Differential effects of secukinumab vs. ustekinumab for treatment of psoriasis on quality of life, work productivity and activity impairment: a structural equation modelling analysis

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What’s already known about this topic?

There are only weak to moderate correlations between Psoriasis Area and Severity Index (PASI) and Dermatology life Quality Index (DLQI) scores.

Factors other than area and severity may play a role in patients’ evaluations of their health-related quality of life (HRQOL).

Patients perceive pain, itching, and scaling to be the most troubling aspects of their psoriasis.

What does this study add?

Both PASI response and improved psoriasis-related symptoms of pain, itching, and scaling have an important role for improvements in HRQOL and work and daily activity.

Improvements in PASI, patient-reported symptoms, HRQOL, and work and daily activity were greater for those patients on secukinumab vs. ustekinumab.
Differential effects of secukinumab vs. ustekinumab for treatment of psoriasis on quality of life, work productivity and activity impairment: a structural equation modelling analysis

Purpose: This study examined direct and indirect (mediated) effects of secukinumab vs. ustekinumab on quality of life, work productivity, and activity impairment based on psoriasis severity and symptoms.

Methods: Analyses were based on data from the CLEAR study. Structural equation modelling (SEM) examined the effects of secukinumab vs. ustekinumab on the Dermatology Life Quality Index (DLQI) and on the Work Productivity and Activity Impairment (WPAI) questionnaire using Psoriasis Area Severity Index (PASI) severity and symptoms (pain, itching, and scaling) as potential mediators. Analyses were conducted primarily for patients achieving PASI 90 response at week 16 (repeated at week 52) and for PASI 50, 75, and 100.

Results: Results at weeks 16 and 52 showed that the effect of treatment on change in DLQI score was mediated by PASI 90 response and by improvements in itching and scaling. Achieving any PASI response as early as week 16 directly resulted in significantly better WPAI scores. At week 52, both PASI response and improvement in scaling directly resulted in significantly better WPAI scores. Pain, itching, and scaling were correlated ($r = 0.51$ to $0.68$); improvement in any of these had a significant effect (directly or indirectly) on WPAI. All results favoured secukinumab over ustekinumab.

Conclusion: The results underscore the important role of both PASI response and improved symptoms on improvements in health-related quality of life and work and daily activity in favour of secukinumab vs. ustekinumab.

Keywords: psoriasis; health-related quality of life; work and activity impairment; structural equation modelling
Introduction

The appearance and lifelong, chronic nature of psoriasis result in considerable burden to patients [1] such as sleep impairment [2], depressive symptoms [3,4], negative self-esteem [1], and reduced work productivity. [5,6].

Assessment of psoriasis severity and response to treatment in clinical trials is typically made using the Psoriasis Area Severity Index (PASI) [7]. However, while PASI provides a composite assessment of the signs and extent of psoriasis, it does not yield information about the effect psoriasis has on patients’ lives [8]. The Dermatology Life Quality Index (DLQI) is the most commonly used instrument to assess the health-related quality of life (HRQOL) of patients with psoriasis [7,9]. However, increasing evidence confirms only weak to moderate correlations between PASI and DLQI [10,11]. This suggests that factors other than objective disease severity may play a role in patients’ evaluations of their HRQOL. Previous research has shown that patients perceive pain, itching, and scaling to be the most troubling aspects of their psoriasis [12,13]. These symptoms are correlated with PASI scores [14] and may affect HRQOL and work and activity impairment.

In a head-to-head clinical trial for the treatment of moderate to severe psoriasis, the CLEAR study, secukinumab has demonstrated sustained greater efficacy versus ustekinumab in clearing skin through week 52; greater improvement in symptoms, HRQOL, work and activity impairment; and a comparable safety profile [15].

The present post hoc analysis from the CLEAR study explored how PASI response and psoriasis symptoms (pain, itching, and scaling) affect HRQOL and work and activity impairment using a sophisticated analytic method, structural
equation modeling (SEM). Further, the analysis explored how these relationships differ between secukinumab and ustekinumab.

**Methods**

**Data**
The data for these analyses came from CLEAR, a 52-week, multicenter, randomized, double-blind, head-to-head, parallel-group superiority trial in moderate to severe psoriasis. At baseline, data were available from 336 patients randomized to secukinumab and 339 randomized to ustekinumab. Details of study methods and efficacy/safety results have been previously reported.[15,16].

**Measures**

*Psoriasis Area Severity Index (PASI)*
The PASI is a clinician-reported measure evaluating the head, trunk, upper limbs, and lower limbs for the severity and body surface area coverage of erythema, thickening (plaque elevation, induration), and scaling (desquamation) [17-19]. Improvement was assessed by the percentage of reduction in PASI total score from baseline at each time point, with specific thresholds of 50% (PASI 50), 75% (PASI 75), 90% (PASI 90) and 100% (PASI 100) reductions being the main criteria for improvement. The PASI response at weeks 16 and 52 were used for this analysis.

*Dermatology Life Quality Index (DLQI)*
The DLQI is a 10-item patient-reported measure evaluating the extent to which quality of life (QOL) has been affected by skin problems in the previous week
Total and subscale scores (Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment) are computed. The total DLQI score ranges from 0 (no effect on patient’s life) to 30 (extremely large effect on patient’s life). The change in DLQI total score at weeks 16 and 52 was used for this analysis.

Work Productivity and Activity Impairment–Psoriasis (WPAI)

The WPAI is a self-administered questionnaire comprised of six questions regarding the effects of psoriasis on the subject’s ability to work and perform regular activities and is based on their experiences in the previous 7 days [21]. Scores were calculated for the percent of impairment in daily activities or while working (“presenteeism”) and work time missed (“absenteeism”). The WPAI scores from weeks 16 and 52 were used in this analysis.

Patient’s assessment of psoriasis-related pain, itching, and scaling

A self-administered, 11-point numeric rating scale (0-10) was used to evaluate the patient’s assessment of pain, itching, and scaling over the past 24 hours. Respondents answered three questions for the assessment of pain, itching, and scaling: “Overall, how severe was your psoriasis-related pain/itching/scaling over the past 24 hours?” A score of 0 represented the absence or null end of the pain, itching, or scale intensity (i.e., no pain, itching, or scaling) and a score of 10 represented the other extreme of pain, itching, or scaling intensity (i.e., pain, itching, or scaling as bad as it could be). Symptom severity scores for psoriasis-related pain, itching, and scaling at weeks 16 and 52 were used in this analysis.
Baseline Covariates

The following covariates, known to potentially drive HRQOL, were also included in the present analyses: age and gender of the patient; body mass index; duration of psoriasis; presence of psoriatic arthritis at baseline; and previous use of biologics/systemics before treatment with secukinumab or ustekinumab in the CLEAR study.

Analyses

The analyses were carried out using SEM, a type of path analysis that involves the use of latent variable (i.e., unobserved variables; also called factors) and manifest variables (i.e., observed variables) to assess the relationships between multiple patient-relevant outcomes simultaneously. [22,23] We used SEM to assess the direct and indirect (i.e., mediated) differential effects of psoriasis treatment (secukinumab vs. ustekinumab), covariates, PASI response, and patient-reported psoriasis-related symptoms (pain, itching, and scaling) on change in DLQI scores from baseline at weeks 16 and 52, and on WPAI scores at weeks 16 and 52. We present PASI 90 results since PASI 90 was the primary efficacy endpoint of the CLEAR study, although the SEM analyses were replicated for PASI 50, 75, and 100 responses.

We hypothesized in the DLQI model that the DLQI Symptoms and Feelings (DLQI-SF) subscale was antecedent to a DLQI Total (Revised) “subscale” combining the remaining five DLQI subscales (Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment subscales; Figure 1). The logic underlying this set of relationships was that changes in PASI response and psoriasis symptoms would first affect the DLQI-SF subscale
(measured by the questions “Over the last week, how itchy, sore, painful, or stinging has your skin been?” and “Over the last week, how embarrassed or self-conscious have you been because of your skin?”); the DLQI-SF subscale would then, in turn, affect the remaining subscales of the DLQI. The five remaining subscales were modelled as alternative measures of a revised latent variable for the DLQI Total.

Three WPAI scores were considered in the SEM model for WPAI: percent of impairment in daily activities, percent of impairment while working (“presenteeism”), and work time missed (“absenteeism”) in the previous 7 days (Figure 2).

Goodness-of-fit tests were used to assess how closely the hypothesized, model-implied relationships fit or represented those in the CLEAR data. In addition to the fit indices, examination of results focused on standardized coefficients (β [i.e., betas] ranging from −1 through 0 to +1, where −1 is a perfect inverse relationship between variables, 0 is no relationship, and +1 is a perfect positive relationship; standardized coefficients are interpreted in a similar way as correlation coefficients); this approach enabled direct comparison of the strength of relationships between the variables included in the DLQI and the WPAI models.

Results

Baseline comparisons

Baseline characteristics and patient-reported outcome scores for patients in the two treatment arms of the CLEAR study were similar (Table 1). These data have been presented elsewhere [16].
Results for the models of the change in DLQI total score from baseline to week 16 and from baseline to week 52 are presented in Figure 3 and Figure 4, respectively. Goodness-of-fit statistics for the DLQI models were all excellent, indicating that the relationships hypothesized in Figure 1 are representative of those in the CLEAR data. Moreover, the fit statistics were much better for the model where DLQI-SF was antecedent to the DLQI Total (Revised) [See Supplemental Information]. This confirms the model hypothesis that if patients feel that their itchy, sore, painful, or stinging skin has improved, or if patients feel less embarrassed or less self-conscious about their skin, they will be more likely to carry out daily activities and personal relationships.

Results of the DLQI model at week 16 showed that the impact of psoriasis treatment on DLQI was not direct but was mediated by both PASI response and psoriasis-related symptoms.

Compared with those treated with ustekinumab, patients treated with secukinumab were significantly more likely to achieve PASI 50/75/90/100 response (β = −0.08, −0.14, −0.22, −0.17, respectively). Achieving PASI 75 or 90 (but not PASI 50 or PASI 100) significantly improved the DLQI-SF subscale which in turn significantly improved the DLQI Total (Revised) subscale (i.e., the combined total of the other five DLQI subscales). Similarly, improvements in pain, itching, and scaling also significantly improved the DLQI-SF subscale (β = 0.18, 0.41, 0.21; all P < 0.05), which in turn significantly improved the DLQI Total (Revised) subscale (β = 0.50; P < 0.05) in favour of secukinumab over ustekinumab. Improvement in itching had the largest effect on the DLQI-SF subscale and on the DLQI Total (Revised) via the DLQI-SF subscale, although pain and scaling were also significant. The DLQI Total (Revised) subscale was
important to patients, with Leisure, Daily Activities, and Personal Relationships subscales being the most important (i.e., they had the highest standardized coefficients).

Similar results were seen with the DLQI models at Week 52.

**WPAI Scores at Week 16 and Week 52**

Results for the WPAI models at week 16 and at week 52 are presented in Figure 5 and Figure 6, respectively. Goodness-of-fit statistics for the WPAI models were all excellent, indicating that the hypothesized relationships in Figure 2 reflect the data very well.

Results of the WPAI models at week 16 showed more complex relationships between the different variables than was seen with the DLQI models and that the impact of psoriasis treatment on WPAI was not direct but was mediated by PASI response.

Psoriasis treatment ($\beta = -0.215$) and scaling ($\beta = -0.257$) directly improved PASI 90 response, and patients treated with secukinumab were more likely to achieve PASI 90 response than those treated with ustekinumab. The effects of improvement in psoriasis symptoms on WPAI scores were completely indirect and were mediated by the improvement in PASI response. When scaling improved, pain and itching improved, and this improvement was more likely for those treated with secukinumab vs. ustekinumab. Compared with ustekinumab, treatment with secukinumab indirectly and significantly improved pain and itching ($r \approx 0.07$ and $0.09$, respectively) via improvements in scaling and, in turn, the observed correlations between improvements in scaling and improvements in pain and itching.
Achieving PASI 90 response directly resulted in less WPAI activity impairment ($\beta = -0.215$) and presenteeism ($\beta = -0.2$). Because WPAI activity impairment and presenteeism are significantly correlated with absenteeism in this model, achieving PASI 90 response also resulted in less absenteeism. Given that scaling has a direct effect on PASI response, improvement in scaling indirectly resulted in lower WPAI activity impairment and less presenteeism.

Results of the models at week 16 were similar for all PASI responses.

The results of the WPAI models at week 52 were somewhat different, with both PASI response and symptoms mediating the effects of psoriasis treatment on WPAI scores.

Patients on secukinumab experienced greater improvements in pain, itching, and scaling, and were more likely to achieve PASI 90 response than those on ustekinumab. Improvement in scaling and the achievement of PASI 90 response directly resulted in lower WPAI activity impairment ($\beta = 0.115, -0.223$, respectively), and less presenteeism at week 52 ($\beta = 0.126, -0.236$, respectively). Improvement in scaling and the achievement of PASI 90 response indirectly resulted in less absenteeism at week 52 because absenteeism was correlated with WPAI activity impairment ($r = 0.264$) and presenteeism ($r = 0.305$) in this model. Pain and itching were directly related to psoriasis treatment and were correlated with scaling (which had direct effects on WPAI activity impairment and presenteeism); therefore, pain and itching indirectly resulted in lower WPAI activity impairment, less presenteeism, and less absenteeism at week 52.

Results of the models at week 52 were similar for all PASI responses.

**Discussion**

This post hoc analysis of the CLEAR 52-week data indicate that the relationships
among psoriasis treatment, PASI response, and psoriasis-related symptoms and HRQOL and work and activity impairment are complex, often involving indirect but significant relationships. The SEM analyses demonstrated that the effect of psoriasis treatment on HRQOL and WPAI are mediated by both PASI response and improvements in patient-reported psoriasis-related pain, itching, and scaling symptoms. Secukinumab showed superior efficacy in clearing skin and relieving symptoms, a finding which resulted in greater positive impact of secukinumab on HRQOL and on WPAI versus ustekinumab.

Clear skin is the ultimate treatment goal and is associated with improved HRQOL. Previously, the effects of improvement in psoriasis symptoms on HRQOL and WPAI were unclear. This analysis provides insight on the importance of relieving bothersome psoriasis symptoms for patients’ lives. Griffiths and colleagues [10] reported weak to moderate correlations between DLQI and PASI total scores and noted that changes in QOL do not appear to be captured by PASI or its subscales. Our results demonstrate that, in alignment with this research, factors other than PASI influence HRQOL and, more specifically, that patient-assessed psoriasis symptoms play an important role in affecting patient outcomes. Whereas Leonardi and colleagues [24] focused on the effects of pruritus severity, the present study included three key psoriasis symptoms noted by patients [12,13] and demonstrated their key role in the patient experience with psoriasis.

In 2013, Lewis-Beck and colleagues [25] were first to inform on the presence of direct relationship between psoriasis symptom (pain, itching, and scaling) severity and HRQOL and work and activity impairment among patients with moderate to severe psoriasis using SEM. However the present analyses go
well beyond this research by using a full structural equation model that simultaneously estimates all hypothesized relationships and evaluates the fit of the hypothesized model to the observed data in the CLEAR study without having to use a two-stage analytic approach. Moreover, our models investigate the differential effects of two active treatments for moderate to severe psoriasis and the effects at different time points, which is rarely explored in SEM analyses to our knowledge.

The confirmation of the hypothesis that the Symptoms and Feelings subscale was antecedent to a latent variable (factor) representing the remaining five subscales of the DLQI Total (Revised) was a notable result. The results of the SEM analyses suggested that improving skin clearance and psoriasis symptoms will first improve the patients’ experience with itchy, sore, painful, or stinging skin and embarrassment with skin before improving other domains of HRQOL, such as daily activities or personal relationships. Although this seems logical, this measurement model of the DLQI should be explored in future research since it appears to be a novel conception of this measure.

Interestingly, the effects of improvement in psoriasis symptoms on WPAI scores were mediated by improvement in PASI response in the models at week 16, but they directly affected WPAI scores at a later time point (i.e., week 52). This finding may indicate that patients first experience the effects of clear skin on their work and activities followed by the additional effects of improvements in their psoriasis symptoms.

We did not find a relationship between PASI 50/100 responses and changes in the DLQI-SF subscale at week 16, or between PASI 50 response and the DLQI-SF subscale at week 52. For PASI 50 response, this may be caused by
the large skew in the distribution of patients, as almost 95% of patients had attained PASI 50 at both time points. Thus, there was little variability for use as a reliable predictor. It is unclear why we did not find a relationship between PASI 100 response and changes in the DLQI-SF subscale at week 16 whereas a relationship was found at week 52. In contrast, all PASI responses were directly related to WPAI scores at week 16 and week 52. It may be explained by the use of actual scores for WPAI rather than changes in scores from baseline, as with the DLQI and PASI. The rationale behind using actual scores in the SEM rather than the change of scores from baseline was based on the fact that the WPAI collects the work and activity experience of the patient during the past 7 days, excluding the current day. We believe it makes more sense to focus on the WPAI scores at weeks 16 and 52, when the measure has a one-week recall at both time points.

We explored whether a psychological variable such as depression could play a role in explaining some of these relationships following recent findings showing an increased likelihood of depressive symptoms or clinical depression among patients with psoriasis, which may have some etiology in the systemic inflammatory condition that increases risk of brain inflammation [4,26,27]. The only measure of depression/anxiety available from the CLEAR study is the single item from the EuroQol EQ-5D that asks about the extent to which the patient feels anxious or depressed today. As an example, the results of the models of the WPAI that included the EQ-5D anxiety/depression variable showed that improvements in pain and scaling directly resulted in less anxiety/depression, which in turn resulted in less activity impairment and impairment while working (presenteeism). However, an argument could be made that improvements in the WPAI also led to improvement of the EQ-5D anxiety/depression domain. It is not...
clear if anxiety or depression is a mediating variable with effects on work and activity impairment or if it is itself an outcome of these QOL domains. Further work is needed to understand the role of anxiety/depression in patients’ outcomes.

Some limitations in the current study are worth noting. As with any SEM, there are implied causal relationships with these models and interpretations of many of the paths in these models are that of causal relationships. However, time ordering was built into the DLQI analyses by using PASI score at weeks 16 and 52, and change from baseline in psoriasis symptoms and DLQI scores. For the WPAI analyses, the WPAI scores at weeks 16 or 52 (reflecting the previous 7 days) were used as outcome variables, along with the covariates of PASI responses from baseline to weeks 16 and 52, and change from baseline in psoriasis symptoms. There is nothing inherently wrong with this approach, particularly when the hypothesized relationships are based on sound logic supported by significant empirical results. Nonetheless, firm causal conclusions must be accepted tentatively.

A second possible limitation is that the CLEAR study was a clinical trial, with specific inclusion/exclusion criteria and controls. It would be valuable to know whether these same relationships hold in real-world situations. In addition, analyses were limited to the variables available in the CLEAR study; other relevant variables might play a role in these relationships, but were not available for these analyses.

The DLQI and WPAI were analysed separately (i.e., in separate models) for two reasons: (1) the models became complex analytically because there were many domains of HRQOL outcomes between the two measures, some of which overlapped in content (e.g., DLQI Daily Activities and Work and School with the
WPAI Activity Impairment and Work Impairment); and (2) the combined models would be visually complex and it would be difficult to see individual paths. Thus, we feel the approach used in this analysis provides the clearest presentation of the complex relationships and yields the same conclusions.

The SEM analyses utilized here represent a powerful and informative analytic method that has helped us obtain a detailed understanding of the differential direct and indirect effects of secukinumab versus ustekinumab on multiple patient-relevant outcomes simultaneously. These analyses underscore the important role of both clear skin and improved psoriasis-related symptoms in affecting the lives of patients with moderate to severe psoriasis; these findings also produce explanatory insights into the greater impact of secukinumab treatment versus ustekinumab in improving patient-reported outcomes.
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Conflict(s) of Interest

DES, BS and KH are employed by RTI Health Solutions. CEMG is a consultant and has received grants from Novartis; has been a paid advisor and/or in receipt of research grants from AbbVie, Actelion, BMS, GSK, Galderma, Janssen, Leo Pharma, MSD, Pfizer, Novartis, Sandoz, Eli Lilly, Regeneron, Roche, L’Oreal, DSM, Clarins, Walgreens Boots Alliance and UCB Pharma. AYF is joint copyright owner of the DLQI: Cardiff University and AYF receive royalties. AYF has received honoraria from Novartis for advisory board membership, and from Galderma, Napp, Sanofi and Eli Lilly. IG and AG are employed by Novartis Pharma, AG, and Novartis Pharmaceuticals Corporation, respectively. YZ is employed by Sun Pharma, but was employed by Novartis Pharmaceuticals Corporation at the time this research was conducted. LP has received grants or honoraria from Abbvie, Almirall Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Novartis, Pfizer, Regeneron, Roche, and Sandoz.

References


Table 1. Baseline Demographics and PRO Scores of the Two Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Secukinumab (N = 336)</th>
<th>Ustekinumab (N = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>45.2 (13.96)</td>
<td>44.6 (13.67)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>229 (68.0)</td>
<td>252 (74.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.4 (19.95)</td>
<td>87.2 (22.11)</td>
</tr>
<tr>
<td>Currently employed at baseline, n (%)</td>
<td>228 (67.7)</td>
<td>225 (66.4)</td>
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Patient-reported outcomes

<table>
<thead>
<tr>
<th></th>
<th>Secukinumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLQI total score</td>
<td>13.4 (7.63)</td>
<td>13.2 (7.57)</td>
</tr>
<tr>
<td>WPAI: Absenteeism</td>
<td>5.39 (14.986)</td>
<td>5.96 (15.672)</td>
</tr>
<tr>
<td>WPAI: Presenteeism</td>
<td>27.31 (26.095)</td>
<td>26.17 (24.304)</td>
</tr>
<tr>
<td>WPAI: Activity impairment</td>
<td>36.87 (29.942)</td>
<td>35.83 (29.186)</td>
</tr>
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DLQI = Dermatology Life Quality Index; PRO = patient-reported outcome; SD = standard deviation; WPAI = Work Productivity and Activity Impairment
Figure 1. Hypothesized Structural Equation Model of Predictors of the DLQI

BMI = body mass index; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index.
BMI = body mass index; PASI = Psoriasis Area Severity Index; WPAI = Work Productivity and Activity Impairment.
Figure 3. PASI 90, Changes in Itching, Pain, and Scaling with Changes in DLQI at Week 16

BMI = body mass index; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index; PSA = psoriatic arthritis; Tx = treatment.
BMI = body mass index; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; PSA = psoriatic arthritis; Tx = treatment.

Note: For both Figures 3 and 4, only paths significant at P ≤ 0.05 are shown. Variables in squares = observed variables; variable in a circle = latent variable. Direct effects are depicted as an arrow emanating from an independent variable leading and pointing to a dependent variable (outcome). An indirect effect is depicted as a mediating variable having an arrow pointing to it from an independent variable but also pointing to yet another dependent variable.
Figure 5. PASI 90 Changes in Itching, Pain, and Scaling With WPAI Activity Impairment, Work Impairment, and Work Time Missed at Week 16

BMI = body mass index; PASI = Psoriasis Area and Severity Index; PSA = psoriatic arthritis; Tx = treatment; WPAI = Work Productivity and Activity Impairment.
Figure 6. PASI 90 Changes in Itching, Pain, and Scaling With WPAI Activity Impairment, Work Impairment, and Work Time Missed at Week 52

BMI = body mass index; PASI = Psoriasis Area and Severity Index; PSA = psoriatic arthritis; Tx = treatment; WPAI = Work Productivity and Activity Impairment.

Note: For both Figures 5 and 6, only paths significant at $P \leq 0.05$ are shown. Variables in squares = observed variables. Direct effects are depicted as an arrow emanating from an independent variable leading and pointing to a dependent variable (outcome). An indirect effect is depicted as a mediating variable having an arrow pointing to it from an independent variable but also pointing to yet another dependent variable.