Does adherence to treatment mediate the relationship between patients’ treatment outcome expectancies and the outcomes pain intensity and recovery from acute low back pain?

Abstract

It is believed that patients’ expectancies about the effectiveness of their treatment influence their treatment outcomes, but the working mechanism is rarely studied in low back pain patients. Theoretical models suggest that adherence to treatment may be an important pathway. The aim of this study was to assess the mediating role of adherence to treatment in the relationship between expectancies and the outcomes recovery and pain intensity in patients with acute low back pain. This study used data from a randomized placebo controlled trial of paracetamol for acute low back pain. Expectancies were measured with the Credibility Expectancy Questionnaire (CEQ). Adherence was measured with a medication diary. Pain intensity was recorded daily in a diary on a 0-10 pain scale and recovery was defined as the first of seven consecutive days scoring 0 or 1 the pain scale. Cox regression (dependent variable: recovery) and linear mixed model analyses (dependent variable: daily pain intensity scores) were performed. The “difference in coefficients” approach was used to establish mediation. 1573 participants were included in current analyses. There was a small but highly significant relationship between expectancies and outcomes; 3.3% of the relationship between expectancies and recovery and 14.2% of the relationship between expectancies and pain intensity was mediated by adherence to treatment. The current study does not convincingly support the theory that adherence is a key pathway in the relationship between treatment outcome expectancies and recovery and pain intensity in this acute low back pain population.

Introduction

Patients’ expectancies are believed to influence treatment outcomes like recovery, pain and activity limitations. Patients may have expectancies for different aspects of their treatment. For example, they may have expectancies regarding the outcome of treatment, regarding the treatment process, and regarding their self-efficacy as it relates to their treatment. For patients with low back pain there is fair evidence that supports the relationship between patients’ outcome expectancies and treatment outcomes. A recent systematic review concluded that negative expectancies regarding recovery are a consistent significant predictor of poor outcome (i.e. recovery and activity limitations) in patients with acute low back pain.

Multiple pathways are proposed through which expectancies may influence outcomes. Perhaps the most-investigated pathway linking expectancies to pain is via the expression of endogenous opioids. Much of this research has been conducted in the context of understanding placebo effects using experimental pain paradigms. However, in clinical situations there may be also behavioral factors that (partly) mediate the relationship between expectancies and outcomes.

The idea that patients’ beliefs or expectancies influence their behavior is central to many of the theoretical models in behavioral medicine and health psychology, such as the health belief model, common sense model and the social cognitive model. Adherence to treatment is such a health behavior that is believed to be affected by patient’s expectancies. The idea is that patients that expect the treatment to be beneficial for their health will put more effort into following the treatment recommendations. Treatment adherence and is essential for the success of many medical treatments. It has been defined by the World Health Organisation as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”. Previously, studies have focused on the relationship between patients’ expectancies and treatment outcomes or on the relationship between patients’ expectancies and adherence. However, to the best of our knowledge in low back pain these relationships have never been studied in a mediation model with respect to taking medication.

Several types of patients’ expectancies and multiple definitions of patients’ expectancies have been proposed previously. In this study we focus on expectancies about treatment outcomes, hereon referred to as “outcome expectancies”, which are defined as “improvements that patients believe will be achieved” from the treatment. We will investigate the mediating role of adherence to treatment in the relationship between outcome expectancies and the outcomes recovery and pain intensity. In order to be able to assess this we first have to assess relationship between patients’ pre-treatment outcome expectancies and recovery and pain intensity. Therefore the first hypothesis to be tested is: There is a statistically significant relationship between patients’ pre-treatment outcome expectancies and recovery and pain intensity from acute low back pain in patients taking...
paracetamol or placebo paracetamol. The second hypothesis is: Part of the relationship between patients’ pre-treatment outcome expectancies and recovery from acute low back pain is mediated by adherence to treatment.

Methods

Design and participants
This study is a secondary analysis of a double dummy, double blind, randomized controlled trial (RCT) investigating the efficacy of paracetamol for acute low back pain\(^{20-22}\). In this RCT participants were provided with advice and randomly assigned to receive up to 4 weeks of either regular (time-contingent) doses of paracetamol, or doses of paracetamol as needed, or placebo.

Patients were eligible to participate if they had a new episode of acute low back pain (defined as pain between the 12\(^{th}\) rib and buttock crease that was shorter than 6 weeks’ duration and preceded by at least 1 month of no pain) with or without leg pain. The pain had to be of at least moderate intensity in the past 24 hours, as measured by a six point scale with the following answering options: no pain, very mild pain, mild pain, moderate pain, severe pain, very severe pain (an adaptation of item 7 of the SF-36). Exclusion criteria were suspected serious spinal pathology; current use of full recommended doses of an analgesic; spinal surgery in the preceding 6 months; contraindication to paracetamol; use of psychotropic drugs for a disorder judged to prevent reliable recording of study information; or pregnant or planning pregnancy. Ethical approval for the study was given by the University of Sydney Human Research Ethics Committee. All participants signed informed consent. More information on the trial design, statistical analysis plan and the results of this study can be found in previously published papers\(^{20-22}\).

Procedures
With the double dummy design each participant was asked to take two types of tablets. Two tablets from the regular-paracetamol box every 6-8 hours (6 tablets per day) and one or two tablets from the as-needed-paracetamol box when needed for pain relief (at least 4-6 hours apart, max 8 tablets per day). Participants in the first group had paracetamol tablets in the regular-paracetamol box and placebo in the as-needed-paracetamol box. Participants in the second group had placebo in the regular-paracetamol box and paracetamol in the as-needed-paracetamol box. For participants in the third group both boxes contained placebo. Participants were asked to continue the study medication until they recovered, or for 4 weeks, whichever came first.

Further, participants in all groups received the advice to stay active and avoid bed rest and reassurance of the favourable prognosis of low back pain according to guidelines. Primary outcome of the trial was recovery, defined as a pain score of 0 or 1 sustained for 7 consecutive days.

Measurements

Expectancies
Treatment outcome expectancy was measured at baseline with the expectancy subscale of the Credibility Expectancy Questionnaire (CEQ). The CEQ is a self-reported six item questionnaire consisting of two subscales that aims to measure treatment credibility (e.g. at this point, how successfully do you think the treatment will be in reducing your complaints) and treatment outcome expectancies (e.g. at this point, how much do you really feel that the treatment will help to reduce your complaints)\(^{19}\). The expectancy subscale contains three items of which the first and third item are scored on a 0-100% scale and the second on a 0-9 scale. To derive a sum ranging from 0-29, scores on first and third item were divided by 10. The CEQ has been shown to be a valid and reliable measurement instrument for patients with low back pain\(^{23}\).

Medication adherence
To measure adherence, participants recorded the number of tablets they consumed daily from each box up until their recovery. For the current study adherence was defined as the number of tablets consumed from the regular-paracetamol box (recommended: 6 per day), as reported by the participant.

Outcomes

Time to recovery
Recovery was defined as the first day a participant scored a 0 or 1 on a 0-10 pain rating scale that was maintained for 7 consecutive days. Time to recovery for each participant was calculated as the number of days from the start of the study period until ‘recovery’.

Pain intensity
Pain intensity was recorded daily in a diary until recovery or for a maximum of 72 days (12 weeks) using a 0-10 pain rating scale (0= no pain – 10 = worst imaginable pain). For the current study only the first 28 days of the pain intensity scores were used as this is the maximum period that patients were treated with paracetamol or placebo paracetamol.
Statistical analysis

The primary analyses of the trial showed no differences between the treatment groups for primary and secondary outcomes nor in baseline parameters and process variables. Thus, data from all three groups were aggregated and regarded as one cohort. This assumption was tested in the current study by adding interaction terms between expectancy and group to all analyses. In the primary analyses of the trial the primary outcome was time until recovery. Secondary outcomes of the trial were pain intensity, disability, function, global rating of symptom change, sleep quality, and quality of life. Process measures consisted of adherence to drugs, concomitant treatment use, work absenteeism, adverse events, and treatment satisfaction. For more detail please see the results paper of the trial.

In figure 1 the conceptual model of mediation in the current study is shown. For both analyses the “difference in coefficients” approach was used to investigate the mediating effect of adherence. This approach assumes that the mediated effect is the reduction in the effect of the independent variable X (outcome expectancy) on the outcome variable Y (time to recovery/pain intensity) when adjusted for the mediator M (adherence). The magnitude of the mediated effect can be estimated by calculating the difference in the coefficients of the effect of X on Y (C) and the effect of X on Y when controlling for M \((C' - C)\)

Figure 1: The conceptual model of mediation

Time to recovery

Patients that did not reach the endpoint of recovery within the four weeks of the trial were censored at day 28. Adherence was defined as the median number of recommended tablets that were actually consumed (calculated per week; day 1-7, day 8-14, day 15-21, day 22-28).

First, a univariate Cox regression analysis (SPSS 20) of the effect of expectancy on time to recovery was performed \((C)\). Secondly, the adherence variables were entered into the model together as a time dependent covariate. To calculate the percentage of the effect of expectancy on recovery that is mediated by adherence to treatment, first the difference in regression coefficient between the univariate analysis \((C)\) and the analysis with adherence as a time dependent covariate \((C')\) was calculated \((C-C')\). The percentage of the effect mediated by adherence was then calculated by \(((C-C') / C) * 100\).

Pain Intensity

As both the pain and adherence variables are measured repeatedly (daily measurements for 28 days) linear mixed-model analysis (also known as multilevel analysis or as random effects model analysis) was chosen as a method for the analysis with pain intensity as an outcome, in these analyses an adjustment is made for the correlation between repeated observations within a subject. This is done by modeling the variability among the subjects. In this study, a random intercept was added to the regression model.

First, a univariate mixed model analysis (xtmixed procedure in Stata 11.2) was performed with the daily pain scores as the dependent variable and expectancy as the independent variable \((C)\). Secondly, the 28 daily adherence to medication variables were added to the linear mixed model to obtain the effect of expectancy on pain intensity when adjusted for adherence \((C')\). Again, the percentage of the effect of expectancies on pain intensity mediated by adherence was calculated by \(((C'-C)/C) * 100\).

Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>group 1</th>
<th>group 2</th>
<th>group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; mean (SD)</td>
<td>44.9 (15.8)</td>
<td>44.4 (15.0)</td>
<td>45.1 (15.9)</td>
<td>45.1 (16.4)</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>46.7</td>
<td>45.1%</td>
<td>47.7%</td>
<td>47.3%</td>
</tr>
<tr>
<td>Baseline pain, mean, 0-10 scale (SD)</td>
<td>6.4 (1.8)</td>
<td>6.3 (1.7)</td>
<td>6.5 (1.8)</td>
<td>6.4 (1.8)</td>
</tr>
<tr>
<td>Pain at 4 weeks; median, 0-10 scale (IQR)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Recovered after 4 weeks</td>
<td>72.8%</td>
<td>72.9%</td>
<td>71.9%</td>
<td>73.7%</td>
</tr>
<tr>
<td>Days until recovery * ; median (IQR)</td>
<td>14 (7; 28)</td>
<td>14 (7; 28)</td>
<td>14 (6; 28)</td>
<td>13 (7; 28)</td>
</tr>
<tr>
<td>Currently employed (% yes)</td>
<td>74.8</td>
<td>74.6</td>
<td>71.3</td>
<td>78.4</td>
</tr>
<tr>
<td>Self-reported adherence; median (IQR)</td>
<td>4.0 (1.6;5.7)</td>
<td>4.0 (1.6;5.6)</td>
<td>3.9 (1.5;5.6)</td>
<td>4.0 (1.5;5.7)</td>
</tr>
<tr>
<td>Days since onset; median (IQR)</td>
<td>6.0 (3.0;14.0)</td>
<td>5.0 (3.0;14.0)</td>
<td>5.0 (2.0;14.0)</td>
<td>5.0 (3.0;14.0)</td>
</tr>
<tr>
<td>Number of previous episodes; median (IQR)</td>
<td>2.0 (0.0;6.0)</td>
<td>2.0 (0.0;5.0)</td>
<td>2.0 (0.0;6.0)</td>
<td>2.0 (1.0;7.0)</td>
</tr>
<tr>
<td>Baseline presence of pain beyond the knee (% yes)</td>
<td>19.4%</td>
<td>19.7%</td>
<td>20.8%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Baseline disability RMDQ mean, range 0-24; (SD)</td>
<td>13.0 (5.5)</td>
<td>12.8 (5.6)</td>
<td>13.1 (5.4)</td>
<td>13.2 (5.4)</td>
</tr>
<tr>
<td>Baseline expectancy CEQ mean, range 0-25; (SD)</td>
<td>21.4 (5.6)</td>
<td>21.2 (5.8)</td>
<td>21.1 (5.5)</td>
<td>21.7 (5.6)</td>
</tr>
</tbody>
</table>

IQR= interquartile range, RMDQ= Roland Morris disability questionnaire, CEQ= credibility expectancy questionnaire, * patients not recovered in the first 4 weeks were censored at day 28 for this study, group 1: paracetamol on a time contingent basis, placebo paracetamol as needed; group 2: placebo paracetamol on a time contingent basis, paracetamol as needed; group 3: placebo paracetamol on a time contingent basis, placebo paracetamol as needed.
Results

From November 2009 to December 2012 4606 patients were screened of which 1652 were included and randomly assigned to one of the three treatment groups. Of these participants 9 were excluded after randomization because they were incorrectly screened. Of the remaining 1643 participants 70 were not included in the current study because they did not complete the expectancy subscale of the CEQ or they did not fill in the medication or pain diary. Characteristics of the 1573 participants are shown in table 1. Participants were on average 45 years old, 46.7% were female, enrolled in the trial 10 days (mean score) after onset of their episode of low back pain, and they had had a mean of 7 previous episodes of low back pain and a baseline pain score of 6.4. About 70% of participants were recovered after 4 weeks which can be seen in the Kaplan Meier curve (Figure 2).

Results for the analysis (Cox regression) with time to recovery as an outcome showed that treatment outcome expectancies had a significant effect on time to recovery (Table 2). A hazard ratio (HR) of 1.03 means that a one point higher score on the baseline measure of expectancies results in a 3% greater probability of recovery at any time during the 4 weeks of the trial. When adherence was added to this model, a very small proportion of the effect disappeared, indicating that a small proportion (3.3%) of the effect of expectancy on time to recovery is mediated by adherence to treatment.

Interaction terms between expectancy and group were none-significant in all analyses indicating that the relationships between expectancy, adherence and outcomes are not significantly different for the three treatment groups.

Post-hoc analyses were performed to find possible explanations for the results above. First the effect of expectancies on adherence was tested with linear mixed models. Results show a trend towards a significant effect, though with a very small magnitude (β = -0.016 p=0.07). Secondly, the effect of adherence to treatment on the outcomes was investigated using similar methods as the primary analyses (Cox regression for time to recovery and linear mixed models for pain intensity). Results show that there in both analyses there was a significant relationship between adherence and outcomes (time to recovery HR= 0.922 p=0.00; pain intensity B=0.453 p=0.00).

Table 2. Results for time to recovery (Cox regression)

<table>
<thead>
<tr>
<th></th>
<th>B (SE)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct association expectancies – recovery (C)</td>
<td>0.030 (0.006)</td>
<td>1.030</td>
<td>1.019 ;1.042</td>
</tr>
<tr>
<td>Model with adherence as covariate (C’)</td>
<td>0.029 (0.006)</td>
<td>1.029</td>
<td>1.018 ;1.041</td>
</tr>
</tbody>
</table>

Proportion of effect mediated by adherence 3.3%

β= beta coefficient; SE= standard error; HR= hazard ratio; 95% CI= 95% confidence interval

Table 3. Results for pain intensity (linear mixed models)

<table>
<thead>
<tr>
<th></th>
<th>B (SE)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct association expectancies – pain intensity (C)</td>
<td>-0.037 (0.009)</td>
<td>-0.054 ; -0.020</td>
</tr>
<tr>
<td>Model with adherence as covariate (C’)</td>
<td>-0.033 (0.009)</td>
<td>-0.050 ; -0.015</td>
</tr>
</tbody>
</table>

Proportion of effect mediated by adherence 10.8%

β= beta coefficient; SE= standard error; 95% CI= 95% confidence interval

The results for pain intensity (linear mixed- model analysis) were similar (table 3). Again, there was a significant effect of expectancies on pain intensity. A one point higher score on the baseline measure of expectancies results in a decrease in pain intensity of 0.037 points on the 0-10 pain intensity scale. In this analysis the proportion of the relationship mediated effect by adherence to treatment was somewhat larger; 14.2%.

Interaction terms between expectancy and group were none-significant in all analyses indicating that the relationships between expectancy, adherence and outcomes are not significantly different for the three treatment groups.

Post-hoc analyses were performed to find possible explanations for the results above. First the effect of expectancies on adherence was tested with linear mixed models. Results show a trend towards a significant effect, though with a very small magnitude (β = -0.016 p=0.07). Secondly, the effect of adherence to treatment on the outcomes was investigated using similar methods as the primary analyses (Cox regression for time to recovery and linear mixed models for pain intensity). Results show that there in both analyses there was a significant relationship between adherence and outcomes (time to recovery HR= 0.922 p=0.00; pain intensity B=0.453 p=0.00).
Discussion

The mediating role of adherence to treatment in the relationship between outcome expectancies and time to recovery and pain intensity was explored. Our results suggest that while adherence to treatment does play a role, it is not likely to be the primary pathway that links expectancies to outcomes in this population.

The magnitude of the mediating effects found in this study should be interpreted in the context of the size of the direct effect. The magnitude of this direct effect of treatment outcome expectancies on recovery was relatively small (B=0.04 and HR=1.03); a 0.04 point difference on the 0-10 point pain scale or 3% higher chance on recovery for each point difference on the expectancy scale, respectively. This effect approaches clinical relevance when the difference in expectancy scores between two patients at baseline is about 10 points on the expectancy subscale. Of this effect, 3.3% or 14.2% is due to the fact that patients with higher expectancy scores adhere better to treatment.

Findings of previous studies in other fields correspond with our finding that adherence likely plays a small role, but that outcome expectancies predicted future health outcomes above and beyond the effects of adherence to treatment. A study in patients undergoing heart transplantation showed that outcome expectancies were related to adherence to a complex post-operative medical regimen. But also that outcome expectancies explained a substantial amount of variance in physical health after surgery, even when adherence and pre-operative health were adjusted for. Recently, Stetler studied in an experimental placebo setting whether initial expectancies influence adherence which then influence subsequent expectancies that affect the placebo response. Results of this study showed that stronger expectancies for the outcome predicted a better outcome, but that adherence and later expectations did not mediate this association.

Findings of our study are consistent with several theoretical models that suggest that beliefs about treatment influence health behavior (including adherence to treatment), but only to a limited extent. Based on these theories we would have expected the mediated effect to be somewhat larger. For instance, Bandura’s social cognitive theory proposes that outcome expectancy is one of the most powerful direct influences on health behavior. In our study, post hoc analysis revealed that the relationship between outcome expectancies and adherence was small. Thus, it is likely that this association between outcome expectancies and adherence caused the mediated effect to be smaller than expected. A possible reason for this is that adherence is a complex behavioral process which is influenced by many factors e.g. environmental and organizational factors. In our study it is therefore plausible that a combination of these other (unmeasured) factors had a greater influence on adherence than outcome expectancies. Further, there may be beliefs other than outcome expectancies which played a role in adherence to treatment. For instance if a patient believes there is a great risk of addiction to pain medication then even if he expects there will be a great benefit of taking them he still might not adhere to recommendations.

Previous literature is equivocal regarding the relationship between expectancies and adherence. A recent systematic review on psychosocial predictors of preventive medication adherence found that only 2 out of 9 studies reported a positive association. Other studies have found clear positive relationships between treatment beliefs/expectancies and adherence. It appears these positive findings are often found in studies that have investigated this relationship in treatments in which the patient has to put more effort, e.g. exercise therapy. It may be that adherence is a stronger mediator of the expectancy effect in these types of treatments. It is plausible the relationship between expectancies and adherence may be stronger for behaviors that demand greater effort from the patient as opposed to a simple regimen of taking a couple of tablets each day, which one might do despite the doubt in its effectiveness. Further research however is needed to confirm this hypothesis.

Our findings indicate that pathways other than adherence may be important in the relationship between expectancies and outcomes in our population. Besides behavioral pathways, Barry Flood hypothesized multiple pathways in the relationship between expectancies and outcomes, namely: 1) triggering of a physiological response, 2) conditioning the patient psychologically to observe certain types of outcomes and ignore others 3) changing the understanding of the disease 4) expectancies acting in concert with anxiety (anxious patients are more likely to be sensitive to pain and adverse outcomes). It is likely that multiple pathways simultaneously play a role and interact, and perhaps the dominant pathway varies according to type of treatment or per type of disorder. For our sample that was treated with paracetamol, it may be that a physiological response from high expectancies, for example endogenous opioid expression, also played a major role. Furthermore, besides taking medication, patients in our study were also given general advice and reassurance. Unfortunately, adherence to this advice was not measured in this study. It may be that adherence to the advice given mediates the relationship between expectancies and outcomes more than the adherence to the study drug. For further research it would be interesting to study which pathway or combination of pathways explains most of the relationship between expectancies and outcomes. Further it would be an interesting exercise to compare the importance of pathways between different types of treatments, for instance active versus passive treatments.

Strengths and limitations

Strengths of this study are first of all the large sample size and minimal loss to follow up, which allowed us to perform repeated measurement analyses yielding good precision and a good interpretability of our estimates. Secondly, our results are robust as evidenced by the fact that both the analyses (recovery and pain intensity) show effects in the same direction, however, they differed somewhat in the proportion of the effect mediated by adherence. These differences might be due to differences in outcome measures or analytical differences between the analyses methods or both. Both the statistical methods are quite complementary. The Cox regression analysis with time to recovery as outcome takes into account the fact that not everyone contributed the same person time. However,
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the daily adherence scores had to be condensed to 4 weekly scores (median per week) and the outcome was binary (recovered vs not recovered) which did not take into account the patients decreasing in pain that are not completely recovered yet. For the mixed models analysis daily, continuous adherence and pain intensity scores could be used which enhances the likelihood that subtle effects are picked up. Also adjustment for dependency of scores within one person could be made, which is more likely to reflect the complexity of the real situation. Mixed models analysis however has the disadvantage that it doesn’t take into account censoring. A limitation of this study is that data from observational studies are not optimal for investigating mediation models because reverse causality is still possible, in our study recovery status (or changes in pain intensity) may have influenced adherence as well. Another limitation is that previous treatment and perceived success of previous treatment were not measured and taken into account in the analyses. Potentially, someone with successful previous treatment may have higher expectations if similar treatment is offered again. Also during treatment, experiencing success (i.e. less pain) may lead to having higher expectancies for the remainder of the treatment, and vice versa. However a recent study concluded that for the majority of patients expectancies do not change dramatically during the further duration of treatment39, and therefore we believe that this probably had a limited influence in our study.

Generalizability of our results may be questioned because of the use of trial data. It could be argued that this leads to a selection of patients with high expectancies of pain medication and a relatively high degree of adherence. On the other hand, the chance of receiving placebo may lower expectations and prevents patients with a strong preference and high expectation for medication to participate in the trial. There is some evidence that expectancies for improvement are on average stronger for patients who believe they are receiving active treatment as compared to those who think they are receiving placebo40.

On the basis of this we recommend that placebo-controlled RCTs measure patient beliefs with respect to the credibility of the treatment to which they have been randomized. This would also assist in interpretation of treatment effects.

Finally, in our study adherence was measured using tablet counts, a global self-reported measure and a self-reported medication diary, these methods all revealed similar findings. In this study the medication diaries were used because the diary data were most complete. Although this is a self-reported method which may be drawn to response biases, daily diaries have been found to be more reliable as compared to more global measures of adherence (e.g. recall of average adherence)41. We therefore think we have relatively reliably measured medication adherence.

Conclusion
Adherence to treatment had a small mediating role in the relationship between treatment outcome expectancies and the outcomes pain intensity and time to recovery from acute low back pain in patients treated with paracetamol or placebo paracetamol.

Reference List

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