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RESEARCH ARTICLE

Wellness of patients with chronic pain is not only about pain intensity

Tamar Gershoni MA[1] | **Dorit Pud PhD**[1] | **Joshua Aviram PhD**[1,2] | **Elon Eisenberg MD, PhD**[3,4]

[1]The Cheryl Spencer Department of Nursing, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel

[2]Faculty of Biology, Technion – Israel Institute of Technology, Haifa, Israel

[3]Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel

[4]Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

Correspondence
Tamar Gershoni, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel.
Email: tamarbr07@gmail.com

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Abstract

Objective: Attaining good outcomes in the management of chronic pain remains a clinical challenge. This study aimed to investigate the relationships between – and the contribution of – pain and related conditions to the wellness of these patients.

Design: A secondary analysis of database of patients with chronic pain treated with medical cannabis (MC) to carry out a one-year prospective follow-up study was conducted. Questionnaires were completed before (T_0), six (T_6), and twelve (T_{12}) months after MC initiation. Data included patients' demographics and questionnaires related to three latent factors: pain intensity measures, related conditions (catastrophizing, sleep disturbance, anxiety, and depression), and wellness parameters (quality-of-life, disability, subjective-health-state). Weighted average of the observed variables (WOBs) were calculated for each latent factor. Longitudinal structural equation modeling (SEM) and mediation analyses were performed to identify predictors and interrelations between the WOBs, respectively.

Results: Participants included 510 patients. All variables were significantly improved from T_0 to T_6 and T_{12}. SEM revealed that related conditions, and to a lesser extent pain, predicted wellness at T_0, T_6, and T_{12} (related conditions: $\beta_0 = 0.55$, $p<0.001$; $\beta_6 = 0.54$, $p<0.001$; and $\beta_{12} = 0.51$, $p<0.001$; pain: $\beta_0 = 0.42$, $p<0.001$; $\beta_6 = 0.18$, $p<0.001$; and $\beta_{12} = 0.25$, $p<0.001$). Mediation analyses demonstrated that the effect of WOB-related conditions was greater than WOB-pain on wellness.

Conclusion: Wellness of patients with chronic pain can be determined not only by pain itself but even more so by the severity of related conditions. Thus, considering a broad spectrum of pain measures and related conditions seems relevant for improving the wellness of patients with chronic pain.

KEYWORDS
chronic pain, related conditions, secondary analysis, wellness

INTRODUCTION

Although a wide array of therapies are employed in the management of chronic pain, attaining good outcomes remains a clinical challenge.[1–4] Millions of patients continue to suffer chronic pain which is typically accompanied by related conditions such as depression, anxiety, and sleep disturbances.[5–8] Chronic pain impacts an individual's sense of self and wellness, physical functioning and quality of life (QoL),[9,10] and may lead to long-lasting emotional disturbances.[11] Due to its multifactorial nature and heterogeneous symptomatology, the precise etiology of this complex phenomenon remains poorly understood.[12,13] Epidemiological and biopsychological studies suggest that a bidirectional relationship exists between chronic pain and related conditions,[14–16] and together these are among the leading causes of functional impairment, disability, and health care expenditures.[17–19] The current approach to managing chronic pain incorporates techniques aimed at addressing chronic pain's multifactorial dynamic nature and the mutual interrelationships between its physiological, psychological, and behavioral dimensions that are necessary for improving functioning and QoL.[20–23]

Moreover, considerable effort has been invested in identifying factors, transcending pain intensity per se, that may affect and even predict the QoL and wellness of patients with chronic pain.[11,24] In fact, several psychological characteristics have been shown to predict good outcomes for chronic pain relief. For example, a low level of anxiety, a stronger belief in personal control,[8,25] and high expectations for recovery[26] have all predicted an improvement in disability and work participation. However, other studies have failed to identify such predictors for improvement.[27–29]

We recently conducted a prospective, large-scale, longitudinal study of patients with chronic pain treated with medical cannabis (MC) aimed to explore the effectiveness and safety of MC for treating this patient's population and to identify patients prone to respond to MC treatment. We demonstrated mild to modest long-term improvement of all investigated measures (including pain and associated conditions); reduction in analgesics use; safety of MC treatment for most patients; and identified measures contributed to the prediction of treatment success.[30] Since the improvement in the wellness of patients with chronic pain is not necessarily related to pain intensity and the magnitude of its reduction only, we conducted this study. Specifically, we aimed to better extend the knowledge on the longitudinal relationships between pain intensity, related conditions, and wellness in this population. Notably, this secondary analysis study is based on part of the former database while not concentrating on the effectiveness of MC or predictors for treatment success. Our working hypothesis was that the improvement in patients' wellness would not be related merely to pain intensity measures and their reduction. Rather, the burden of related conditions and the extent of their attenuation over time will contribute to patients' wellness as well.

MATERIALS AND METHODS

Study population

Eligible patients were Hebrew speaking, aged >18 years, were scheduled to begin medical cannabis to treat any form of chronic non-cancer pain and had given signed informed consent for study participation.

Instruments

Online survey

Data collection was carried out by a secured online survey technology Qualtrics® (version 12018).

Study questionnaires

Data included patients' self-reported questionnaires relating to the following four categories: (I) Pain intensity: the least and worst pain during the last week, current pain intensity, the average of six positional weekly pain intensities scores (ie, resting in bed, turning in bed, sitting, transitioning from sitting to standing, standing, and walking), and the Short-Form McGill Pain Questionnaire (SF-MPQ).[31] The Hebrew translation of the SF-MPQ was cross-validated by four fluent Hebrew speakers, all of whom were clinicians in the field of pain. This was done to ensure that the Hebrew words conveyed the same meaning as the English original[32]; (II) Related conditions: the Pain Catastrophizing Scale (PCS).[33] The Hebrew version has been validated and presented good validity. The total Cronbach's α score for the PCS Hebrew version entire scale was 0.86[34]; The Pittsburgh Sleep Quality Index (PSQI),[35] the Hebrew version has shown adequate reliability and good validity (Cronbach's $\alpha = 0.72$)[36]; the General Anxiety Disorder 7-Item (GAD-7) scale.[37] Its Cronbach α was found to be ranged from 0.85 to 0.92 for the Hebrew version,[38] and the Beck Depression Inventory (BDI).[39,40] This questionnaire has been widely used in Hebrew and has been reported to have good predictive validity (Cronbach's $\alpha = 0.89$)[41]; (III) Wellness: The Health-Related Quality of Life (EQ-5D) questionnaire has developed by the EuroQol group and consists from two items with different scores: The first item is five statements regarding the patients' mobility, self-care, activities, pain/discomfort, anxiety/depression (QoL) and the second item that asked the patient to indicate his/her subjective quality of life on a scale of 0–100 (subjective-health-state).[42] Total Cronbach's α

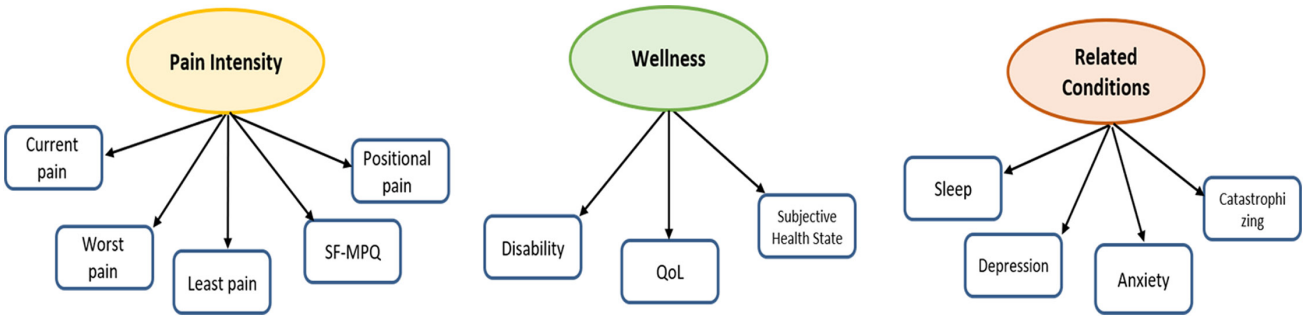

FIGURE 1 Latent variables. Each colored ellipse represents a latent variable – yellow: pain; brown: related conditions; green: wellness. Blue boxes represent observed variables composited a latent variable.

score for the Hebrew version is very high (Cronbach's α = 0.85).[43] The Pain Disability Index (PDI)[44] and its internal consistency for the Hebrew version were found by Lerman et al.[8] in their study examining chronic pain patients to be Cronbach's α in a range between 0.88 and 0.91, (IV) Demographics: age, gender, family status, employment, co-morbidities, education, pain etiology, and pain duration.

Study design

This multi-center, prospective, long-term study was approved by the ethics committees of the University of Haifa (#278/15) for physicians practicing in private clinics. Institutional ethics committees (Rambam Health Care Campus #0272-15-RMB and the Chaim Sheba Medical Center #3670-16-SHC) approved the study for physicians employed by these public hospitals.

This was a pure observational study with no interventional component whatsoever, so similar to other observational studies,[45–50] registration at the Clinical Trials Register was not required. Importantly, no recognizable information on participating patients is published in this article.

This study was conducted between December 2015 and October 2019. Participating physicians (pain specialists, rheumatologists, or orthopedic surgeons) who regularly complete applications for MC use and who agreed to join the study team, presented the study procedure to eligible patients. A written informed consent was obtained from those who agreed to participate in the study and was sent to the investigator along with the patient's diagnosis and contact information. Patients were contacted by an investigator and were asked to complete the questionnaires listed above at each of the following six time-points: baseline (before MC treatment initiation; T_0); at 1, 3, and 6 months (T_6); and at 9 and 12 months (T_{12}) following the initiation of MC treatment. For the purpose of this secondary analyses study, we used the data collected at three representative time points: baseline, and at 6 and 12 months only. No financial compensation was offered to participating patients.

Statistical analysis

Only patients who had completed the entire study protocol with minimal missing data (not more than 10% per participant) were included in the statistical analyses. The changes between the three time points (ie, deltas) were assessed using the Wilcoxon signed-rank test. The normality of data distribution was assessed using the Shapiro–Wilk test. In order to evince a general score per each of the three latent factors, weighted averages of the observed variables (WOBs) were normalized to a 0–10 scale. As such, scores from each of the self-reported questionnaires' scores of the three latent factors were linearly transformed on their ranges to "equalize" the influence of variables with different scale lengths on the latent variables. To examine the effect and the contribution of pain intensity and related conditions on wellness at the three time points, a longitudinal Structural Equation Model (SEM) was performed. The SEM included age, gender, the number of concurrent pain etiologies, and the number of comorbidities as exogenic demographic characteristics. Three latent variables on the original scales without the transformation were generated: Pain intensity, Related conditions, and Wellness. Each of them has been driven from the relevant questionnaires (Figure 1). The following indices were used to evaluate model fit: the *comparative fit index* (CFI)[51]; Bentler-Bonett's *non-normed fit index* (NFI)[52]; and *root-mean-square error of approximation* (RMSEA).[53] When running the models, we arrived at the most parsimonious models by eliminating nonsignificant pathways.[54]

Two models of mediation analyses were conducted to assess associations between the three WOBs (pain intensity, related conditions, and wellness). For this purpose, changes in the WOBs (Δ, delta) between T_0 and T_6, T_6 and T_{12}, and T_0 and T_{12} were calculated for each latent factor. Since no changes were observed in all WOBs between T_6 and T_{12}, delta scores from T_0 to T_{12} was used. In both models, Δwellness was the dependent variable. However, in model A, Δpain intensity was the independent variable and Δrelated conditions was the mediated variable, and vice versa in Model B. The mediation models were calculated using a 5000 Bootstrap sampling with a 95%

confidence level and Bias Corrected method.[55] Missing data were estimated by using the series mean imputation. Data analyses were conducted using IBM SPSS statistics software version 25, IBM SPSS Amos version 25, and PROCESS SPSS.

RESULTS

Of the 602 patients who completed the 12 months follow-up questionnaires, 510 had minimal missing data and were included in these secondary analyses study. The sample included 293 males (57.5%) with mean ± SD age of 47.5 ± 14.8 years (range 19–95 years). The average pain duration was 9 ± 9.7 years, ranging between 1 and 70 years. The most common pain etiology was neuropathic pain (74%, n = 381). Fifty-two percent were diagnosed with a single pain etiology. Seventy-seven percent (n = 395) consumed analgesic medications at baseline, and 57% (292 patients) reported comorbidities (Table 1).

Figure 2A–C demonstrate the results of all variables that were included in the three latent factors at each time point: pain intensity (A), related conditions (B), and wellness (C). In addition, it shows the calculated WOB of each latent factor. As can be seen, each variable was significantly improved from T_0 to T_6 and from T_0 to T_{12}. No changes were observed in those variables between T_6 and T_{12}. Similarly, all three WOBs (pain intensity, related conditions, and wellness) were significantly improved from T_0 to T_6 (Z(df = 472) = −15.1, p<0.001; Z(df = 488) = −15.8, p<0.001; and Z(df = 493) = −15.1, p<0.001, respectively) and from T_0 to T_{12} (Z(df = 458) = −15.2, p<0.001; Z(df = 486) = −16.1, p<0.001; and Z(df = 494) = −15.9, p<0.001, respectively). Pearson correlations between the observed variables presented high stability effect throughout the three time points (r = 0.28–0.78).

The longitudinal SEM model

To examine the contribution of pain intensity and related conditions on wellness across the three time points, a SEM was performed. The model evinced an adequate fit (χ^2 = 1884.473, df = 684, ρ<0.001, CMIN/DF = 2.711, NFI = 0.853, CFI = 0.901, RMSEA = 0.058). Omitting non-significant parameters, the most parsimonious mode was achieved. Within the time points related conditions at T_0, T_6 and T_{12} predicted wellness at each time point (β_0 = 0.55, p<0.001; β_6 = 0.54, p<0.001; and β_{12} = 0.51, p<0.001, respectively) greater than pain intensity (β_0 = 0.42, p<0.001; β_6 = 0.18, p<0.001; and β_{12} = 0.25, p<0.001, respectively). Along the time points, related conditions at T_0 predicted wellness at T_6 as well as at T_{12} (β = −0.27, p<0.001 and β = −0.29, p<0.001, respectively). As for pain intensity, at T_0 it was failed to predict wellness at T_6. Nonetheless, wellness at T_{12} was predicted by pain intensity at T_6 (β = −0.15, p<0.001), but to a lesser extent than it was predicted by the related conditions at the same time point (β = −0.29, p<0.001).

Furthermore, each of the three latent factors significantly predicted the equivalent latent variable during the following time point. Among the exogenic variables (ie, gender, age, number of pain etiologies, number of comorbidities), only age was found to negatively predict 'related conditions' (β = −0.18, p<0.001). See Figure 3.

TABLE 1 Characteristics of the study sample (n = 510).

	Mean (SD) range
Age (years)	47.5 (14.8) 19–95
Pain duration (years)	9 (9.7) 1–70
	N (%)
Gender	
Male	293 (57.5)
Female	217 (42.5)
Family status	
Single	89 (17.5)
Married	319 (62.6)
Divorced	76 (14.9)
Widowed	20 (3.9)
Missing	6 (1.1)
Education	
Elementary	25 (4.9)
High school	187 (36.7)
Academic	156 (30.6)
Other	142 (27.8)
Pain etiology[a]	
Neuropathic	381 (74.7)
Musculoskeletal	229 (45)
Nociplastic	83 (16.3)
Visceral	52 (10.2)
Headache	56 (11)
Number of pain etiologies	
One	266 (52.2)
Two	186 (36.5)
>Two	58 (11.3)
Comorbidities	
Yes	295 (57.8)
Type of analgesic at T_0[a]	
OTC analgesics	121 (23.7)
NSAIDs	103 (20.2)
Weak opioids	151 (29.6)
Strong opioids	240 (47)
Anticonvulsants	179 (35.1)
Antidepressants	157 (30.8)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over the counter.

[a]Pain etiology and type of analgesics at T_0 do not add up to 100% due to concomitant etiologies/analgesics.

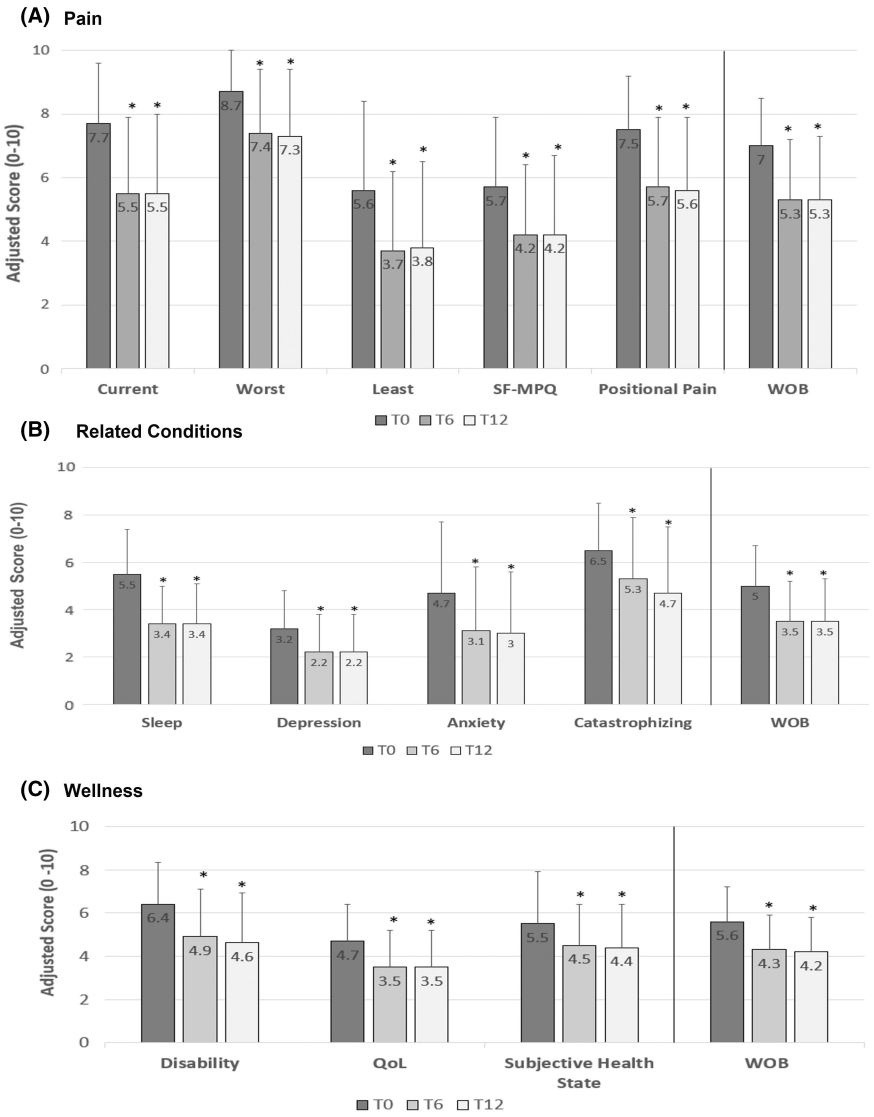

FIGURE 2 Mean±SD of study parameters and weighted observed variables (WOB's) at each time point (A: Pain; B: Related conditions; C: Wellness). Each color represents a specific follow-up time point. T_0: Baseline (dark gray), T_6: 6 months (light gray), T_{12}: 12 months (white). SF-MPQ, total score of the Short-Form McGill Pain Questionnaire; WOB, weighted observed variable. All scores were adjusted to a 0–10 scale; *$p<0.001$ between each time point and T_0. The numbers on the bars represent the mean score of each measure at a particular time point. Error bar values are SD.

Mediation analyses

At the next stage, two models of mediation analyses were conducted to assess associations between the three WOBs (pain intensity, related conditions, and wellness). Figure 4 demonstrates the results of two mediation models. Model A: ΔWOB pain intensity (independent), ΔWOB-related conditions s (mediator), and ΔWOB wellness (dependent) (Figure 4A). Model B: ΔWOB-related conditions (independent), ΔWOB pain intensity (mediator), and ΔWOB wellness (dependent) (Figure 4B). The indirect effect ($a*b$) in model A is larger than $a*b$ of model B ($a*b = 0.15$, $p<0.001$, 95% CI 0.11–0.20 vs. $a*b = 0.09$, $p<0.001$, 95% CI 0.05–0.14). The total effect in Model A is lower than in Model B ($c = 0.34$, $p<0.001$, 95% CI 0.26–0.42 vs $c = 0.44$, $p<0.001$, 95% CI 0.37–0.52). Conversely, in Model B, the direct effect (c') of ΔWOB-related conditions on ΔWOB wellness when ΔWOB pain intensity is the mediator is larger than the direct effect (c') of ΔWOB pain intensity on ΔWOB wellness when ΔWOB-related conditions are the mediator in model A ($c' = 0.36$, $p<0.001$, 95% CI 0.28–0.43 vs. $c' = 0.19$, $p<0.001$, 95% CI 0.11–0.27). According to a linear regression, the adjusted R^2 of ΔWOB-related conditions is 0.25 versus only 0.18 for ΔWOB pain intensity. Both regression models are significant ($F(\text{df} = 386) = 138.9$, $p<0.001$ versus $F(\text{df} = 385) = 77.34$, $p<0.001$, respectively).

DISCUSSION

The main findings of the present study indicate that the level of – and improvement in – patients' wellness are not related merely to pain intensity and the magnitude of its

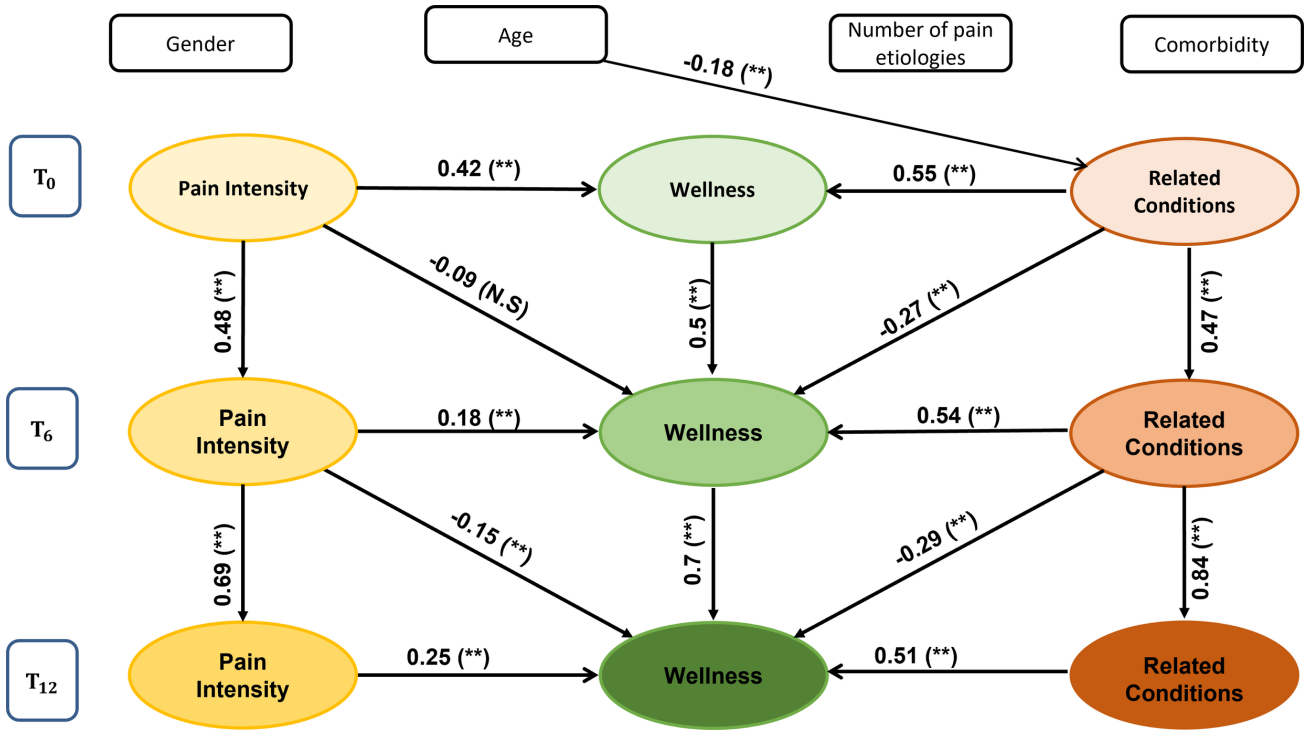

FIGURE 3 The longitudinal SEM model. Each colored ellipse represents a latent variable – yellow: pain intensity; brown: related conditions; green: wellness. Color shading represents the time points: Light: T_0; intermediate: T_6; and dark: T_{12}. Linear arrows represent direct predictions. Horizontal arrows predict wellness by pain or related conditions in the current time point. Vertical arrows predict the parallel latent variable in the next time point. Skew arrows predict wellness in the next wave. Only statistically significant associations are presented by arrows.

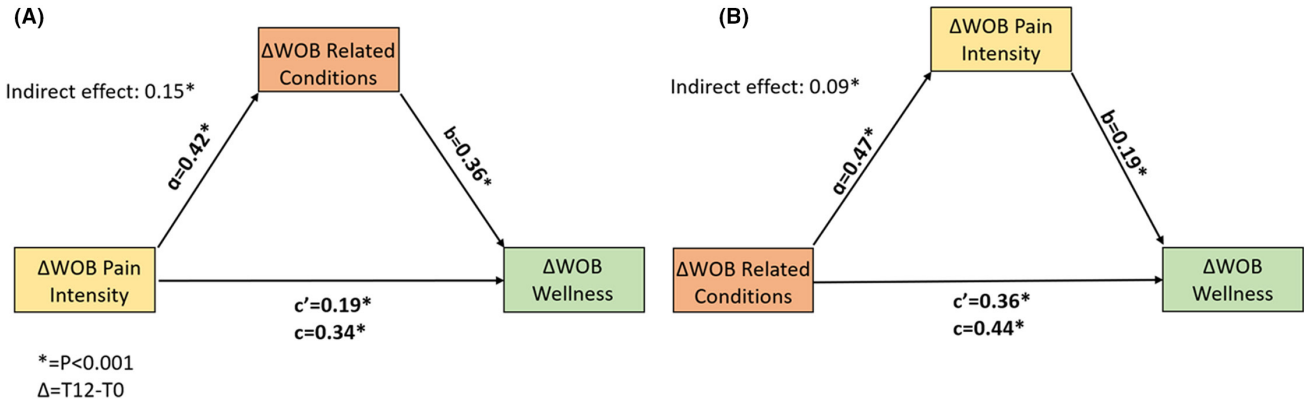

FIGURE 4 Mediation analyses. Model A: Δpain intensity (independent), Δrelated conditions (mediator) Δwellness (dependent). Model B: Δrelated conditions (independent), Δpain intensity (mediator) Δwellness (dependent) $\Delta = T_{12}–T_0$; *$p<0.001$.

reduction. Rather, the level of related conditions and the extent of their attenuation over time contribute to patients' wellness and to its improvement to a greater extent than pain intensity per-se.

In the present study, we created a latent variable entitled 'wellness' that incorporated three major aspects of patient-reported outcomes: quality of life, physical functioning, and subjective health state. Since the main goal of chronic pain management is improving these outcomes,[24,56,57] we believe that consolidating them into one latent variable of a patient's wellness is appropriate.

Traditionally, effective treatment of chronic pain meant reducing its intensity. Indeed, in early 2000, the European Pain Federation – EFIC declared that living free of pain is a fundamental human right.[58] The evidence for adopting this approach is the standard FDA requirement to demonstrate reduction in pain intensity as a primary outcome in clinical trials of patients with chronic pain.[59,60] Many patients with chronic pain still regard reduced pain intensity as a pre-requisite for their wellness. However, this approach has been criticized over the past several years, more so since the identification

of the opioid crisis in North America. Subsequently, Sullivan and Ballantyne[24] argued that pain intensity should not be a primary emphasis in the assessment and treatment of patients with chronic pain, since it may result in establishing the wrong goal for care and impede the understanding of health care providers regarding the essence of chronic pain. Rather, suffering and disability have been suggested to be more closely associated with the meaning of chronic pain.[24]

Our findings likewise indicate that at all three time points, wellness is more closely associated with related conditions rather than with pain intensity itself. Similarly, the improvements in wellness showed stronger associations with the improvement in related conditions than with pain intensity reduction. This was demonstrated by using two different statistical approaches (SEM and mediation analyses). Moreover, the descriptive data in Figure 2 shows that even if the level of each related conditions was mild to moderate at baseline (3–6.5; adjusted scale 0 = 10), and the entire related conditions load was only 5, their effect on wellness was more pronounced than that of pain measures which were more severe at baseline (4.2–8.7; adjusted scale 0 = 10).

Findings from some previous studies that examined the impact of chronic pain and related conditions on patient outcomes (eg, QoL, functioning) were in the same line as in our study. However, most of them were cross-sectional in nature and with associations tested at a single time point.[61–64] For example, in a cross-sectional study, Furrer et al.[61] investigated associations between subjective well-being, pain, and catastrophizing in nearly 100 individuals with physical disabilities. It was found that greater subjective well-being showed significantly lower pain intensity via mediating effect of lower pain catastrophizing. In another cross-sectional study, Lame et al.[62] searched for predictors of quality of life in over 1200 patients with chronic pain and showed that pain catastrophizing was strongly associated with quality of life, and stronger than pain intensity itself. Such cross-sectional studies are limited in providing insights on variables that are evaluated and compared over time; these can only be tested using a longitudinal study design. Only a few studies have examined these relationships longitudinally. For example, Hawker et al.[65] examined the interrelationships of pain, depression, fatigue, and disability among patients with chronic pain for 3 years and found that pain determined a subsequent depressed mood through its effect on fatigue and disability. In another study, Lerman et al.[8] tested longitudinally patients with chronic pain and showed that high levels of depression and anxiety may worsen pain and disability. Mutubuki et al.[66] examined the longitudinal relationships between pain severity, disability, and QoL among patients with chronic low back pain found that pain is longitudinally related to disability with a stronger impact than to QoL. To the existing knowledge raised by those previous study, the current study adds a broader view of the longitudinally relationships between the domains by exploring greater amount of variables and using two different statistic approach to confirm the results.

Compelling evidence from numerous studies has shown that the co-occurrence of chronic pain with other related conditions, each by itself and reciprocally, contribute to functional impairment, work-related disability, and reduced QoL.[8,67–77] By observing patients with chronic pain longitudinally, the current study displays the ongoing vicious cycle of multiple related conditions, pain intensity, and impaired wellness. Additionally, the composition of related conditions into different clusters (WOB's of pain intensity and related conditions) sets the stage for demonstrating the relative contribution of these two latent factors to the latent factor of wellness over time. Perhaps this finding may suggest a direction to the "chicken and egg" dilemma: is wellness determined by chronic pain which in turn causes other related conditions, or is it the related conditions' load that defines wellness and consequently affects chronic pain? Our results may support the latter as the more likely direction of events.

Several potential strengths of the present study may deserve further consideration. First, the study included only patients who completed the entire study protocol. This is why we did not have to handle the common methodological shortcoming of cohort studies of missing data. As mentioned, there is a detailed description elsewhere of all the patients who participated in the study, emphasizing the efficacy and safety of MC.[30] Second, the relatively large sample size enabled us to execute longitudinally SEM at three time points. The advantage of this statistical model is that it allowed us to define latent variables, which each encompassed a few relevant observed variables. This model was therefore able to express the theoretical idea better than by evaluating each observed variable separately. Third, the results provided by the two statistical models of mediation analyses and SEM agreed, and so verify our findings.

This study has several limitations. First, this study was based on a database of patients with chronic pain treated with MC, so its effect on most latent variable was obvious. Yet, the aim of the present study was to investigate the effect of pain intensity and related conditions on wellness longitudinally. Nonetheless, the fact that this specific cohort of patients was treated with MC may limit the generalization of the findings to other populations of patients with chronic pain. Second, the effects of other medications taken concomitantly were not controlled and could be a potential bias. Lastly, the calculation of the weighted average of each questionnaire in each category (WOB's) was based on the assumption that each one of them has an equal weight. However, it should be noted that the SEM model was based on the original variables' scores (ie, unadjusted to a 0–10 scale) of each of the three latent factors, and not on the calculated WOBs. Hence,

due to these limitations, further studies are warranted to verify our findings.

In conclusion, the study can strengthen the recognition that the wellness of patients with chronic pain is associated with and even affected not only by pain intensity itself but more so by the severity of the related conditions. Thus, assessing a broad spectrum of pain measures and related conditions seems relevant for improving the wellness of patients with chronic pain. Moreover, in terms of treating of co-occurring pain and related conditions, clinicians should evaluate the use and effectiveness of pharmacologic and non-pharmacologic interventions for these symptoms. Further studies examining additional related conditions and aspects of wellness, and testing cohorts of patients with chronic pain not under MC treatment, can further strengthen our results and allow us to generalize our conclusions.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare. The study was partially funded by research grants from the Israeli Pain Association (IPA) and TEVA Pharmaceutical Industries Ltd. These sponsors had no role or influence on the study or on this submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

INFORMED CONSENT

Bareket Schiff-Keren, Miriam Ogintz, Simon Vulfsons, Tamar Yashar, Haim-Moshe Adahan, Silviu Brill, Howard Amital, Itay Goor-Aryeh, Dror Robinson, Leslie Green, Refael Segal, Yacov Fogelman, Oren Tsvieli, Ofir Morag, Vadim Tashlykov, Roee Sheinfeld, and Ruth Goor contributed to the study by locating compatible patients and obtaining written informed consent at their institutions.

ORCID

Tamar Gershoni https://orcid.org/0000-0002-0083-5716

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