The minimally important difference (MID) for patient-reported outcomes including pain, fatigue, sleep and the Health Assessment Questionnaire Disability Index (HAQ-DI) in primary Sjögren's syndrome

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Abstract

Objectives

We wanted to determine the MID for the HAQ, pain, fatigue, sleep and global VAS (0-100mm) in Sjögren's syndrome (SS) using a patient-reported overall health status anchor.

Methods

Patients with a diagnosis of primary Sjögren's syndrome (pSS) who had answered a standardised questionnaire at two consecutive visits including an overall health status question: "How would you describe your overall status since your last visit: much better, better, the same, worse, much worse?" were included. The MID was calculated as the mean change between visits for those who rated their disease as better or worse. Scales on VAS were from 0 (best) to 100 (worst).

Results

Forty patients met the inclusion criteria (97% female, mean age 58 years, mean disease duration 10 years). The mean baseline HAQ was 0.68. Ten rated their status as better and 14 as worse than the previous visit. MID estimates for improvement / worsening (SD) respectively were: -7.4 (27.8) / 20.7 (20.0) for pain VAS, -6.2 (28.3) / 15.2 (21.8) for fatigue VAS, -24.0 (24.0) / 15.2 (28.0) for sleep VAS, -0.18 (0.23) / 0.14 (0.30) for HAQ and -23.1 (21.6) / 16.4 (20.9) for global VAS. Spearman's rho correlation coefficients for the patient-reported outcomes were 0.38 (pain VAS), 0.54 (fatigue VAS), 0.55 (sleep VAS), 0.39 (HAQ), and 0.57 (global VAS), $p<0.05$.

Conclusion

The MID for pain and fatigue are greater for worsening than improvement. A small change in the HAQ is detected as a change in status by the patient. This knowledge may aid those who treat SS and in designing intervention studies.

Key words

primary Sjögren's syndrome (pSS), Sjögren's syndrome (SS), minimal important difference (MID), Health Assessment Questionnaire Disability Index (HAQ-DI), patient-reported outcomes, health-related quality of life, pain, fatigue, global assessment, sleep disturbance

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disorder that is characterised by inflammation and damage to secretory glands, primarily the lacrimal and salivary glands. The symptoms include dry eyes and mouth, which causes itching and burning of the eyes, fissures and ulceration of the tongue and severe dental caries. Sjögren's can also involve various other systems causing painful symptoms and fatigue that can be disabling. For example, Riente *et al*. discovered ultrasound evidence of bone erosions and inflammatory arthritis in patients with Sjögren's syndrome (1). As well, in a study by Voulgarelis, Tzioufas and Moutsopoulos, approximately 40-50% of patients with primary Sjögren's syndrome (pSS) had extraglandular involvement. Some of these manifestations included interstitial nephritis, vasculitis and non-Hodgins lymphoma, which can result in higher mortality in this population (2). Autoantibodies including anti-Ro (SSA), anti-La (SSB), ANA (anti-nuclear antibody) and RF (rheumatoid factor) are common in Sjögren's syndrome. Sjögren's syndrome affects mostly older women with approximately ninety percent of individuals with Sjögren's syndrome being female and the mean age of onset in the forties and fifties (3).

Pain and fatigue have an undeniable negative impact on quality of life (4, 5). For example, approximately 67% of patients with Sjögren's syndrome have severe fatigue leading to a considerable decrease in quality of life (4). Since Sjögren's syndrome is a chronic disease with no permanent cure, improving quality of life becomes an important clinical treatment goal. We have identified patients with pSS in our practice of rheumatologists in London ON and reported on Sjögren's patients with and without inflammatory arthritis (6). Patient-reported outcomes such as pain, fatigue, sleep and global health are measured with visual analogue scales (VAS) and functional impairment can be measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). The HAQ-DI is a self-report tool that assesses the patient's functional capacity. (7). Functional capacity is determined by the patient's self-reported ability to perform activities of daily living such as dressing, eating, rising, walking and others. The HAQ-DI is an important assessment tool because it provides a validated and sensitive measurement of the impact of an illness on a patient's functioning. As mentioned, visual analogue scales can be used to measure patient outcomes such as pain, fatigue, sleep and global health. These self-reported scales encompass the impact of an illness on global health, function and symptoms such as pain, fatigue, and sleep.

In clinical practice, it is essential to know what amount of change the patient perceives as a noticeable and meaningful difference. This is known as the minimal important difference (MID). The MID is defined as the smallest difference in a symptom that a patient perceives as a change, either an improvement or worsening (8, 9). Determining the MID for a particular disease can be extremely useful. It can be used to evaluate the effectiveness of a treatment in research and clinical trials. The MID can also help establish whether a statistically significant outcome is perceived by the patient as a clinically relevant change. In order to calculate the MID, an anchor approach is typically used. The anchor approach involves linking patient-reported outcomes (*i.e*. HAQ-DI, pain, fatigue, sleep and global health) to an external measure such as a patient or a physician global assessment rating. There is no known MID for Sjögren's syndrome with respect to patient-reported variables.

In the current study, we identified patients with Sjögren's syndrome from a rheumatology outpatient clinic and determined the MID estimates for HAQ-DI (both improvement and worsening) and for patient outcomes such as pain, fatigue, sleep and global health (both improvement and worsening). We hypothesized that the MID scores would be different bidirectionally (improvement and worsening).

Methods

This study was approved by the University of Western Ontario (UWO) ethics board. The data originate from patients

seen at the St. Joseph's Hospital Rheumatology clinic, which is affiliated with UWO. At each visit, patients routinely completed the HAQ-DI, VAS for pain, fatigue, sleep and global health and a patient global assessment rating. Patients were diagnosed with pSS by their treating rheumatologist, so it was a clinical diagnosis. Minor salivary gland biopsies were not always performed and were not necessarily available in the rheumatologists' medical records. Those with secondary Sjögren's, such as RA patients, were excluded as were overlaps such as Sjögren's and SLE co-existing. Hepatitis C, HIV and sarcoidosis were ruled out if clinically suspected. To be included, the patient outcomes of interest had to be completed on two consecutive visits, which were no more than sixteen months apart. Thus the patients had to be able to read English and understand the questions. Data were extracted from the patients' medical records by a trained individual and entered into an Excel spreadsheet and an SPSS database.

In addition to completing the HAQ-DI (0 scored as no disability and 3 scored as severe disability), patients also completed the VAS for pain, fatigue, sleep and global health (0 as no problem and 100 as worst). These outcomes were anchored to a patient global assessment rating in a 5-point Likert scale, "How would you describe your overall status from the last visit?" on a scale labeled: *much better, better, same, worse, much worse*. Patients who reported *better* or *worse* were within the minimally changed subgroups. Thus, the MID calculation was based on the changes in HAQ-DI, pain, fatigue, sleep and global health in those patients who indicated that they were *better* or *worse* than at their last visit. These were compared to the changes in scores for the other subgroups (*much better, same* and *much worse*). Patients were blinded to data they had completed from the previous visit.

The change in HAQ-DI was calculated as follows: HAQ-DI from most recent visit – HAQ-DI from previous visit. Thus, a negative value reflects an improved HAQ-DI and a positive score reflects a worsening HAQ-DI. The change in the VAS pain, fatigue, sleep and global health were calculated as: VAS score from most recent visit – VAS score from previous visit. Similarly to the HAQ-DI change, a negative value reflected an improved patient outcome and a positive value reflected a worsened patient outcome.

The change in the anchor question and the change in the patient outcome scores should have a significant correlation coefficient in order to be useful. In order to assess this, the Spearman Correlation Coefficients between the patient global assessment score (anchor question on a 5-point Likert scale) and the change patient outcomes (HAQ-DI, VAS pain, fatigue, sleep and global health) were computed. To assess the usefulness of an anchor, change in the anchor and change in the HAQ-DI and VAS scores should have a correlation of at least >0.37. The correlation coefficient of >0.37 corresponds to an effect size of 0.80 (large effect as proposed by Cohen) (10). SPSS software was used for the analysis, where $p<0.05$ was considered statistically significant. Results were reported in mean (SD) values. Similar methodology has been used in other rheumatic diseases to calculate the MIDs for patient centred outcomes (11-16).

Table I. Baseline and follow-up characteristics of the primary Sjögren's patients.

Characteristic	Baseline mean (SD)	Follow-up mean (SD)
Age (yrs)	58 (15)	
Gender	97% (female)	
Fibromyalgia	20%	
Inflammatory arthritis	30%	
Disease duration (yrs)	10	
Visit time interval	7.4 (4.4)	
Pain (0–100)	35.5 (27.2)	40.3 (29.0)
Fatigue (0–100)	54.1 (27.4)	53.4 (28.6)
Sleep (0–100)	45.4 (30.2)	42.5 (32.7)
Global health (0–100)	43.1 (23.8)	41.7 (26.2)
HAQ-DI (0–3)	0.68 (0.66)	0.67 (0.64)
Anti-nuclear antibody (ANA) positive	94%	
SSA (Ro) positive	76%	
SSB (La) positive	51%	
Rheumatoid Factor (RF) positive	78%	
Medications		
Pilocarpine orally	15%	
Antidepressant use	23%	
Prednisone	10%	
Azathioprine	8%	
Hydroxychloroquine	3%	
Methotrexate	10%	
Leflunomide	5%	

Missing values for lab results were excluded from calculation of percentages.

Results

On the review of patient files, 40 patients with pSS were identified with consecutive visits and nearly complete data. The baseline characteristics included: mean age (SD) of 57 years (15 years); mean disease duration of 10 years; 97% were women; 20% had fibromyalgia and 30% had inflammatory arthritis; ANA was positive in 94%; 76% were anti-Ro/SSA positive, 51% were anti-La/SSB positive, and rheumatoid factor occurred in 78%. The medication use at first visit is seen in Table I. The mean (SD) follow-up between visits was 7 months (4 months) (Table I). The VAS scales of pain, fatigue, sleep and global health were scored on 0-100mm, with 0 as no disability and 100 as maximum disability. At baseline, 10% reported no pain and 2.5% reported maximum pain; 5% reported no fatigue and 7.5% reported maximum fatigue; 7.5% reported no problems with sleep and 2.5% reported maximum sleep problems; and 5% reported no problems with global health and 5% reported maximum global health problems. The mean (SD) baseline scores were: pain 35.5 (27.2), fatigue 54.1 (27.4), sleep 45.4 (30.2), global health 43.1 (23.8) and HAQ-DI

Table II. Spearman correlations for the anchor question compared to the HAQ-DI and the VAS scales of pain, fatigue, sleep and global health.

Outcome	Spearman correlation to overall anchor question
Pain (0-100)	0.38*
Fatigue (0-100)	0.54**
Sleep (0-100)	0.55**
Global Health (0-100)	0.57**
HAQ-DI	0.39*

*$p<0.05$, **$p<0.01$

Table III. MID for the pain, fatigue and sleep and global health VAS and HAQ-DI in the single site, London, ON

Patient rated overall status (n)	Pain (0–100 VAS) Change mean	Fatigue (0–100 VAS) Change mean	Sleep (0–100 VAS) Change mean	Global Health (0–100 VAS) Change mean	HAQ-DI (0–3) Change mean
Much better (3)	-32.0	-48.3	-28.3	-22.0	-0.54
Better (10)	-7.4	-6.2	-24.0	- 23.1	-0.18
Same (14)	7.14	0.79	0.86	4.9	0.09
Worse (10)	20.7	15.2	15.2	16.4	0.14
Much worse (3)	11.0	9.3	15.7	3.7	0.04

Negative values indicate improvement and positive values indicate worsening.

Table IV. Standard deviation and confidence intervals for MID in pain, fatigue and sleep and global health VAS and HAQ-DI in the single site, London, ON.

Patient rated overall status (N)	Pain SD [95% CI]	Fatigue SD [95% CI]	Sleep SD [95% CI]	Global Health SD [95% CI]	HAQ-DI (0-3) SD [95% CI]
Much better (3)	45.7 [-145.6 to 81.6]	17.6 [-92.0 to -4.7]	44.8 [-139.7 to 83.0]	7.2 [-39.9 to -4.1]	0.63 [-2.1 to 1.0]
Better (10)	27.8 [-28.8 to 13.9]	28.3 [-26.5 to 14.1]	24.0 [-41.2 to -6.8]	21.6 [-38.6 to -7.6]	0.23 [-0.34 to -0.01]
Same (14)	9.5 [1.7 to 12.6]	18.7 [-10.0 to 11.6]	19.4 [-10.3 to 12.1]	19.5 [-6.4 to 16.2]	0.35 [-0.11 to 0.29]
Worse (10)	20.0 [6.4 to 35.0]	21.8 [-0.41 to 30.8]	28.0 [-4.9 to 35.3]	20.9 [1.45 to 31.4]	0.30 [-0.08 to 0.35]
Much worse (3)	14.2 [-24.2 to 46.2]	13.7 [-24.6 to 43.2]	7.4 [-2.64 to 34.0]	21.7 [-50.3 to 57.7]	0.19 [-0.43 to 0.52]

0.68 (0.66). At follow-up, the mean (SD) scores were: pain 40.3 (29.0), fatigue 53.4 (28.6), sleep 42.5 (32.7), global health 41.7 (26.2) and HAQ-DI 0.67 (0.64). Of the sample, 7.5% reported being *much better*, 25% reported being *better*, 35% reported being the *same*, 25% reported being *worse* and 7.5% reported being *much worse*.

The Spearman correlation coefficient for the anchor question and change in outcomes were: pain 0.38, fatigue 0.54, sleep 0.55, global health 0.57, HAQ-DI 0.39 (p <0.05) (Table II). There was an extremely robust correlation between the anchor question and overall global health, 0.57 (p<0.01). The MID was calculated for the change in overall status at the second visit. All outcomes were statistically related to the 5 point Likert scale for the change in overall status and the correlations were at least of the desired strength (0.37). The MIDs are shown in Table III.

Patients who answered *better* or *worse* on the anchor question had a larger change on the VAS scales and the HAQ-DI than the patients who answered *same* on the anchor question. For pain, patients who answered *better* or *worse* had a larger change score of -7.4 (27.8) and 20.7 (20.0), respectively, compared to those who answered *same,* who had a change score of 7.14 (9.5). Similarly for fatigue, those who answered *better* or *worse* on the anchor question had a larger change score of -6.2 (28.3) and 15.2 (21.8) compared to the patients who answered *same,* 0.79 (18.7). For sleep, the *better* and *worse* groups had a bigger change score, -24.0 (24.0) and 15.2. (28.0), than the *same* group, 0.86 (19.4). For global health, the *better* and *worse* groups also had a larger change score, -23.1 (21.6) and 16.4 (20.9), than the *same* group, 4.9 (19.5). Finally, for the HAQ-DI, the *better* and *worse* groups had a larger change score, -0.18 (0.23) and 0.14 (0.30), compared to 0.09 (0.35) for the *same* group (negative is improved and positive is worsening). Numbers are very small in *much better* and *much worse* so the estimates should be interpreted with caution. There are bidirectional differences where on pain and fatigue it takes more pain to worsen than improve, whereas in sleep and global status it takes numerically more to report as better than worse. For HAQ the change may be similar for worsening and improving.

Discussion

The MID for patient-reported outcomes in Sjögren's have not previously been described. The MID is extremely important since it can be used to interpret the relevance of statistically significant differences in clinical and research trials. The MID can determine if statistically significant differences are likely to be perceived by patients as clinically significant changes.

In the present study, we determined the MID by comparing patient outcomes on two consecutive visits to a patient determined global score. Most previous studies have calculated the MID by comparing patient-reported changes to an objective measure such as physician assessment or a disease scale. Revicki *et al*. recommended utilising several different anchors concurrently, both patient-reported anchors and objective clinician or disease scale anchors (17). The authors also supported placing the most weight on patient-reported anchors since the outcomes being compared are most relevant to the patient and should thus be interpreted from the patient's perspective. We also utilised a longitudinal design as opposed to a cross sectional design. The longitudinal design is more sensitive to change since each patient acts as

their own control. Any external noise is decreased and changes observed are more likely significant. Comparing the current methodology to another study using a different methodology demonstrates similar results for fatigue (in our study the MID was -6.2 and 15.2 and in the other study it was -6.7 and 17, so the results were nearly identical) (18). Also, in a cross sectional RA study the MID for HAQ improvement was 0.22 and we found ours to be 0.18, which is quite comparable (19).

In our results, for both pain and fatigue, the MID scores showed that a small change would be perceived by the patient as an improvement and a large change would be needed for a worsening to be noticed. Our MID scores for pain were -7.4 for improvement and 20.7 for worsening. These results are similar to those in other studies (13). In one study that examined the MID in patients with ankylosing spondylitis (AS) the MID for pain was -6.93 for improvement and 18.97 for worsening. Similarly, for fatigue our MID scores were -6.2 for improvement and 15.2 for worsening. These results are similar to the MID for a sample of patients with rheumatoid arthritis (12). The MID for fatigue in RA patients was -8.2 to -11.3 for improvement and 11.3 to 12.6 for worsening. The MID results for both pain and fatigue imply that treatments which impact either pain or fatigue have great potential to make clinically significant changes for the patient.

The MID values for sleep, global health and HAQ-DI showed that a relatively similar change would be needed for the patient to appreciate an improvement or a worsening. The MID scores for HAQ-DI were -0.18 for an improvement and 0.14 for a worsening. These results are comparable to the MID for HAQ-DI in both ankylosing spondylitis and lupus (13, 14). For example, in ankylosing spondylitis, the MID for HAQ-DI was -0.14 for an improvement and 0.22 for a worsening. For sleep, our MID score for improvement was -24.0 and 15.2 for worsening. Finally, for global health our MID was -23.1 for improvement and 16.4 for worsening. Similar results were obtained in RA and psoriatic arthritis (11, 12, 16).

The Spearman's correlations for fatigue and sleep were particularly robust at 0.54 and 0.55 respectively, with both values significant at $p<0.01$. These results are supported by other research studies which demonstrate that those with pSS have significantly increased daytime fatigue and sleep disturbances (20, 21). In one study, those with pSS were compared to healthy controls and control patients who had rheumatoid arthritis. Those who had pSS had more difficulty falling asleep, more nighttime awakenings, increased severe daytime fatigue and felt less rested after sleep than the healthy or rheumatoid arthritis controls (20). It seems that these factors especially impact patient related outcomes and how a patient perceives their overall health status.

This study has limitations. The number of patients included in the analysis was only 40 but the results are comparable to other studies in connective tissue diseases (CTDs) and inflammatory arthritis (11-16). Patients had to read English to participate in the study. In future studies, it may be worthwhile to include data from other practices in several different cities in order to bolster the sample size and improve generalisability. In addition, the average disease duration was 10 years. Thus, the current results may not apply to those who have been recently diagnosed with pSS. A further limitation of this study is the difference in timing between the HAQ-DI and the VAS scales. The HAQ-DI asked for changes over the last week while the VAS scales inquired about changes since the last visit. Most patients had an average time of 7 months between visits. Thus, forgetting and recall bias could have skewed the results somewhat. In any retrospective question, the individual is prone to recall bias. As well, the patient's current status while answering the question can influence the result. Patient recall may actually be quite good as most patients rated themselves the same and the mean changes between visits overall were small (see Table I). Most trials are at least 6 months long, so a change score from beginning to end would be relevant in a 6- to 12-month time frame, thus the between visits time interval is likely a strength. Another possible limitation stems from our method of determining the MID. We used a patient-reported global health question as an anchor instead of an objective anchor, such as a clinician assessment. As mentioned, there is much debate in the literature around what constitutes a suitable anchor. Most authors support using both a patient-reported anchor and an objective anchor. (22). Thus, the addition of an objective anchor such as a disease scale or a clinician assessment would have been useful to further refine our MID determination. Lastly, in the current study, the features examined (pain, fatigue, sleep and HAQ-DI) are not specific to Sjögren's syndrome and can be found in many rheumatologic diseases. Patients with multiple illnesses may experience symptoms of pain, fatigue and difficulty with sleep that are not necessarily attributable to Sjögren's syndrome. In future studies the addition of a VAS scale measuring overall dryness (sicca manifestations) could be added and would be more specific to Sjögren's syndrome. In the present study, only approximately 20% of patients had concurrent fibromyalgia and only 30% had concurrent inflammatory arthritis. However, despite these limitations, the MID found in this study was similar to the MID in other inflammatory arthritis and connective tissue disease studies (12-16). There is a normal distribution between the ratings of *same, better, much better* and *worse* and *much worse* so this is reassuring where patient expectations likely did not markedly alter the results.

In conclusion, in this study we determined the MID scores for the patient-reported outcomes of pain, fatigue, sleep, global health and HAQ-DI. The MID scores determined in this study were bidirectional. Overall, it seems that the MID scores show that for both pain and fatigue, a relatively small change was perceived as an improvement. The perception of a small change as a clinically significant improvement means that treatments that improve pain and fatigue will result in clinically significant results. For sleep, global health and the HAQ-DI, the MID scores for both improvement and worsening were rela-

tively similar. Finally, the correlation coefficients for sleep and fatigue show a robust correlation between overall health status and the patient outcomes of fatigue and sleep. The robust correlations imply that the patient outcomes of fatigue and sleep are very intimately related to how patients experience their disease. Utilising the MID scores determined from this study can be extremely useful when evaluating the efficacy of new treatments for pSS in both clinical practice and in research settings.

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