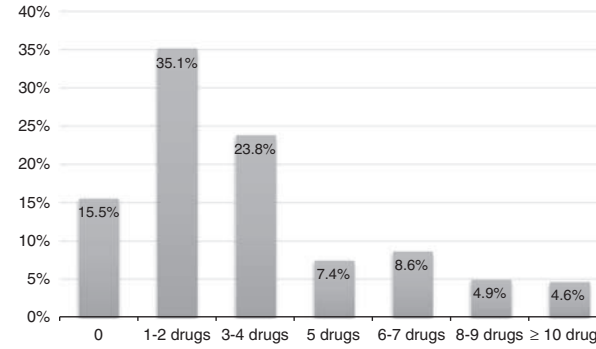

FIGURE 1. Number of medications taken per patient.

TABLE 2. Patients Comorbidities

Group Diseases (ICD-11)	n (%)
Metabolic diseases	118 (29)
Cardiovascular diseases	103 (25.3)
Mental-behavioral disorders	52 (12.8)
Respiratory disorders	38 (9.3)
Neoplasm	30 (7.4)
Renal disease	6 (1.5)
Other chronic disease*	55 (13.5)
Multiple comorbidities	110 (27)

*Arthrosis, chronic pain, neurological disorders, connective tissue disease, and other rheumatological diseases.

ICD-11 indicates International Statistical Classification of Diseases and Related Health Problems, 11th Revision.

Outcomes

At 12 months, the percentage of flares, need to switch or add new IBD treatment, hospitalizations and surgeries were identified in 24.6%, 18.2%, 6.6%, and 5.2% of patients, respectively. There were no significant differences between the PP population with these poor disease outcomes after adjusting for severity of IBD.

Regarding IBD treatment, nonadherence was evaluated in 387 patients, and was presented in 14.3%. Furthermore, undertreatment was documented in 6.4% of cases. The rates of undertreatment (18.7% vs. 3.6%, $P<0.001$) and nonadherence (26.6% vs. 12%, $P<0.02$) were significantly higher among the PP population at 12 months. In the multivariate analysis performed to identify factors associated with undertreatment and treatment nonadherence, PP was the only factor associated with nonadherence (OR: 2.24, 95% CI: 1.13-4.54, $P = 0.02$).

DISCUSSION

Our results show that PP is also present in IBD patients, with a prevalence of 1 in 5 patients, and reaching 48% in patients older than 62 years old. This highlights the fact that PP is a global problem and a common clinical issue in this population.

Compared with other chronic diseases, PP in IBD patients does not appear to be more prevalent. Viktil et al[38] reported the prevalence of PP in a cohort of 313 patients with rheumatic diseases at nine hospitals; 60% of patients used 5 or more drugs, the most frequent being corticosteroids and NSAIDs. In a systematic review and meta-analysis performed in a type 2 diabetes population, the rate of PP varied between 6.9% and 93.4%.[39] These variations may be explained by age (most studies included older patients), other population characteristics and, again, the

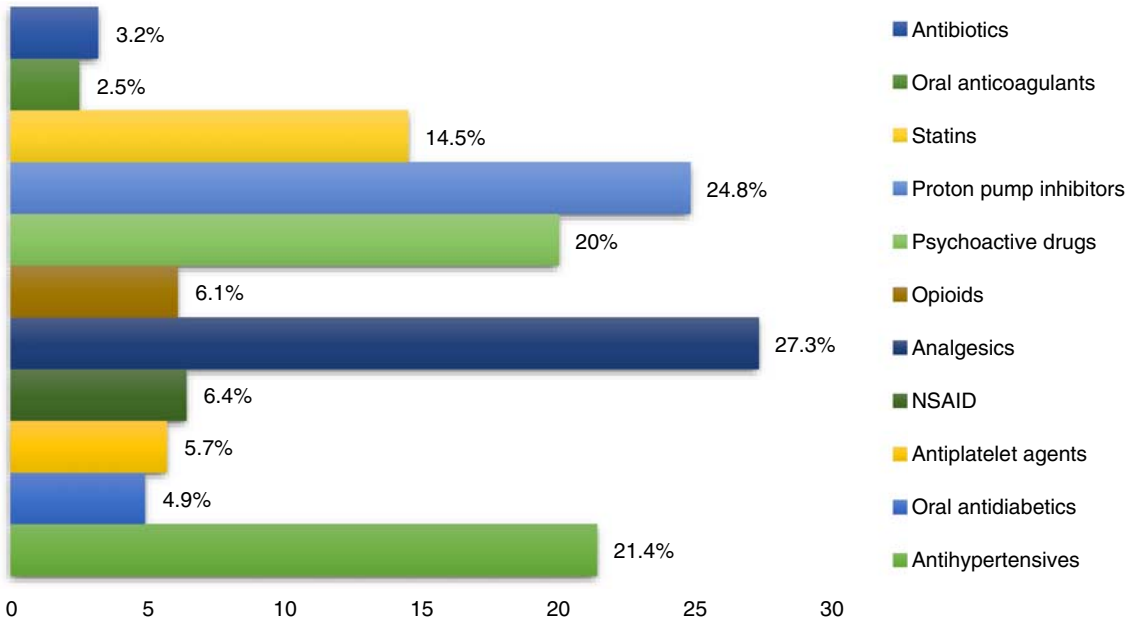

FIGURE 2. Drug use by class. NSAID indicates nonsteroidal anti-inflammatory drug.

definition of PP. However, in most of the studies, PP was defined as the concurrent use of 5 or more drugs.

Nowdays, 3 studies have explored previously the role of PP in IBD.[40–42] Cross and colleagues identified a prevalence of PP (≥ 5 medications) of 49.8% over 291 Crohn's disease patients included. The most widely consumed drugs were vitamin and mineral supplements (55.3%). In other clinical series of 457 patients with ulcerative colitis PP was present in 29.8%. It is likely that the high rate of PP observed in these series were mainly due to the inclusion of over-the-counter drugs.[40,41] Parian and Ha[42] evaluated the prevalence of PP in an older IBD population (190 patients with ≥ 65 y old), considering PP as the use of ≥ 10 drugs it was present around 43% of them. Our results confirm that older age is associated with a potential higher risk of PP too (OR: 3.54).

TABLE 3. Factors Associated With Polypharmacy

Variables	Univariate Analysis (*P*)	Multivariate Analysis [OR (95% CI)]	*P*
Sex	0.79		
IBD type	0.153		
Age > 62 y old	0.001	3.54 (1.67-7.51)	0.001
Tobacco	0.43		
Extraintestinal manifestations	0.164		
Associated comorbidity	0.001	10.1 (2.14-47.56)	0.003
Metabolic disease	0.001	1.44 (0.66-3.14)	0.35
Cardiovascular system	0.001	0.87 (0.38-1.98)	0.736
Mental-behavioral disease	0.001	2.3 (1.01-5.26)	0.047
Respiratory system	0.001		
Renal disorders	0.002		
Neoplasms	0.001		
Multimorbidity	0.001	3.53 (1.46-8.51)	0.005
Dependence	0.001	2.61 (0.65-10.48)	0.175

CI indicates confidence interval; IBD, inflammatory bowel disease; OR, odds ratio.

Another important finding in our study is the high prevalence of chronic comorbidity; more than half of patients presented at least 1 associated chronic disease. These results are consistent with the Swiss series, in which cardiovascular and metabolic disease were the most prevalent comorbidities.[26] In our series, psychiatric disorders were also considerable, present in 13% of patients. These results are in line with those shown in the systematic review published by Mikocka-Walus et al,[27] in which the pooled mean proportions of anxiety and depression were 19.1% and 21.2%, respectively. Importantly, the concomitant presence of these chronic conditions requires the use of some drugs to control symptoms according to clinical guidelines that often do not take into account patients with chronic multimorbidity, contributing to the appearance of drug addiction problems.[43]

The most frequently used drug class in our series was analgesics. Pain and discomfort are a common issue, and analgesics the most widely used drug to control them, especially in self-medication.[44] A French study published in 2016 described trends in analgesic use compared with other European countries using national databases, showing that analgesic consumption had increased in the last 10 years up to 121 defined daily doses per 1000 inhabitants; France was the third ranked country in use after the UK and Spain.[45] In a recent Spanish anonymous survey on self-medication with analgesics conducted in 546 patients with ulcerative colitis, around one half of patients declared that they had used them in the past year.[46] The second most commonly used drug class was PPIs. In the United States, PPIs represent the third most commonly prescribed drug.[47] Despite well-defined indications regarding the use of PPIs, this group continues to grow worldwide, highlighting the need to reestablish correct use of this drug class.[48,49] As

gastroenterologists, it is very important to establish and reassess the indications for PPIs in IBD patients for several reasons, such as some intestinal adverse events, small intestinal bacterial overgrowth, a possible association with the development of microscopic colitis and, finally, the risk of presenting *Clostridioides difficile* infection.[50–52]

Our results show that patients consumed a low but non-negligible proportion of NSAIDs (6.4%), opioids (6.1%) and other high-risk drugs (6.1%). Cross et al[53] reported a rate of opioid use in Crohn's disease patients of 13.1%. Opioids can be prescribed in IBD for temporary pain relief in specific situations such as postoperative pain. However, it was found that both adolescents and young adults with IBD had a higher prevalence of chronic opioid therapy compared with the general population (up to 18.2%), mainly to control disease activity and pain, despite the risk of narcotic bowel syndrome, dependence, psychiatric comorbidities, lower quality of life, and high risk of infections.[54–57]

Our findings also confirm that PP is associated with advanced age, comorbidities and multimorbidity.[6,14,38,41,42] Previous clinical series reported that female sex was associated with PP (OR: 2.4, 95% CI: 1.5-4.0).[40,41] Nevertheless, we found no differences between sex, tobacco use, or disease severity. Psychiatric disorders were a specific comorbidity associated with PP in multivariate analysis of our series (OR: 2.3, 95% CI: 1.01-5.26; $P = 0.0047$). This finding was previously reported in a retrospective study of 1205 elderly patients without IBD, in which depression was an independent predictive factor for PP (OR: 4.5, 95% CI: 3.2-6.5, $P < 0.001$).[58] Moreover, Wang et al[41] found PP was also associated with psychiatric disorders (32%).

This series evaluated IBD outcomes associated with PP at 12 months, finding no significant differences between patients taking PP and non-PP users, even when stratified by disease activity.[40] Wang and colleagues evaluated clinical outcomes in ulcerative colitis patients related with PP and could correlated with a higher risk of flare (OR: 4) in patients with major PP during 5 years of follow-up. However, hospitalizations, surgery and therapy escalation were not significantly associated.[41] It is possible that our short term of follow-up could interfered in our results.

We also evaluated the risk of treatment nonadherence, because this is a real problem in several published series in IBD. The overall prevalence of medication nonadherence ranged between 7% and 27%, depending on the study design, definitions, and populations.[59] Among a number of factors that have been associated with treatment nonadherence in IBD patients, PP has been poorly explored. Kane et al[60] evaluated the nonadherence rate in an ulcerative colitis series under mesalamine treatment. Of 94 patients, 40% presented mesalamine nonadherence, and a history of >4 prescriptions were associated with nonadherence (OR: 2.5, 95% CI: 1.4-5.7). Our study showed that IBD patients taking >5 drugs presented a high rate of IBD therapy nonadherence. This was the only factor associated with treatment nonadherence in the multivariate analysis.

Our study presents limitations. First, it is a cross-sectional and retrospective study that could interfere in the estimation of PP. We also used the most widely accepted definition of PP, although experts do not yet know whether or not PP is a dynamic concept. We estimated concomitant drug use in a cross-sectional evaluation using an electronic drug prescription program, though the length of time that patients were under PP might be even more important. Second, our results come from a single-center series, so we cannot infer what is happening in other regions, countries or even continents, where there are differences regarding drug use. Finally, treatment nonadherence and undertreatment were evaluated under medical criteria and by reviewing clinical records. Certainly, there is no accepted gold standard for measuring treatment adherence, and all tools presented deficiencies.[59] Taking into account the retrospective design, we used self-reporting, considering medication adherence as a percentage of over 80%. This cutoff has also been used in many IBD studies, and we often refer to it as we are concerned about this aspect.

Nevertheless, this study has some strengths. It provides further evidence regarding PP in IBD patients, for which there is little data. Furthermore, it represents the largest IBD series published up to date, which includes many IBD phenotypes.

In conclusion, PP is also a problem in chronic digestive diseases such as IBD, mainly affecting older patients and patients with comorbidities. This scenario could interfere with appropriate IBD treatment, therapeutic adherence and, finally, therapeutic success. Consequently, efforts should be made to include these variables in IBD studies, and to take them into consideration for the management of IBD patients in clinical practice.

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REFERENCES

1. Taghy N, Cambon L, Cohen JM, et al. Failure to reach a consensus in polypharmacy definition: an obstacle to measuring risks and impacts—results of a literature review. *Ther Clin Risk Manag*. 2020;16:57–73.
2. Masnoon N, Shakib S, Kalisch-Ellett L, et al. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17:230.
3. Qato DM, Alexander GC, Conti RM, et al. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA*. 2008;300:2867–2878.
4. Bjerrum L, Sogaard J, Hallas J, et al. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. *Eur J Clin Pharmacol*. 1998;54:197–202.
5. Thomas HF, Sweetnam PM, Janchawee B, et al. Polypharmacy among older men in South Wales. *Eur J Clin Pharmacol*. 1999;55:411–415.
6. Junius-Walker U, Theile G, Hummers-Pradier E. Prevalence and predictors of polypharmacy among older primary care patients in Germany. *Fam Pract*. 2007;24:14–19.
7. Beard JR, Officer A, de Carvalho IA, et al. The World report on ageing and health: a policy framework for healthy ageing. *Lancet*. 2016;387:2145–2154.
8. World Health Organization. Ageing and Health. Available at: www.who.int/news-room/fact-sheets/detail/ageing-and-health. Accessed November 17, 2020.
9. United Nations. World Population Ageing. Available at: www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Report.pdf. Accessed November 17, 2020.
10. Organization for Economic Co-operation and Development. Trends in Severe Disability Among Elderly People. Available at: www.oecd.org/social/soc/38343783. Accessed November 17, 2020.
11. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet*. 2015;385:549–562.

12. European Patients' Forum. EU Reflection on Chronic Disease. Available at: www.eu-patient.eu/globalassets/policy/chronic-disease/epf-chronic-diseases-consultation-response-2012.pdf. Accessed November 17, 2020.
13. Lai S, Gao J, Zhou Z, et al. Prevalences and trends of chronic diseases in Shaanxi Province, China: evidence from representative cross-sectional surveys in 2003, 2008 and 2013. *PLoS One*. 2018;13:e0202886.
14. Menditto E, Gimeno Al, Moreno A, et al. Patterns of multimorbidity and polypharmacy in young and adult population: systematic associations among chronic diseases and drugs using factor analysis. *PLoS One*. 2019;14:e0210701.
15. Lindblad CI, Hanlon JT, Gross CR, et al. Clinically important drug disease interactions and their prevalence in older adults. *Clin Ther*. 2006;28:1133–1143.
16. Fried TR, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc*. 2014;62:2261–2272.
17. Pasina L, Brucato AL, Falcone C, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs Aging*. 2014;31:283–289.
18. Blanco-Reina E, Ariza-Zafra G, Ocaña-Riola R, et al. Optimizing elderly pharmacotherapy: polypharmacy vs. undertreatment. Are these two concepts related? *Eur J Clin Pharmacol*. 2015;71:199–207.
19. Lalic S, Sluggett JK, Ilomaki J, et al. Polypharmacy and medication regimen complexity as risk factors for hospitalization among residents of long-term care facilities: a prospective cohort study. *J Am Med Dir Assoc*. 2016;17:1067.e1–1067.e6.
20. Leelakanok N, Holcombe AL, Lund BC, et al. Association between polypharmacy and death: a systematic review and meta-analysis. *J Am Pharm Assoc*. 2017;57:729–738.
21. Katz S, Pardi DS. Inflammatory bowel disease of the elderly: frequently asked questions [FAQs]. *Am J Gastroenterol*. 2011;106:1889–1897.
22. Lakatos PL, David G, Pandur T, et al. IBD in the elderly population: results from a population-based study in Western Hungary, 1977–2008. *J Crohns Colitis*. 2011;5:5–13.
23. Hussain SW, Pardi DS. Inflammatory bowel disease in the elderly. *Drugs Aging*. 2010;27:617–624.
24. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.
25. Duricova D, Pedersen N, Elkjaer M, et al. Overall and cause-specific mortality in Crohn's disease: a meta-analysis of population-based studies. *Inflamm Bowel Dis*. 2010;16:347–353.
26. Bahler C, Schoepfer AM, Vavricka SR, et al. Chronic comorbidities associated with inflammatory bowel disease: prevalence and impact on healthcare costs in Switzerland. *Eur J Gastroenterol Hepatol*. 2017;29:916–925.
27. Mikocka-Walus A, Knowles S, Keefer L, et al. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2016;22:752–762.
28. Park SW, Jun Kim T, Young Lee J, et al. Comorbid immune-mediated diseases in inflammatory bowel disease: a nation-wide population-based study. *Aliment Pharmacol Ther*. 2019;49:165–172.
29. Gomollón F, Dignass A, Annese V, et al. on behalf of ECCO, 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis*. 2017;11:3–25.
30. Magro F, Gionchetti P, Eliakim R, et al. for the European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis*. 2017;11:649–670.
31. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther*. 2008;46:72–83.
32. Roughead L, Semple S, Rosenfeld E. Literature review: Medication safety in Australia, prepared by the Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, Adelaide, SA, for the Australian Commission on Safety and Quality in Health Care, ACSQHC, Sydney, NSW, Australia; 2013. Available at: www.safetyandquality.gov.au/. Accessed November 17, 2020.
33. World Health Organization. International Classification of Diseases (ICD). Available at: www.who.int/classifications/icd/en/. Accessed November 17, 2020.
34. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet*. 1980;1:514.
35. Walmsley RS, Ayres RCS, Pounder RE, et al. A simple clinical colitis activity index. *Gut*. 1998;43:29–32.
36. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on therapeutics in crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14:4–22.
37. Sicilia B, García-López S, González-Lama Y, et al. GETECCU 2020 guidelines for the treatment of ulcerative colitis. Developed using the GRADE approach. *Gastroenterol Hepatol*. 2020;43:1–57.
38. Viktil KK, Enstad M, Kutschera J, et al. Polypharmacy among patients admitted to hospital with rheumatic diseases. *Pharm World Sci*. 2001;23:153–158.
39. Al-Musawe L, Martins AP, Raposo JF, et al. The association between polypharmacy and adverse health consequences in elderly type 2 diabetes mellitus patients; a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2019;155:107804.
40. Cross RK, Wilson KT, Binion DG. Polypharmacy and Crohn's disease. *Aliment Pharmacol Ther*. 2005;21:1211–1216.
41. Wang J, Nakamura TI, Tuskey AG, et al. Polypharmacy is a risk factor for disease flare in adult patients with ulcerative colitis: a retrospective cohort study. *Intest Res*. 2019;17:496–503.
42. Parian A, Ha CY. Older age and steroid use are associated with increasing polypharmacy and potential medication interactions among patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21:1392–1400.
43. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380:37–43.
44. Turunen JHO, Mäntyselkä PT, Kumpusalo EA, et al. Frequent analgesic use at population level: prevalence and patterns of use. *Pain*. 2005;115:374–381.
45. Hider-Mlynarz K, Cavalié P, Maison P. Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe. *Br J Clin Pharmacol*. 2018;84:1324–1334.
46. Rodríguez-Lago I, Mesonero F, Cañas M, et al. P371 Self-medication with analgesics in ulcerative colitis: results of a patient survey. *J Crohns Colitis*. 2020;14:S349–S350.
47. Pallarito K. How safe are popular reflux drugs? Experts debate evidence linking acid-blockers to possible bone, heart problems. US News World Rep*ort*; 2009.
48. Savarino V, Dulbecco P, De Bortoli N, et al. The appropriate use of proton pump inhibitors (PPIs): need for a reappraisal. *Eur J Intern Med*. 2017;45:160–168.
49. Corsonello A, Lattanzio F, Bustacchini S, et al. Adverse events of proton pump inhibitors: potential mechanisms. *Curr Drug Metab*. 2018;19:142–154.
50. Lanas-Gimeno A, Hijos G, Lanas A. Proton pump inhibitors, adverse events and increased risk of mortality. *Expert Opin Drug Saf*. 2019;18:1043–1053.
51. Law EH, Badowski M, Hung YT, et al. Association between proton pump inhibitors and microscopic colitis. *Ann Pharmacother*. 2017;51:253–263.
52. Deshpande A, Pant C, Pasupuleti V, et al. Association between proton pump inhibitor therapy and *Clostridium difficile* infection in a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10:225–233.
53. Cross RK, Wilson KT, Binion DG. Narcotic use in patients with Crohn's disease. *Am J Gastroenterol*. 2005;100:2225–2229.
54. Buckley JP, Cook SF, Allen JK, et al. Prevalence of chronic narcotic use among children with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2015;13:310–315.

55. Wren AA, Bensen R, Sceats L, et al. Starting young: trends in opioid therapy among US adolescents and young adults with inflammatory bowel disease in the Truven markets can database between 2007 and 2015. *Inflamm Bowel Dis*. 2018;24:2093–2103.
56. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol*. 2006;4:621–630.
57. Hanson KA, Loftus EV, Harmsen WS, et al. Clinical features and outcomes of patients with Inflammatory bowel disease who use narcotics: a case-control study. *Inflamm Bowel Dis*. 2009;15:772–777.
58. Yuruyen M, Yavuzer H, Demirdag F, et al. Is depression a predictive factor for polypharmacy in elderly? *Bull Clin Psychopharmacol*. 2016;26:374–381.
59. Lenti MV, Selinger CP. Medication non-adherence in adult patients affected by inflammatory bowel disease: a critical review and update of the determining factors, consequences and posible interventions. *Expert Rev Gastroenterol Hepatol*. 2017;11:215–226.
60. Kane SV, Cohen RD, Aikens JE, et al. Prevalence of non-adherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol*. 2001;96:2929–2933.