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Regular Article

Changing mindsets about methotrexate in the rheumatology clinic to reduce side effects and improve adherence: a randomized controlled trial

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Abstract

Background: Patients' negative expectations about medication can exacerbate side effect burden leading to low adherence and persistence. A novel intervention involves targeting mindsets about non-severe symptoms; reframing them as encouraging signs of medication working.

Purpose: This study aimed to assess whether a brief symptom-mindset intervention can improve symptom experience and adherence in patients starting methotrexate to treat an inflammatory rheumatic disease.

Methods: A randomized controlled trial was conducted with patients starting methotrexate. Participants were randomly assigned (1:1) to a mindset intervention or standard information control condition. Symptom mindset was assessed after 4 weeks to check intervention efficacy. The primary outcome was symptom experience after 4 weeks. Secondary outcomes were adherence and motivation to take methotrexate (4 weeks), as well as continuation and C-reactive protein (12 weeks).

Results: Forty-seven participants were randomly assigned to the intervention ($n = 24$) or control group ($n = 23$). All participants completed the study. After 4 weeks, compared to the control group, intervention participants endorsed more positive symptom mindsets, experienced less symptom burden (mean difference −2.70 [95% CI, −4.50, −0.90] $P = .005$), fewer general symptoms (3.53 [−6.99, .79] $P = .045$) and a similar number of methotrexate-specific symptoms (−0.79 [−2.29, 0.71] $P = .295$). The intervention group had better motivation and adherence to methotrexate at 4 weeks and better continuation, and C-reactive protein at 12 weeks than the control group. There was no difference in side effect attribution.

Conclusions: In patients starting methotrexate, a mindset intervention reframing the role of non-severe side effects is a promising approach for improving symptom experience and early stage medication persistence.

Lay summary

The side effects patients experience when they start a new medication are a major barrier to adherence and treatment success in rheumatology. This study explored whether a brief (7.15-min) mindset intervention reframing common side effects as positive signals from the body that medication is working could improve patients' early experiences of low-dose methotrexate. Participants were recruited after seeing their rheumatologist and being prescribed methotrexate to treat an inflammatory rheumatic condition. Participants were randomly allocated to the mindset intervention condition or to a standard information control condition, which included a 5.00-min video framing side effects as an unfortunate part of taking methotrexate. Compared with the standard information control group, the mindset intervention group had more positive mindsets about methotrexate symptoms, found them less burdensome, experienced fewer general symptoms and a similar number of symptoms specific to methotrexate. The mindset intervention group also had more motivation and better adherence to methotrexate after 4 weeks and were more likely to be taking methotrexate and have lower levels of C-reactive protein after 12 weeks. These findings support brief mindset-based interventions that give a truthful, positive explanation for the role of common side effects for medications like methotrexate to improve patients' early treatment outcomes.

Key words: arthritis; methotrexate; medication adherence; mindset; side effects (treatment).

Introduction

Inflammatory rheumatic diseases encompass a set of chronic conditions characterized by intrusive day-to-day symptoms like joint pain, stiffness, and swelling, and by long-term inflammatory risks such as heart and lung diseases. Low-dose methotrexate has been a first-line treatment for many inflammatory rheumatic diseases for over 30 years. Methotrexate is prescribed to prevent or decelerate disease progression

long-term, although early signs of efficacy are observable via reduction in C-reactive protein levels (a routinely monitored biological marker of systemic inflammation).[1,2] Alongside methotrexate's well-established clinical efficacy, the medication is less expensive and has a favorable safety profile relative to other disease modifying antirheumatic drugs (DMARDs).[3,4] However, in contrast to the positive clinical perspective, patients often view methotrexate as toxic due to the side effect burden, or ineffective due to the relatively long interval between starting treatment and experiencing a noticeable improvement in their rheumatic disease.[5,6] Although people taking methotrexate can have severe reactions that require intervention or cessation (eg, hepatoxicity or bone marrow suppression), these are monitored through blood test surveillance.[7,8] People starting methotrexate are more likely to experience other common but medically non-severe symptoms (eg, nausea and mental fog) that can provoke anxiety and diminish quality of life.[9] Side effects are a significant predictor of early non-adherence and discontinuation of methotrexate, often within the first 3 months.[8–10]

Telling people about potential side effects of treatment is essential to the informed consent process. However, doing so can generate negative expectations and cause anxiety, increasing the likelihood of a nocebo response, where common symptoms are misattributed as side effects.[11,12] Nocebo effects and their clinical implications are well documented in the context of inflammatory rheumatic diseases,[13] and negative expectations towards treatment are a strong predictor of DMARD side effects, over and above disease, treatment, and sociodemographic factors.[14] An important challenge, therefore, is how clinicians can inform patients about the nature of methotrexate without causing potential harm, or risk discouraging the use of this effective treatment.

Previous research indicates that side effect experience can be influenced by the way that information is framed and delivered.[15,16] One promising strategy for improving symptom experience and burden, and therefore improving treatment adherence, involves addressing mindsets about the nature of common, non-severe symptoms. Mindsets are core beliefs about the nature of a domain (eg, illness or stress) and how things work, and previous research has demonstrated their significant influence on treatment experience and interpretation of side effects.[17,18] In most clinical circumstances, people are merely informed about side effect risk, without being given information about their meaning. Without such information, people may adopt mindsets about side effects that are negative, untrue, or unhelpful (for example, believing that experiencing side effects must mean that a medication is harmful or ineffective), further contributing to the problems of non-adherence and negative treatment experience. In many cases, however, this interpretation of side effects is not warranted. For example, localized swelling and mild fever following vaccination can be a sign of an adaptive immune response,[19] and nausea following chemotherapy whilst unpleasant, is a sign of the treatment actively killing fast-growing cells in the body.[20]

In the case of methotrexate, side effects are generally interpreted negatively by patients. However, they may also be interpreted as evidence of the medication being active in the body.[21] Thus, where appropriate, people can instead be informed about the potentially positive meaning of common non-life-threatening side effects; that they can be an indication of the treatment working with the body as intended. Focusing on mindsets involves instilling adaptive beliefs that hold room for complexity; people can believe side effects are unpleasant while still holding the mindset that these symptoms are a sign the treatment is active. The approach upholds the ethical necessity to inform patients about side effects whilst encouraging a truthful and adaptive mindset about the meaning of non-severe reactions that can help them persist through difficult moments in treatment.

Early studies have shown that people who receive this symptom-mindset messaging alter their mindsets about side effects and, as a result, experience less symptom anxiety and burden, fewer side effects, and report stronger intentions to engage with treatment compared to those who hear the standard message that symptoms are unfortunate aspects of treatment.[18,22] One randomized controlled trial (RCT) tested the symptom-mindset intervention with 50 children and their families undergoing 6 months of oral immunotherapy for severe peanut allergies.[23] Describing non-severe symptoms as signs of desensitization to the allergen increased adherence, reduced anxiety and symptom burden, and resulted in a greater increase in peanut-specific blood IgG4 levels compared to a standard information control group.

The current study is a single-center, parallel 2-armed RCT exploring whether a brief intervention encouraging the mindset that non-severe symptoms can be positive signals of methotrexate working in the body, compared with a standard information control group, could improve early treatment experience and outcomes for patients starting methotrexate to treat an inflammatory rheumatic condition. The primary study hypothesis was that the mindset intervention would improve patients' symptom experience (including number of reported symptoms and proportion attributed as methotrexate side effects, and burden of symptoms) after 4 weeks, compared to the standard messaging used to give information to patients starting methotrexate. The efficacy of the intervention for targeting mindsets was also assessed by measuring symptom mindsets after 4 weeks. Secondary hypotheses were that the mindset intervention would increase patients' motivation to take methotrexate, and improve self-reported adherence at 4 weeks, and result in better treatment continuation rates and improvement in C-reactive protein levels at 12 weeks, compared to the standard messaging about methotrexate.

Methods

Study design and sample size

Adult patients starting methotrexate to treat an inflammatory rheumatic condition were randomized to either a mindset intervention or standard information control condition. Data were collected at baseline, immediately after viewing one of 2 study videos (either a mindset intervention video, or standard information video) and then after 4 weeks and 12 weeks. Ethical approval was obtained from the Health and Disability Ethics Committee (20/STH/52) and locality approval from the Auckland District Health Board (A+8863).

A power analysis was conducted using G*Power to establish a target sample size. We aimed to detect a small- to medium-effect ($d = 0.3$) based on prior research involving mindset-based interventions.[23,24] With 80% power and significance of $P < .05$ (2-sided), we established that 48 participants were needed for between-group analyses. To account for attrition (20%), we initially aimed to recruit 58 participants. However, the excellent retention in the study meant that 47 participants were eventually recruited.

Participants

Individuals were recruited from an outpatient rheumatology clinic in Auckland, New Zealand, following their standard clinic appointment where they were prescribed methotrexate. Eligible participants were adults between the ages of 18 and 80 years old, able to converse and write in English, had access to a phone, and were diagnosed with an inflammatory rheumatic condition for which methotrexate was being prescribed for the first time. People were not eligible to participate if they had taken methotrexate for another condition in the past. All participants were given a $30.00 shopping voucher.

Randomization and masking

Eligible participants were randomly allocated (1:1) into a mindset intervention group or standard information control group following informed consent and completion of the baseline questionnaire. Randomization was completed by an independent researcher using a random number generator and contained in sequentially numbered opaque envelopes. Due to the nature of the intervention, it was not possible for the researchers to be blinded to participants' group allocation beyond consent and baseline assessment processes. Participants remained blinded to the study hypotheses and group allocation for the duration of the study.

Procedure

Potential participants were identified by rheumatology staff during a clinical appointment and were told the study was evaluating the effect of different types of information on early methotrexate experiences. All eligible and willing participants provided written informed consent at an in-person meeting with a member of the research team at the rheumatology clinic (n = 28), or electronically using Qualtrics during a Zoom call (n = 19). Participants completed a baseline questionnaire before being randomized to either a "*symptoms as positive signals*" mindset intervention group, or a standard information "*symptoms as side effects*" control group. Participants completed a post-video questionnaire after seeing their assigned video. Two weeks later, participants were contacted by phone for a short (5-min) booster session, reminding them of the group-specific message they received about the role of non-severe methotrexate symptoms. After 4 weeks, participants completed the follow-up questionnaire online. Twelve weeks following enrollment in the study, participant's clinical records were accessed for information about continuation of methotrexate, any reason provided for discontinuation, and C-reactive protein (CRP) levels.

Study conditions

Participants were shown a short group-specific video featuring a clinician providing identical basic information about methotrexate, including what to expect when starting the treatment, distinguishing between severe and non-severe symptoms, reiterating the importance of surveillance blood tests, and providing guidance for effective symptom management (Figure 1). See electronic Supplementary Material 1 for links to both study videos. The mindset intervention video (7.15-min) used the word "symptoms" throughout and encouraged participants to think of non-severe symptoms as a positive signal of methotrexate working with their body. This mindset was further explained by using a metaphor likening taking a dose of methotrexate to an athlete completing a training session (they might have sore muscles short term, but this is a good sign of developing strength). Participants were encouraged to devise a personal method of remembering the '*symptoms as positive signals*' mindset. The clinician acknowledged that some people will not experience symptoms and that this does not mean methotrexate is less effective.

The standard information group video (5.00-min) used the term "side effects" in place of "symptoms" throughout and offered participants an explanation for non-severe side effects that matched the standard messaging provided by clinicians and the clinic's methotrexate information sheets (side effects are uncomfortable but will not have a long-term effect on health). Participants were also encouraged to think about personal methods of managing methotrexate side effects.

After seeing the video, participants were given an information sheet to take home summarizing the video content specific to their allocated group (see electronic Supplementary Material 2). The basic content for both videos matched methotrexate information sheets provided by the rheumatology clinic. Mindset intervention messaging and all study materials were reviewed by rheumatology specialists (for accuracy), as well as patients with experience taking methotrexate for an inflammatory rheumatic disease (for acceptability).

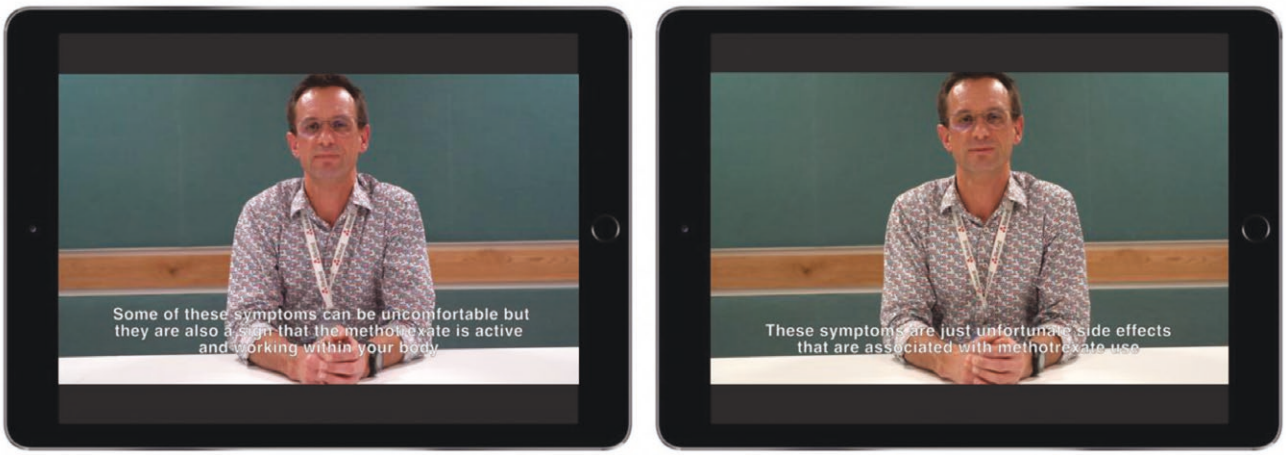


Figure 1. Screenshots of the "symptoms as positive signals" Mindset Intervention video (left) and symptoms as side effects' Standard Information control video (right), displaying the similarity of the video format and design.

Measures

Demographic and clinical characteristics

At baseline, participants reported their age, gender, ethnicity, educational attainment, and overall perceived general health compared to others of their age (0 "poor"–10 "excellent"). Rheumatic disease diagnosis was ascertained from clinical records.

Symptom mindsets

The intention of the intervention was to instill the mindset that nonsevere symptoms can be a sign of methotrexate's efficacy. To check intervention efficacy, this mindset was measured after 4 weeks. Participants were first asked if they had experienced symptoms after taking a dose ("yes" or "no"). Participants who indicated experiencing symptoms were then asked: "*How much do you think these symptoms were a sign that your body is getting stronger?*" (0 "not at all"–10 "definitely/extremely"). Participants who indicated not experiencing symptoms answered one symptom-mindset item: "*How well do you think the treatment is working for you after dosing?*" (0 "very badly"–10 "very well"). The questions used to assess symptom mindset have shown adequate sensitivity in previous studies.[22,23]

Primary outcome measures: symptom experience

The primary outcome was symptom experience, which included perceived symptom burden at 4 weeks, as well as change in reported general and methotrexate-specific symptoms between baseline and 4 weeks, and attribution of experienced symptoms as methotrexate side effects at 4 weeks. For perceived symptom burden, participants who indicated experiencing symptoms after methotrexate doses were asked: "*How much do your methotrexate side effects bother you?*" (0 "not at all"–10 "definitely/extremely").

The Side Effect Attribution Scale (SEAS)[25] was used to measure the number of general and methotrexate-specific symptoms all participants reported at baseline and at the 4-week follow-up. All participants were asked to complete the SEAS regardless of whether or not they reported experiencing symptoms after methotrexate doses at 4 weeks, as measured in the aforementioned item. The first part of the SEAS presents a standard list of 50 common symptoms (e.g., sore throat, back pain) and respondents answer "yes" or "no" to experiencing each over the past 4 weeks. The rheumatology clinic's standard methotrexate information sheet listed 11 common side effects of methotrexate, 7 of which are included in the SEAS (nausea, vomiting, diarrhea, skin rashes, fatigue, tiredness, and headaches) and the remaining 4 (sore mouth, mental fog, hair loss, and sensitivity to the sun) were added to the symptom list for this study making a total of 54. These 11 symptoms were regarded as methotrexate-specific symptoms, and the remaining 43 were regarded as general symptoms.

The second part of the SEAS was used at the 4-week follow-up to assess the proportion (%) of the general and methotrexate-specific symptoms participants experienced that they believed to be a side effect of methotrexate. Part 2 of the SEAS asks respondents to rate the likelihood of each symptom they experienced being a methotrexate side effect (1 "definitely not a side effect"–5 "definitely a side effect"). Responses of >4 "probably a side effect" were coded as side effects, and responses of <3 "unsure" we coded as the symptom not being attributed to methotrexate.[25]

Secondary outcome measures

Secondary outcomes included self-reported adherence and motivation to take methotrexate (4 weeks), and continuation of methotrexate and CRP levels (12 weeks).

Adherence

Adherence was assessed after 4 weeks with a 4-item scale based on previous research.[26] Past research has found the scale to have good internal consistency ($\alpha = .76$) and to correlate with self-reported missed doses in previous week ($r = 0.60$-0.67).[26] The internal consistency in the current study was $\alpha = .96$. Due to the known social-desirability bias in self-report adherence measures,[27] adherence was assessed as a categorical variable ("adherent" or "non-adherent") whereby any reported deviation from full-adherence across the 4 items was deemed "non-adherent."

Motivation

Motivation towards methotrexate was assessed with 2 items at baseline, immediately after seeing the assigned video, and after 4 weeks. One item asked about perceived safety, and the other about expressed motivation to use methotrexate (0 "not at all"–10 "extremely"). Scores from the 2 items were summed to generate a total score out of 20 ($r = 0.738$).

Continuation of methotrexate

After 12 weeks, Chart View clinical records were used to ascertain continuation of methotrexate and any reason provided for discontinuation. All participants were seen for follow-up assessment with the rheumatology clinic as part of standard care, except for one who did not attend and was discharged from the service. Continuation and ongoing prescription of methotrexate were therefore confirmed with the rheumatologist's assessment, who could view the national health system pharmacy dispensing records and cross-check with the patient.

CRP

CRP (measured in mg/L) was assessed as an exploratory biomarker of disease activity (with higher levels suggestive of greater systemic inflammation) through laboratory blood test results conducted every 2 weeks as standard surveillance for methotrexate toxicity and efficacy. Available blood test results were accessed closest to the date of the baseline assessment and those closest to the 4-week and 12-week follow-ups.

Statistical analysis

IBM SPSS (v.29) was used for analyses. Bootstrapping was used when assumptions of normality were violated for self-report data, and CRP data was Log_2 transformed with a constant (+1) added. Chi-square tests of independence were conducted on categorical outcomes (adherence, continuation). Independent samples *t*-tests and mixed-model ANOVA were used to test single-measure (symptom mindsets, effectiveness, side effect attribution) and repeated-measure (motivation, general and methotrexate-specific symptom reporting, CRP) continuous outcome variables, respectively. The Bonferroni correction for multiple tests

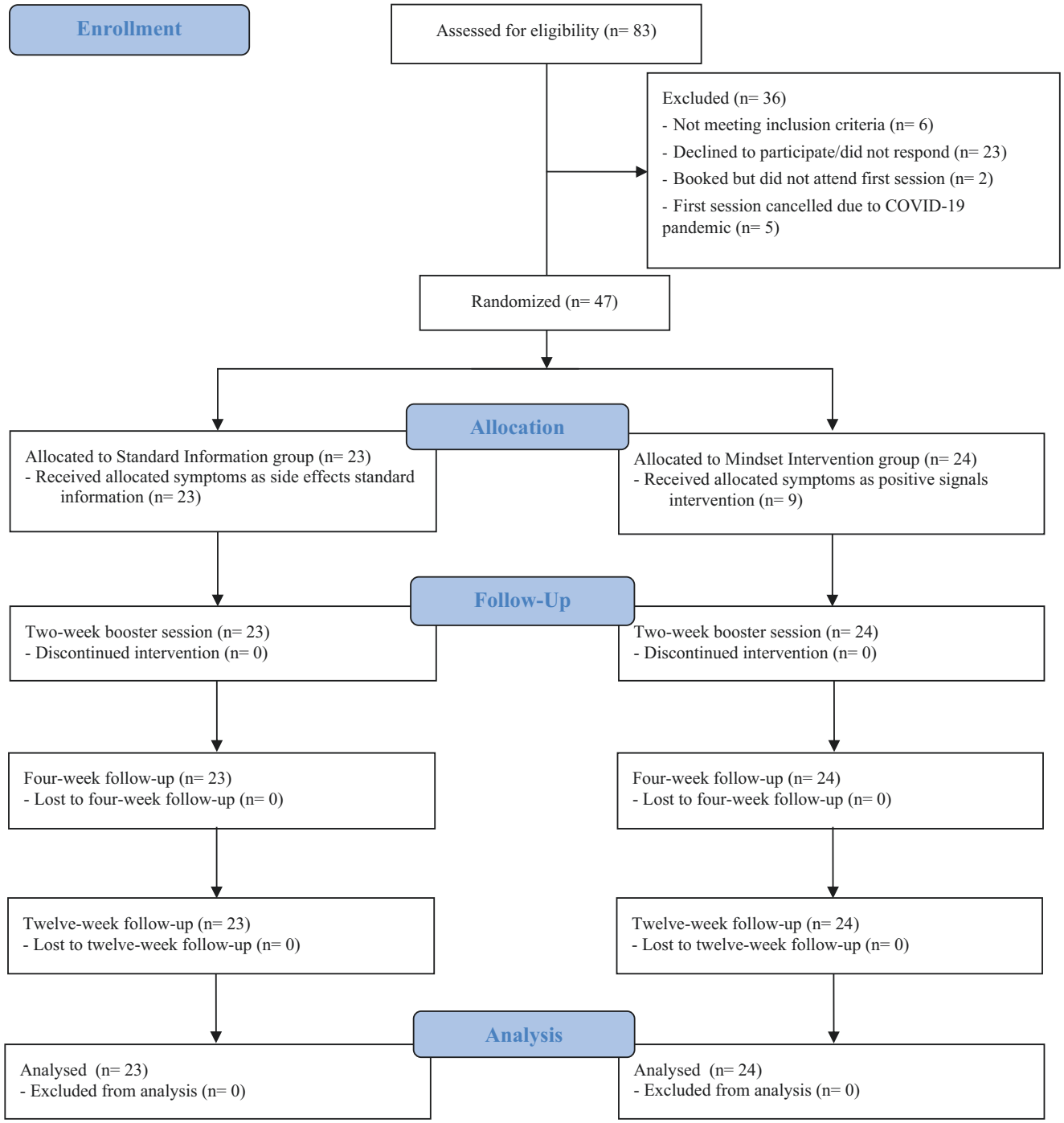


Figure 2. CONSORT flow diagram of participants in the trial.

was applied to post hoc pairwise comparisons to reduce the chance of type 1 error.

Results

Participant recruitment and baseline characteristics

Between July 29, 2020 and May 7, 2023, 83 patients prescribed methotrexate were screened, of whom 36 (43%) were excluded. Reasons for exclusion included not meeting the inclusion criteria (for example being unable to converse fluently in English) (n = 6), declining to participate/not contacting the research team after being told about the study by their rheumatologist (n = 23), failing to attend the first session (n = 2), or the first session was canceled due to the COVID-19 pandemic (n = 5). Forty-seven patients (57%) gave informed consent and were randomly assigned to the mindset intervention (n = 24) or standard information control group (n = 23) (Figure 2). All 47 participants completed the study and were included in primary endpoint analyses. Most participants were female (35 [74%]), with a mean age of 54 years ± 15.7, identified as New Zealand European (28 [59%]), and reported a tertiary education (23 [49%]). Participants were mainly diagnosed with rheumatoid arthritis (20 [42%]), or psoriatic arthritis (15 [32%]) (Table 1).

Table 1 | Characteristics of study participants.

	Mindset intervention patients $n = 24$	Standard information participants $n = 23$	Total sample $n = 47$
Age (years), *M* (*SD*)	51.8 (15.0)	55.6 (16.4)	53.6 (15.7)
Range	27-78	24-80	24-80
Gender			
Female	16 (67%)	19 (83%)	35 (74%)
Male	8 (33%)	3 (13%)	11 (23%)
Gender Diverse	0 (0%)	1 (4%)	1 (2%)
Ethnicity			
New Zealand European	12 (50%)	16 (69%)	28 (59%)
Other	6 (25%)	4 (17%)	10 (21%)
Pacific peoples	3 (12%)	2 (9%)	5 (11%)
Indian	2 (8%)	0 (0%)	2 (4%)
Chinese	0 (0%)	1 (4%)	1 (2%)
Māori	1 (4%)	0 (0%)	1 (2%)
Education			
Primary	0 (0%)	1 (4%)	1 (2%)
Secondary	6 (25%)	9 (39%)	15 (32%)
Tertiary	14 (58%)	9 (39%)	23 (49%)
Post-Graduate	4 (17%)	4 (17%)	8 (17%)
General health (rating), *M (SD)*	6.1 (2.0)	6.3 (2.0)	6.2 (2.0)
Condition being treated by methotrexate			
Rheumatoid arthritis	10 (42%)	10 (43%)	20 (42%)
Psoriatic arthritis	7 (29%)	8 (35%)	15 (32%)
Spondyloarthritis	4 (17%)	3 (13%)	7 (15%)
Polymyalgia rheumatica	3 (12%)	1 (4%)	4 (8%)
Giant cell arteritis	0 (0%)	1 (4%)	1 (2%)

Unless otherwise indicated, all values demonstrate *n* (%).
Abbreviations: M, mean; SD, standard deviation.

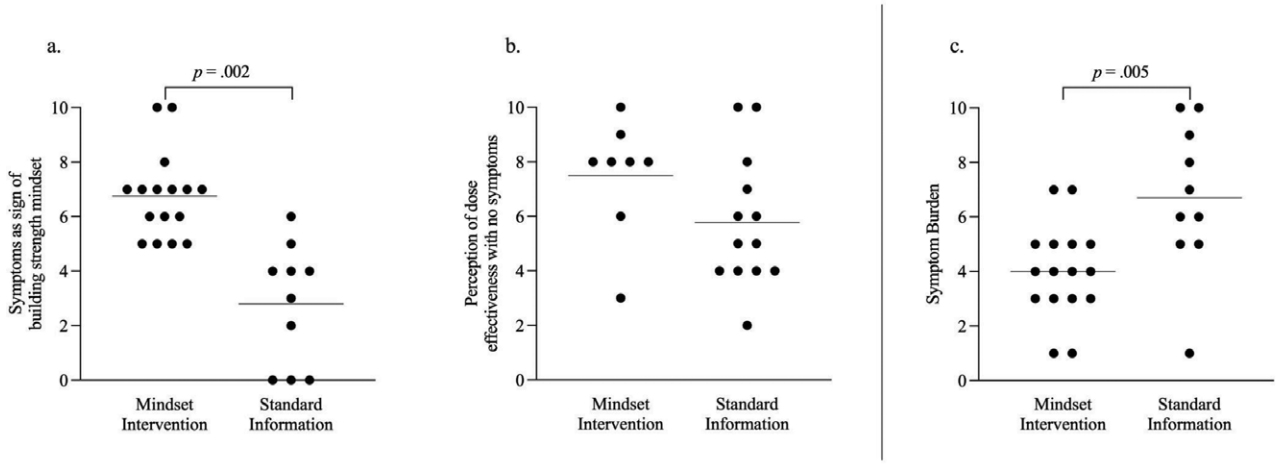
Intervention efficacy check: change in symptom mindsets

Amongst participants who reported experiencing symptoms following methotrexate doses ($n = 26$) at 4 weeks, the mindset intervention group reported greater endorsement of the target mindset that non-severe symptoms could be positive signals of the body building strength, compared to the standard information group (mean difference 3.95 [95% CI, 2.46, 5.49]) (Figure 3A). Additionally, amongst participants who experienced no symptoms after dosing ($n = 21$) at 4 weeks, there was no significant difference between groups in belief of methotrexate's effectiveness (mean difference 1.73 [95% CI, −0.45, 3.91]) (Figure 3B). See Table 2 for additional detail.

Primary outcome: symptom experience

The primary outcome of symptom experience first explored perceived burden of symptoms amongst participants who responded "yes" to experiencing symptoms following methotrexate doses ($n = 26$) at 4 weeks. The mindset intervention group reported that the symptoms they experienced after a methotrexate dose were less burdensome compared to the standard information group (mean difference −2.70 [95% CI, −4.50, −0.90]) (Figure 3C). Amongst all participants ($n = 47$), there was a significant difference in the trajectory of the number of general symptoms experienced by condition, from baseline to 4 weeks ($p = .021$) (see graph in electronic Supplementary Material 3). At baseline both groups reported experiencing a similar number of general symptoms in the prior 4 weeks (mean difference 0.72 [95% CI, −3.19, 3.34]). However, by the 4-week follow-up, the standard information group reported a slight increase in their experience of general symptoms, whereas reported general symptoms decreased in the mindset intervention group (mean difference −3.53 [95% CI, −6.99, −0.08]). The symptoms that increased most between baseline and 4-week follow-up for the standard information group compared to the mindset intervention group were stomach pain, back pain, anxiety, eye or vision problems, and dizziness. At 4 weeks, there was no significant difference between groups in the proportion of reported general symptoms they attributed as side effects of methotrexate (mean difference 0.05 [95% CI, −0.12, 0.21]) (Table 2).

Amongst all participants ($n = 47$), the number of methotrexate-specific symptoms reported did increase between baseline and the 4-week follow-up for both groups. This increase was statistically significant for the standard information group (mean difference 1.09 [95% CI, 0.32, 1.85] $P = .006$), but not for the mindset intervention group (mean difference 0.54 [95% CI, −0.21, 1.29] $P = .153$). There was no significant difference in trajectory of the number of methotrexate-specific symptoms experienced by condition, from baseline to 4 weeks ($P = .416$), with both groups reporting a similar number of methotrexate-specific



Note: (a) Participants reporting symptoms from methotrexate: Degree to which symptoms are seen as signs of the body gaining strength (n=26). (b) Participants reporting no symptoms from methotrexate: Perceived effectiveness of methotrexate after dosing (n=21). (c) Participants reporting symptoms from methotrexate: Perceived burden of methotrexate symptoms (n=26). Dots represent individual participant scores. Grey lines show mean scores for each group. Results with $p < .05$ denoted on figures.

Figure 3. Symptom mindset outcomes (A & B) and symptom burden (C).

symptoms at baseline (mean difference –0.25 [95% CI, –1.48, 1.00]) and at the 4-week follow-up (mean difference –0.79 [95% CI, –2.29, 0.71]) (see graph in electronic Supplementary Material 4). There was no significant difference between groups in the proportion of reported methotrexate-specific symptoms attributed as side effects of the medication (mean difference –0.005 [95% CI, –0.22, 0.21]). See Table 2.

Further detail regarding number of general and methotrexate-specific symptoms reported in the SEAS by those who did and did not report experiencing symptoms after methotrexate doses can be found in electronic Supplementary Material 5.

Secondary outcomes

Motivation

For secondary outcomes, motivation to take methotrexate increased after watching the assigned study video for both the mindset intervention group (mean difference 2.21 [95% CI, 1.35, 3.06] $P < .001$), and the standard information group (mean difference 2.30 [95% CI 1.43, 3.18] $P < .001$). Following this, there was a significant decrease in motivation between the postvideo timepoint and the 4-week follow-up for the standard information group (mean difference –2.09 [95% CI, –3.24, –0.93] $P = .002$), and a non-significant decrease for the mindset intervention group (mean difference –0.63 [95% CI, –0.51, 1.76] $P = .817$). Overall, the trajectory of motivation between baseline and 4 weeks was similar for both groups ($P = .159$), however after 4 weeks, motivation to take methotrexate was higher in the mindset intervention group compared to the standard information group (mean difference 2.09 [95% CI, 0.14, 4.04]) (Table 2; see graph in electronic Supplementary Material 6).

Adherence

At the 4-week follow-up, one of 24 mindset intervention participants (4.2%) reported nonadherence to methotrexate, compared to 9 of 23 standard information participants (39.1%), $P = .004$, indicating that the mindset intervention increased methotrexate adherence (Figure 4A; Table 2).

Continuation

At the 12-week follow-up, 2 of 24 mindset intervention participants (8.3%) had discontinued methotrexate, compared to 8 of 23 standard information participants (34.8%), $P = .036$. Of the 2 mindset intervention participants who discontinued, one instance was clinician-initiated (deranged liver function), and one was patient-initiated (prescription unfilled and no-show at follow-up clinics). Reasons for discontinuation for the 8 standard information participants included 3 patient-initiated cases (burden of non-severe methotrexate symptoms), 3 instances of joint decision-making (evidence of mildly deranged liver function paired with patient-reported burden of nonsevere methotrexate symptoms), and 2 clinician-initiated cases (deranged liver function). For the sake of stringency, the analysis was rerun excluding the 3 cases where discontinuation was clinician initiated and the effect remained significant $P = .042$. Taking adherence and continuation results together, these provide preliminary evidence that the mindset intervention increased the likelihood of continuing methotrexate through the first 3 months of treatment (Figure 4B; Table 2).

CRP

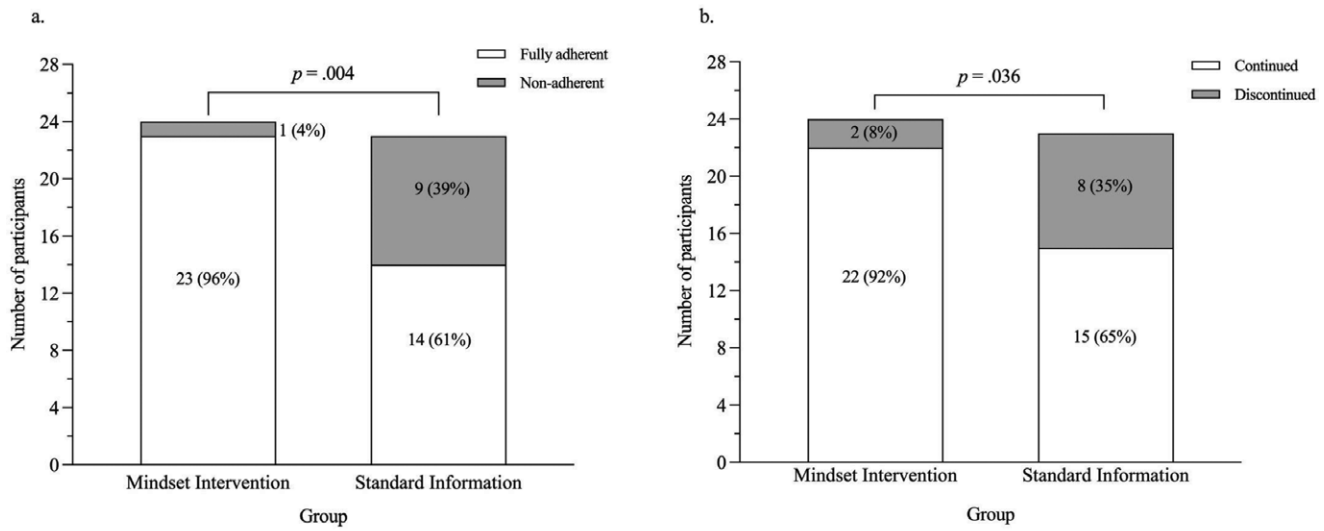
CRP data were missing for 6 participants at one or more time points. Analyses were conducted on the remaining sample ($n = 41$; mindset intervention $n = 21$, standard information $n = 20$). The average number of days between a study assessment point and the closest blood test was 4.4 days for baseline, 5.1 days for the 4-week follow-up, and 13.1 days for the 12-week follow-up. Overall, there was a significant difference in the trajectory of CRP by condition over time ($P = .036$). CRP decreased between baseline and the 4-week timepoint for the mindset intervention group (mean difference –0.68 [95% CI, –1.06, –0.30] $P < .001$), but not for the standard information group (mean difference –0.35 [95% CI, –0.74, –0.04] $P = .089$). CRP remained stable for the mindset intervention group between the 4- and 12-week timepoints

Table 2 | Group means and difference between groups for study outcomes at each timepoint.

	Mindset intervention *n* = 24 *M* (*SD*)	Standard information *n* = 23 *M* (*SD*)	Between-group difference			
			Test statistic (*df*)	*P*-value	Effect size *d* [c]	Mean difference (95% CI)
Symptom mindsets						
Symptoms experienced after MTX doses at 4 weeks [*n* = 26]						
Positive symptoms mindset endorsement[a]	6.75 (1.57) [*n* = 16]	2.80 (2.20) [*n* = 10]	*t* = 5.35	**.002**	2.16	3.95 (2.46, 5.49)
No symptoms experienced after MTX doses at 4 weeks [*n* = 21]						
MTX effectiveness	7.50 (2.14) [*n* = 8]	5.77 (2.42) [*n* = 13]	*t* = 1.66	.113	0.75	1.73 (–0.45, 3.91)
Symptom experience (primary outcome)						
Symptoms experienced after MTX doses at 4 weeks [*n* = 26]						
Symptom burden	4.00 (1.71) [*n* = 16]	6.70 (2.75) [*n* = 10]	*t* = –3.10	**.005**	1.25	–2.70 (–4.50, –0.90)
General symptoms			*F* = 5.69 (1, 45)[b]	**.021**	0.71	
Baseline number of general symptoms reported	9.33 (5.47)	9.26 (5.64)		.965	0.01	0.72 (–3.19, 3.34)
4-week number of general symptoms reported	7.25 (5.01)	10.78 (6.67)		**.045**	0.60	–3.53 (–6.99, –0.78)
Proportion of general symptoms attributed as MTX side effects at 4 weeks[a]	0.32 (0.31)	0.27 (0.30)	*t* = 0.56	.570	0.16	0.05 (–0.12, 0.21)
MTX-specific symptoms			*F* = 1.05 (1, 45)[b]	.311	0.31	
Baseline number of MTX-specific symptoms reported	2.63 (2.24)	2.87 (1.96)		.693	0.12	–0.25 (–1.48, 1.00)
4-week number of MTX-specific symptoms reported	3.17(2.46)	3.96 (2.65)		.295	0.31	–0.79 (–2.29, 0.71)
Proportion of MTX-specific symptoms attributed as MTX side effects at 4 weeks[a]	0.43 (0.42)	0.43 (0.43)	*t* = –0.04	.970	0.01	–0.005 (–0.23, 0.22)
Secondary outcomes						
Motivation to take MTX			*F* = 2.47 (1, 45)[b]	.091	0.47	
Baseline	14.33 (3.13)	13.61 (3.56)		.462	0.22	0.73 (–1.24, 2.69)
Postvideo	16.54 (252)	15.91 (2.78)		.411	0.24	0.63 (–0.90, 2.16)
4-week follow-up	15.92 (3.22)	13.83 (3.42)		**.036**	0.63	2.09 (0.14, 4.04)
Nonadherence to MTX at 4 weeks						
4-week follow-up, *n* (%)	1 (4.2%)	9 (39.1%)	χ^2 = 8.57	**.004**	φ = 0.43	8 (34.9%)
Discontinuation of MTX at 12 weeks						
12-week follow-up, n (%)	2 (8.3%)	8 (34.8%)	χ^2 = 4.91	**.036**	φ = 0.32	6 (26.5%)
CRP (log2) [*n* = 41]			*F* = 3.65 (1, 39)[b]	**.036**	0.61	
Baseline	2.53 (1.71) [*n* = 21]	2.30 (1.46) [*n* = 20]		.649	0.12	0.23 (–0.78, 1.24)
4-week follow-up	1.85 (1.30) [*n* = 21]	1.95 (1.46) [*n* = 20]		.819	0.06	–0.10 (–0.97, 0.78)
12-week follow-up	1.63 (1.16) [*n* = 21]	2.17 (1.82) [*n* = 20]		.266	0.40	–0.54 (–1.49, 0.42)

Abbreviations: df, degrees of freedom; M, mean; MTX, methotrexate; SD = standard deviation.
Bold *P*-values denote statistical significance at α = .05. Group descriptive statistics *M* (*SD*) unless otherwise noted as *n* (%).
Analyses completed on the full sample (*n* = 47) unless otherwise noted as [*n*].
[a]Bootstrapped test used as data violated normality assumptions.
[b]Represents the group-by-time interaction effect.
[c]Effect sizes computed using Cohen's *d*, excepting Phi (φ) for chi-square tests of independence as noted.

(mean difference –0.22 [95% CI, –0.72, 0.29] *P* = .864), and the reduction in CRP was significant over the 3 months (mean difference –0.90 [95% CI, –1.48, –0.31] *P* < .001). In contrast, there was no significant change in CRP for the standard information group between the 4- and 12-week timepoints (mean difference 0.22 [95% CI, –0.21, 0.88] *P* = .876) and the overall difference in CRP over the 3 months was nonsignificant (mean difference –0.13 [95% CI, –0.73, 0.29] *P* = 1.000) (Table 2; see graph in electronic Supplementary Material 7).



Note: (a) Self-reported adherence to methotrexate measures at four weeks. (b) Continuation of methotrexate assessed at 12 weeks. Results with $p < .05$ denoted on figures.

Figure 4. Adherence (A) and continuation (B) of methotrexate.

Discussion

This study demonstrates that a brief intervention targeting mindsets about common symptoms of low-dose methotrexate can improve patient's early experiences of treatment for an inflammatory rheumatic condition. The intervention, comprised of a 7.15-min educational video, successfully instilled the mindset that non-severe symptoms can be positive signals of methotrexate working to build the body's strength and was also associated with reduced general symptoms, improved experience, and better early treatment outcomes as measured by adherence, continuation, and CRP.

The intervention group reported fewer general symptoms (eg, eye/vision problems and backpain) compared to those who heard the standard explanation that side effects are unfortunate aspects of treatment. These findings align with a wider body of research demonstrating the influential role of negative beliefs in shaping greater burden and number of non-specific symptoms,[11,17] and DMARD-related side effects.[14] Importantly, the type of symptoms most effected by the intervention were "non-specific" symptoms (ie, those unlikely to be driven by methotrexate's active ingredients). This makes sense because whilst general symptoms are commonly experienced amongst the whole population, when starting a new medication the nocebo phenomena demonstrates that they are frequently misattributed as side effects due to increased bodily-monitoring and vigilance.[12,14,28] In contrast, there was no difference between the groups in the number of methotrexate-specific symptoms (eg, mental fog and nausea). However, those in the mindset intervention group who did report symptoms after taking methotrexate doses reported that they were less burdensome. Therefore, whilst the intervention group still experienced some non-severe methotrexate side effects, the messaging improved their experience. These findings echo previous findings exploring the role of symptom mindsets in shaping experiences of symptoms associated with other medications.[22,23] Medications almost always come with side effect warnings, however, merely informing people about their likelihood leaves room for negative interpretations. Offering a potential underlying purpose for adverse experiences can diffuse catastrophizing interpretations and offer reassurance,[29] which in turn helps people to persist through challenging treatment periods.[18]

The effect of the intervention on the number of symptoms and side effects and the burden of them are important outcomes on their own, as they improve patient experience of medication. But they are also particularly notable in the clinical context. Firstly, reducing symptom experience lessens the seeking of and cost for healthcare services[30,31] Secondly, symptom experience and side effect distress can lead to non-adherence and to patient-initiated DMARD changes.[9,14] Relatedly, reducing symptom experience and burden may have a positive impact on long-term acceptance of treatments, as existing research links prior treatment side effect experience with poorer acceptance of future treatment.[14,32] The current study reinforces the importance of addressing side effect concerns. Receiving the intervention was associated with better methotrexate adherence and continuation. Additionally, the pattern of CRP results showing greater decrease for the intervention group compared to the standard information group lends support to the better methotrexate adherence reported by the intervention group, and gives a preliminary indication that the mindset intervention can have an important beneficial impact on disease state. Finding ways to improve adherence rates in rheumatology are critical because non-adherence early in treatment is linked with higher healthcare service cost, medication costs including switches to more expensive and burdensome DMARDs, escalation in disease activity, and diminished quality of life.[33,34]

Both groups reported greater motivation to take methotrexate after seeing their respective study video. Although motivation appeared to drop after 4 weeks, the intervention group showed greater motivation to take methotrexate compared to the standard information group. This finding fits somewhat with existing literature, which regards motivation as a core factor for adherence to long-term medication.[35] However, the downward trajectory in stated motivation seen in the current study may align more with wider psychological research demonstrating the gap between attitude and enacted

behavior, whereby additional factors like perceived task difficulty (taking methotrexate and dealing with its effects) could have a more influential role on behavior (adherence/continuation).[36]

Taken together, the symptom-mindset strategy, and this 7-min intervention, help to address the challenge of balancing the ethical requirement to inform people about potential side effects, without simultaneously causing undue harm or undermining the uptake of an effective treatment. Importantly, the nuance of the messaging distinguishes non-severe symptoms from severe reactions, targeting the former and preserving patient safety by stressing need for routine surveillance for the latter. An understandable concern about framing symptoms as positive signals of treatment efficacy is the potential detrimental impact on patients who do not experience them.[18] In this study, the intervention group rated methotrexate equally effective as the standard information group when common side effects of the DMARD were not experienced. These results replicate past findings and offer further evidence that instilling this mindset about the potentially positive role of non-severe symptoms does not undermine or damage expectations of a treatment's effectiveness in patients who do not report experiencing side effects.[22,23] Ultimately, the symptom-mindset approach could reasonably be employed in the context of clinical appointments where methotrexate is prescribed.

The mindset intervention video included reassurance that not experiencing common methotrexate symptoms does not mean the treatment is less effective. The results showing the benefit of the intervention and the similarity between both groups in perceived effectiveness are notable as they indicate that this necessary reassurance did not undermine the core mindset targeted by the intervention. Future research should explore whether omitting the message has a meaningful impact on those who do not experience symptoms and/or increases the convincingness of the "symptoms-as-positive-signals" mindset for those who do experience non-severe symptoms.

On a broader level, the current study adds to growing research demonstrating the benefits of attending to patient's mindsets about chronic illness and treatment as a means of improving health outcomes.[17] Existing symptom-mindset-based intervention research has raised the question of the optimal "dose" and format required to instill an adaptive symptoms mindset and change treatment outcomes whilst balancing brevity and practicality. The present study is the second to utilize a brief, video-based intervention format,[22] but found larger effects on outcomes that align more with the findings of the seminal face-to-face 6-month-long intervention.[23] There are several potential explanations. Firstly, the personalized element (coming up with a personal metaphor for remembering *how* symptoms can be positive signals from the body) could be important for generating connection and triggering a reevaluation of preexisting cognitive schema about potential symptoms (by providing self-relevant evidence in favor of the new, desirable mindset). Secondly, and possibly in addition, a degree of personal interaction with a healthcare provider who endorses the intervention message may increase its overall convincingness and believability.[11,37] Howe and colleague's[23] original study was delivered face-to-face in a clinical setting, and the current study, although fundamentally video-based, incorporated a discussion about the personal symptom metaphor with a study researcher during the first session, which the prior video-based intervention study testing this approach did not.[22] Thirdly, it could be that the approach works best for medications that people have only passing/second-degree familiarity with (for example, seeing a friend's experience with methotrexate) but without existing first-hand related experience (for example, symptom mindsets may be harder to shift in people who have previous experience taking methotrexate, or with other DMARDs). Each of these areas could be explored in future research.

Based on the results of the present study and existing research, further testing of evidence-based psychosocial interventions targeting detrimental treatment beliefs in rheumatology is warranted.[14,38] In particular, the long-term impact on treatment outcomes for inflammatory rheumatic diseases is yet to be ascertained. Study designs should incorporate longer follow-up periods to explore how long the benefits of these interventions last.

Findings should be considered in light of limitations. The reduced sample size and imprecision of when CRP was measured (ie, the highly variable distance of available blood test results to each timepoint) represent a significant limitation, and these results should be interpreted cautiously. However, the observed pattern in CRP aligns with past research, which found a beneficial influence of the symptoms-mindset approach on physiological markers of oral immunotherapy treatment response.[23] Therefore, the current findings support the inclusion of rigorous exploration of treatment biomarkers in future research. In particular, the mechanisms underlying the connection between the mindset approach and biomarkers should be explored. As a biomarker directly targeted by methotrexate, adherence is likely to be a strong driver behind the observed effect on CRP. However, it is notable that this is the second study to observe an impact on immune function,[23] which can also be influenced by psychosocial factors (eg, stress).[39] Psychosocial mechanisms are an intriguing possibility that should be researched in a systematic and rigorous nature. A further consideration is that all methods of measuring adherence are associated with known limitations.[40] In this study, adherence was measured via self-report, for which there is a known chance of social-desirability bias.[27] Both the CRP and continuation findings support that the intervention had a positive impact on people's adherence to methotrexate. Nonetheless, future research should aim to replicate this finding using alternative methods such as medication monitoring devices. Further, it should be noted that symptoms mindsets and symptom burden were assessed with single items for the sake of brevity and reducing burden on participants. These items were used in past symptom-mindset research,[22,23] but are not based on validated scales. An important direction for future research will be developing reliable and valid measures for measuring symptom and other health-related mindsets.

Recruitment was also challenging for this study. Initial plans were to recruit patients face-to-face after the clinical appointment where methotrexate was prescribed. However, the recruitment period coincided with the COVID-19 pandemic. Sudden restrictions caused cancelation of study sessions. Once the study was amended to allow for remote recruitment, the online and administrative barriers reduced clinician's referral of patients, and their participation. Notably, the study had a 100% completion rate for recruited participants. Relatedly, remote recruitment primarily relied on patients contacting a researcher to express interest in the study. Therefore, the

study sample may represent people highly motivated to participate in research and may not be generalizable to the full population prescribed methotrexate for inflammatory rheumatic disease.

To conclude, this study supports growing evidence that truthfully framing nonsevere symptoms of some medications as positive signals from the body can instill more useful mindsets about those side effects and, as a result, positively impact treatment outcomes including symptom experience, motivation to take medication, adherence, continuation, and disease state. Methotrexate is a cornerstone treatment for long-term care of many inflammatory rheumatic diseases, whether alone or in conjunction with other DMARDs. Large-scale assessment of this approach in the context of rheumatology and other chronic illness is warranted. Improving people's experiences of medications like methotrexate, prescribed for chronic illnesses, improves quality of life and long-term health, whilst also saving healthcare system resources, time, and expense.[11,13,17,33] This intervention approach can enhance patient's experiences of treatment early on in their diagnosis, and incorporation into standard practice has the potential to result in clinically meaningful improvements in treatment adherence and persistence.

Supplementary material

Supplementary material is available at *Annals of Behavioral Medicine* online.

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Author contributions

Rachael Yielder (Conceptualization [lead], Data curation [lead], Formal analysis [lead], Writing—original draft [lead], Writing—review & editing [lead]), Kari Leibowitz (Conceptualization [supporting], Methodology [supporting], Visualization [supporting], Writing—review & editing [supporting]), Alia Crum (Conceptualization [lead], Methodology [supporting], Supervision [supporting], Visualization [supporting], Writing—review & editing [supporting]), Paul Manley (Methodology [supporting], Resources [supporting], Visualization [supporting], Writing—review & editing [supporting]), Nicola Dalbeth (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Project administration [supporting], Supervision [equal], Visualization [supporting]), and Keith Petrie (Conceptualization [lead], Methodology [lead], Project administration [lead], Supervision [lead], Writing—original draft [supporting], Writing—review & editing [supporting])

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Conflicts of interest

None declared.

Transparency statements

Study registration: ANZCTR, Identifier ACTRN12620000483954. *Analytic plan pre-registration*: The analysis plan was not formally pre-registered. *Analytic code availability*: There is no analytic code associated with this study. *Materials availability*: Some materials used to conduct the study are available in the supplementary materials. Any other materials will be made available from the lead author upon reasonable request; researchers should contact the lead author for requests. *Ethical approval*: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data availability

Deidentified aggregated data analysis will be made available from the lead author upon reasonable request; researchers should contact the lead author for requests.

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