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Validity and utility of a single-item patient-reported measure of treatment-related bother in rheumatoid arthritis: A cross-sectional OMERACT study

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ABSTRACT

Objectives: To assess the construct validity of a modified single-item measure of bother due to side effects (the GP5 item) from the Functional Assessment of Chronic Illness Therapy (FACIT) system by comparing it to current symptomatic side effects from the Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO—CTCAE) reported by patients with rheumatoid arthritis (RA).
Methods: Through a cross-sectional, web-based survey we collected information on the frequency of symptomatic side effects and bother from side effects related to RA medications. We applied multiple correspondence analysis (MCA) to reduce 80 symptomatic side effects into key dimensions (≥5% of the total variance each). We then examined associations among key dimensions, individual items, the sum of current side effects, and the single-item bother measure using Spearman rho.

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Results: A total of 560 patients participated in the online survey. Our scree plot showed a clear elbow point after the first dimension, indicating that keeping just one dimension captured the most meaningful information. This overall side effect burden score appeared to reflect a broad concept influenced by a variety of symptomatic side effects, each having only a negligible to weak impact.
Conclusions: Our results may indicate that individuals have diverse experiences of side effects, allowing the global index to capture these variations, even when they differ across patients. Thus, a single-item burden measure to side effects can potentially serve as a useful summary indicator, shedding light on the impact of symptomatic side effects experienced by RA patients.

Introduction

In biomedical research, harms (often also described as "adverse events" [AEs] or "side effects") provide essential context for evaluating the benefit-risk ratio of interventions. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), collect AE data to ensure healthcare product safety and take necessary regulatory actions, such as recalls or safety alerts [1]. The Consolidated Standards of Reporting Trials (CONSORT) statement uses harms to emphasize comprehensive reporting of all negative outcomes, ensuring a clear communication of risks and benefits [2,3]. It is crucial to explicitly report patient-important harms, which may differ from those that clinicians document [4].

The use of patient-reported outcomes (PROs), which are direct reports of symptoms by patients, has gained prominence as the "gold standard" for capturing the patient voice. This shift was accelerated by the FDA's 2009 guidance on PRO measures for medical development and has influenced initiatives like the National Cancer Institute's (NCI's) PRO data systems [5]. In rheumatology, the Outcome Measures in Rheumatology (OMERACT) initiative [6] has successfully developed Core Outcome Sets (COS) for many rheumatologic and musculoskeletal conditions (RMDs) [7,8] and has explicitly included the patient perspective since 2002 [9]. Even though patients with rheumatoid arthritis (RA) report side effects to be the main reason for not taking their methotrexate (MTX) [10], a suitable measurement instrument for assessing patient-reported side effects for RMDs has not been ascertained [11] and the extent to which bother of treatment-related symptoms is associated with outcomes, such as treatment-discontinuation and quality of life, is largely unknown.

At the OMERACT meeting in May 2023, there was increasing recognition of the need for a global outcome measure to summarize patient experiences with side effects from anti-rheumatic drugs or other treatments [12]. A pragmatic, comprehensive safety/harm outcome measure could assess patients' burden of side effects to treatment. We therefore investigated the association between a modified single-item bother measure from the Functional Assessment of Chronic Illness Therapy (FACIT) system and RA patient-reported current symptomatic side effects included in the Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO—CTCAE). The PRO—CTCAE is a standardized system developed by the U.S. National Cancer Institute to capture 80 symptomatic treatment-related adverse events directly from patients. The FACIT system includes a general measure of a single-item of bother to symptomatic side effects from treatment – the GP5 item [13] – which is included in the Physical Well-Being subscale in various FACIT instruments e.g., the Functional Assessment of Cancer Therapy - General (FACT-G) [14], and could serve as a useful summary of patients' overall bother to treatment-related symptomatic side effects. Thus, developing and validating such a single-item bother measure for RMDs would enable reporting of overall impact of patient perceived side effects associated with their treatment.

Our primary objective was to establish the construct validity of this single-item bother measure by comparing it to the harm related dimensions derived through latent variable modeling (multiple correspondence analysis [MCA]) of the PRO—CTCAE. We assessed correlations between the single-item bother measure and these more theoretically related latent variables. The rationality of our study was to recommend the GP5 item as a valid candidate measure to be provisionally endorsed by OMERACT for assessing overall burden of medication side effects in clinical trials of patients with RMDs. Even though the PRO—CTCAE is developed within cancer, it was selected as the anchor instrument because it is a validated and widely used measure designed to capture patient-reported symptoms. We expected higher GP5 bother scores observed among patients reporting higher frequency of PRO—CTCAE symptoms. We hypothesized a positive Spearman rank correlation $\geq$0.30, as suggested by the COSMIN group [15,16], between the modified single-item bother measure and the sum of current symptomatic side effects, and we then mapped which domains were contributing to the measure.

Methods

The OMERACT Safety Working Group (SWG) is working to improve the patients' reports of harmful treatment related symptoms, allowing for a more comprehensive, patient-centered evaluations of harmful treatments through standardized symptom reporting systems in clinical trials [17]. Two (MV and PR) patient research partners (PRPs) were involved in the present study from planning stage to submission of the manuscript. By participating in discussions during planning and on results, and by reviewing and providing feedback on the manuscript draft, the PRPs ensured that the study was relevant to patients. To follow this patient-centered approach we will use the term "side effect" in this study, even though this term suggests causality, as this term is more widely used in lay populations [18]. Furthermore, we will add the term "symptomatic", as this refers to symptoms (i.e., distinct from 'signs') that are apparent to the patient [19]. Finally, we will use the term "bother" or "overall bother" when referring to patients' overall burden of one or more symptomatic side effect(s) from treatment. The PRO—CTCAE uses the term "AEs", but as described, we are using the term "side effects" – and additionally, we use the term "current (symptomatic) side effects" which refers to those the patient reported as experiencing within the past week. To aim for proper assessment of construct validity in our study, we used the OMERACT handbook and checklists for construct validity [20–22]. Our Statistical Analysis Plan is available as **Supplemental File 1**. We report the findings of this study according to the COSMIN Reporting guideline for studies on measurement properties of patient reported outcome measures version 2.0 [23].

Study design

We used data from an exploratory online cross-sectional survey conducted in Canada of adults with self-identified RA [24]. Using the PRO—CTCAE and the GP5 item, Hazlewood et al. collected information on the frequency of symptomatic side effects and bother due to side effects related to participants' RA medications. To list potential symptomatic side effects in Hazlewood et al.'s study, the PRO—CTCAE quick guide to the item library [25] was customized to the survey.

Online survey

The survey opened with questions about socio-demographics and

current RA medication use. Then the complete list of 80 PRO—CTCAE symptomatic side effects was presented, and participants were asked to indicate which of the items (described as "side effects" in the survey) they had experienced while taking their RA medications in the a] past seven days and b] at any point in time. Free-text fields also allowed participants to write any other harmful event they experienced to their RA medical treatment. At the end, they were also asked a single question to indicate the extent to which they were "bothered by side effects of their RA medications" (from 1 = "*not at all*" to 5 = "*very much*"). The question was a slightly modified version ("*how much are you bothered by side effects of your rheumatoid arthritis medications*") of the GP5 item from the FACIT system ("*I am bothered by side effects of treatment*"). We will call this patients' overall bother.

Participants

After recruiting 29 people in an academic rheumatology Calgary clinic, with 23 completing the survey, further recruitment was shifted to online approaches to address recruitment challenges during the contact restrictions in first wave of the COVID-19 pandemic [24]. The web-based survey was promoted on social media through Canadian arthritis patient advocacy groups, inviting individuals diagnosed with RA who were receiving treatment from a rheumatologist and using at least one RA treatment to participate. A total of 913 people began the survey, and 575 (63%) completed it. In total, 598 people completed the survey, either in clinic or online, with 560 (94%) reporting the use of at least one RA medication (NSAIDs or DMARDs, including prednisone) and included in the analysis.

Ethics

The survey was conducted using Qualtrics survey software and approved by the University of Calgary Conjoint Research Ethics Board (REB no. 18–0597). Approval for conducting this follow-up was also approved by the same ethics board (REB no. 24–0093). Participants in the survey viewed a consent form on the survey's first page, and implied consent was obtained upon completion. Participants could navigate back to previous pages at any time to modify their previous responses. While IP addresses were not recorded, cookies were utilized to prevent multiple submissions from the same IP address. The survey was deemed complete upon reaching the final page.

Statistical methods

Descriptive statistics summarized participant characteristics and the frequency of current and ever-occurring side effects. In our analysis, we used participants' reports of current symptomatic side effects, as we considered these best reflected overall side effect of bother and were less prone to recall bias. MCA was employed as a dimensionality reduction technique to transform the original 80 current symptomatic side effects reported by participants into a new set of dimensions, capturing the most significant information from the 80 items reported while reducing dimensionality. The proportion of variance explained by the dimensions was used to decide whether a dimension could be included for further analysis. A cutoff of 5% of the total variance explained was used to define the existence of a dimension. The contents of the included dimensions were evaluated based on the top contributions of each of the 80 items reported by participants as occurring in the past 7 days.

To develop an overarching frame for the top contributors (e.g. those contributing more than 1%) to dimensions not related to PRO—CTCAE categories, the 80 items were categorized by an author (TH) not familiar with PRO—CTCAE categories. Subsequently, the contribution of each item, and the categories led to an overarching framework. For sensitivity, and to further investigate an overarching frame, we asked Chat Generative Pretrained Transformers (ChatGPT) to do a categorization of the 80 items and their contribution to the dimension. Our ChatGPT work was supported by the newest Large Language Model (LLM) from OpenAI available in Denmark (as of March 19th, 2025) ChatGPT 4.5. For reporting our results of our ChatGPT categorization we used the reporting guideline for the use of Generative Artificial intelligence tools in MEdical Research (GAMER) [26].

The strength of the correlation among each of the 80 current symptomatic side effects reported by participants (as dichotomies), the single-item measure of overall bother due to side effects, the sum of current side effects experienced in the past 7 days, and the dimensions from the MCA, expressed as Spearman rho, was explored. As suggested by Prion and Haerling, we interpreted the Spearman rho results of 0 to ±0.20 as negligible, ±0.21 to ±0.40 as weak, ±0.41 to ±0.60 as moderate, ±0.61 to ±0.80 as strong, and ±0.81 to ±1.00 as very strong [27]. Lastly, the Spearman rank correlation between participants' overall bother, the sum of current side effects experienced in the past 7 days, and the included dimensions from the MCA, were evaluated. All analyses were conducted with R statistical software (version 4.3.2), specifically the packages Tidyverse and FactoMineR.

Results

Participant demographics are detailed in Table 1. Participants had a mean age of 44 years, the median RA disease duration was five years, and 530 (95%) of the participants were women. The median number of medications taken was five, including three for RA medications. Nonsteroidal anti-inflammatory drugs (NSAIDs) were utilized by 316 (56%), and 181 (32%) used prednisone. Methotrexate (MTX) emerged as the predominant conventional synthetic DMARD, used by 318 (57%), while 226 (40%) of participants were on biologic DMARDs (bDMARDs), and 60 (11%) were on JAK inhibitors.

The sum of current side effects reported by participants in the past 7 days due to RA medications varied considerably. Among the participants, 36 (6%) reported no side effects, 71 (13%) experienced 1 to 5 side effects, 82 (15%) reported 6 to 10, 158 (28%) reported 11 to 20, and 213 (38%) experienced more than 20 current symptomatic side effects. As listed in Table 1, the responses to the overall bother due to side effects revealed a diverse distribution among participants. Specifically, 65 individuals (12%) indicated "not at all" bothered, while 117 (21%) reported "a little bit". A total of 159 participants (28%) rated their bother as "somewhat", 137 (25%) as "quite a bit", and 82 (15%) expressed being "very much" bothered by side effects. This suggests that while some participants experienced minimal annoyance, a substantial portion reported significant discomfort related to treatment side effects. The distribution of prevalences of the 80 items including associations between medication use and odds of symptomatic AEs has previously been reported by Hazlewood et al. [24].

The scree plot in Fig. 1 visually represents the eigenvalues derived from the MCA of the 80 current symptomatic side effects, aiding in determining the number of latent variables that could be justified. The plot displayed a clear elbow point after the first dimension, suggesting that the optimal number of dimensions to retain is one. By observing the steep drop in eigenvalues, and using a cutoff of 5% explained variance, it was possible to identify the latent construct (i.e., Dimension 1) that contributed meaningfully to the variance in the data. In this case, it was the first dimension with no others meeting the criteria. That means we have one "side effect burden score", and no other constructs (such as just "neurological" or just "gastrointestinal" side effects) appears to impact the outcome.

Box 1 explains terminology used in MCA. Because Dimension 1 in the MCA was the only meaningful contributor to the variance, the subsequent analyses focused on this dimension alone and its relationship to participants' overall bother and the sum of current side effects.

Fig. 2 shows results of our MCA illustrating the current symptomatic side effects experienced by participants and their contributions (i.e., importance) to our dimension of multiple correspondence. Our thematic interpretations of the dimension were based on the highest

Table 1
Participant demographics in the intention-to-infer-from population.

Characteristic		N
Age, yrs, mean (SD)	44 (13)	488
Gender, n (%)		560
Male	28 (5)	
Female	530 (95)	
Diverse/Prefer not to answer	2 (0.4)	
Disease duration, yrs, median (IQ)	5 (2–12)	560
Disease duration, n (%)		560
<2 yrs	144 (26)	
2 to <5 yrs	151 (27)	
5 to <10 yrs	96 (17)	
> 10 yrs	169 (30)	
Total no. of medications, median (IQ)	5 (3–8)	559
Total no. of RA medications, median (IQ)	3 (2–5)	560
Current RA medication, n (%)		560
NSAIDs	316 (56)	
Prednisone	181 (32)	
MTX	300 (54)	
MTX oral	185 (33)[a]	
MTX sc	133 (24)[a]	
Hydroxychloroquine	218 (39)	
Sulfasalazine	97 (17)	
Leflunomide	72 (13)	
bDMARD	226 (40)	
JAK inhibitor	60 (11)	
Sum of current side effects, median (IQ)	17 (8–26)	560
Sum of current side effects, n (%)		560
0	36 (6)	
1–5	71 (13)	
6–10	82 (15)	
11–20	158 (28)	
>20	213 (38)	
Sum of ever side effects, median (IQ)	17 (8–28)	560
Sum of ever side effects, n (%)		560
0	28 (5)	
1–5	66 (12)	
6–10	91 (16)	
11–20	145 (26)	
>20	230 (41)	
Overall bother due to side effects, median (IQ)	2 (1–3)	560
Overall bother due to side effects, n (%)		560
Not at all	65 (12)	
A little bit	117 (21)	
Somewhat	159 (28)	
Quite a bit	137 (25)	
Very much	82 (15)	

[a] 18 people reported being on both oral and SC MTX. bDMARD: biologic disease-modifying antirheumatic drug; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RA: rheumatoid arthritis; SC: subcutaneous; yrs: years.

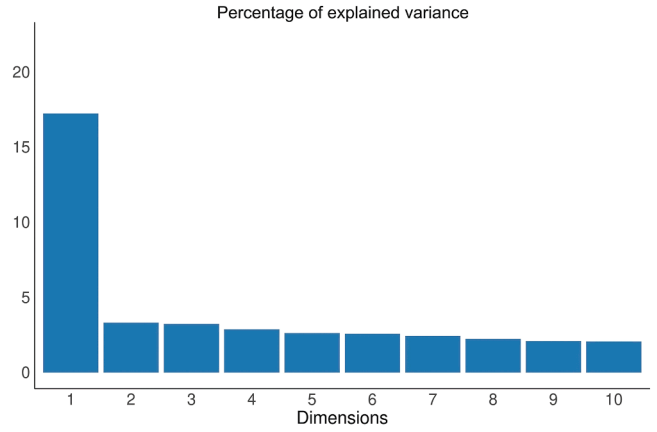

Fig. 1. Scree plot representing the eigenvalues derived from the MCA of the 80 current symptomatic side effects.

contributions, and we set the cutoff to 1% as illustrated in Fig. 2.

The results of our overarching framework, based on the author categorization and the ChatGPT categorization, led to similar results (**Supplemental File 2**). The categories indicated that the broad dimension was strongly influenced by a psychological domain (e.g., memory, concentration, and anxiety) followed by a physical domain (e.g., aching muscles, swelling, and pain), and a sensory domain (e.g., chills, numbness and tingling, and dizziness). Therefore, the overarching framework of the dimension supported a psychological, physical, and sensory disruption of patient well-being. The full prompt and answer from ChatGPT can be found in **Supplemental File 2**.

Associations with patients' overall bother due to side effects

A correlation matrix, employing Spearman's Rho, which demonstrated the mutual associations between the 80 current symptomatic side effects in 14 categories included in PRO—CTCAE, participants' overall bother due to side effects, and the sum of current side effects is presented in **Supplemental File 3**. The coefficients revealed varying strengths of association, indicating the specific current symptomatic side effects that were most closely related to the overall bother due to side effects experienced by participants.Table 2 provides valuable insights into the relationships among the side effects that had the most impact on participants' overall bother: Eleven specific items were weakly correlated to participants' overall bother due to side effects, while other correlations were classified as negligible ($r < 0.2$). "Anxiety" ($r = 0.30$) "Nothing could cheer up" ($r = 0.28$) and "Sad" ($r = 0.28$) constitute the PRO—CTCAE category of "Mood" and were the most important items.

Associations with the sum of current side effects

Table 3 shows the relationships among the ten items that had the most impact on the sum of current side effects reported by participants. "Aching joints" ($r = 0.68$), "Pain" ($r = 0.66$), and "Aching muscles" ($r = 0.64$) were the most important items and constitute the PRO—CTCAE category of "Pain" together with "Headache", which appeared to be the 9th most important ($r = 0.56$). These were followed by "Memory" ($r = 0.62$) and "Concentration" ($r = 0.61$), which also were among the highest correlated to participants' overall bother and constitute the PRO—CTCAE category of "Attention/Memory". Correlations between each of the 80 items and the sum of current side effects are shown in **Supplemental File 3**. Of the 80 items, 0 (0%), 6 (8%), 31 (39%), 35 (44%), and 8 (10%) had very strong, strong, moderate, weak, and negligible correlation, respectively.

Associations with sum of current side effects and MCA dimension

There was a relation ($r = 0.35$, $p < 0.001$) between participants' overall bother due to side effects and the sum of current side effects experienced by participants as indicated in Fig. 3a. Likewise, the relation between participants' overall bother due to side effects and the MCA dimension in Fig. 3b was also significant ($r = 0.35$, $p < 0.001$).

Discussion

This study suggest that patients' rating of the overall bother due to side effects, measured with an instrument such as the modified GP5 item, provides validity evidence supporting the use of a single-item bother measure, which is capturing a broad concept influenced by a variety of symptomatic side effects, each of which individually has a negligible to weak impact on overall bother due to side effects in patients with RA. Our results present very low correlations, which may indicate that individuals have more diverse experiences - allowing the global index to capture these variations, even when they differ across patients. Thus, patients' overall bother appears to reflect the cumulative burden of side effects, which is influenced by multiple symptoms, as no

Box 1
Multiple correspondence analysis (MCA) terminology.

Multiple correspondence analysis (MCA): A way to find patterns in data like mapping out relationships between different characteristics.

Dimensions in MCA: A dimension represents an underlying pattern that summarizes how side effects are experienced across various patients.

Eigenvalues: How much a dimension (i.e., pattern) explains in the data.

One meaningful dimension in MCA: Results that indicate only one meaningful dimension through MCA suggest that there is no need to worry about multiple competing constructs i.e., modeling or predictions can focus on a single latent variable, which makes interpretation and use in clinical settings much easier (e.g., one "side effect burden score").

single symptom alone can accurately represent the overall burden experienced by patients. Still, patients' level of bother increased as patients reported more symptoms, and this in turn also raised the overall dimension.

Our findings underscore the critical need to capture patient experiences with treatment of RMDs. By establishing the construct validity of patients' overall bother due to side effects through latent variable modeling, including multiple correspondence analysis, we have elucidated harm-related constructs that reflect the complex nature of side effects in RA patients. Even though we cannot be sure that all symptoms are equally experienced to be bothersome by patients, and we lacked information about treatment duration and beneficial response to treatment, the correlations observed between patients' overall bother and theoretically related outcomes enhance our understanding of how symptomatic side effects impact patients' well-being and quality of life. Additionally, comparisons with latent variables derived from a Canadian RA patient dataset reinforce the GP5 index's utility as an example of a valuable tool for clinicians and researchers alike. A patient-centered approach to measuring both the number and impact of symptomatic side effects can yield more comprehensive assessments of treatment side effects.

We analyzed our data using factor analysis, and to prevent overestimation as our data were categorical, we used MCA (over Principal Component Analysis [PCA], which is appropriate for continuous data). Our primary MCA dimension explained 17% of variance which supports a single-dimension solution based on the elbow criterion; however, given the complexity of treatment-related side effects, additional aspects may provide a clinically meaningful structure. One likely reason for the relatively low variance explained is the inherently diverse nature of patient-reported symptomatic side effects, as they differ widely in type (e.g., physical, cognitive, emotional), frequency, and severity across individuals, making it difficult for a single latent factor to account for the full range of variability. Additionally, the GP5 item aggregates the subjective impact of side effects, which are shaped by individual thresholds for tolerance, treatment expectations, and contextual factors - aspects that may not be tightly linked across a common latent structure. Thus, a single dimension, though informative, likely captures only the dominant thematic axis (e.g., psychological burden) while leaving substantial heterogeneity unexplained.

Our study showed that mood changes (i.e., "anxiety", "nothing could cheer up" and "sad") were mostly associated with patients' overall bother, and these symptoms also constitute the PRO—CTCAE category of "mood". Such emotional side effects may be mostly subjective and less observable to others [28], and thus evident only by self-report. Our categorization, conducted by both the authors and ChatGPT, further showed that psychological, physical, and sensory categories were linked to patients' overall bother. These categories also mainly included primarily subjective symptomatic side effects [28], such as anxiety (psychological domain), pain (physical domain), and chills (sensory domain). Pain is also a subjective experience, and our analysis of the ten most impactful items on the sum of current side effects indicated that "aching joints", "pain", and "aching muscles" were the most significant, along with "headache," which ranked ninth in importance. To the contrary, symptoms such as "nail loss", "hand-foot syndrome", "ejaculation problem", "difficulty erection", and "bed sores" may be observable to the patient or others [28], and were among those having the weakest association with patients' overall bother and the smallest contribution to the dimension. However, some of these had very low prevalence, Still, symptoms like "pain" can cause emotional distress and might impact every minute of the day, whereas symptoms such as "nail loss" may only be bothersome when one thinks about them. Therefore, e.g., "pain" might also be more associated with patients' overall bother than e.g., "nail loss".

The PRO—CTCAE category of pain encompasses these items, reinforcing that the overall burden is a subjective experience, that must be assessed by the individual who is actually experiencing the symptoms. Further, "memory" and "concentration", that constitute the PRO—CTCAE category of "attention/memory" - were also among the highest correlated with patients' overall bother due to side effects and can also be considered primarily subjective without observable components. These findings support the assumption that the GP5 is capturing patients' lived harm experiences in our sample of adults with RA. However, some of the burden (i.e., side effects such as aching joints and pain) are also symptoms of RMD, and therefore may also be disease driven, especially as the disease progresses and new symptoms appear. These may be attributable to the current, or a new therapy, reflecting suboptimal disease control rather than perceived harm.

Our study has some limitations. We followed largely the original statistical analysis plan, but we also used categorization conducted by author and ChatGPT, which should be seen as exploratory. Such large language models (LLMs) pose challenges for reproducibility and transparency because they don't always produce the same results, and it's difficult to know what data they were trained on or how they make decisions. Therefore, comparing our results of categorization made by humans and LLMs might be influenced by differences in reasoning, inconsistency, and lack of explainability. Our study also included patients with RA, but the PRO—CTCAE and GP5 item are both developed in cancer and, to our knowledge, none of them have been previously validated in any RMDs. Likewise, we used data from RA patients alone, as opposed to looking at a greater number of patients with RMDs, however, patients with inflammatory arthritis tend to present with similar symptoms and receive similar treatments [29]. Further, the MCA-selected dimension explains only 17% of the variance; this suggests that there is a large share of the patient experience regarding side effects that are highly heterogeneous or even patient-specific and may not be possible to capture with a single dimension. This heterogenous nature of "bother" will require more efforts to seek and summarize terms or may need to settle for a few critical terms such as psychological, physical, and sensory themes. Finally, a limitation is local dependency among items, as conceptually overlapping items (e.g.: "pain" and subtypes of pain such as "aching joints", "aching muscles", and "headache"; and different types of depressed mood such as "nothing could cheer up", "sad", and "anxiety") may have violated the assumption of item independence. As we didn't use "super items" that group related items, our results of associations with overall bother and sum of current side effects may be inflated. Our findings do not constitute OMERACT endorsement of the GP5 bother measure in patients with RMDs, but they add valuable knowledge in evaluating this candidate measure to assess patients' overall burden due to medication side effects.

Our results suggest that the single-item burden measure to side

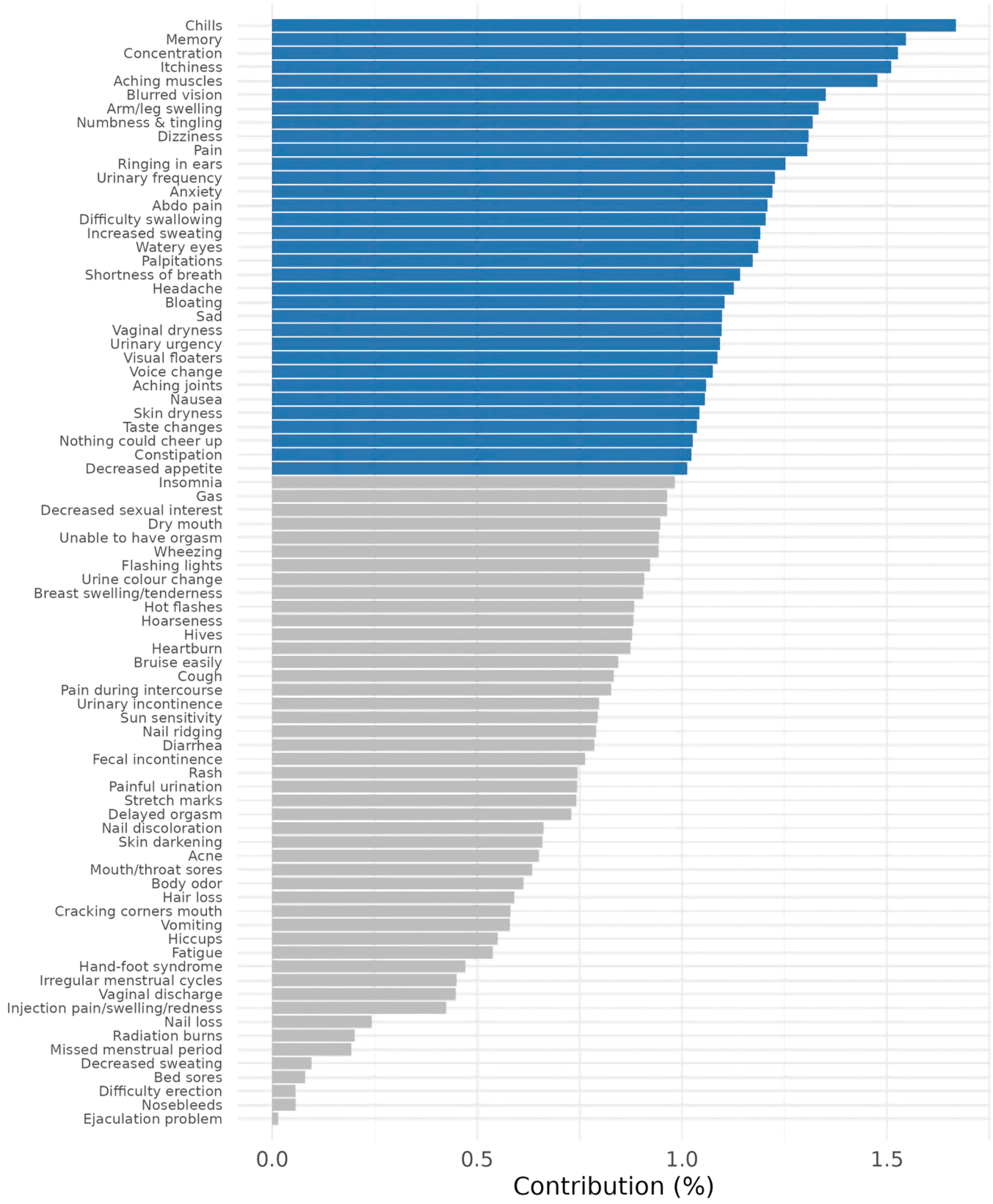

Fig. 2. Contributions of all 80 current symptomatic side effects to the primary dimension. Items contributing >1% are illustrated in blue.

effects could potentially serve as a useful summary indicator, shedding light on the impact of symptomatic side effects experienced by patients with RMDs. Integrating such an instrument into clinical practice may help healthcare providers explore patient concerns more effectively and support meaningful informed discussions about treatment choices. Furthermore, the implications of this work may extend to the development of tailored instruments for RMDs, enhancing our understanding of patient-reported outcomes and the safety profile of RA therapies. Future

Table 2
Items with some correlation to participants' overall bother due to side effects.

Item	Overall bother
Anxiety	0.30
Nothing could cheer up	0.28
Sad	0.28
Nausea	0.27
Concentration	0.26
Memory	0.26
Increased sweating	0.25
Bloating	0.24
Strech marks	0.21
Aching joints	0.21
Aching muscles	0.20

Correlations are expressed as Spearman rho.

Table 3
Items with some correlation to the sum of current side effects.

Item	Sum of current side effects
Aching joints	0.68
Pain	0.66
Aching muscles	0.64
Memory	0.62
Concentration	0.61
Fatigue	0.60
Anxiety	0.58
Insomnia	0.57
Headache	0.56
Numbness & tingling	0.54

Correlations are expressed as Spearman rho.

research should aim to validate a single-item index evaluating the "bother" "impact of side effects in patients across diverse populations and treatment modalities, ensuring its applicability in various clinical settings. Investigating when side effects lead to patients' discontinuation of treatment are other future areas. Longitudinal studies are also needed to elucidate the temporal relationship between treatment-related symptoms and overall patient well-being, providing a more comprehensive view of the side effects associated with RA medications.

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Ethics approval

The study was approved by the University of Calgary Conjoint Research Ethics Board (REB# 24-0093).

Declaration of competing interest

Dorthe B. Berthelsen: None; emerging leader of the OMERACT Safety Working Group.
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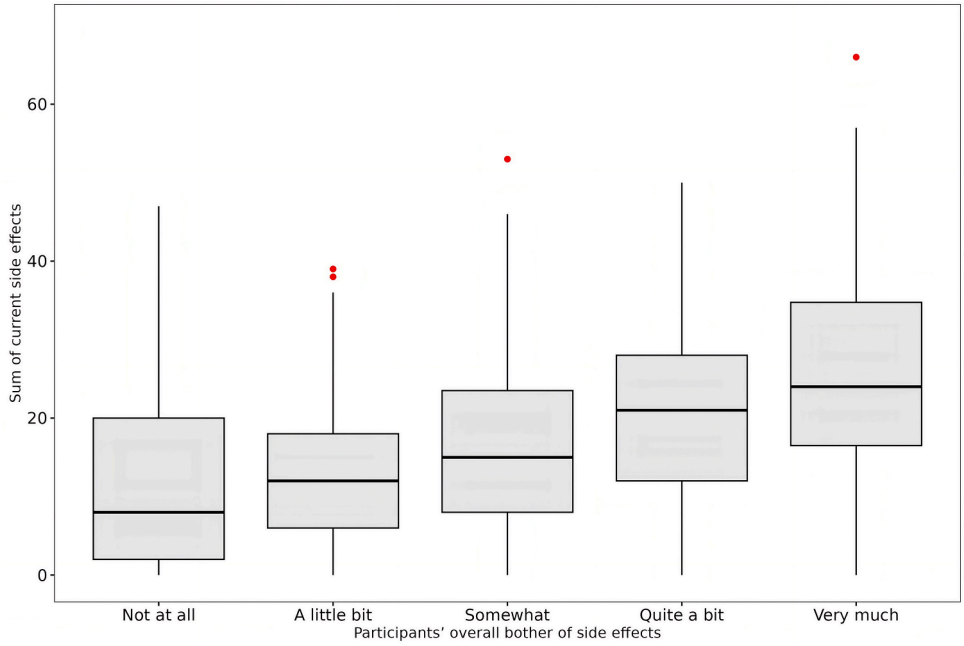

Fig. 3a. Boxplot of participants' overall bother of side effects and sum of current side effects. Dots indicate outliers.

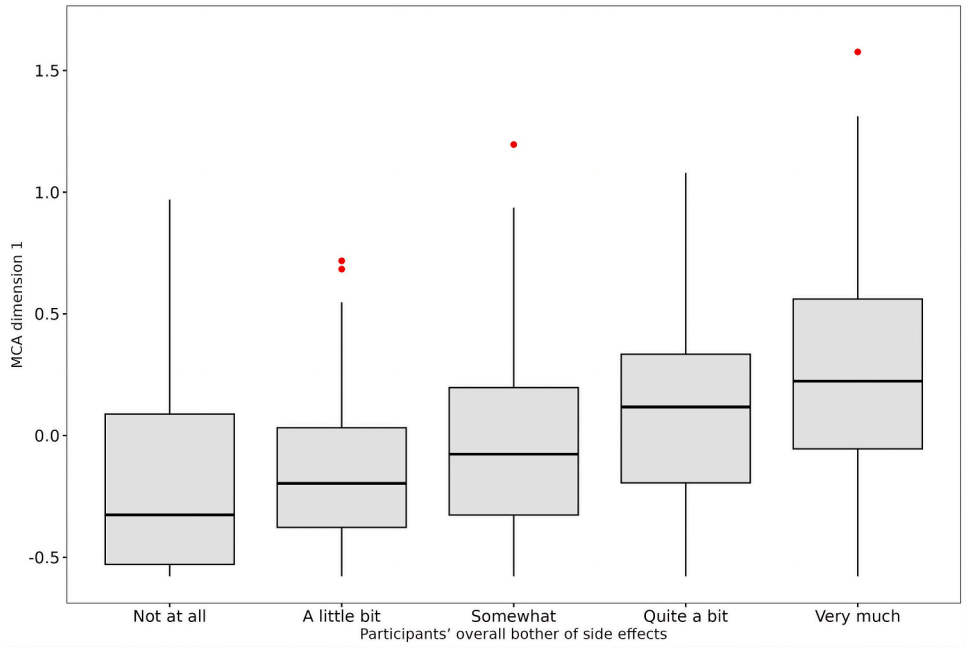

Fig. 3b. Boxplot of the overall bother index and MCA dimension 1. Dots indicate outliers.

USA Inc., Frictionless Solutions, Schipher, Crealta/Horizon, Medisys, Fidia, PK Med, Two labs Inc., Adept Field Solutions, Clinical Care options, Putnam associates, Focus forward, Navigant consulting, Spherix, MedIQ, Jupiter Life Science, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; the National Institutes of Health; and the American College of Rheumatology. JAS has received institutional research support from Zimmer Biomet Holdings. JAS received food and beverage payments from Intuitive Surgical Inc./Philips Electronics North America. JAS owns stock options in Atai life sciences, Kintara therapeutics, Intelligent Biosolutions, Acumen pharmaceutical, TPT Global Tech, Vaxart pharmaceuticals, Atyu biopharma, Adaptimmune Therapeutics, GeoVax Labs, Pieris Pharmaceuticals, Enzolytics Inc., Seres Therapeutics, Tonix Pharmaceuticals Holding Corp., Aebona Pharmaceuticals, and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JAS is on the speaker's bureau of Simply Speaking. JAS was a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies. JAS serves on the FDA Arthritis Advisory Committee. JAS previously served as a member of the following committees: member, the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee and the co-chair of the ACR Criteria and Response Criteria subcommittee

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2026.152983.

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