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Frequency of Symptomatic Adverse Events in Rheumatoid Arthritis: An Exploratory Online Survey

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ABSTRACT. ***Objective.*** To generate initial data on the frequency and effect of symptomatic adverse events (AEs) associated with rheumatoid arthritis (RA) drug therapy from the patient perspective.

Methods. We conducted an exploratory online survey asking patients with RA to indicate whether they currently or had ever experienced the 80 different symptomatic AEs included in the Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Results were summarized to report their frequency, and regression models were used to estimate their associations with RA medication use and overall bother.

Results. The 560 patients who completed the survey and reported taking ≥ 1 RA medication (disease-modifying antirheumatic drugs [DMARDs], steroids, nonsteroidal antiinflammatory drugs [NSAIDs]), had a mean disease duration of 8 years, and were on a wide range of DMARDs. The number of symptomatic AEs experienced in the past 7 days was none (6%), 1–10 (28%), 11–20 (28%), and > 20 (38%). Overall, most participants reported that side effects bothered them somewhat (28%), quite a bit (24%), or very much (15%). In multivariable regression analyses, current prednisone and NSAID use were associated with the greatest number of current side effects (26 and 22, respectively). Many of the strongest associations between current symptomatic AEs and medication use aligned with known side effect profiles.

Conclusion. In this exploratory online survey, patients with RA reported frequent symptomatic AEs with their medications that are bothersome. Further work is needed to develop and validate a measure for use in patients with rheumatic disease.

Key Indexing Terms: adverse effects, antirheumatic agents, drug-related side effects and adverse reactions, patient-reported outcome measures, rheumatoid arthritis

People with rheumatic diseases (RDs) typically require life-long treatment. When deciding how much of their medication to take and whether to take it, people weigh the benefits against the effect of their medications on their lives.[1] Patients commonly list symptomatic adverse events (AEs) or side effects as key reasons when choosing to take less medication.[2] People also learn to adjust their lives to manage the symptomatic AEs they experience, and the cumulative burden of these may have a considerable effect on quality of life over time.[1]

In clinical trials for RDs, AEs are typically graded using the

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Common Terminology Criteria for Adverse Events (CTCAE)[3] or the Rheumatology Common Toxicity Criteria.[4] These approaches rely on reporting from physicians and/or trained research personnel, but do not capture information on bothersome side effects from the perspective of patients.[5] In oncology, the Patient-Reported Outcomes of the CTCAE (PRO-CTCAE; https://healthcaredelivery.cancer.gov/pro-ctcae)[6] was created to allow patients to self-report presence, absence, frequency, severity, and interference from an item bank of 80 symptomatic AEs for patients in cancer clinical trials. It was developed with patient involvement using rigorous qualitative and quantitative methods and has been extensively validated in 30 languages.[7] Investigators can select subsets of symptomatic AEs from the item library relevant for their purpose, depending on the disease and treatments being studied. The intention is not to replace the CTCAE but rather to provide a patient-reported measure to complement existing drug safety information.[6]

The objectives of this study were to describe the frequency of symptomatic AEs listed in the PRO-CTCAE item library in patients with rheumatoid arthritis (RA), identify important items not currently included, and evaluate associations with RA medication use. While the PRO-CTCAE was developed for cancer trials, the extensive symptom library and overlapping medications (steroids, methotrexate [MTX], and injectable medications) provided a rationale for using it as a source for potential symptoms, with an overall aim to generate initial data that could be used to inform the future development of a rheumatology-specific instrument.

METHODS

Study design. We conducted a cross-sectional, web-based survey for adults with self-identified RA to collect information on the frequency of symptomatic AEs (side effects; we use these terms interchangeably) from their RA medications. We did not administer the PRO-CTCAE but rather used the PRO-CTCAE quick guide to the item library as a list of potential symptomatic AEs for our custom survey (https://healthcaredelivery.cancer.gov/pro-ctcae/item-library.pdf).[6]

Survey development. The survey included questions about sociodemographics, current RA medication use, and the complete list of 80 PRO-CTCAE symptomatic AEs, including free-text fields asking patients to write any other side effects they attributed to their RA medications (full survey in Supplementary Material, available with the online version of this article). Patients were asked to indicate the presence/absence of each symptomatic AE (described as "side effects" in the survey) experienced due to their RA medication in the past 7 days and ever. They were also asked a single question at the end to indicate the extent to which they were "bothered by side effects of your RA medications" (1 = "not at all" to 5 = "very much").[8] We chose to include the full list of symptoms in the PRO-CTCAE because it included a wide range of symptoms that encompassed most known side effect profiles. We had pilot-tested giving the PRO-CTCAE domain list in earlier qualitative work with patients in Australia, US, and Canada and received a very positive response from patients.[1] Side effects that were clearly unrelated to RA medications (radiation burns, bed sores) were not removed but rather served as internal controls, where we would not expect any positive responses.

Administration and ethics. The 14-page online survey was hosted using Qualtrics survey software (Qualtrics) and was approved by the University of Calgary Conjoint Research Ethics Board (REB no. 18-0597). Participants viewed the consent form on the first page of the survey and implied consent was obtained on completion of the survey. Participants could go back to previous pages to change their answers. IP addresses were not recorded, but the survey software used cookies to prevent multiple responses from the same IP address. The survey was considered complete when they reached the last page. No incentives were provided.

Sample population. The survey sample initially included patients with RA receiving treatment at an academic rheumatology clinic in Calgary, Alberta. However, in response to recruitment challenges during the first wave of the coronavirus disease 2019 (COVID-19) pandemic, the web-based survey was advertised on social media through Canadian arthritis patient advocacy groups, inviting individuals to participate who were diagnosed with RA, receiving treatment from a rheumatologist, and using ≥ 1 RA treatment.

Patient and public involvement. Two patient partners (DR, LP) were involved throughout the study, including survey development, pretesting, recruitment, interpretation of findings, and preparation of the manuscript. Additionally, the Arthritis Research Canada's Arthritis Patient Advisory Board reviewed the survey prior to dissemination and assisted with recruitment.

Data analysis. Descriptive statistics were used to summarize participant characteristics and the frequency of current and past side effects. We evaluated the overall bother of side effects in relation to the number of side effects currently experienced (last 7 days) reported through Spearman rank correlation, with overall bother as the dependent variable.

We explored the association between each of the 80 symptomatic AEs reported by patients in the last 7 days (dependent variable) and current RA medication use using multivariable logistic regression. Medications were categorized as nonsteroidal antiinflammatory drugs (NSAIDs), prednisone, MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide (LEF), biologic disease-modifying antirheumatic drugs (bDMARDs), and Janus kinase (JAK) inhibitors. Each of the 80 regression models included all 8 medications/medication classes as independent variables, and thereby evaluated the independent association with each RA medication/medication class. These analyses were viewed as exploratory, as causation cannot be inferred, given the cross-sectional nature of the survey. However, in a valid instrument of patient-reported side effects, we would expect to see some alignment between medication use and known side effect profiles. To prevent overfitting, we limited the multivariable regression models to symptomatic AEs that were reported with a frequency of ≥ 15%. All analyses were conducted using R statistical software (version 3.6.1; R Foundation for Statistical Computing).

Sensitivity analyses. We identified respondents who reported taking implausible medication combinations (> 1 advanced therapy; both oral and subcutaneous [SC] MTX) or reported either of 2 side effects that should not be associated with RA medications (skin burns from radiation and bed sores). We recognized that some of these responses may be valid (eg, patients may be switching between oral and SC MTX when they travel) or may reflect an error for that question and not the whole survey. Therefore, these patients were included for the main analyses but were excluded in a sensitivity analysis for our regression analyses. Finally, we examined whether symptomatic AE differed by sex/gender where expected (eg, vaginal dryness), again recognizing that while these symptomatic AEs could occur in patients who self-identified as either male or female, the frequency should be different.

RESULTS

Following the recruitment of 29 people in clinic in Calgary (23 of whom completed the survey), the survey was hosted online, where 913 people started it and 575 (63%) completed it. Of the 598 total people who completed the survey either in clinic or online, 560 (94%) reported taking ≥ 1 RA medication (NSAIDs or DMARDs including prednisone) and were included in this analysis. Demographics of the participants are presented in

Table 1. Patient characteristics.

	N = 560
Age, yrs, mean (SD)	44.3 (12.6), missing = 72
Gender, n (%)	
Female	530 (95)
Male	28 (5)
Diverse	1 (< 1)
Prefer not to answer	1 (< 1)
Disease duration, yrs, mean (SD)	8.1 (9.7)
Disease duration, yrs, n (%)	
< 2	144 (26)
2 to < 5	151 (27)
5 to < 10	96 (17)
≥ 10	169 (30)
Total no. of medications[a], mean (SD)	5.9 (3.7), missing = 1
Total no. of RA medications, mean (SD)	1.7 (1.0)
Current RA medications, n (%)	
NSAIDs	316 (56)
Prednisone	181 (32)
MTX	300 (54)
Oral	185 (33)[b]
SC	133 (24)[b]
Hydroxychloroquine	218 (39)
Sulfasalazine	97 (17)
Leflunomide	72 (13)
bDMARD	226 (40)
JAK inhibitor	60 (11)

[a] Includes non-RA medications. [b] 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.

Table 1. Most were women (95%) and the mean age was 44 years. Participants were on a mean number of 6 total medications, of which 2 were for RA. NSAIDs were used by 56% and prednisone by 32% (21 and 3 patients were using NSAIDs or prednisone alone, respectively, with no other DMARDs). The most common conventional synthetic (cs)DMARD used was MTX (54%), split between oral and SC routes; other csDMARDs were less common (Table 1). bDMARDs were used by 40% and JAK inhibitors by 11% (Table 1).

Frequency of symptomatic AEs. The number of symptomatic AEs participants reported experiencing in the past 7 days due to RA medicines ranged widely (see Supplementary Figure 1 for histogram of side effect frequency, available with the online version of this article). Thirty-six participants (6%) reported no side effects, 71 (13%) reported between 1–5 side effects, 82 (15%) between 6–10 side effects, 158 (28%) between 11–20 side effects, and 213 (38%) reported > 20 side effects.

The frequency of each side effect is presented in Figure 1. Of the 80 side effects, 45 (56%) were experienced in the past 7 days by ≥ 15% of patients. Side effects with the highest frequency included those that overlapped with common symptoms reported with RA (eg, fatigue, aching joints), as well as typical side effects associated with medications (eg, nausea, hair loss).

Overall bother of symptomatic AEs attributed to RA medications. Thirty-nine percent of participants reported being "quite a bit" or "very much" bothered by side effects of their RA medications in the past 7 days (Table 2). Bother increased with the number of side effects reported (Table 2), although patients stating they were "not at all" bothered by their side effects still reported a median of 8 symptomatic AEs.

Association between medication use and symptomatic AEs. Results for the multivariable models evaluating the association between medication use and the 45 symptomatic AEs with a frequency ≥ 15% are presented in Table 3 and Table 4 (symptomatic AEs with a statistically significant association are shown). Current prednisone had a statistically significant positive association with the greatest number of symptomatic AEs (n = 26), followed by NSAIDs (n = 22), SSZ (n = 8), MTX (n = 4), JAK inhibitors (n = 4), bDMARDs (n = 2), and HCQ (n = 2). LEF, which was only used by 72 participants, did not have a statistically significant association with any of the 45 symptomatic AEs evaluated. Many of the associations, particularly the ones with the largest effect sizes, aligned closely with known side effect profiles of medications. Current use of MTX was associated with experiencing nausea, hair loss, and difficulties with memory and concentration. Current HCQ use was most strongly associated with sun sensitivity, and bDMARDs with bruising easily (black and blue marks). Current prednisone and NSAID use were associated with a wide range of side effects.

Sensitivity analyses. Of the 560 patients, 44 (8%) failed ≥ 1 of the tests of internal validity (taking both SC and oral MTX [n = 18], taking > 1 bDMARD [n = 26], or reporting bed sores [n = 5] or radiation burns [n = 10] as side effects of their RA medications). When these patients were excluded from the analyses, the associations between medications and side effects were largely the same (Supplementary Tables 1–2, available with the online version of this article). A notable exception was an association between leflunomide and numbness and tingling (odds ratio [OR] 1.15, 95% CI 1.01–1.32)], and diarrhea [OR 1.14, 95% CI 1.01–1.30). Side effects showed expected associations with gender (Supplementary Table 3).

Free-text responses. Eighty-nine patients provided a total of 119 additional side effects they have attributed to their medications (ever) as a free-text response. Some (n = 32) overlapped with items in the PRO-CTCAE, and the remaining are summarized in Table 5. These included AEs/diagnoses (eg, cancer, diabetes) as well as additional symptomatic AEs.

DISCUSSION

Our study suggests that real-world patients using common RA treatment regimens report many symptomatic AEs that they attribute to their RA medications. Collectively, these side effects are substantially bothersome to many patients. Taken together, this exploratory study suggests a potentially large, underrecognized burden of symptomatic AEs that people with RA attribute to their RA medications. While the cross-sectional nature of our study prevents causal inference, the associations observed between current medication use and side effects in the past 7 days found many expected AEs. This supports the importance

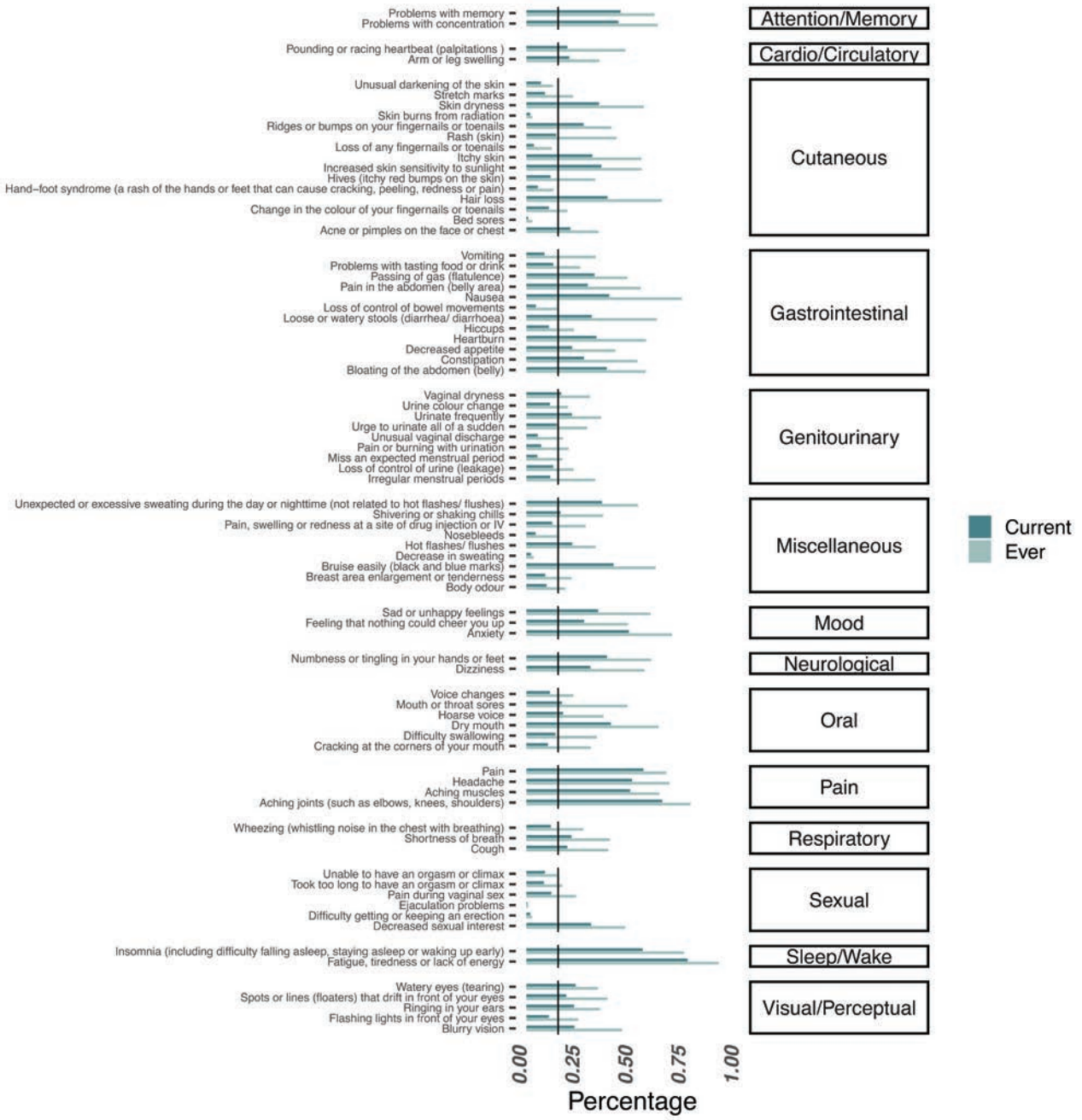

Figure 1. Frequency of symptomatic adverse events in patients with rheumatoid arthritis. The vertical line indicates a frequency of 15%. IV: intravenous.

Table 2. Overall bother of symptomatic AEs attributed to RA medications (past 7 days).

	Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
n (%)	65 (12)	117 (21)	159 (28)	137 (24)	82 (15)
No. of side effects*, median (IQR)	8 (2–20)	12 (6–18)	15 (8–24)	21 (12–28)	24 (17–35)

* Spearman rank correlation 0.35 ($P < 0.001$) for a trend across ordered groups. AE: adverse event; RA: rheumatoid arthritis.

Table 3. Multivariable association between medication use (conventional, biologic, and targeted synthetic DMARDs) and odds of symptomatic AEs.

Methotrexate, n = 300		HCQ, n = 218		Sulfasalazine, n = 97		bDMARD, n = 226		JAKi, n = 60	
Nausea	1.18 (1.09–1.28)	Sun sensitivity	1.17 (1.08–1.28)	Nothing could cheer up	1.18 (1.07–1.30)	Bruise easily	1.17 (1.08–1.27)	Dry mouth	1.19 (1.04–1.36)
Concentration	1.10 (1.02–1.20)	Gas	1.10 (1.01–1.19)	Sad	1.16 (1.04–1.29)	Itchiness	1.09 (1.01–1.18)	Acne	1.19 (1.06–1.32)
Memory	1.10 (1.02–1.20)	Nothing could cheer up	0.92 (0.85–0.99)[a]	Insomnia	1.13 (1.02–1.27)	Dizziness	0.89 (0.82–0.96)[a]	Diarrhea	1.15 (1.01–1.30)
Hair loss	1.09 (1.01–1.19)	Sad	0.90 (0.83–0.98)[a]	Watery eyes	1.13 (1.02–1.24)			Hoarseness	1.12 (1.01–1.24)
				Dry mouth	1.12 (1.00–1.25)				
				Decreased sexual interest	1.11 (1.01–1.23)				
				Shortness of breath	1.10 (1.01–1.21)				
				Chills	1.09 (1.01–1.19)				

Side effects with frequency ≥ 15% and statistically significant association. Values are expressed as OR (95% CI). [a] Denotes medication use was associated with lower odds of reporting the side effect. bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; HCQ: hydroxychloroquine; JAKi: Janus kinase inhibitor; OR: odds ratio.

of collecting side effect reports directly from patients. Further work is required to develop an RA or rheumatology-specific instrument.

For this work, we utilized all symptoms contained in the PRO-CTCAE symptom item bank.[6] Importantly, the PRO-CTCAE was developed to collect symptomatic AEs in oncology clinical trials. However, several aspects make it appealing as an initial list to build from for a rheumatology-specific inventory. It offers a reasonably comprehensive list that covers most common medication-related symptoms patients experience. While 2 side effects are clearly unrelated to RA medications (eg, radiation burns, bed sores), we decided to include the full list of side effects as they provided additional checks of internal validity. These could be removed from an RA-specific instrument, as could others that may not be relevant to RA medications. Importantly, the free-text responses also highlighted potential missing side effects such as "brain fog," "dry eyes," "mood swings," and others that respondents attributed to their RA medications. Additional work is needed to clarify the range of side effects that are important to patients and that should be routinely collected in people with RA and other RDs. Including patients in this process will be essential.

Strengths of our study include collecting side effects directly from the patient, the relatively large sample size, and including patients as research partners throughout the process from study design to interpretation of results. While our study was cross-sectional and therefore cannot evaluate causation, many of the strongest associations observed were in line with expected side effects. We found a large number of side effects associated with prednisone and NSAID use. Some of these likely reflect the true burden of side effects that are common with both NSAIDs and prednisone in RDs.[9,10] Prior work has found patients and physicians place different importance on AEs from glucocorticoid (GC) use,[11] so a patient-reported collection of side effects may supplement the routine monitoring of AEs, which has been recommended for patients taking GCs even at low doses.[12] Some of these side effects, however, may be related to active RA, as patients taking NSAIDs or prednisone are more likely to have active (or recently active) disease. While we asked patients to indicate which side effects they had experienced "as a result of taking your RA medications", assigning attribution of symptoms is challenging.[13,14] Understanding attribution would need to occur through longitudinal and/or interventional studies. Regardless, this highlights the importance of understanding patient-reported side effects; a high perceived burden of symptomatic side effects may shift the risk/benefit balance when patients decide to reduce or stop a medication.[15]

Our study has limitations. We recruited patients online, so it was not possible to know how many people viewed the invitation or to calculate a response rate. It is possible there was a self-selection bias, with patients experiencing more side effects being more likely to respond to the survey. We had no information about disease activity or other clinical data, including comorbidities and other non-RA medications, which would have provided more context to the findings. Few men completed

Table 4. Multivariable association between medication use (NSAIDs and prednisone) and odds of symptomatic AEs.

NSAIDs, n = 316		Prednisone, n = 181	
Pain	1.25 (1.16–1.36)	Headache	1.18 (1.08–1.29)
Aching muscles	1.24 (1.14–1.34)	Increased sweating	1.17 (1.07–1.27)
Aching joints	1.19 (1.10–1.29)	Constipation	1.17 (1.08–1.27)
Headache	1.15 (1.06–1.25)	Pain	1.16 (1.07–1.27)
Anxiety	1.15 (1.06–1.25)	Aching joints	1.15 (1.06–1.26)
Insomnia	1.13 (1.04–1.23)	Palpitations	1.15 (1.07–1.24)
Concentration	1.13 (1.04–1.23)	Abdominal pain	1.15 (1.06–1.25)
Fatigue	1.12 (1.05–1.21)	Fatigue	1.14 (1.06–1.23)
Numbness and tingling	1.11 (1.03–1.21)	Sad	1.14 (1.04–1.24)
Constipation	1.11 (1.03–1.20)	Arm/leg swelling	1.14 (1.06–1.22)
Memory	1.11 (1.02–1.21)	Anxiety	1.14 (1.04–1.24)
Urinary frequency	1.10 (1.03–1.18)	Memory	1.13 (1.04–1.24)
Itchiness	1.10 (1.02–1.19)	Bruise easily	1.13 (1.04–1.24)
Abdominal pain	1.10 (1.02–1.19)	Bloating	1.13 (1.03–1.23)
Gas	1.10 (1.02–1.19)	Nothing could cheer up	1.13 (1.04–1.22)
Arm/leg swelling	1.10 (1.03–1.17)	Hoarseness	1.12 (1.05–1.20)
Chills	1.10 (1.03–1.17)	Blurred vision	1.12 (1.04–1.21)
Sad	1.09 (1.01–1.18)	Hot flashes	1.12 (1.04–1.20)
Hot flashes	1.09 (1.02–1.17)	Decreased appetite	1.12 (1.04–1.20)
Urinary urgency	1.09 (1.03–1.15)	Insomnia	1.12 (1.02–1.22)
Nausea	1.09 (1.00–1.18)	Numbness and tingling	1.11 (1.01–1.21)
Bloating	1.09 (1.00–1.18)	Concentration	1.10 (1.01–1.20)
		Decreased sexual interest	1.09 (1.01–1.19)
		Sun sensitivity	1.09 (1.00–1.19)
		Shortness of breath	1.09 (1.01–1.17)
		Visual floaters	1.07 (1.00–1.15)

*Side effects with frequency (≥ 15%) and statistically significant association reported. Values are expressed as OR (95% CI). AE: adverse event; NSAID: nonsteroidal antiinflammatory drug.

Table 5. Additional symptomatic AEs provided by participants not captured in PRO-CTCAE.

Side Effect	n
Infections or infectious symptoms (eg, sinus infection/ congestion, urinary tract infections)	13
Change in weight (gain or loss) or appetite	12
Other miscellaneous (e.g. malaise, issues with wound healing/clotting, vivid dreams, stomach lesions, infertility)	13
Other AEs (eg, TIA, NSIP, neuropathy, cancer, diabetes, osteoporosis)	9
Dry eyes	7
Other cutaneous (eg, skin lightening, water pimples/blisters, skin necrosis)	7
Brain fog/feeling slow or lethargic/clumsy/ditzy	7
Other neurological (eg, tremors, muscle weakness, muscle cramping, visual disturbance)	6
Other mood (eg, mood swings, irritability, panic attacks)	4
Temperature fluctuations/sensitivity (eg, fever, hot/cold sensitivity)	4
Allergy	3
Other cardio/metabolic (eg, blood pressure, lipid changes)	2

AE: adverse event; NSIP: nonspecific interstitial pneumonia; PRO-CTCAE: Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events; TIA: transient ischemic attack.

the survey and owing to the method of collection, our sample is largely limited to computer-literate patients who are active members of online patient groups. Future research would benefit from targeting the specific experiences of older and male patients, perhaps through in-clinic recruitment with both paper-based and electronic methods of data collection. We did not include a measure of severity for each side effect as we were concerned about question fatigue with an online survey, so were unable to determine which side effects were the most bothersome. We did include a single-response item of overall medication bother,[8] which showed a strong correlation with the number of side effects. However, adding a measure of severity or bother for each side effect is clearly needed to understand the burden associated with specific RA medications. In our study, patients

who reported they were "not at all bothered" by side effects still reported a median of 8 side effects.

How to best measure side effects is controversial. Nonspecific symptoms that are generally not serious are common in placebo recipients in clinical trials[16] and 75–90% of the general adult population report ≥ 1 symptom at any given time, similar to rates observed in our study.[17,18] Checklists of side effects have been shown to result in many more side effects being reported than open-ended elicitation and may therefore lead to overreporting.[19,20] However, patients have been shown to underreport side effects to clinicians, and this underreporting can result in preventable AEs.[5,21,22] Open-ended questioning by a trained research assistant, with subsequent mapping to common terminology (eg, CTCAE[3] or Medical Dictionary for Regulatory Activities [MedDRA][23]), is the standard in regulatory clinical trials. However, this can be challenging to implement in clinical studies and in practice. Another option is free-form unstructured reporting by patients; by keeping a diary, for example. Traditionally, this method has posed challenges, but with the advent of mobile app technology and push notifications, real-time collection of patient-reported outcomes through electronic diaries has shown promise.[24] Including some measure of side effect ("bother" or "burden") for each side effect, and allowing free-text additions may also help mitigate the limitations of a checklist, and support patients and clinicians in having an informed discussion about which side effects are having the most life impact.

In summary, our results show the promise of a patient-reported inventory of side effects for patients with RA. Our results suggest the frequency and burden of side effects in RA medicines merit further study. Next steps from this work would be to identify a prioritized candidate list of side effect domains with further input from patients and clinicians, and to evaluate the optimal way to ask about side effect severity and burden in trials. Broader input is needed from international patients and other RDs.[25] The instrument would then need to be validated through longitudinal or interventional studies, while also capturing data on medication use and adherence, disease-related measures (eg, disease activity and duration), comorbidities, and other potential confounding variables.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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