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ORIGINAL REPORT

# Treatment patterns and health care costs of mebeverine-treated IBS patients: a case-control study†

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## SUMMARY

**Background** Irritable bowel syndrome (IBS) is a functional disorder affecting the quality of life of patients. In the Netherlands, mebeverine is currently the only medical treatment registered for IBS, although its efficacy is considered disputable.
**Objective** To assess treatment patterns and associated health care cost in mebeverine users relative to matched controls.
**Methods** A matched case-control study was performed using pharmacy data. Cases were mebeverine users as proxy for IBS patients. Controls were non-mebeverine users and matched to cases by age, gender and pharmacy. Prevalence and incidence of mebeverine use, concomitant drug use and hospitalizations were assessed in 3431 cases and 3431 controls. Concomitant drug use and hospitalizations was also assessed in a subgroup of 1222 users of mebeverine and laxatives (proxy for constipation-IBS) and their controls.
**Results** Twelve per 1000 residents were ever-dispensed mebeverine in 1998. One-third of these mebeverine users used laxatives concomitantly. Concomitant drug use and hospitalizations were increased in mebeverine users. The odds ratio for hospitalizations for gastrointestinal reasons was increased predominantly in mebeverine users with concomitant laxative use (OR:8.7; 95%CI [4.3–17.3]). Excess yearly costs for all concomitant medications were €94 [95%CI €79–€109] and for hospital admissions €120 [€74–€166] per mebeverine user. In mebeverine users with concomitant laxative use these costs were €136 and €251 respectively.
**Conclusions** In treated IBS patients, concomitant drug use and hospitalizations are increased relative to matched controls. Medical resource use and associated health care costs are particularly increased in mebeverine users using laxatives. The total mean excess cost per patient per year is €482. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — mebeverine; irritable bowel syndrome; matched case control study; incidence; laxatives; hospital morbidity; co-medication; health care costs

## INTRODUCTION

IBS entails a group of functional bowel disorders in which abdominal discomfort or pain is associated with a change of bowel habit and features of disordered defecation. The aetiology of IBS is still largely unclear and pathogenic mechanisms are only partly understood. IBS patients can be identified on the basis of Rome-II criteria.[a] Besides symptoms of abdominal

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[a]At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features: (1) relieved with defecation; and/or (2) onset associated with a change in frequency of stool and/or (3) onset associated with a change in form (appearance) of stool.



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pain, and diarrhoea and/or constipation, patients suffer more than healthy individuals from symptoms like nausea, headache, backache, anxiety, sleep disturbances and tiredness.[1] Symptoms in IBS patients are most likely to arise from a complex interaction of physiological, psychological and social factors.[2–4] Because of the variety of symptoms and the lack of specific causal treatment patients with IBS have a poorer quality of life and a higher health care utilization than persons without the disorder.[1,5,6]

The irritable bowel syndrome (IBS) is one of the most prevalent gastrointestinal disorders in Western societies. Approximately 10–20% of the general population in the Western World suffers from IBS or related syndromes, and it affects females more often than males.[7] The annual incidence is approximately 1–2%. The prevalence remains stable because the onset of symptoms is balanced by symptom loss; up to 50% of the patients show symptom improvement over time. Only a minority seeks professional care. Pain severity as well as psychological distress in part determine health-care seeking.[7] The relatively low rate of health care consumption might also be explained by the absence of a treatment that effectively targets the symptomatology of IBS.

The lack of one specific pathogenic mechanism impedes the development of specific causal treatments. Drugs investigated in randomized controlled clinical trials include smooth muscle relaxants, bulking agents, prokinetic agents, antidiarrheals and psychotropic agents.[8] However, trials in IBS are notoriously difficult, as the condition being treated is polymorphous. Consequently, there are many possible endpoints, and most therapies have so far been at most only marginally better than placebo.[8,9] In the Netherlands, drug treatment of IBS is currently not advised due to the lack of evidence concerning efficacy.[10] The antispasmodic agent mebeverine (Duspatal®) is the only drug registered for the treatment of IBS in the Netherlands but its position is under debate.[11,12] Recently, there is much interest in the use of agents with an effect on serotoninergic transmission as new therapeutics. Acting primarily through 5-HT3 and 5-HT4 receptors, serotonin elicits changes in motor function and possibly visceral sensation.[13–15] The economic impact of IBS is considerable, for instance, representing a multi-billion-dollar problem in the United States.[7] The excess morbidity of IBS patients may result in complex drug use patterns and increased hospital morbidity contributing to the economic impact of IBS. The aim of the present study was therefore to estimate the excess costs due to comedication and hospital admission in mebeverine users and, more specifically, in mebeverine users who suffer from constipation and use laxatives.

## MATERIALS AND METHODS

### *Data sources*

Data for this study were obtained from the PHARMO medical record linkage system in the Netherlands.[16] The PHARMO medical record linkage scheme includes the drug-dispensing records of community pharmacies and hospital discharge records of all 400 000 community-dwelling inhabitants of 12 population-defined areas in the Netherlands.[16] For all residents, the drug-dispensing histories are linked to the hospital discharge records of the same patient, using a probabilistic algorithm, based on characteristics such as date of birth, gender and a code for the general practitioner. Validation showed that these registries are linked with a sensitivity and specificity exceeding 95% which is comparable to record linkage systems based on unique personal identifiers. The computerized drug-dispensing histories contain data concerning the dispensed drug (using ATC codes (Anatomical Therapeutic Chemical (ATC) classification system)), type of prescriber, dispensing date, dispensed amount, prescribed dose regimens and the prescription length. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures and dates of hospital admission and discharge. All diagnoses were coded according to the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification).

### *Selection of patients*

Patients, 15–74 years of age, who were dispensed mebeverine at least once in 1998 were selected as cases. A control group of subjects who did not use mebeverine in 1997 and 1998 was extracted from the patient roster files, with 1 control matched for age, gender and pharmacy. Cases and controls without a first dispensing of any drug before 1 January 1998 and those with less than two dispensings in 1998 were excluded. New starters of mebeverine were defined as those patients that filled a first prescription for mebeverine in 1998 and did not fill a prescription for mebeverine in 1996 and 1997.

### *Incidence and prevalence of mebeverine use*

The yearly prevalence of prescription of mebeverine was determined by assessing the number of

 

prescriptions per 1000 residents in 1998. The incidence rate of new starters on mebeverine was estimated in 1998. A patient was defined as a new starter of mebeverine when he started mebeverine use in 1998 without a valid dispensing for mebeverine in 1996 and 1997. The incidence rate was calculated by counting the number of new starters of mebeverine in 1998, divided by the number of residents in 1998.

All dispensings of mebeverine were converted into episodes of continuous consecutive use. To reconstruct periods of uninterrupted drug use the following corrections were made:

1. In case of overlap of two repeat prescriptions the 'overlap' days were added to the episode.
2. In case of interruptions between two prescriptions of less than 30 days, the episode was considered to be uninterrupted.

Additionally, the incidence rate of new starters on mebeverine, who also used laxatives, was estimated. These patients started mebeverine in 1998 without a valid dispensing for mebeverine in 1996 and 1997 and the period before the first dispensing and also used laxatives in 1998.

### *Concomitant drug use*

Concomitant drug use was assessed for both cases and controls in 1998. The assessment was performed for medication for IBS and related symptomatology and for other medications. The identification of drugs used to treat IBS-related symptomatology was based on the review by Jailwala *et al*.[8] These drugs include laxatives (e.g. bulking agents), agents affecting motility and/or visceral perception, psychotropic agents and analgesics. Other medications, such as drugs for acid secretion inhibiting drugs, antacids and antibiotics that are indirectly linked to IBS (symptomatology) were also included.[17–19] All other drugs were considered as non-IBS related. Drugs were grouped on the therapeutic level of the ATC-code.

### *Hospital morbidity*

Hospital discharge records were obtained for cases and controls from the PHARMO database in 1998. Primary diagnoses were identified and grouped on basis of the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification). Cases and controls were divided in ever-hospitalized and non-hospitalized for each ICD-9 major category.[20] Differences between cases and controls in hospitalization for the different ICD-9 major categories were analyzed.

### *Excess costs of concomitant medication and hospitalization*

For every prescription of a (concomitant) drug the reimbursed costs were obtained from the data files. The costs of hospitalizations were calculated using the nationwide collection scheme of diagnoses. From this database, all admissions with a principal discharge diagnosis as defined in the section describing the case-control study with hospitalization as an outcome were selected for the Netherlands. For each admission, the costs of the hospital charges i.e. admission day cost, the costs of diagnostic and therapeutic procedures and the specialist fee for procedures, tests, operations and visits were calculated per hospital and summarized. All costs were based on charges made to third party payers. Admission day costs were the costs of a single hospital and year specific admission day and included all costs not related to visits to medical specialists or procedures. Cost of each specific procedure and specialist consultation fees were based on year-specific charges to third party payers.[16,21]

### *Statistical analyses*

Conditional logistic regression modeling was used for comparison of use of drugs among cases and controls. Drug groups (ATC code, therapeutic level) were analyzed together in the logistic regression model when they were significantly associated with mebeverine use or had an odds ratio $<0.7$ or an odds ratio $>1.5$.[22] Differences in costs between cases and controls were analyzed by calculating the mean and 95% confidence intervals for all drugs and drug groups. Conditional logistic regression modeling was also used for the comparison of cases and controls with respect to hospital morbidity for the main ICD9-CM categories. Major ICD9-CM categories (major classification categories) were analyzed together in the logistic regression model when they were significantly associated with mebeverine use or had a rate ratio $<0.7$ or a rate ratio $>1.5$.[22] Conditional logistic regression modeling for comparing cases and with respect to concomitant drug use and hospital morbidity was also performed as sub-analyses in the subgroup of cases using mebeverine and laxatives and their matched controls.

## RESULTS

### *Incidence and prevalence of mebeverine use*

A total of 3431 persons filled at least once a prescription for mebeverine in 1998, of which 2519 were female (73.4%) and 912 (26.6%) men. The yearly prevalence of prescription of mebeverine was 12 per 1000 residents. Of the 3431 persons that filled a prescription for mebeverine, 2337 persons filled a first prescription of mebeverine since 2 years (new starters). The overall incidence rate was 8.4 per 1000 residents, 12 and 5 per 1000 for women and men respectively.

The 3431 patients included 1222 patients (35.6%) who also used laxatives in the same year. In this subgroup, mebeverine was mainly prescribed in one episode (69.3%) and the duration of the episode was 60 days or less in 906 patients (82.6%) (Table 1).

### *Concomitant drug use*

More than 20 different types of drugs were significantly associated with use of mebeverine (at least one prescription) or with an odds ratio $<0.7$ or $>1.5$. Use of laxatives showed the highest odds ratio (OR: 7.3; 95%CI [6.0–8.7]). Frequently used laxatives used were bulking agents (psyllium extracts) and osmotic agents (Table 2).

In the subgroup of mebeverine and laxatives consumers, the use of prokinetics (OR: 1.9 [1.3–2.6]), anxiolytics (OR: 1.4 [1.1–1.7]), hypnotics (OR: 1.6 [1.2–2.1]) and NSAIDs (OR: 1.6 [1.3–1.9]) was significantly increased in the cases. Also the use of proton pump inhibitors, $H_2$-antagonists (OR: 2.4 [1.9–3.1]) and antacids (OR: 2.5 [1.7–3.8]) was significantly associated with the use of mebeverine and laxatives. Other medications such as iron and antihaemorrhoid preparations were also associated with the use of mebeverine and laxatives (Table 3).

### *Hospital morbidity*

Mebeverine use was significantly associated with increased hospitalization during the study period (OR: 1.5 [1.3–1.7]), especially for diagnoses in the ICD9 major categories neoplasms (140–239), digestive system (520–579) and symptoms/signs (780–799). Excess morbidity in the major ICD-9 diagnosis neoplasms could be partly contributed to hospitalization for malign and benign neoplasms of the gastrointestinal system (ICD-9 codes 152, 153, 154 and 211.3).

Hospital morbidity for the ICD-9 categories 520–579 and 780–799 was studied in more detail (Table 3). When all hospitalizations for gastrointestinal and IBS-related complaints (530–540, 555–570, 787, 7890) were regarded as one group, the number of admissions was clearly increased in mebeverine cases when compared to the matched controls (OR: 5.4 [3.4–8.6]). This effect was most pronounced in the subgroup of mebeverine and laxatives consumers (OR: 8.7 [4.3–17.3]), in particular in the category 'other diseases of the GI tract and peritoneum' (OR: 18.5 [4.5–76.9]), where for instance 12 patients (11 cases, 1 control) were hospitalized with a primary diagnosis irritable colon (ICD-9 code 5641).

Table 1. Number and duration of mebeverine prescriptions and episodes in mebeverine (and laxative) use

| Characteristics | Mebeverine users ($n = 3431$) *n* (%) | Mebeverine and laxative users ($n = 1222$) *n* (%) |
|---|---|---|
| Number of prescriptions per patient | | |
| 1 | 2158 (62.9) | 674 (55.2) |
| 2 | 616 (18.0) | 253 (20.7) |
| 3–10 | 622 (18.1) | 276 (22.7) |
| >10 | 35 (1.0) | 19 (1.6) |
| Average duration per prescription | | |
| 1–15 days | 3472 (53.6) | 1237 (47.1) |
| >15–30 days | 1951 (30.1) | 898 (34.2) |
| >30–60 days | 578 (8.9) | 244 (9.3) |
| >60 days | 477 (7.4) | 246 (9.4) |
| Number of treatment episodes per patient | | |
| 1 | 2543 (74.1) | 847 (69.3) |
| 2 | 551 (16.1) | 239 (19.6) |
| >2 | 337 (9.8) | 136 (11.1) |
| Average duration per treatment episode | | |
| 1–15 days | 2534 (52.0) | 824 (45.5) |
| >15–30 days | 1170 (24.0) | 419 (23.1) |
| >30–60 days | 557 (11.4) | 254 (14.0) |
| >60 days | 611 (12.6) | 316 (17.4) |

 

Table 2. Concomitant drug use in cases and controls

| Medication for treatment of IBS or IBS-related symptomatology (ATC code) | Mebeverine users ($n = 3431$) | | | Mebeverine and laxative users ($n = 1222$) | | |
|---|---|---|---|---|---|---|
| | Cases N (%) | Controls N (%) | Odds ratio (95%CI)[1] | Cases N (%) | Controls N (%) | Odds ratio (95%CI)[1] |
| Mebeverine (A03AA04) | 3431 (100) | 0 | | 1222 (100) | 0 | |
| Laxatives (A06A) | 1222 (35.6) | 225 (6.6) | 7.3 (6.0–8.7)[§] | 1222 (100) | 225 (18.4) | |
| Agents affecting motility and/or visceral perception | | | | | | |
| Prokinetic agents (A03F) | 550 (16.0) | 201 (5.9) | 2.2 (1.8–2.7)[§] | 246 (20.1) | 92 (7.5) | 1.9 (1.3–2.6)[§] |
| Peripheral opioid agonist (A07D) | 156 (4.5) | 100 (2.9) | 1.4 (1.0–1.9)[§] | 43 (3.5) | 36 (3.0) | 0.9 (0.5–1.5) |
| Psychotropic agents | | | | | | |
| Anxiolytics (N05B) | 943 (27.5) | 672 (19.6) | 1.2 (1.0–1.3) | 393 (32.2) | 244 (20.0) | 1.4 (1.1–1.7)[§] |
| Hypnotics and sedatives (N05C) | 592 (17.3) | 412 (12.0) | 1.1 (0.9–1.3) | 276 (22.6) | 157 (12.9) | 1.6 (1.2–2.1)[§] |
| Antidepressants (N06A) | 429 (12.5) | 330 (9.6) | 1.0 (0.8–1.2) | 174 (14.3) | 126 (10.3) | 0.9 (0.6–1.2) |
| Analgesics | | | | | | |
| NSAIDs (M01A) | 1709 (49.8) | 1332 (38.8) | 1.3 (1.2–1.5)[§] | 680 (55.7) | 485 (39.7) | 1.6 (1.3–1.9)[§] |
| Analgesics (N02B) | 937 (27.3) | 654 (19.1) | 1.2 (1.0–1.3)[§] | 379 (31.0) | 244 (20.0) | 1.2 (1.0–1.5) |
| Dyspeptic agents | | | | | | |
| Antacids (A02A) | 295 (8.2) | 113 (3.3) | 1.4 (1.1–1.9)[§] | 157 (12.9) | 45 (3.7) | 2.5 (1.7–3.8)[§] |
| Acid secretion inhibitors (A02B) | 999 (29.1) | 442 (12.9) | 2.2 (1.9–2.6)[§] | 435 (35.6) | 174 (14.2) | 2.4 (1.9–3.1)[§] |
| Systemic antimicrobial agents | | | | | | |
| Tetracyclines (J01A) | 607 (17.7) | 487 (14.2) | 1.0 (0.8–1.2) | 239 (19.6) | 151 (12.4) | 1.1 (0.9–1.5) |
| Beta-lactam antibiotics (J01C) | 612 (17.8) | 540 (15.8) | 0.9 (0.8–1.1) | 247 (20.2) | 197 (16.1) | 0.9 (0.7–1.2) |
| Sulphonamides/trimethoprim (J01E) | 363 (10.6) | 223 (6.5) | 1.3 (1.0–1.6)[§] | 137 (11.2) | 90 (7.4) | 1.0 (0.7–1.4) |
| Macrolides/lincosamides (J01F) | 349 (10.2) | 218 (6.4) | 1.2 (1.0–1.5) | 151 (12.4) | 69 (5.6) | 1.5 (1.1–2.1)[§] |
| Fluoroquinolones (J01M) | 219 (6.4) | 110 (3.2) | 1.3 (1.0–1.8) | 100 (8.2) | 40 (3.3) | 2.0 (1.2–3.2)[§] |
| Other antimicrobial agents | | | | | | |
| Gynaecology (G01A) | 247 (7.2) | 158 (4.6) | 1.3 (1.0–1.7)[§] | 96 (7.9) | 55 (4.5) | 1.3 (0.9–2.0) |
| Urinary tract (G04A) | 222 (6.2) | 128 (3.5) | 1.4 (1.1–1.9)[§] | 89 (7.3) | 59 (4.8) | 1.1 (0.7–1.6) |
| Other medication | | | | | | |
| Blood/cardiovascular system | | | | | | |
| Iron preparations (B03A) | 166 (3.8) | 131 (4.8) | 0.9 (0.7–1.2) | 77 (6.3) | 35 (2.9) | 1.8 (1.1–2.9)[§] |
| Anti-haemorrhoid preparations (local) (C05A) | 164 (4.8) | 101 (2.9) | 1.1 (0.8–1.5) | 78 (6.4) | 38 (3.1) | 1.7 (1.0–2.6)[§] |
| ACE-inhibitors (C09A) | 145 (4.2) | 208 (6.1) | 0.6 (0.5–0.8)[§] | 55 (4.5) | 88 (7.2) | 0.5 (0.3–0.8)[§] |
| Dermatology | | | | | | |
| Corticosteroids (D07X) | 491 (12.2) | 430 (10.5) | 1.0 (0.8–1.2) | 89 (7.3) | 51 (4.2) | 1.1 (0.8–1.4) |
| Respiratory tract | | | | | | |
| Decongestives (R01A) | 517 (12.5) | 428 (15.1) | 1.0 (0.9–1.2) | 214 (17.5) | 145 (11.9) | 1.3 (1.0–1.7)[§] |
| Systemic antihistamines (R06A) | 321 (9.4) | 371 (10.8) | 0.6 (0.5–0.7)[§] | 189 (15.5) | 151 (12.4) | 0.9 (0.7–1.2) |

[1]Conditional logistic regression was used with all 24 drugs in one model.
[§]Drugs significantly associated with use of mebeverine ( $p < 0.05$).

### *Excess costs of concomitant medication and hospitalization*

Costs for co-medication and hospitalization were increased in mebeverine users compared to their matched controls; excess costs were €94 and €120 per case per year on average respectively (Table 4). In the subgroup of mebeverine and laxative users mean excess costs for concomitant medication were €136 Euro per case, and per year, relative to matched controls (Table 4). Especially acid secretion inhibiting drugs (proton pump inhibitors and $H_2$-antagonists) (€80), prokinetics (€14) and NSAIDs (€10) contributed to these excess costs. Additionally, excess costs for hospitalization and specialists were €251 per case per year in this particular subgroup. In total, excess costs for cases—including mebeverine and laxative use—were €482 per case per year.

## DISCUSSION

The results of our study clearly indicate that co-medication and hospitalization are increased in mebeverine users. Use of medical resources and associated

 

Table 3. Number of cases and controls hospitalized for gastrointestinal and IBS related complaints

| ICD-9-CM groups | Mebeverine users ($n = 3431$) | | | Mebeverine and laxative users ($n = 1222$) | | |
|---|---|---|---|---|---|---|
| | Cases number (%) | Controls number (%) | OR (95% CI[1]) | Cases number (%) | Controls number (%) | OR (95% CI[1]) |
| All hospitalizations for gastrointestinal and IBS-related complaints (530–540, 555–570, 787, 7890) | 114 (3.3) | 22 (0.6) | 5.4 (3.4–8.6[§]) | 79 (6.5) | 10 (0.8) | 8.7 (4.3–17.3[§]) |
| Diseases of oesophagus, stomach and duodenum; non-infectious enteritis and colitis, appendicitis (530–540, 555–559) | 37 (1.1) | 10 (0.3) | 3.0 (1.5–6.1[§]) | 22 (1.8) | 4 (0.3) | 3.9 (1.3–11.7[§]) |
| Other diseases of the intestines and peritoneum (560–569) | 48 (1.4) | 5 (0.2) | 9.8 (3.5–27.4) | 45 (3.7) | 3 (0.3) | 18.5 (4.5–76.9[§]) |
| GI tract symptoms and abdominal pain (787 and 7890) | 40 (1.2) | 9 (0.3) | 3.9 (1.9–8.1[§]) | 22 (1.8) | 4 (0.3) | 4.4 (1.4–12.9[§]) |

[1]All ICD9-CM groups were tested in a conditional logistic regression model. The main group of all hospitalizations for GI and IBS-related complaints was tested separately in a model while the subgroups were analyzed simultaneously in a model.
[§]Hospitalisations for ICD9-CM categories that were significantly associated with use of mebeverine and laxatives, ($p < 0.05$).

health care costs are predominantly increased in mebeverine users also using laxatives. Given a total population of 16 millions residents in the Netherlands in 1998, we estimated that approximately 140 000 mebeverine users generated an amount of 48 million Euro per year of total excess costs, due to concomitant medication (including mebeverine) and hospitalization. Constipation-predominant IBS patients were responsible for more than 60% of these costs, it was estimated that the excess medical costs in this group were €31 million. This shows that constipation-predominant IBS is costly to society.

In the present study, use of the antispasmodic drug mebeverine was used to identify patients with IBS. The estimated incidence of use of mebeverine was 8.4 per 1000 in 1998 while the annual incidence of IBS probably is 10–20 per 1000.[1,7] Therefore, identifying IBS patients based on prescription data of mebeverine seems to underestimate the number of patients with IBS. This is in line with findings from others, which

Table 4. Medication and hospitalization costs for cases and controls in Euro

| | Mebeverine users ($n = 3431$) | | | Mebeverine and laxative users ($n = 1222$) | | |
|---|---|---|---|---|---|---|
| | Cases | Controls | Excess costs for cases total (cost per patient) | Cases | Controls | Excess costs for cases total (cost per patient) |
| Costs for (c)-IBS medication | | | | | | |
| Mebeverine | 134 983 | 0 | 134 983 (39) | 57 755 | 0 | 57 755 (47) |
| Laxatives | 64 303 | 11 519 | 52 784 (15) | 64 303 | 4765 | 59 538 (49) |
| Costs for co-medication for treatment of IBS or IBS-related symptomatology (excluding mebeverine and laxatives) | 652 777 | 382 885 | 269892 (79) | 311 357 | 145 740 | 165 617 (136) |
| Costs for hospitalization for GI and IBS-related complaints | | | | | | |
| Hospitalization costs | 474 002 | 89 535 | 384 467 (112) | 331 320 | 45 634 | 285 686 (234) |
| Specialist costs | 31 457 | 5061 | 26 396 (8) | 23 085 | 2793 | 20 292 (17) |
| Total | 1 357 523 | 489 001 | 868 522 (253) | 787 821 | 198 932 | 588 888 (482) |

 

suggest that only 25% of persons with this condition seek medical care.[10,12,23]

Our data indicate that most patients were only treated once with mebeverine, which in the Netherlands is the only drug registered for the treatment of IBS.[11] When the use of mebeverine was analyzed in more detail in the group of mebeverine and laxatives users, it was obvious that, in contrast to the chronic use of laxatives, mebeverine was only used for a short period. This may reflect treatment of IBS exacerbations or the awareness of Dutch physicians that the efficacy of mebeverine is limited. Moreover, short-course treatment with mebeverine is advised in the major Dutch IBS management guidelines.[10,11]

Our data demonstrate that patients using mebeverine had a high concomitant drug use compared to controls independent of age and gender. In one third of our patients, constipation was present and treated with laxatives. In another 20% of patients diarrhoea was predominant and the most commonly prescribed agents were psyllium extracts. Additionally, prokinetic agents like cisapride and domperidone and the antidiarrheal agent loperamide were prescribed more often in the users of mebeverine compared to controls. There was also a large group of cases using NSAIDs regularly. It is most likely that these were prescribed to treat abdominal pain, although other indications cannot be ruled out. In the subgroup of patients using mebeverine and laxatives the use of NSAIDs is even more prominent. It may be speculated that in this subgroup constipation related pain complaints will lead to an additional use of NSAIDs when compared to patients who only use mebeverine. In the subgroup of mebeverine and laxative users also the use of anxiolytics and hypnotics was significantly increased compared to the controls, indicating that this is probably a group of patients with more severe co-morbidity. Many IBS patients also have symptoms consistent with functional dyspepsia.[24] This can explain the increased use of proton pump inhibitors, $H_2$-antagonists and antacids by patients with mebeverine compared to controls.

Mebeverine users were hospitalized more often than their controls. Excess hospital morbidity was mostly associated to IBS-related symptoms. In the subgroup of mebeverine and laxative users and their matched controls differences between cases and controls were even more prominent. It is difficult, however, to extract the mechanism of the causal relation between use of mebeverine and laxatives and increased hospitalization. It may be suggested that in some cases the initial diagnosis of IBS, which was established in the first line, proved to be false. Subsequently, these cases were admitted to the hospital for other indications with a similar pattern of symptoms. Nevertheless, some of these cases were also diagnosed as IBS patients in the hospital. Concomitant medication led to high additional prescription costs for IBS patients. Per IBS patient €94 was reimbursed in excess, when the mebeverine prescription itself was excluded. These excess costs were even higher in mebeverine users who also used laxatives (€135), indicating that these patients probably have a more severe form of IBS than the average user of mebeverine. The relatively large contribution of acid secretion inhibiting drugs to the excess costs was caused by the relative high prices for these agents; mean monthly reimbursement costs for treatment were between €30 and €50 in 1998.[11] Excess costs for hospitalization were also high, in mebeverine and laxative users more than €250. When the excess costs for all mebeverine users were related to yearly prevalence of prescription (12 per 1000), we estimated for the total Dutch population that the excess medical costs, due to concomitant medication (including mebeverine) and hospitalization, were €48 million (95% CI €39–58 million) in 1998. Constipation-predominant IBS patients were responsible for more than 60% of these costs. On the basis of the assumption that one third of all mebeverine users also use laxatives, it was estimated that the excess medical costs, due to concomitant medication (including mebeverine) and hospitalization, for the total population were €31 million (95% CI €24–38 million).

The total medical costs for IBS patients are most likely even higher. Firstly, no additional costs could be calculated due the visits to the GP and/or the specialist. Secondly, we have no information on IBS patients who visited the GP but did not receive medication and were only advised to change their lifestyle. Finally, the total medical costs are probably only a small part of total economic burden caused by IBS; it is estimated that the annual economic burden of IBS is $US41 billion in the eight most industrialized countries.[25]

In conclusion, previous epidemiological studies indicated that IBS is common in the Dutch population whereas our study showed that only a percentage of these patients is treated with mebeverine. Our data also indicated that, especially in the group of mebeverine and laxatives users, in contrast to the chronic use of laxatives, mebeverine was only used for a short period. Importantly, we showed that concomitant drug use and hospital morbidity is increased in mebeverine users when compared to non-mebeverine users. This was even more pronounced in patients using mebeverine and laxatives. Thus, constipation-predominant IBS patients, treated with mebeverine and laxatives, on

 

KEY POINTS

- Medical resource use and associated health care costs are particularly increased in mebeverine users using laxatives.
- The total mean excess cost per c-IBS patient per year is €482.

average are €480 per year more costly then their matched control counterparts.

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## REFERENCES

1. Donker GA, Foets M, Spreeuwenberg P. Patients with irritable bowel syndrome: health status and use of health care services. *Br J Gen Pract* 1999; **49**: 787–792.
2. Haubrich WS. Clinical features of the irritable bowel syndrome. *Gastrointest Endosc* 1980; **26**: 24S–25S.
3. Kay L, Jorgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J Intern Med* 1994; **236**: 23–30.
4. Kay L, Jorgensen T, Jensen KH. [Irritable colon among 30–60-year old subjects. A cohort study of 4581 Danes]. *Ugeskr Laeger* 1995; **157**: 3476–3480.
5. Osterberg E, Blomquist L, Krakau I, Weinryb RM, Asberg M, Hultcrantz R. A population study on irritable bowel syndrome and mental health. *Scand J Gastroenterol* 2000; **35**: 264–268.
6. Lea R, Whorwell PJ. Quality of life in irritable bowel syndrome. *Pharmacoeconomics* 2001; **19**: 643–653.
7. Talley NJ. Irritable bowel syndrome: definition, diagnosis and epidemiology. *Baillieres Best Pract Res Clin Gastroenterol* 1999; **13**: 371–384.
8. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med* 2000; **133**: 136–147.
9. Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. *Am J Med* 1999; **107**: 91S–97S.
10. van der Horst HE, Meijer JS, Muris JWM. NHG-Standard Prikkelbaar Darm Syndroom. *Huisarts Wetenschap* 2001; **44**: 58–65.
11. Anonymous. *Farmacotherapeutisch Kompas*. Amstelveen; 1999.
12. van der Horst HE. Het prikkelbaredarmsyndroom: is er een plaats voor medicamenteuze therapie. *Geneesmiddelenbulletin* 2001; **36**: 15–21.
13. Talley NJ. Drug therapy options for patients with irritable bowel syndrome. *Am J Manag Care* 2001; **7**: S261–S267.
14. Muller-Lissner SA, Fumagalli I, Bardhan KD, *et al.* Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001; **15**: 1655–1666.
15. Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2000; **118**: 463–468.
16. Herings RM, Klungel OH. An epidemiological approach to assess the economic burden of NSAID-induced gastrointestinal events in The Netherlands. *Pharmacoeconomics* 2001; **19**: 655–665.
17. Holtmann G, Goebell H, Talley NJ. Functional dyspepsia and irritable bowel syndrome: is there a common pathophysiological basis? *Am J Gastroenterol* 1997; **92**: 954–959.
18. Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *Br Med J* 1999; **318**: 565–566.
19. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *Br Med J* 1997; **314**: 779–782.
20. Anonymous. *Classificatie Van Ziekten, Systematisch*. (3rd edition). SIG Zorginformatie: Utrecht, The Netherlands; 1999.
21. Wiedijk I, Spierings P. *Technische Brochure: Opbouw en Organisatie Van Het CBV-Bestand*. Stichting CBV: Leiden; 1999.
22. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989; **79**: 340–349.
23. Horwitz BJ, Fisher RS. The irritable bowel syndrome. *N Engl J Med* 2001; **344**: 1846–1850.
24. Su YC, Wang WM, Wang SY, *et al.* The association between Helicobacter pylori *infection and functional dyspepsia in patients with irritable bowel syndrome. Am J Gastroenterol* 2000; **95**: 1900–1905.
25. Camilleri M, Williams DE. Economic burden of irritable bowel syndrome. Proposed strategies to control expenditures. *Pharmacoeconomics* 2000; **17**: 331–338.

 