Polypharmacy in Patients With Inflammatory Bowel Disease

Prevalence and Outcomes in a Single-center Series

Francisco Mesonero, MD, Cristina Fernández, APN, Eugenia Sánchez-Rodríguez, MD, Ana García-García Paredes, PhD, Carla Senosiain, MD, Agustín Albillos, PhD, and Antonio López-Sanromán, PhD

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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problems, notably psychiatric disorders and other autoimmune diseases. The high prevalence of older IBD patients, and the fact that most of these patients will become even older over the coming years, 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) 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. 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. 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 APICHN was developed by the Australian Commission on Safety and Quality in Health Care, 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). Of these, we selected as significant 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) 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.

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 χ² 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).

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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 (27.9)      |
| Strictureing (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)       |

**TABLE 2. Patients Comorbidities**

| Group Diseases (ICD-11) | n (%) |
|-------------------------|-------|
| Metabolic diseases      | 118 (29)|
| Cardiovascular diseases | 101 (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)|

*Arthritis, 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.

FIGURE 1. Number of medications taken per patient.

6.1% (mainly opioids). The most common inappropriate prescriptions were for benzodiazepines, neuroleptics, opioids and antihistamines 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.

**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[3] 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%. These variations may be explained by age (most studies included older patients), other population characteristics and, again, the...
definition of PP. However, in most of the studies, PP was defined as the concurrent use of 5 or more drugs.

Nowadays, 3 studies have explored previously the role of PP in IBD. 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. Parian and Ha 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).

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. 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, 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.

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. 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. 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. The second most commonly used drug class was PPIs. In the United States, PPIs represent the third most commonly prescribed drug. 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.

### 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.
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 al53 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).50,51 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 al41 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 al60 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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