Patient-Reported Nausea and Fatigue Related to Methotrexate: A Prospective, Self-Controlled Study in the ArthritisPower® Registry

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ABSTRACT

Introduction: The magnitude and frequency of temporally related methotrexate (MTX)-associated side effects in rheumatoid arthritis (RA) or psoriatic arthritis (PsA) patients are difficult to quantify using traditional research methods. As proof of concept designed in part to implement digital data collection for remote patient monitoring, we conducted a study implementing self-controlled case series analytic methods to understand MTX-related symptoms in RA or PsA.

Methods: In study phase 1, adults with RA or PsA from the ArthritisPower® Registry (past or current oral MTX users) participated in a cross-sectional survey. In phase 2, current MTX users participated in a longitudinal study and completed the Patient-Reported Outcomes Measurement Information System (PROMIS®) 1-day nausea/vomiting and fatigue measure. Within-person change in PROMIS scores between risk (6–36 h post-dose) and control (96–144 h post-dose) windows were compared using mixed models.

Results: The baseline survey was completed by 671 participants (mean age: 54 years, 88% female, 92% white, 79% with RA). Among current MTX users (353/671 [53%]), most reported MTX-associated side effects (216/353 [61%]), most frequently fatigue (161/353 [46%]). Among phase 2 participants with (n = 39) and without (n = 84) baseline nausea, mean increase in PROMIS nausea was 5.1 units (P < 0.0001) and 0.7 units (P = 0.135), respectively; among those with (n = 51) and without (n = 72) baseline fatigue, mean increase in PROMIS fatigue was 3.9 units (P = 0.003) and 0.4 units (P = 0.554), respectively.

Conclusions: Digital remote patient monitoring presents an opportunity to detect and address medication tolerability in real time. Using a novel study design to control for between-person confounding, the magnitude of nausea and fatigue experienced by participants with RA and PsA temporally related to weekly MTX use was substantial.

Keywords: Adverse events; Fatigue; Methotrexate; Nausea; Patient-reported outcome measures
**INTRODUCTION**

Methotrexate (MTX) remains a frequently used therapy for patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) due to its cost-effectiveness and clinical benefits in both populations [1–5]. As the cornerstone of therapy for RA and PsA, its use is codified in recommendations to clinicians from the American College of Rheumatology about “Choosing Wisely” [6]. Other treatment options including biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic (ts)DMARDs are more effective when used in combination with MTX at a group level. Despite its well-known benefits, MTX use is associated with a number of adverse events (AEs), including nausea, fatigue, gastrointestinal (GI) toxicity, and mouth sores, as well as more serious, albeit rare, AEs such as liver toxicity and bone marrow suppression [5, 7, 8]. These rare AEs, as well as poor tolerability in some patients, may make the use of MTX burdensome for some individuals [9–11]. The impact of these safety and tolerability considerations may be appreciable. Indeed, past studies have shown that as many as 50% of RA and PsA patients discontinue MTX within 6 months to 2 years of treatment due to intolerance and GI symptoms [12–17], either with or without their physicians’ knowledge [9–11]. A recent review of trials in RA found that non-serious medication-related AEs were not consistently reported [18].

Currently, a gap exists in patient-centric studies that focus on the patient experience with MTX, including beliefs regarding its benefits and behavioral distress and anxiety experienced by patients in anticipation of their upcoming dose. An important feature of MTX use is that some symptoms may be temporally related to its weekly administration [19]. For example, patients may experience nausea, fatigue, or malaise within a few days after MTX dosing, which may subsequently improve over time until the next weekly dose is given. This pattern is particularly difficult to study in clinical trials or with traditional study designs (e.g., a cohort study) because it would require multiple study visits within the same week, which is

### Key Summary Points

**Why carry out this study?**

Methotrexate is an important treatment option prescribed by physicians to optimize disease control in patients with RA or PsA; however, patients often experience bothersome side effects, notably fatigue and nausea, which are temporally related to weekly MTX dosing and may result in poor adherence and suboptimal disease management. Such data may be difficult to capture in routine care settings if symptoms fluctuate from day to day. Digital remote patient monitoring presents an opportunity to detect and address medication tolerability in real time.

**What was learned from this study?**

We used a self-controlled case series study design using electronic patient-reported outcome measures (e-PROMs) to generate real-world evidence regarding patients’ experiences and perceptions of treatment side effects and found that the majority of current MTX users report side effects, such as fatigue and nausea, with mean changes exceeding a minimally important difference.

Gastrointestinal (GI) side effects, such as stomach upset and pain, may play a more substantial role in patients’ decisions to discontinue MTX compared to other side effects.

Healthcare practitioners should consider the burden of MTX use in patients who may be bothered by side effects on a weekly basis but are not forthcoming in disclosing these symptoms to their clinician.

A smartphone-based strategy that implements remote patient monitoring to capture medication-related symptoms appears both feasible and acceptable to patients.
something that may be infeasible from a par-
ticipant burden perspective. A digital, app-based
method for data collection from patients
between office visits may improve accessibility
and patient participation for a study or a clinical
remote patient monitoring system that requires
multiple data collection points within the same
week.

Facilitating the implementation of such a
digital data collection strategy, previous studies
conducted in patients living with chronic con-
ditions have indicated that the National Insti-
tutes of Health–developed Patient Reported
Outcomes Measurement Information System
(PROMIS®) can reliably capture important
patient experiences across the domains of
physical, mental, and social health. The PRO-
MIS scales are available in both a fixed short
form as well as a computer-adaptive testing
format and have shown robust psychometric
properties [13]. For example, the PROMIS fati-
gue instruments have been shown to be reliable,
well correlated with, and responsive to change
in RA disease activity [20, 21].

As a proof-of-concept study of a novel digital
health strategy to capture medication-related
symptoms and using a novel continuous self-
controlled case series study design to control for
between-person confounding, we collected data
from a smartphone app at different time points
before and after administration of MTX. This
study aimed to assess the following outcomes:
to characterize the frequency of various both-
ersome symptoms associated with MTX use; to
examine patients’ overall satisfaction with
MTX; and to identify meaningful worsening in
nausea or fatigue occurring shortly after weekly
MTX administration using validated outcome
measures.

METHODS

Study Population

Participants were recruited from within the
ArthritisPower® Patient-Powered Research Net-
work Registry. ArthritisPower is a collaboration
between the nonprofit Global Healthy Living
Foundation (the parent organization of the
CreakyJoints® arthritis patient community) and
academic researchers at the University of Ala-
bama at Birmingham. It enrolls adult patients
with RA, PsA, or other rheumatic, skin, and
musculoskeletal conditions interested in par-
ticipating in research studies and has grown to
34,164 patients to date. The current study was
an ancillary study of the registry (Advarra IRB
Protocol #00033156) during which eligible
ArthritisPower members opted in for additional
data collection. Because this was a sub-study
that did not go beyond collection and analysis
of patient-reported outcome or other observa-
tional data being routinely collected by the
registry, no additional consent or addendum to
consent was required. The study was conducted
in accordance with ethical principles of the
Declaration of Helsinki 1964, and its later
amendments.

Eligibility for this ancillary study required
ArthritisPower registry participation (US resi-
dents: aged ≥ 19 years; Puerto Rico residents:
aged ≥ 21 years) with a self-reported physician
diagnosis of RA or PsA and an invitation to
participate in a cross-sectional survey (phase 1
of the study) via e-mail. Phase 1 participants
were current or past users of oral MTX; current
users were then invited to participate in the
longitudinal phase of the study (phase 2), which
required current MTX use, with at least 1 dose
taken in the prior month, and use of MTX
for < 10 years. In the absence of data indicating
a tolerance threshold for duration of MTX
therapy, the 10-year limit was chosen to strike a
balance between possible adjustment to MTX
tolerance over time and enabling adequate
participation in the survey. MTX use was per-
mitted either alone (i.e., monotherapy) or in
combination with other DMARDs. Rolling
recruitment of participants occurred from May
2019 to April 2020.

Survey Phases

The flow of the survey phases is shown in
Fig. 1A. Phase 1 participants completed a cross-
sectional survey online (see Supplementary
Material, Phase 1 Survey Questions) using the
health insurance portability and accountability
act-compliant SurveyMonkey platform, which included questions on what symptoms or side effects they have or had previously experienced while taking MTX, and the five-item specific-

Fig. 1 A Flow of the participants in the phase 1 and phase 2 surveys and B study design for the self-controlled case series analysis over 3 weeks. MTX methotrexate
necessity scale from the beliefs about medicine questionnaire [22].

Participants opting in for the phase 2 longitudinal study were asked to complete another brief baseline survey and patient-reported outcome assessments (Table S1). Phase 2 baseline survey assessments included questions pertaining to current MTX use such as dose and brand, timing of the RA or PsA diagnosis, and general physical and mental state associated with MTX dosing (Figure S1). During the 3-week observation period, participants were asked to record the exact date and time that they took MTX for each subsequent week, and then complete up to 6 (i.e., twice-weekly for 3 weeks) electronic patient-reported outcome measures (e-PROMs), both at 6–36 h after taking MTX (the “risk window”) and 96–144 h after taking MTX (the “control window”) (Fig. 1B). Risk and control windows were selected based on the expected temporal relationship between MTX use and peak onset of these symptoms. This study design is termed a continuous self-controlled case series (SCCS) [23] and compares participants’ health state in the risk window with that in their control window. SCCS models are typically used with a binary outcome, but a continuous SCCS design was employed here, as done in other studies. Because participants serve as their own controls, this study design avoids typical between-person confounding because all-time invariant factors (e.g., age, sex, comorbidities, concomitant RA medications) are perfectly balanced within the same individual.

Four health domains were assessed in the phase 2 longitudinal survey: (1) physical health using a modified version of the PROMIS GI nausea and vomiting instrument; PROMIS Fatigue, PROMIS Physical Function, and PROMIS Pain Interference short forms; (2) mental health using the PROMIS Anxiety and Applied Cognition Abilities short forms; (3) social health using the PROMIS Ability to Participate in Social Roles and Activities short forms; and (4) MTX tolerance and satisfaction using the Methotrexate Intolerance Severity Score (i.e., MISS) questionnaire. Although PROMIS includes a four-item instrument for nausea (https://www.healthmeasures.net/index.php), the time referent for 1 of the questions (“In the past 7 days, how often did you throw up or vomit?”) was unsuitable for a daily e-PROM. Thus, we removed that question and scored the remaining three items using the custom instrument scoring feature available for PROMIS instruments (https://www.assessmentcenter.net/ac_scoringservice) (Table S1). Although it may vary slightly across health domains and patient populations, the minimally important difference (MID) in PROMIS instruments for a group mean change is typically considered to be approximately 2–3 units, and a five-unit change for individual patients [24–26]. We conducted two analyses that considered either a within-person change of > 3 units as the MID for nausea and fatigue, and a within-person change of > 5 units.

**Statistical Analysis**

We conducted descriptive analysis using paired t tests, one-sided comparisons for continuous variables, and Chi-square tests for categorical variables. Within-person change in PROMIS scores between the risk and control windows were analyzed using mixed models for repeated measures and stratified by whether participants reported nausea or fatigue with MTX at baseline in their response to Yes/No questions: “Do you commonly feel fatigue within a day of taking methotrexate compared with other times?”; “Do you commonly have gastrointestinal symptoms, like nausea or vomiting, within a day of taking methotrexate compared with other times?”. We also included an interaction term with the baseline score. Detecting a significant difference in the within-person change in the 1-day PROMIS GI nausea and vomiting score or the PROMIS fatigue score was determined at the 5% level (P < 0.05), with 95% confidence intervals. All analyses were performed using SAS 9.4 software (SAS Software, Cary, NC, USA).
RESULTS

Participant Characteristics: Phase 1

Invitations to participate were e-mailed to 17,981 eligible members in the ArthritisPower Registry and 2378 eligible members in the CreakyJoints community. Up to two e-mail reminders were sent to non-responders. E-mails were opened by 26.1% (5318/20,359) of members, and the registration link was accessed by 26.6% (1416/5318) of those who saw the e-mail. A total of 1347 members agreed to participate and 671 eligible members completed the phase 1 survey (Fig. 1A). Of the 671 respondents who completed the survey, 528 (78.7%) reported physician-diagnosed RA and 193 (28.8%) reported PsA; 50 (7.5%) respondents reported both RA and PsA. Among the eligible patients, 353 (52.6%) were taking oral MTX at the time of survey administration (i.e., current users) and 318 (47.4%) were prior users who had discontinued. Most respondents were female (88.4%), with a mean (standard deviation [SD]) age of 54.0 (11.6) years, and white (92.4%). Mean (SD) duration of MTX treatment among current users was 4.9 (6.2) years; nearly all users (96.6%) took folic acid concurrently. Among current MTX users (N = 353), about half (48.2%) agreed that their life would be impossible without MTX, 66.0% believed that MTX protects them against worsening disease, and 44.5% believed that they would be very sick without MTX (Fig. 2). However, among current MTX users, 79.6% agreed that they would stop taking MTX if their RA or PsA was well controlled and their doctors said it was okay to stop taking it.

A significantly higher percentage of past versus current MTX users reported experiencing at least one side effect that they related to the medication (78.9 vs. 61.2%; \( P < 0.0001 \)) (Table 1), and among past users (N = 318), 65.1% said they stopped taking MTX because of unwanted side effects they thought were related to MTX. Fatigue was the most common side effect reported among both subgroups of patients and experienced by 45.6% of current and 44.7% of past users. Compared with current users of MTX, patients who discontinued MTX (i.e., past users; asked to recall their symptoms based on prior use of MTX) reported a significantly higher incidence of GI side effects, including nausea (40.3 vs. 30.6%; \( P = 0.009 \)) and abdominal pain (22.3 vs. 14.7%; \( P = 0.011 \)). A significantly higher proportion of past versus current users also reported experiencing malaise related to their MTX dose (27.4 vs. 16.1%; \( P < 0.001 \)). In addition, when current and past users of MTX were questioned on whether they believe that they experienced nausea/vomiting or fatigue within 1 day of MTX dosing, past users reported a higher incidence rate for both nausea/vomiting (50.0 vs. 38.2%) and fatigue (70.4 vs. 67.1%).

Participant Characteristics: Phase 2

Among the 353 individuals eligible for the phase 2 study, 198 (56.1%) participants signed up and completed the baseline characteristics form (Fig. 1B). A total of 175 (88.4%) participants joined the cohort and completed the phase 2 longitudinal survey (baseline characteristics), of which 136 (77.7%) provided the date of their next MTX dose.

Continuous Self-Controlled Case Series Analysis

In total, 123 participants provided any e-PROM data in the risk and control windows and were thus eligible for the SCCS analysis; within-week paired PROMIS nausea data were provided by 84 participants and within-week paired PROMIS fatigue data were provided by 85 participants. In terms of cohort characteristics, 77.2% were living with RA and 27.6% were living with PsA, with a mean (SD) baseline PROMIS Global score of 40.6 (7.0). Mean (SD) age was 51.7 (11.8) years, 87.0% of patients were female, and 93.5% were white. Mean (SD) duration of MTX treatment among current users was 2.6 (3.9) years. Among participants, 39.8% were on a biologic DMARD and 59.3% were on a non-biologic DMARD only (Table 2). At baseline, 58 (47.2%) reported nausea and/or fatigue in the phase 2 survey.
Among the 39 participants reporting MTX-associated nausea on their baseline survey, 25 contributed 43 paired sets of observations over the next 3 weeks; the mean increase in the PROMIS nausea score was 5.1 units (95% CI 3.1, 7.1; \( P < 0.0001 \)) (Table 3; Fig. S2). Among the 84 participants without baseline nausea, 59 contributed 110 paired sets of observations; the mean increase in PROMIS nausea was 0.7 units (95% CI 0.2, 1.6; \( P = 0.135 \)). Among the 51 participants reporting MTX-associated fatigue on their baseline survey, 35 contributed 62 paired sets of observations; the mean increase in PROMIS fatigue score was 3.9 units (95% CI 1.9, 6.0; \( P = 0.0003 \)). Among the 72 participants without fatigue at baseline, 50 contributed 92 paired sets of observations; the mean increase in PROMIS fatigue was 0.4 units (95% CI 0.0, 1.8; \( P = 0.554 \)). There was a small but significant interaction between baseline score and time (Fig. S3). Of the participants reporting MTX-associated nausea at baseline, 41% (16/39) experienced worsened nausea with an MID \( > \) 3 units compared with 24% (20/84) who did not report nausea at baseline. Of the participants reporting MTX-associated fatigue at baseline, 41% (21/51) experienced worsened fatigue with an MID \( > \) 3 units compared with 36% (26/72) who did not report fatigue at baseline (Fig. 3). Using an alternative cutoff for MID of \( > \) 5 units, the corresponding proportions were 31% (12/39) and 17% (14/84) for nausea and 39% (20/51) and 29% (21/72) for fatigue.

**DISCUSSION**

The entirely virtual nature of this longitudinal study is promising for future research with RA and PsA patients adopting remote patient monitoring as an essential component of digital health, where out-of-office data capture from patients is critical. Participants were prompted to specify the date of their weekly MTX dose and received reminders to complete e-PROMs on the ArthritisPower smartphone app or web-based equivalent during the risk and control windows. This innovation in the way that clinical trials and real-world studies can be conducted shows that a study design with no involvement from clinical sites, and dependent only upon patients’ use of smartphone technology, is feasible. Moreover, the within-person study design is novel and avoids all time-invariant confounding that would otherwise accompany a traditional cohort design [23, 27, 28]. Particularly in an era of widespread
| Characteristics | All participants, N = 671 | Currently on MTX, n = 353 | Previously on MTX, n = 318 | P value* |
|-----------------|--------------------------|---------------------------|--------------------------|----------|
| Female, n (%)   | 593 (88.4)               | 313 (88.7)                | 280 (88.1)                | 0.803    |
| Age, years, mean (SD) | 54.0 (11.6)         | 53.4 (11.7)               | 54.7 (11.5)               | 0.130    |
| White, n (%)    | 620 (92.4)               | 326 (92.4)                | 294 (92.5)                | 0.961    |
| College graduate, n (%) | 290 (43.2)          | 155 (43.9)                | 135 (42.5)                | 0.704    |
| Employment status, n (%) |                   |                           |                           |          |
| Employed (full-time, part-time, or self-employed) | 323 (48.1)           | 188 (53.3)                | 135 (42.5)                | 0.005    |
| Current RA/PsA therapy, n (%) |                  |                           |                           |          |
| Non-biologic DMARDs onlya | 281 (41.9)          | 190 (53.8)                | 91 (28.6)                 | < 0.0001 |
| Biologic DMARDs | 383 (57.1)               | 163 (46.2)                | 220 (69.2)                | < 0.0001 |
| Corticosteroids only | 7 (1.0)             | 0 (0.0)                   | 7 (2.2)                   | 0.005    |
| Duration of current MTX use, years, mean (SD) | 4.9 (6.2)           | 4.9 (6.2)                 | –                        | –        |
| Current folic acid use, n (%) |                   |                           |                           |          |
| BMI, kg/m², mean (SD) | 31.9 (7.9)           | 32.2 (8.4)                | 31.5 (7.2)                | 0.251    |
| Side effectsa, n (%) |                   |                           |                           |          |
| Anyb | 467 (69.6)             | 216 (61.2)                | 251 (78.9)                | < 0.0001 |
| Fatigue | 303 (45.2)            | 161 (45.6)                | 142 (44.7)                | 0.804    |
| Nausea | 236 (35.2)            | 108 (30.6)                | 128 (40.3)                | 0.009    |
| Hair thinning | 225 (33.5)           | 121 (34.3)                | 104 (32.7)                | 0.667    |
| Brain fog | 197 (29.4)            | 111 (31.4)                | 86 (27.0)                 | 0.211    |
| Hair loss | 163 (24.3)            | 83 (23.5)                 | 80 (25.2)                 | 0.620    |
| Malaise | 144 (21.5)           | 57 (16.1)                 | 87 (27.4)                 | < 0.001  |
| Mouth sores/ulcers | 138 (20.6)          | 70 (19.8)                 | 68 (21.4)                 | 0.619    |
| Difficulty sleeping | 124 (18.5)          | 80 (22.7)                 | 44 (13.8)                 | 0.003    |
| Abdominal pain | 123 (18.3)            | 52 (14.7)                 | 71 (22.3)                 | 0.011    |
| Diarrhea | 112 (16.7)            | 56 (15.9)                 | 56 (17.6)                 | 0.545    |
| Loss of appetite | 84 (12.5)            | 37 (10.5)                 | 47 (14.8)                 | 0.093    |

* Denotes statistical significance; P < 0.05

** by comparison between currently and previously on MTX

a by comparison between currently and previously on MTX

b by comparison between currently and previously on MTX

| Δ Adis |
technology availability and social distancing to mitigate the risk of a highly transmissible infection (e.g., COVID-19), this study demonstrates the capacity and willingness of patients (particularly those who may be susceptible to increased risk due to autoimmune conditions and associated immunomodulatory treatment) to use a digital platform for research that can easily be extended to remote patient monitoring as an essential component of telehealth and digital health care. In addition, as treatment paradigms shift towards an informed decision-making model, the incorporation of patients’ views and experiences will be increasingly important [18], and remote approaches to collecting these data will be used more frequently. If these approaches were used routinely in clinical care settings, patient motivation to participate in efforts like this may increase as they become more familiar with the technology, particularly if encouraged to do so by their clinicians who may be able to provide improved care by having patient’s data between office visits.

As has been observed previously [29], people taking MTX to manage RA or PsA commonly experience bothersome side effects, notably nausea and fatigue, which are temporally related to weekly MTX dosing. These AEs associated with chronic medication use are often combined with pre-existing fatigue, which is an important symptom experienced by patients with rheumatic diseases such as RA and PsA. Based on this study’s findings, only half to two-thirds of patients taking MTX acknowledge its role in achieving optimal disease control yet were nevertheless still taking it. While only patients with intolerable side effects with MTX should be switched to alternative csDMARDs or b/tsDMARDs, if their clinician is able to have insights into tolerability problems, it allows dose adjustments or alteration in the route of administration (e.g., to SQ injection) if needed.

Indeed, of the current MTX users (353/671 [53%]), most of the participants reported side effects associated with MTX (216/353 [61%]), of which fatigue was the most frequent (161/353 [46%]). Among participants in the phase 2 longitudinal study reporting baseline fatigue (n = 35 with 62 observations) or nausea (n = 25 with 43 observations), the mean increase in PROMIS nausea score was 5.1 units (P < 0.0001) and the mean increase in PROMIS fatigue score was 3.9 units (P = 0.0003), both exceeding the MID. Because 5 units represents a half SD change on PROMIS instruments, a 4- or 5-unit change would be noticeable and clinically relevant for most patients [24–26]. As expected, differences in PROMIS scores were not significant among participants without baseline symptoms. It is notable that only about one-third of patients in this sample experienced meaningful worsening of nausea or fatigue in the day following their weekly MTX dose, with a magnitude of that change exceeds the MID. Thus, stratifying by self-reported symptoms not

### Table 1 continued

| Characteristics | All participants, N = 671 | Currently on MTX, n = 353 | Previously on MTX, n = 318 | P value* |
|-----------------|--------------------------|---------------------------|---------------------------|----------|
| None of the above | 2 (0.3) | 0 (0.0) | 2 (0.6) | 0.136 |

**Phase 1 study**

*Statistical significance between groups of participants who are currently on MTX and were on MTX in the past, P < 0.05; t tests were performed for continuous variables and Chi-square tests for categorical variables; P values are nominal in nature and should be interpreted in an exploratory manner

aSelection of side effects mentioned below were not mutually exclusive except for the “none of the above” option

bExperience of any side effect that participants believed was related to taking MTX (includes other related side effects not listed in Table 1)

**BMI body mass index, DMARD disease-modifying anti-rheumatic drug, MTX methotrexate, PsA psoriatic arthritis, RA rheumatoid arthritis, SD standard deviation**

*Statistical significance between groups of participants who are currently on MTX and were on MTX in the past, P < 0.05; t tests were performed for continuous variables and Chi-square tests for categorical variables; P values are nominal in nature and should be interpreted in an exploratory manner

aSelection of side effects mentioned below were not mutually exclusive except for the “none of the above” option

bExperience of any side effect that participants believed was related to taking MTX (includes other related side effects not listed in Table 1)
only provides evidence for convergent validity
of the quantitative PROMIS scores but also helps
avoid failing to identify important symptoms
that are bothersome to a large minority of
patients yet may be obscured if only reporting
at a group level.

It is also noteworthy that although the SCCS
design has been used to study the impact of
different treatment options on disease flares and
infection risk [30, 31], not many rheumatology
studies of medication-related symptoms have
used it. We would refer readers to the

Table 2 Characteristics of participants reporting MTX-related fatigue or nausea (SCCS survey at baseline)

| Characteristics                                      | All participants, N = 123 | No nausea or fatigue from MTX, n = 65 | Report nausea and/or fatigue from MTX, n = 58 | P value* |
|------------------------------------------------------|---------------------------|-------------------------------------|-----------------------------------------------|---------|
| Female, n (%)                                        | 107 (87.0)                | 58 (89.2)                           | 49 (84.5)                                     | 0.61    |
| Age, years, mean (SD)                                | 51.7 (11.8)               | 52.3 (12.6)                         | 51.1 (10.9)                                   | 0.56    |
| White, n (%)                                         | 115 (93.5)                | 63 (96.9)                           | 52 (89.7)                                     | 0.21    |
| Bachelor’s degree or higher, n (%)                   | 62 (50.4)                 | 33 (50.8)                           | 29 (50.0)                                     | 1.00    |
| Employed (full-time, part-time, self-employed), n (%)| 67 (54.5)                 | 37 (56.9)                           | 30 (51.7)                                     | 0.69    |
| Condition, n (%)                                     |                           |                                    |                                               |         |
| RA                                                   | 95 (77.2)                 | 51 (78.5)                           | 44 (75.9)                                     | 0.90    |
| PsA                                                  | 34 (27.6)                 | 17 (26.2)                           | 17 (29.3)                                     | 0.85    |
| Years since RA/PsA diagnosis, mean (SD)              | 5.9 (6.7)                 | 6.2 (7.8)                           | 5.6 (5.4)                                     | 0.63    |
| Current RA/PsA therapy, n (%)                        |                           |                                    |                                               | 0.77    |
| Biologic DMARDs                                      | 49 (39.8)                 | 27 (41.5)                           | 22 (37.9)                                     |         |
| Non-biologic DMARDs only                             | 73 (59.3)                 | 37 (56.9)                           | 36 (62.1)                                     |         |
| Duration of current MTX use, years, mean (SD)        | 2.6 (3.9)                 | 2.6 (3.8)                           | 2.8 (4.0)                                     | 0.78    |
| Baseline patient global PROMIS score, mean (SD)      | 40.6 (7.0)                | 41.4 (7.2)                          | 39.8 (6.7)                                     | 0.19    |
| Side effect experienced, n (%)                       |                           |                                    |                                               |         |
| Fatigue                                             | 51 (41.5)                 | 0                                   | 51 (87.9)                                     | < 0.001 |
| Nausea                                              | 39 (31.7)                 | 0                                   | 39 (67.2)                                     | < 0.001 |

*Statistical significance between groups of participants who report no nausea or fatigue and those who report nausea and/or fatigue, P < 0.05; t tests were performed for continuous variables and Chi-square tests for categorical variables; P values are nominal in nature and should be interpreted in an exploratory manner; SD values reported are 1 SD below population mean (for PROMIS scores, the population mean = 50, SD = 10)
Strengthening the Reporting of Observational Studies in Epidemiology (i.e., STROBE) guidelines for good reporting of observational data that may make it particularly suitable for the assessment of certain health outcomes [32, 33]. In particular, the SCCS design is well suited to the assessment of temporal associations between transient exposures and symptoms and AEs [23], particularly those with abrupt onset such as those examined in this study.

The findings of this study should be considered in the context of certain limitations. Patients were recruited via an online community; therefore, there may be some bias in the patients who took part. For example, individuals who have experienced MTX-associated side effects might be more likely to participate in a study like this one, which may increase the frequency of these symptoms in the cohort. We acknowledge attrition between the various phases of the study but nevertheless note a substantial number of patients who reported no nausea or fatigue and participated in the longitudinal aspect of the study. Attrition in a digital health study similar to this is likely to decrease if patients are encouraged by their treating physician to participate and if the results are to be used for clinical care, as current ArthritisPower initiatives could facilitate in the future. Our findings may not be representative of all US patients with these conditions and are based on participants’ self-reported diagnosis.

### Table 3  Change in PROMIS scores from risk to control window, stratified by baseline nausea and fatigue (n = 123)

| Baseline selection | Patientb | Number of paired observations/patient, n<sup>c</sup> | Mean (95% CI) risk<sup>d</sup> | Mean (95% CI) control<sup>e</sup> | Mean change<sup>f</sup> (95% CI) | P value<sup>g</sup> |
|-------------------|----------|-----------------------------------------------|-------------------------------|-------------------------------|-------------------------------|---------------|
| PROMIS nausea     |          |                                               |                               |                               |                               |               |
| Yes               | 39       | 43/25                                         | 56.9 (55.2, 58.6)             | 51.8 (50.1, 53.4)             | 5.1 (3.1, 7.1)                | < 0.0001      |
| No                | 84       | 110/59                                        | 44.3 (43.6, 45.0)             | 43.6 (43.0, 44.2)             | 0.7 (−0.2, 1.6)               | 0.135         |
| PROMIS fatigue    |          |                                               |                               |                               |                               |               |
| Yes               | 51       | 62/35                                         | 61.1 (59.6, 62.6)             | 57.1 (55.7, 58.6)             | 3.9 (1.9, 6.0)                | 0.0003        |
| No                | 72       | 92/50                                         | 49.4 (48.3, 50.4)             | 48.9 (48.0, 49.9)             | 0.4 (1.0, 1.8)                | 0.554         |

CI confidence interval, N sample size, PROMIS Patient-Reported Outcomes Measurement Information System, SD standard deviation

<sup>a</sup>Statistical significance of change in PROMIS nausea and fatigue scores in risk window (6–36 h) from control window (96–144 h) following oral MTX dose where participants serve as their own control and each observation is from a pair of PROMIS scores in the same week, *P* < 0.05; *t* tests were performed for continuous variables; *P* values are tests of the null hypothesis that there is no within-person change between risk and control. Note that the above estimates include an interaction term between the baseline score and time.

<sup>b</sup>Selection on baseline (phase 1) survey (e.g., “Do you commonly feel fatigue within a day of taking methotrexate compared with other times?”)

<sup>c</sup>Total number of phase 2 participants who made the indicated selection on baseline (phase 1) survey

<sup>d</sup>Number of paired risk-control PROMIS nausea/fatigue observations within the same week over the number of unique phase 2 participants who provided them

<sup>e</sup>Mean (SD) risk score for paired observations

<sup>f</sup>Mean (SD) control score for paired observations

<sup>g</sup>Mean change (CI) in PROMIS nausea/fatigue score between risk and control windows, calculated from mixed models analysis
treatment, and experiences. In addition, recall bias is a well-known limitation of self-reporting and may have impacted the results obtained from the cross-sectional survey contributed by past MTX users but would not affect the prospective, longitudinal component of the study deployed among current MTX users. Because the cutoff point at which patients become tolerant to side effects associated with MTX is unknown, we made a somewhat arbitrary decision about MTX duration and tolerance, initially specifying a 3-year cutoff, then increasing it to a 10-year cutoff. This was done to ensure adequate sample size while limiting the number of patients who had well-established MTX tolerance. Sample size did not allow us to examine the impact of duration of MTX therapy on tolerance, but we speculate that limiting it to patients on MTX for a shorter duration or new users may result in greater PROMIS score changes than what was observed here, and a higher proportion of patients with bothersome MTX-associated symptoms. Our results may thus reflect a conservative estimate of nausea, fatigue, and other MTX-associated symptoms. Finally, the limited sample size did not allow for a detailed analysis of shorter versus longer duration of MTX use.

Future research is needed to better understand the effective implementation of digital strategies and remote patient monitoring to improve detection of suboptimal patient experience with medications due to associated tolerability issues. We would anticipate a framework such as that used in this study, deployed as part of routine clinical care, can improve patient–physician communication and subsequent medication adherence and has the potential to significantly impact clinical outcomes.

**CONCLUSIONS**

Digital remote patient monitoring presents an opportunity to detect and address medication tolerability in real-time. In patients living with chronic autoimmune conditions such as RA and PsA, MTX is an important treatment option often prescribed by physicians to optimize disease control. However, many patients experience undesirable, temporarily-based side effects, resulting in poor adherence, which may lead to suboptimal disease management.

In this self-controlled cohort of RA and PsA patients, we show that patients frequently experienced MTX side effects such as nausea and fatigue. Further research is required to manage patient perception and experience of MTX use, and improvements in treatment...
adherence are likely to have a significant impact on long-term clinical outcomes. A smartphone-based strategy that implements remote patient monitoring to capture medication-related symptoms appears both feasible and acceptable to patients.

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Compliance with Ethics Guidelines. The study was conducted in accordance with ethical principles of the Declaration of Helsinki 1964, and its later amendments. The study protocol was approved by Advarra Institutional Review Board (Advarra IRB Protocol #00033156). The current study was an ancillary study of the registry during which eligible ArthritisPower members opted in for additional data collection. Because this was a sub-study that did not go beyond collection and analysis of patient-reported outcome or other observational data being routinely collected by the Registry, no additional consent or addendum to consent was required.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-
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REFERENCES

1. Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2014;(6):Cd000957.

2. Mease P. Methotrexate in psoriatic arthritis. Bull Hosp Jt Dis. 2013;71(Suppl 1):S41–5.

3. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Rheumatol. 2019;71(1):5–32.

4. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1–26.

5. Wilsdon TD, Whittle SL, Thynne TR, Mangoni AA. Methotrexate for psoriatic arthritis. Cochrane Database Syst Rev. 2019;1(1):Cd012722.

6. Five Things Physicians and Patients Should Question American College of Rheumatology Choosing Wisely; 2019. https://www.choosingwisely.org/societies/american-college-of-rheumatology/.

7. Husted JA, Tom BD, Schentag CT, Farewell VT, Gladman DD. Occurrence and correlates of fatigue in psoriatic arthritis. Ann Rheum Dis. 2009;68(10):1553–8.

8. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J Med Chem. 2018;158:502–16.

9. De Cuyper E, De Gucht V, Maes S, Van Camp Y, De Clerck LS. Determinants of methotrexate adherence in rheumatoid arthritis patients. Clin Rheumatol. 2016;35(5):1335–9.

10. Hope HF, Hyrich KL, Anderson J, et al. The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. Rheumatology (Oxford). 2020;59(1):213–23.

11. Nikipherou E, Negoeescu A, Fitzpatrick JD, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol. 2014;33(5):609–14.

12. Bakker MF, Jacobs JW, Welsing PM, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2012;156(5):329–39.

13. Curtis JR, Bykerk VP, Aassi M, Schiff M. Adherence and Persistence with Methotrexate in Rheumatoid Arthritis: A Systematic Review. J Rheumatol. 2016;43(11):1997–2009.

14. Curtis JR, Zhang J, Xie F, et al. Use of oral and subcutaneous methotrexate in rheumatoid arthritis patients in the United States. Arthritis Care Res (Hoboken). 2014;66(11):1604–11.

15. Lie E, van der Heijde DM, Uhlig T, et al. The effectiveness and retention rates of methotrexate in psoriatic arthritis with methotrexate-treated patients with rheumatoid arthritis as a reference population. Ann Rheum Dis. 2010;69(4):671–6.

16. Schnabel A, Herlyn K, Burchardi C, Reinhold-Keller E, Gross WL. Long-term tolerability of
methotrexate at doses exceeding 15 mg per week in rheumatoid arthritis. Rheumatol Int. 1996;15(5):195–200.

17. Verstappen SM, Bakker MF, Heurkens AH, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. Ann Rheum Dis. 2010;69(6):1044–8.

18. Costello R, David T, Jani M. Impact of adverse events associated with medications in the treatment and prevention of rheumatoid arthritis. Clin Ther. 2019;41(7):1376–96.

19. Patil P, Parker RA, Rawcliffe C, et al. Methotrexate-induced nausea and vomiting in adult and young adult patients. Clin Rheumatol. 2014;33(3):403–7.

20. Bingham CO III, Gutierrez AK, Butani A, et al. PROMIS Fatigue short forms are reliable and valid in adults with rheumatoid arthritis. J Patient Rep Outcomes. 2019;3(1):14.

21. Cook KF, Jensen SE, Schalet BD, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. J Clin Epidemiol. 2016;73:89–102.

22. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Phychol Health. 1999;14:1–24.

23. Petersen I, Douglas I, Whitaker H. Self-controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515.

24. Beaumont JL, Davis ES, Fries JF, Curtis JR, Cella D, Yun H. Meaningful change thresholds for Patient-Reported Outcomes Measurement Information System (PROMIS®) fatigue and pain interference scores in patients with rheumatoid arthritis. J Rheumatol. 2021;48(8):1239–42.

25. Khanna D, Hays RD, Shreiner AB, et al. Responsiveness to change and minimally important differences of the patient-reported outcomes measurement information system gastrointestinal symptoms scales. Dig Dis Sci. 2017;62(5):1186–92.

26. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. J Clin Epidemiol. 2011;64(5):507–16.

27. Gault N, Castañeda-Sanabria J, De Rycze Y, Guillo S, Foulon S, Tubach F. Self-controlled designs in pharmacoepidemiology involving electronic healthcare databases: a systematic review. BMC Med Res Methodol. 2017;17(1):25.

28. Grosso A, Douglas I, MacAllister R, Petersen I, Smeeth L, Hingorani AD. Use of the self-controlled case series method in drug safety assessment. Expert Opin Drug Saf. 2011;10(3):337–40.

29. Curtis JR, Xie F, Mackey D, et al. Patient’s experience with subcutaneous and oral methotrexate for the treatment of rheumatoid arthritis. BMC Musculoskelet Disord. 2016;17(1):405.

30. Nagra NS, Robinson DE, Douglas I, et al. Antibiotic treatment and flares of rheumatoid arthritis: a self-controlled case series study analysis using CPRD GOLD. Sci Rep. 2019;9(1):8941.

31. Wiese AD, Griffin MR, Stein CM, Mitchel EF Jr, Grijalva CG. Opioid analgesics and the risk of serious infections among patients with rheumatoid arthritis: a self-controlled case series study. Arthritis Rheumatol. 2016;68(2):323–31.

32. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology. 2007;18(6):805–35.

33. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–9.