

## Influence of gastrointestinal events on treatment of osteoporosis in Asia-Pacific women: Perspectives from physicians in the MUSIC OS-AP study



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### ABSTRACT

**Background:** The objectives of the physician survey component of the MUSIC OS-AP study were to describe physicians' approaches to treatment of women with postmenopausal osteoporosis and to understand the influence of gastrointestinal (GI) events on treatment in clinical practice.

**Methods:** Physicians were recruited from 5 Asia-Pacific countries. Questionnaires collected information about physicians' standard practices for treatment of patients with osteoporosis, as well as their perspectives on the influence of GI events on osteoporosis treatment approaches.

**Results:** A total of 59 physicians participated in the study. The most frequently prescribed or recommended treatments were vitamin D (84% of patients), calcium (82%), and oral bisphosphonates (59%). When choosing a medication for treatment-naïve patients, GI sensitivity was often or always a factor for 79% of physicians. Among physicians not prescribing pharmacologic treatment, a mean of 18% of non-prescriptions were due to GI sensitivity. For patients with pre-existing GI conditions, physicians most frequently ranked use of non-oral osteoporosis medication as the first treatment strategy (47%), followed by co-prescription with a proton pump inhibitor or other gastro-protective agent (31%). For patients developing GI symptoms after starting pharmacologic treatment, the most frequently first-ranked management strategy was to check if patients were taking their osteoporosis medication correctly as prescribed (64%), followed by temporary discontinuation of the medication (i.e., a drug holiday) until GI events have resolved (31%) and co-prescription with a proton pump inhibitor or other gastroprotective agent (24%).

**Conclusions:** These results suggest that GI events influence the prescribing practices of physicians in the Asia-Pacific region and sometimes result in non-treatment of women with osteoporosis.

### 1. Introduction

Osteoporosis is prevalent in the Asia-Pacific region, and the prevalence and burden of osteoporosis-related fractures are expected to increase over the coming decades as the populations of Asia-Pacific countries become older (Mithal et al., 2014). To reduce the risk of fracture, national and international guidelines recommend pharmacologic treatment for patients with an osteoporotic fracture, with evidence of low bone mineral density (BMD; generally corresponding to a T-score  $\leq -2.5$ ), or with a combination of low BMD and increased

fracture risk (National Osteoporosis Foundation, 2014; Meeta et al., 2013; Royal Australian College of General Practitioners, 2010; Kanis et al., 2013; Taiwanese Osteoporosis Association, 2010).

Gastrointestinal (GI) events are also prevalent in Asia-Pacific countries (Chang et al., 2012; Ghoshal et al., 2011; Peppas et al., 2008), and such events have been shown to be exacerbated by treatment for osteoporosis in Asian populations (Mok et al., 2013; Peng et al., 2014). Studies from the United States have found that a history of GI events can reduce the likelihood of initiating anti-osteoporosis treatment (Modi et al., 2015a; Colon-Emeric et al., 2007). However, little is

**Abbreviations:** BMD, bone mineral density; GI, gastrointestinal; MUSIC, medication use patterns, treatment satisfaction, and inadequate control of osteoporosis study

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known about the influence of GI events on treatment practices in the Asia-Pacific region.

Osteoporosis treatment guidelines from Australia (Royal Australian College of General Practitioners, 2010) note the potential side effects of bisphosphonate use, but other than this, there is little guidance available for Asia-Pacific physicians regarding patients with a history of GI events. The Medication Use Patterns, Treatment Satisfaction, and Inadequate Control of Osteoporosis Study in the Asia-Pacific Region (MUSIC OS-AP) (Modi et al., 2015b) included a physician questionnaire that allowed us to assess the relationship between patients' GI history and physicians' prescribing practices. This article describes Asia-Pacific physicians' approaches to the management of osteoporosis patients with GI events and identifies the physician-reported factors associated with the decision of whether or not to treat osteoporosis with pharmacotherapy in clinical practice.

## 2. Methods

### 2.1. Study design

The 3-component design of MUSIC OS-AP has been described in a previous publication (Modi et al., 2015b). In the component reported here—the physician questionnaire—physicians' management of female osteoporosis patients was examined cross-sectionally, with an emphasis on the role of GI events in treatment decisions.

### 2.2. Study sample

Prior to the commencement of the prospective component of the MUSIC OS-AP study, each investigator completed a short physician questionnaire. Physicians from 5 Asia-Pacific countries (Australia, India, Korea, New Zealand, and Taiwan) were selected for participation via assessment of their experience in conducting clinical research, interest in participation, and ability to dedicate time and resources to the study. All study sites completed ethics reviews according to their local ethics board requirements.

### 2.3. Study outcomes

The questionnaire collected information about the physician's standard practices for treatment of patients with osteoporosis. Physicians were asked how often they witnessed GI events (e.g., heartburn, upset stomach, nausea, or pain) and how often GI sensitivity impacted their decision to prescribe osteoporosis treatment and their choice of medication. Treatment strategies for patients who had pre-existing GI events or developed GI events after starting osteoporosis therapy were queried (e.g., prescribe a gastroprotective agent, recommend a drug holiday, or switch to another medication). The text of the questions is provided as a footnote to each table and figure.

### 2.4. Statistical analysis

The analyses were descriptive in nature, and no statistical comparisons were performed. Continuous variables are reported as mean percentage values, or as medians and ranges (minimum and maximum values). For survey questions with categorical responses (e.g., always, often, sometimes, rarely, and never), the percentage of physicians responding in each category is reported.

## 3. Results

### 3.1. Study participants

A total of 59 physicians completed the questionnaire: 20 from Australia/New Zealand, 15 from India, 15 from Korea, and 9 from Taiwan (Table 1). Sixteen worked at primary care clinics and 43 at

**Table 1**  
Number of physicians by country.

Country	N (%) physicians
Australia/New Zealand	20 (33.9)
India	15 (25.4)
Korea	15 (25.4)
Taiwan	9 (15.3)

specialty centers.

### 3.2. Treatment and non-treatment of osteoporosis

When choosing a medication for treatment-naïve patients, renal insufficiency, menopausal status, and age were always a consideration for 54%, 49%, and 41% of physicians, respectively (Fig. 1). GI sensitivity was often or always a consideration for a combined 79% of physicians (Fig. 1). The most frequently prescribed or recommended treatments (Table 2) were vitamin D (84% of patients), calcium (82% of patients), and oral bisphosphonates (59% of patients).

Among physicians not prescribing pharmacologic treatment (Table 3), the most common reason for not treating osteoporosis was the patient's unwillingness to take the medication (42% of the time), followed by abnormal renal function (21%). GI sensitivity was a reason 18% of the time (Table 3).

### 3.3. Physicians' observations regarding GI events

The GI events most frequently observed by physicians among their treated patients were upset stomach/indigestion (observed sometimes or often by 88% of physicians) and heartburn/acid reflux (observed sometimes or often by 85% of physicians; Fig. 2). Bloating was observed sometimes or often by 57% of physicians (Fig. 2). Physicians reported that a median (range) of 20% (0–75%) of patients had experienced upper GI events and 10% (0–40%) had experienced lower GI events before starting pharmacologic treatment, whereas they estimated that 10% (1–50%) of patients experienced a new GI event after starting treatment. New GI events were reported to commence within the first month of treatment by 75% of physicians and within the first 3 months of starting treatment by 98% of physicians.

### 3.4. Treatment strategies in patients with GI events

For patients with pre-existing GI conditions, physicians most frequently ranked use of non-oral osteoporosis medication as the first treatment strategy (47% of physicians), followed by co-prescription with a proton pump inhibitor or other gastro-protective agent (31%) and modification of the frequency or dosing of the drug (17%; Fig. 3a). For patients with GI symptoms developing after starting pharmacologic treatment, the most frequently first-ranked treatment strategy was to check if the patient was taking their osteoporosis medication correctly as prescribed (64% of physicians), followed by temporary discontinuation of the medication (i.e., a drug holiday) until GI events have resolved (31%) and co-prescription with a proton pump inhibitor or other gastroprotective agent (24%; Fig. 3b).

## 4. Discussion

This analysis of data from the physician questionnaire of MUSIC OS-AP provides novel insights into the role of GI events in the typical prescribing practices of a sample of physicians for osteoporotic women in the Asia-Pacific region. GI events, although not the most frequently considered factor, did appear to affect physicians' decision to treat and the types of treatment prescribed. Physicians reported using different treatment strategies depending on the patient's history of GI events.

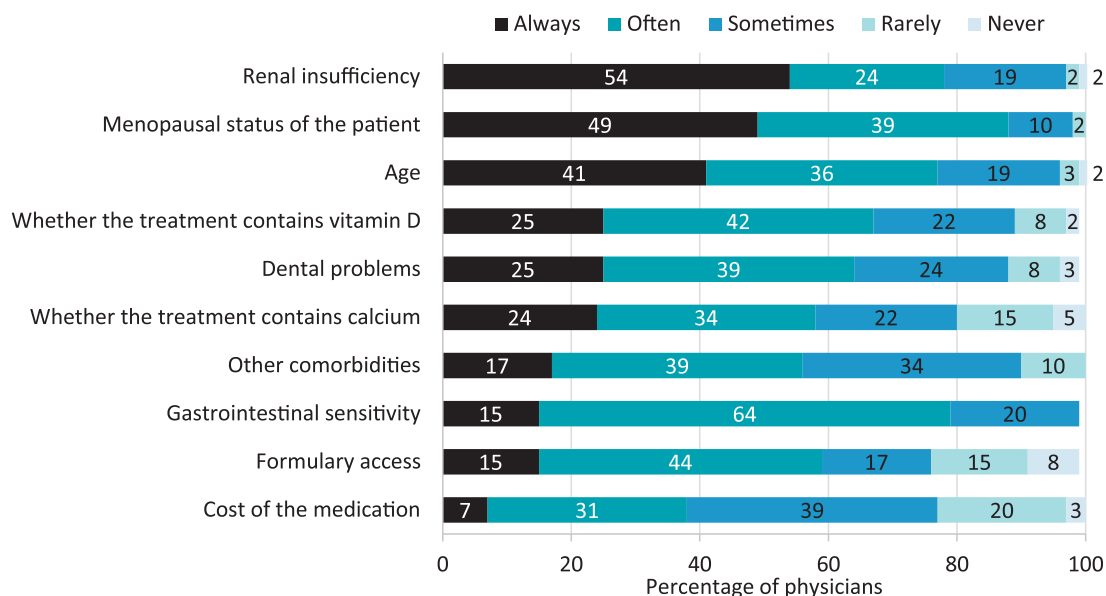


Fig. 1. Factors that impact osteoporosis therapy among treatment-naïve patients.<sup>a</sup>

<sup>a</sup>Survey question: when choosing an osteoporosis medication for treatment-naïve postmenopausal women aged 50 years or older, how often do the following factors impact your choice? Renal insufficiency was defined as creatinine clearance < 35 mL/min.

Table 2

Percentage of patients to whom physicians prescribe or recommend one or more of the listed osteoporosis therapies.<sup>a</sup>

Therapy	Mean percentage of patients
Vitamin D	84
Calcium	82
Oral bisphosphonate therapy <sup>b</sup>	59
Calcitriol	27
Denosumab	19
Injectable bisphosphonate therapy <sup>c</sup>	17
Selective estrogen receptor modulators <sup>d</sup>	12
Calcitonin or elcatonin	10
Parathyroid hormone or teriparatide	8
Strontium	8
Estrogen or hormone therapy	8

<sup>a</sup> Survey question: think about the last 20 postmenopausal women aged 50 years or older you diagnosed with osteoporosis. In approximately what percentage of these women did you prescribe or recommend the following bone-related treatments?

<sup>b</sup> Risedronate, alendronate, ibandronate, and etidronate.

<sup>c</sup> Pamidronate, zoledronic acid, and ibandronate.

<sup>d</sup> Raloxifene and bazedoxifene.

Table 3

Reasons for non-treatment.<sup>a</sup>

Reason	Mean percentage of non-prescriptions
Patient is unwilling to take for medical or other reasons	42
Patient has abnormal renal function (e.g. creatinine clearance < 35 mL/min)	21
Gastrointestinal sensitivity	18
Despite low BMD, absolute fracture risk is low	17
Physician is unwilling to prescribe for medical or other reasons	11

<sup>a</sup> Survey question: when you do not prescribe a pharmacological treatment (including calcium, vitamin D, estrogen and HRT) for a treatment-naïve postmenopausal woman aged 50 years or older with osteoporosis, how often (in percentage terms) would this be due to the following reasons?

Similar effects of GI events on osteoporosis treatment have been reported in US studies, where a GI diagnosis was a common reason (28% of untreated patients) for not initiating bisphosphonate therapy in a cross-sectional study of osteoporosis patients aged 25 years and older (Kamneva et al., 2011) and osteoporosis patients aged 50 years and older included in an analysis of nursing home residents with a history of GI events (esophagitis, peptic ulcer disease, or dysphagia) were less likely to receive osteoporosis therapy than patients without a history of GI events (Colon-Emeric et al., 2007).

Physicians in the Asia-Pacific region showed a preference for non-prescription therapies, such as vitamin D and calcium. However, they estimated that up to 59% of their patients were receiving prescription pharmacotherapies such as bisphosphonates and denosumab. This treatment rate is consistent with published treatment rates of up to ~63% in Korea (Kim et al., 2012; Lee et al., 2014; Kung et al., 2013) and 29% in Australia (Eisman et al., 2004).

For physicians in MUSIC OS-AP, the primary considerations when deciding to treat osteoporosis patients were renal function, menopausal status, and age. These factors differed somewhat from a recent survey of US physicians, which showed that, when deciding whether to prescribe bisphosphonates, known risk factors for osteoporotic fracture, such as fracture history, glucocorticoid use, and BMD test scores, were the major considerations for physicians (Gu et al., 2016). However, a previous survey of 100 physician members the Korean Society for Bone and Mineral Research (KSBMR) found that 99% used BMD measurements when making treatment decisions (Ha et al., 2014), and a survey of 114 Australian general practitioners found that rates of both prescription and non-prescription treatment were higher in patients with a history of osteoporotic fracture (Inderjeeth and Smeath, 2010), indicating that doctors in the Asia-Pacific region do consider fracture risk factors when treating their patients. MUSIC OS-AP differed from these previous surveys by focusing specifically on the role of GI events in prescribing decisions.

According to physicians in MUSIC OS-AP, the most common reason for not treating osteoporosis was the patient's unwillingness to take the medication. US patient surveys have shown that experience of side effects and fear of side effects are associated with patient unwillingness to initiate osteoporosis therapies (Lindsay et al., 2016; Yu et al., 2015). Consistent with the supposition that such side effects would include GI events, physicians in MUSIC OS-AP estimated that GI sensitivity was the

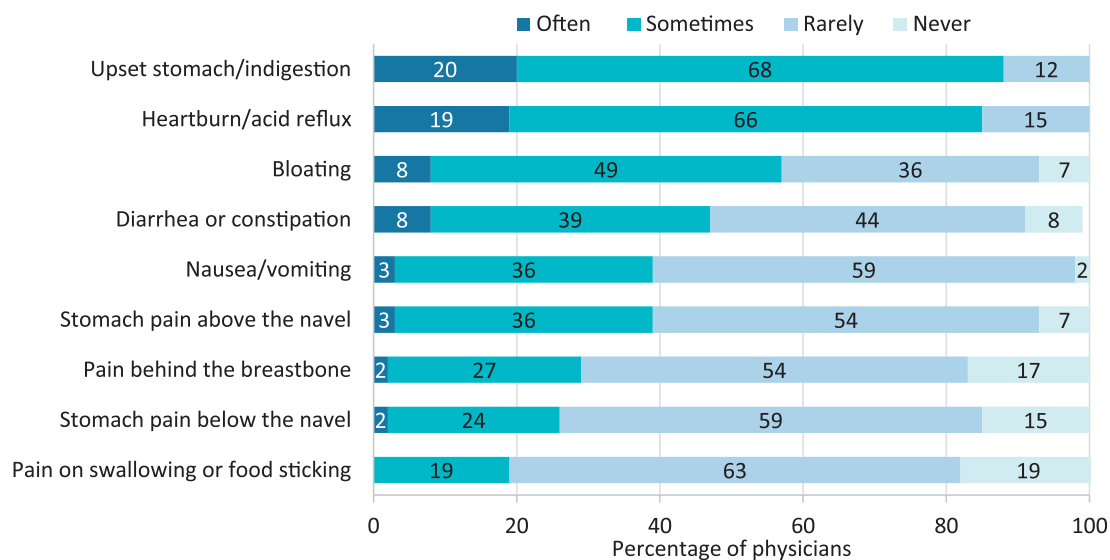


Fig. 2. Frequency of gastrointestinal events among treated patients.<sup>a</sup>

<sup>a</sup>Survey question: how often do you see the following gastrointestinal events in postmenopausal women aged 50 years or older who are receiving osteoporosis treatment?

reason for non-treatment in about one fifth of cases. Similarly, Australian physicians surveyed regarding the management of minimal trauma hip fracture patients reported that gastroesophageal reflux would be a contraindication for bisphosphonate treatment (Levinson and Clay, 2009).

In the KSBMR survey described above, physicians identified a lack of patient awareness (50%), restrictions by health insurance (47%), and the costs of medication (28%) as the biggest barriers to osteoporosis treatment (Ha et al., 2014). Similarly, a 2010 survey of 247 physician attendees of the first Asian regional osteoporosis meeting of the International Osteoporosis Foundation identified lack of awareness among physicians and patients as the most important barrier to osteoporosis care (Korthoewer and Chandran, 2012). Awareness was not assessed in MUSIC OS-AP, but, consistent with the KSBMR survey, formulary access (access to certain, specified medications) and medication costs were found to be often or always a consideration for 59% and 38% of physicians, respectively, in the current study.

Physicians in MUSIC OS-AP estimated that 20% and 10% of patients had experienced upper and lower GI events, respectively, before starting pharmacologic treatment. These results are consistent with the findings from the 2005–2008 Nutrition and Health Survey in Taiwan, in which 33.2% of adult women had functional GI disorders (Chang et al., 2012) and with other population-based studies from Asia and Australia that report GI event rates around 10–20% (Ghoshal et al., 2011; Peppas et al., 2008).

Almost half (47%) of physicians in MUSIC OS-AP reported that, for patients with pre-existing GI conditions, prescription of non-oral osteoporosis medication is the first treatment strategy. Among US physicians, although injectable bisphosphonate formulations are gaining popularity, oral bisphosphonates still appear to be the preferred type of prescribed treatment (Gu et al., 2016). Another commonly used strategy in MUSIC OS-AP was modification of the frequency or dosing of the drug, reported as a first-choice strategy by 17% of physicians. This is consistent with US studies showing that less frequent dosing decreases the occurrence of gastrointestinal symptoms in patients taking bisphosphonates (Binkley et al., 2009; Derman et al., 2009) and with a study from Korea reporting better composite treatment satisfaction scores in monthly versus weekly bisphosphonate users (Oh et al., 2012). For patients with GI symptoms developing after starting pharmacologic treatment, 31% of physicians in the current study reported temporary discontinuation of the medication (i.e., a drug holiday) until GI events have resolved as their preferred strategy. This

agrees with the practices of US physicians, most of whom reported incorporating a drug holiday into their prescribing regimen in a recent survey (Gu et al., 2016).

One limitation of the physician questionnaire of MUSIC OS-AP was its small sample size, which did not allow the assessment of differences between physicians from different countries and between physicians of various specialties. Also, as noted above, the questions were focused on the role of GI events in treatment practices, and thus did not address other topics commonly reported in other physician surveys (e.g., whether risk factors for fracture such as fracture history or BMD influenced treatment decisions). However, this focus allowed MUSIC OS-AP to provide new information on how physicians deal with GI events when managing their osteoporosis patients. Finally, the cross-sectional survey design is limited by the accuracy of physician recall.

## 5. Conclusion

In conclusion, the results of this study show that GI events influence the prescribing practices of physicians in the Asia-Pacific region and sometimes result in non-treatment of women with osteoporosis.

## Disclosures

A. Modi, XY, and S. Sen are employees of Merck & Co., Inc. A. Modi and S. Sen own stock in the company. S. Sajjan was an employee of Merck & Co., Inc. and owned stock in the company at the time of the study.

PRE has received research funding from Merck & Co., Inc., Amgen, Novartis, GlaxoSmithKline, and Eli Lilly and honoraria from Merck & Co., Inc., Amgen, and ViiV Healthcare.

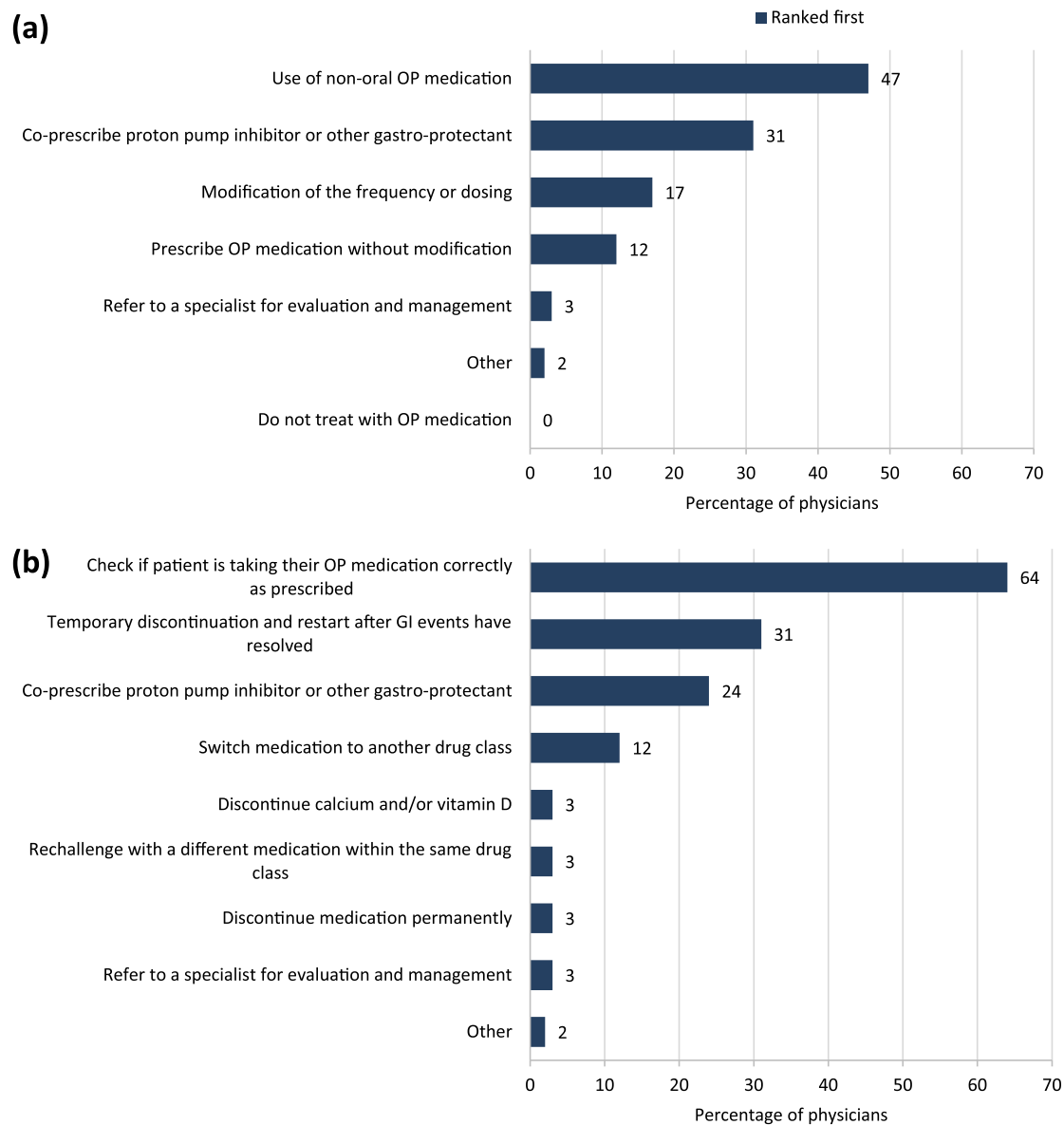
SB is employed by Optum and has received financial remuneration from Merck & Co., Inc. to participate in the study.

MSL, YKM, A. Mithal have no conflicts of interest to report.

The study was funded by Merck & Co., Inc. Other than through the employer relationship disclosed, Merck & Co., Inc. did not have a role in the study design, data collection, interpretation of the data, in writing of the manuscript, and in the decision to submit the manuscript for publication.

## Authors' contributions

Conception and design of the study: A. Modi, PRE, MSL, YKM, A.



**Fig. 3.** Physician treatment approaches for (a) patients with pre-existing GI conditions and (b) patients developing GI symptoms after starting treatment.<sup>a</sup>

GI, gastrointestinal; OP, osteoporosis

<sup>a</sup>Panel (a) Survey question: If one of your female patients is a candidate for osteoporosis medication(s) and has pre-existing GI events, please rank (from 1, 2, 3...) the normal sequence of treatment options you would select. Panel (b) Survey question: If one of your female patients taking osteoporosis medication(s) develops a GI event, please rank (from 1, 2, 3...) the normal sequence of treatment options you would select.

Mithal, and S. Sajjan.

Analysis and/or interpretation of the data: A. Modi, X. Yang, SB, S. Sen, and S. Sajjan.

Drafting and revision of the manuscript: A. Modi, PRE, MSL, YKM, A. Mithal, X. Yang, SB, S. Sen, and S. Sajjan.

Approval of the final version of the manuscript: A. Modi, PRE, MSL, YKM, A. Mithal, X. Yang, SB, S. Sen, and S. Sajjan.

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