

Can Daily Self-Assessment Induce a Learning Effect Mitigating Pain Evaluation Error in Randomized Clinical Trials?

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Introduction and Motivation

Assessment of patients' pain represents the majority of efficacy endpoints in osteoarthritis (OA) randomized clinical trials (RCTs). The intrinsic subjectivity of pain may render this assessment difficult and could lead to a small evaluation error. Mitigation of this error could therefore help to increase the quality of study data.

The main objective of this analysis was to estimate the pain evaluation variability and its evolution over time during the course of a clinical trial. In particular, we assessed the learning effect associated with a daily repetition of the pain self-assessment on the evaluation error made by the subjects.

Overall, this analysis confirms the importance of a pre-baseline run-in period for the subjects to learn how to rate their own pain.

Study Design and Measures

Study Design:

- Single Osteoarthritis study involving 64 patients (ECT 2017-001028-23);
- 3 months of blinded placebo treatment b.i.d. as add-on therapy;

Daily measure of pain scores:

- Average Pain Score (APS);
- Worst Pain Score (WPS);
- Lowest Pain Score (LPS).

Monthly measure of the Brief Pain Inventory (BPI) including:

- APS item of the BPI (BPI-APS);
- WPS item of the BPI (BPI-WPS);
- LPS item of the BPI (BPI-LPS);
- Total score of BPI-Severity (BPI-Sev).

Modeling the Evaluation Error

We assumed that the recorded APS could be modeled as a signal disrupted by an error, the evaluation error:

$$APS = Signal + \epsilon$$

The importance of the evaluation error could be estimated using the estimator of its variance:

$$Var(\epsilon_i) = Var(APS_i) - Cov(APS_i, APS_{i+1})$$

where ϵ_i is the error at day i , and APS_i is the APS recorded at day i .

Direct and Indirect Measures of Evaluation Error

Direct

The evaluation error was computed for all the pain assessments at each day (or visit).

Indirect

We evaluated the evolution of the consistency in the pain assessment by computing:

- the auto-correlation* of the pain scores from one day to the next;
- the correlation between* different pain measures.

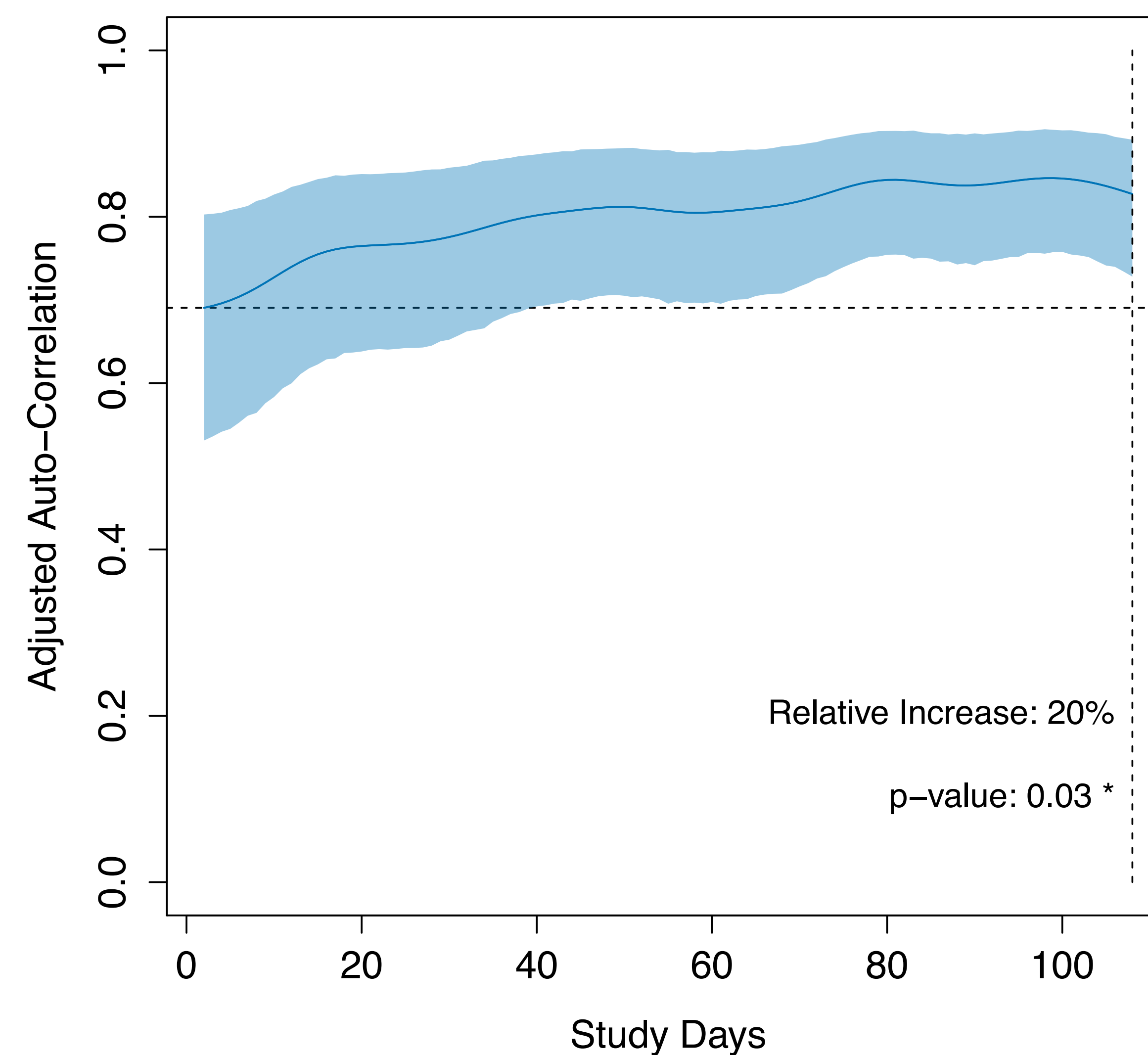
* These correlations were adjusted to only consider an increase of the correlation due to a decrease of the error.

Reduction of the Error of the Daily APS

The results for the daily APS showed:

- An **important reduction (> 50%) of the evaluation error** between the beginning and the end of the study.
- A **significant increase (>20%) of the adjusted auto-correlation** as a consequence.

Figure 1: Evolution of the Adjusted Auto-Correlation of the Daily APS During the Study



Error and Consistency of all the Endpoints

Univariate Analysis

The daily measures and the BPI-Sev presented a significant increase of their adjusted auto-correlation during the study due to a decrease of their Evaluation Error.

Table 1: Significativity of the Increase of Adjusted Auto-Correlation and Decrease of the Error During the Study

	Measures	APS	WPS	LPS	BPI-Sev
	P-Value	<0.05	<0.1	<0.01	<0.05
Increase of Auto-Correlation		>20%	>10%	>10%	>20%
Decrease of Error		>50%	>50%	>50%	>75%

Bivariate Analysis

The adjusted correlations between the daily measures and the BPI scores (BPI-Sev and the corresponding item in the BPI) increased during the study.

Table 2: Significativity of the Increase of Adjusted Correlation Between Efficacy Measures

	BPI-XPS	BPI Severity
Weekly APS	33% (p-val < 0.05)	37% (p-val < 0.01)
Weekly WPS	36% (p-val < 0.01)	18% (p-val > 0.1)
Weekly LPS	40% (p-val < 0.001)	32% (p-val < 0.05)

* BPI-XPS : BPI-APS for APS, BPI-WPS for WPS, and BPI-LPS for LPS.

Conclusion

The results presented here demonstrate

- A reduction over time of the evaluation error of daily pain measurements;
- A decrease in the evaluation error of the other pain assessments (e.g., BPI-Severity);
- An increase of the correlation between different endpoints assessing pain.

This would suggest that the learning effect by a daily self-recording of pain would help the subjects to assess their pain consistently.

This emphasizes the importance of a daily pain evaluation, in particular in a run-in pre-baseline period allowing:

- A reduction of the evaluation error;
- A better estimation of the placebo and treatment responses;
- Without excluding any subjects at baseline.