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Opioid abusers' ability to differentiate an opioid from placebo in laboratory challenge testing*

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Abstract

Background—Abuse liability assessments influence drug development, federal regulation, and clinical care. One suggested procedure to reduce variability of assessments is a qualification phase, which assesses whether study applicants adequately distinguish active drug from placebo; applicants failing to make this distinction are disqualified. The present analyses assessed differences between qualification phase qualifiers and non-qualifiers.

Methods—Data were collected from 23 completers of the qualification phase of an abuse liability study. Opioid abusing participants received 30 mg oxycodone and placebo orally on separate days, and were characterized as qualifiers (vs. non-qualifiers) if their peak visual analog scale liking rating for oxycodone was at least 20 points higher than placebo's peak rating. Groups were compared on demographic characteristics, drug history, and physiologic, subject and observer ratings.

Results—61% of participants were qualifiers and 39% were non-qualifiers. Groups had similar demographic characteristics, drug use histories, and pupillary constriction responses. However, unlike qualifiers, non-qualifiers had an exaggerated placebo response for the liking score ($p=0.03$) and an attenuated oxycodone response for the liking score ($p<.0001$). Non-qualifiers' failure to differentiate oxycodone versus placebo was evident for subject and observer ratings.

Conclusion—Different subjective responses to identical stimuli support the use of a qualification phase in abuse liability assessments. Further research should explore objective measures that may better account for these differences, determine optimal qualification criteria, and explore the developmental course of drug use. This study also documents certain opioid abusers fail to differentiate 30 mg of oxycodone from placebo, a phenomenon deserving further study.

Keywords

abuse liability; qualification; opioids; placebo; discrimination

*Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

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1. INTRODUCTION

The Food and Drug Administration (FDA) considers an assessment profile to determine the proper scheduling of a new drug. This profile includes pre-clinical, human subject, pharmacokinetic, and overdose data (Schoedel and Sellers, 2008). Human subject data include abuse liability testing. Draft FDA guidelines have been created for investigators and reviewed in previous publications (e.g., Balster and Bigelow, 2003); a recent revision provides specific abuse liability procedure guidelines (CDER, 2010). Without standardized procedures, variation in abuse liability testing could occur, which could introduce variability in abuse liability testing results.

Methodology recommendations exist which could improve abuse liability testing (McColl and Sellers, 2006). One recommendation is the use of a qualification phase, intended to ensure that each study participant can adequately differentiate the test drug from placebo (Schoedel and Sellers, 2008). Abuse liability assessment studies ideally enroll experienced, non treatment-seeking drug abusers (Griffiths et al., 2003). Expert consensus, as reflected in guideline recommendations, identifies experienced drug abusers as more likely to provide meaningful, lower false positive ratings, and lower false negative results than non-drug-abusers. Once participants are enrolled, physiologic, subjective and observer ratings are gathered after randomized, within-subject administration of a placebo and a compound of known abuse liability within a class resembling the compound under investigation. Qualification phases use these ratings to confirm that each participant adequately distinguishes active drug from placebo before proceeding into the main study.

This paper presents results from the qualification phase of an abuse liability study. These analyses aimed to determine the distinguishing characteristics between qualifying and non-qualifying participants with active opioid abuse histories, and to determine the consistency of non-qualifying participants' drug responses across subjective, observer, and physiological measures.

2. METHODS

2.1 Participants

26 residential research unit participants entered into the two-day qualification phase of an abuse liability study (Tompkins et al., 2010). Participants were non-dependent polydrug abusers with recent illicit opioid use, but no more than 20 days of use within the thirty days preceding enrollment. Participants were between the ages of 18–65 and in good health (determined by medical history and physical examination). Women were either postmenopausal or on birth control. Applicant exclusion occurred in cases of study condition non-compliance, pregnancy, opioid withdrawal signs, allergies to opioids, prescription medication use within 7 days of study enrollment, or over-the counter medication use within 2 days of study enrollment. Participants provided negative urine drug tests, urine pregnancy tests, and blood alcohol levels before enrollment. Participants refrained from alcohol and grapefruit/grapefruit juice twenty-four hours before enrollment, refrained from caffeine and xanthine products during the study, and abstained from nicotine beginning 1 hour before test dosing and until 4 hours after study drug dosing each day.

2.2 Study Procedure

The main residential abuse liability study used a randomized, seven-way crossover, double blind, active and placebo controlled design (Tompkins et al., 2010). The primary study goal was to compare subjective effects of a novel opioid agonist/antagonist combination product to the subjective effects of oxycodone alone. Secondary goals were to determine safety and physiologic profiles of single doses of this novel compound. The present report provides

analyses of data from the qualification-phase. Each participant received oral challenge doses of 30 mg of oxycodone or placebo on two separate days in a double-blinded, randomized fashion.

2.3 Measures

Demographic data (age; gender; race; weight; height; body mass index [BMI]; past drug use [30-day and total lifetime years] of opioids, cocaine, benzodiazepines, alcohol, and cannabis) were collected. Physiologic measurements (pupil diameter and vital signs [heart rate; blood pressure; respiratory rate; oxygen saturation]) were recorded 30 minutes before drug administration, 30 minutes after drug administration, and at 30 minutes intervals thereafter, up to 3.5 hours. Pupil size was chosen as a physiologic measure because it is a sensitive index of opioid agonist effects (Murray et al. 1983). Subject and observer ratings were recorded at each timepoint. Subject ratings included opioid agonist effects (itchy skin; turning of stomach; nodding; relaxed; pleasant sick; talkative; heavy or sluggish feeling; dry mouth; active; carefree; drunken; good mood; energetic) and antagonist effects (sleepy; flushing; sweating; watery eyes; runny nose; chills; shaky; gooseflesh; restless; agitated). Observer ratings (nodding; scratchy; magnitude of drug effect; restlessness; talkative; sleep/sedated; energetic; irritable; friendly; vomiting; drunken; nervous) were collected. Ratings were on 5-point scales with zero indicating “not at all” and four indicating “extremely.” Subjects also completed 100-point visual analog scales (VAS) ratings (any drug effect; high; good effects; bad effects; liking; sick) at post-dosing time points. To qualify for the main abuse liability phase of the study, a participant’s peak VAS liking rating for the active drug needed to be at least 20 points higher than the corresponding rating for placebo.

2.4 Data Analysis

Categorical and continuous demographic data were compared between the two groups using Fisher’s exact tests and t-tests respectively. Time-course analyses were conducted which included between drug condition and between group t-test comparisons of the average ratings at each timepoint and times-to-peak for each variable. Dose agonist effects were described calculating the sum of the subject agonist ratings and the sum of observer agonist ratings at each timepoint.

Peak agonist effects were described using the peak change from baseline for each measure; however, as there was no baseline for VAS scales, the peak VAS rating was used for these measures. The peak change for each measure was compared between drug conditions and between groups using a repeated measures regression model with planned comparisons. ANCOVAs were then performed on these comparisons using lifetime and 30-day opioid use as covariates. An ANOVA was also performed to determine the order effect of drug administration (oxycodone on the first qualification day versus placebo) on the peak change for pupil size, liking, subject agonist sum, and observer agonist sum.

3. RESULTS

3.1 Participant Characterstics

Three of the initial 26 enrollees were disqualified; one was unable to complete the qualification phase due to acute health problems and two were disqualified due to missing data. Of the remaining 23 participants, those with an oxycodone liking score 20 points or greater than their placebo liking score were designated “qualifiers” (n=14); others were designated “non-qualifiers” (n=9). The 20-point difference was pre-specified and was based upon a review of historical data from other studies that had examined the relative magnitude of effects produced by mu agonist opioids.

Both groups were predominantly males (89% of non-qualifiers, 93% of qualifiers [p=1.0]). Groups reported similar demographics and 30-day drug use histories. There was a statistical trend towards qualifiers having longer lifetime drug use histories[1]. However, the pattern of ANCOVAs performed using lifetime and 30-day opioid use as covariates was generally the same as similar analyses that did not account for these covariates. Of the 28 comparisons that were significant (Table 1) in the original analysis, four of the 28 changed to trends to significance (i.e., were initially $p<0.05$, and now <0.10) in the re-analysis. Given these findings, opioid use differences did not appear to have a significant effect on pupillary constriction responses and ratings outcomes.

3.2 Time Course

Before dosing, both groups had similar baseline pupil diameters, vital signs, and subject and observer agonist ratings (VAS measures were not assessed at baseline). The qualifier's time course analysis (right column of figure 1) demonstrated a significantly greater response for active versus placebo conditions for pupil size, VAS liking rating, subject agonist, and observer agonist ratings at all time points after dose administration, except at 0.5 hours for the subject agonist ratings.

Both groups demonstrated greater pupil constriction in the active versus placebo condition at all post-drug time points (figure 1, top panels), and had similar vital sign values in both drug session conditions at all timepoints. Of the physiological indices, only pupil diameter showed sufficient effect to warrant further comparison of the drug-versus-placebo response of qualifiers and non-qualifiers. Despite similar physiological responses, the non-qualifiers differed markedly from qualifiers in subjective and behavioral responses as assessed with the VAS liking rating, subject agonist, and observer agonist ratings (Drug x Group interactions for these measures were statistically significant: $p<0.0001$, $p=0.019$, and $p=0.002$, respectively). At no timepoint did non-qualifiers' drug response for any of these measures significantly exceed their placebo response.

3.3 Peak Values

Both groups had similar peak pupil constriction responses in the active oxycodone condition and a similar absence of pupil constriction in the placebo condition (table 1). Despite a similar objective physiological response, non-qualifiers had an exaggerated subjective response to placebo and an attenuated subjective response to oxycodone. Non-qualifiers' peak VAS liking rating of placebo was 26 points higher than that of qualifiers (Table 1; $p=0.031$); and conversely, their peak VAS liking rating of oxycodone was 58 points lower than that of qualifiers (table 1; $p<0.0001$). Non-qualifiers also had lower peak oxycodone change from baseline ratings than qualifiers on both the subject agonist and observer agonist ratings (table 1; 5 points lower, $p=0.024$; and 3 points lower, $p=0.01$, respectively). There was no effect of order for drug administration on the selected variables.

4. DISCUSSION

A large proportion (39%) of qualification phase completers failed to differentiate between oxycodone and placebo based on the criteria of a 20-point difference on the VAS liking ratings. This difference appears to result from both an attenuated oxycodone response but also an exaggerated response to the placebo condition. A previous study that conducted abuse liability qualification-phases with different criteria demonstrated an identical failure rate (39%; Busto et al., 1999) while another study with more stringent qualification criteria

[1]Supplementary demographics table can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

demonstrated a substantial failure rate (26%; Setnick et. al, 2011). These rates of failure to differentiate suggest that opioid abuse liability studies should include qualification-phase verification of participants' ability to differentiate adequately between active drug and placebo, even in target groups that have a history of opioid use disorders. Excluding non-qualifiers from abuse liability evaluations may improve the sensitivity and/or validity of testing.

The failure to differentiate was not just a failure to answer questionnaires properly; observers similarly failed to note intoxication differences between active drug and placebo. Observers necessarily rely on the behavior and appearance of participants in making their assessments. Observer ratings confirm that non-qualifiers did not appear differentially intoxicated in the active versus placebo sessions. The differential drug-versus-placebo response of non-qualifiers was limited to the study's subjective and behavioral measures; physiological responses did not differentiate the groups. Future research may further refine the specific measures and cut-off criteria that are most sensitive and cost-effective for qualification purposes.

The different subjective responses of qualifiers and non-qualifiers to the oxycodone condition highlight the fact that time courses for developing tolerance to subjective vs. physiologic [pupil diameter] effects can vary. Therefore, tolerance cannot be categorically eliminated as an explanation for the reported findings. The similarity of the two groups' drug use histories and pupillary constriction responses to oxycodone and the exaggerated placebo response in non-qualifiers raises the likelihood of a multi-factorial explanatory model. In addition to tolerance, non-qualifier responses may also be influenced by non-pharmacological factors such as personality and the environment, factors that have been noted to potentially influence other effects of opioids (Mintzer and Stitzer, 2002; Mintzer et al., 2005). Future research on this phenomenon may want to examine such factors as cytochrome P450 activity (Stamer et al., 2005) and pain sensitivity (Tompkins and Campbell, 2011), and certainly needs to explore the etiology and development of failure to differentiate active drug from placebo, whether the failure to differentiate is trait-like or state-like (i.e., persistent across time and circumstances, or fluctuating with current circumstances).

Beyond implications to abuse liability qualification phase methodology, the present study documents a phenomenon deserving study in its own right: the failure of a substantial proportion of drug abusers to differentiate active drug from placebo. This phenomenon is not limited to opioids. Evidence exists that some drug abusers fail to differentiate between placebo and amphetamine (Shram et al., 2011; Johanson et al., 1998), and similarly sedatives (DeWit and Griffiths, 1991). Future studies may examine other drug classes (e.g., cannabinoids) for this phenomenon and attempt to determine if the current results would be replicated in prescription opioid abusers (vs. the mixed prescription opioid and heroin users in the present study).

Though the present analyses focused on persons unable to distinguish active drug from placebo, evidence exists that many drug users are able to make this distinction under training conditions (e.g., human drug discrimination studies; for example, see: Preston and Bigelow, 2000). These drug discrimination study findings may reflect participants trained to distinguish conditions. This study highlights how even experienced drug users may not be able to discriminate active drug from placebo. Further research on factors that distinguish qualifiers from non-qualifiers, and the etiologies of these group differences may be valuable and enlightening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend. 2003; 70:S13–S40. [PubMed: 12759195]

Busto UE, Zawertailo LA, Kaplan HL, Sellers EM. Identifying appropriate subjects for abuse liability studies using prestudy pharmacological testing. Can J Clin Pharmacol. 1999; 6:103–110. [PubMed: 10519736]

Center for Drug Evaluation and Research (CDER). Guidance for Industry: Assessment of Abuse Potential of Drugs. Center for Drug Evaluation and Research, Food and Drug Administration; Rockville, Maryland 20852: 2010. p. 13-14.

De Wit H, Griffiths R. Testing the abuse liability of anxiolytic and hypnotic drugs in humans. Drug Alcohol Depend. 1991; 28:83–111. [PubMed: 1679388]

Duke AN, Bigelow GE, Lanier RK, Strain EC. Discriminative stimulus effects of tramadol in humans. J Pharmacol Exp Ther. 2011; 338:255–262. [PubMed: 21467190]

Griffiths RR, Bigelow GE, Ator NA. Principles of initial experimental drug abuse liability assessment in humans. Drug Alcohol Depend. 2003; 70:S41–S54. [PubMed: 12759196]

Johanson C, Preston K. The influence of an instruction on the stimulus effects of drugs in humans. Exp Clin Psychopharmacol. 1998; 6:427–432. [PubMed: 9861557]

McColl S, Sellers EM. Research design strategies to evaluate the impact of formulations on abuse liability. Drug Alcohol Depend. 2006; 83:S52–S62. [PubMed: 16554125]

Mintzer MZ, Copersino ML, Stitzer ML. Opioid abuse and cognitive performance. Drug Alcohol Depend. 2005; 78:225–230. [PubMed: 15845327]

Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend. 2002; 67:41–51. [PubMed: 12062778]

Murray RB, Adler MW, Korczyn AD. The pupillary effects of oploids. Life Sci. 1983; 33:495–509. [PubMed: 6136886]

Preston KL, Bigelow GE. Effects of agonist-antagonist opioids in humans trained in a hydromorphone/not hydromorphone discrimination. J Pharmacol Exp Ther. 2000; 295:114–124. [PubMed: 10991968]

Schoedel KA, Sellers EM. Assessing abuse liability during drug development: changing standards and expectations. Clin Pharmacol Ther. 2008; 83:622–626. [PubMed: 18212799]

Setnik B, Roland CL, Cleveland JM, Webster L. The abuse potential of Remoxy(®), an extended-release formulation of oxycodone, compared with immediate-and extended-release oxycodone. Pain Med. 2011; 12:618–31. [PubMed: 21463474]

Shram MJ, Sellers EM, Romach MK. Oral ketamine as a positive control in human abuse potential studies. Drug Alcohol Depend. 2011; 114:185–193. [PubMed: 21109365]

Stamer UM, Bayerer B, Stüber F. Genetics and variability in opioid response. Eur J Pain. 2005; 9:101–104. [PubMed: 15737794]

Tompkins D, Campbell C. Opioid-induced hyperalgesia: clinically relevant or extraneous research phenomenon? Curr Pain Headache Rep. 2011; 15:129–136. [PubMed: 21225380]

Tompkins DA, Lanier RK, Harrison JA, Strain EC, Bigelow GE. Human abuse liability assessment of oxycodone combined with ultra-low-dose naltrexone. Psychopharmacol (Berl). 2010; 210:471–480.

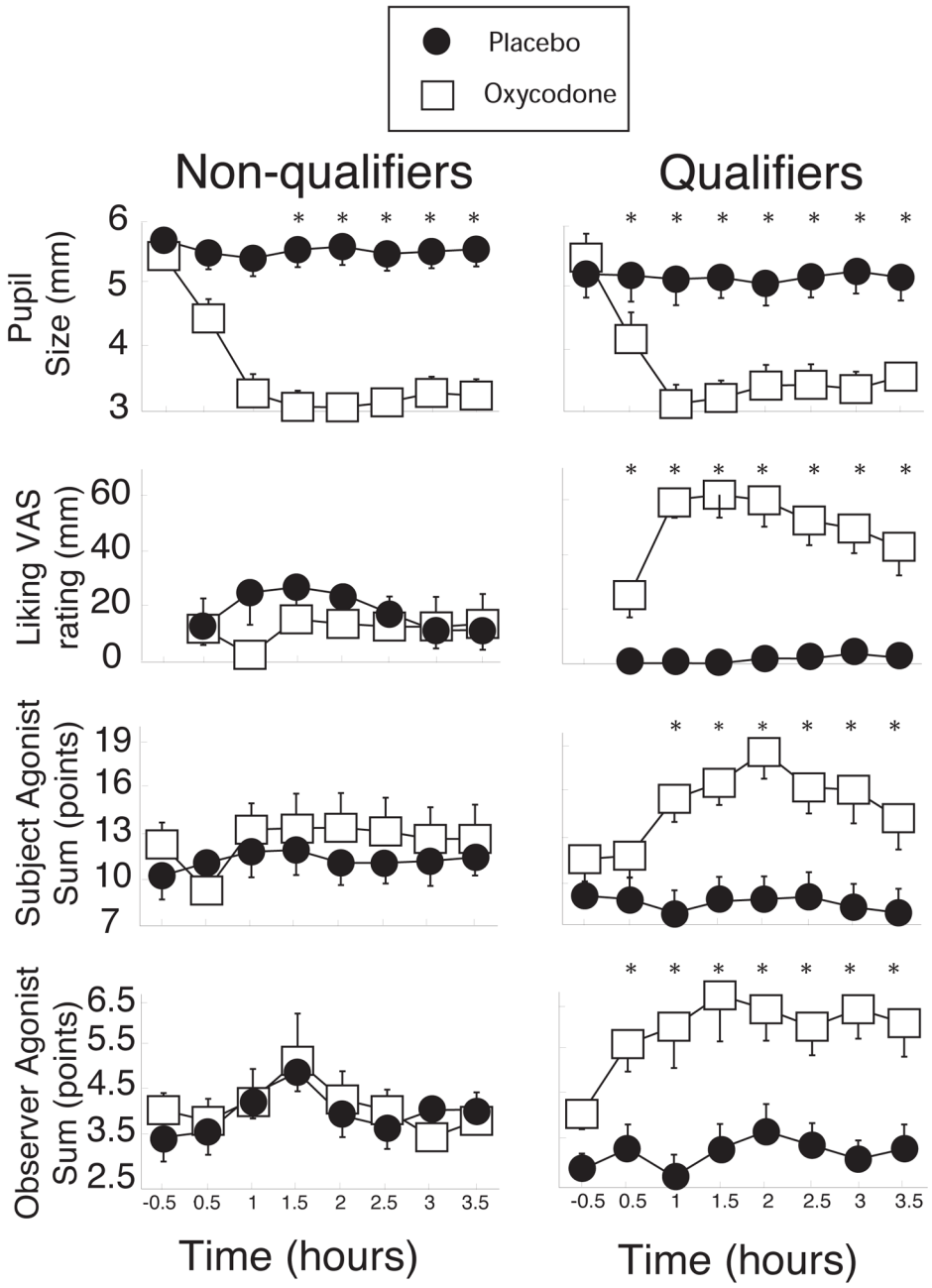

Figure 1.
Non-qualifier and qualifier time-course graphs of the oxycodone and placebo conditions for the main variables assessed in the study's qualification phase. Asterisks (*) signify within-group difference between oxycodone and placebo conditions.

Table 1

Baseline and peak values with planned comparison statistics

	Mean Values (SEM)				Planned Comparisons (p values)			
	Non-qualifiers		Qualifiers		Placebo vs. Active			
Measure:	**Placebo**	**Active**	**Placebo**	**Active**	**Non-qualifiers**	**Qualifiers**	**Placebo vs. Placebo**	**Active vs. Active**
Baseline								
Pupil diameter (mm)	5.2 (0.4)	5.5 (0.4)	5.7 (0.3)	5.5(0.4)	0.348	0.274	0.352	0.963
Subject Agonist Sum	10.0 (1.4)	11.9 (1.3)	8.8 (1.5)	11.1 (1.4)	0.246	0.086	0.570	0.701
Observer Agonist Sum	3.6 (0.5)	4.1 (0.4)	2.9 (0.3)	4.0 (0.3)	0.301	**0.013**	0.202	0.8936
Peak values								
Pupil diameter (mm)*	−0.4 (0.2)	−2.6 (0.4)	−0.6 (0.1)	−2.6 (0.3)	**<0.0001**	**<0.0001**	0.612	0.963
Subject Agonist Sum*	2.6 (1.8)	2.3 (1.2)	0.9 (0.7)	7.4 (1.7)	0.916	**0.001**	0.438	**0.024**
Observer Agonist Sum*	1.4 (0.5)	1.4 (0.8)	1.4 (0.4)	4.2 (0.8)	1.000	**0.002**	0.987	**0.010**
Liking score^{v}	30.1 (12.1)	14.7 (10.8)	3.7 (3.5)	72.3 (7.0)	0.134	**<0.0001**	**0.031**	**<0.0001**
Drug Effect^{v}	24.3 (8.6)	11.9 (6.6)	3.2 (3.1)	63.4 (7.9)	0.221	**<0.0001**	**0.039**	**<0.0001**
High^{v}	23.6 (8.9)	11.2 (7.4)	3.4 (3.2)	62.4 (8.2)	0.246	**<0.0001**	0.061	**<0.0001**
Good Effect^{v}	31.6 (12.6)	14.4 (10.8)	3.4 (3.4)	70.9 (6.7)	0.102	**<0.0001**	**0.022**	**<0.0001**
Bad Effect^{v}	1.6 (0.8)	0.9 (0.4)	0.1 (0.1)	14.0 (7.3)	0.928	**0.027**	0.831	0.058
Sick^{v}	0.8 (0.7)	0.4 (0.2)	0.3 (0.2)	10.0 (5.1)	0.948	**0.024**	0.915	**0.046**
Time to peak (hrs)								
Pupil diameter	1.9 (0.3)	1.3 (0.2)	1.8 (0.3)	1.8 (0.2)	0.192	0.831	0.632	0.292
Subject Agonist Sum	1.7 (0.4)	1.4 (0.2)	1.2 (0.2)	1.9 (0.2)	0.501	**0.012**	0.185	0.221
Observer Agonist Sum	0.9 (0.2)	1.6 (0.4)	1.7 (0.3)	1.7 (0.3)	0.233	1.000	0.078	0.706
VAS liking^{v}	1.0 (0.3)	1.6 (0.4)	0.9 (0.2)	1.6 (0.2)	0.227	**0.048**	0.706	0.891
Drug Effect^{v}	1.2 (0.3)	1.1 (0.3)	0.7 (0.2)	1.7 (0.2)	0.710	**0.010**	0.144	0.119
High^{v}	1.0 (0.3)	1.1 (0.3)	0.8 (0.2)	1.7 (0.2)	0.900	**0.023**	0.625	0.098
Good Effect^{v}	1.0 (0.3)	1.2 (0.4)	0.7 (0.2)	1.8 (0.2)	0.596	**0.002**	0.356	0.093
Bad Effect^{v}	0.6 (0.1)	0.7 (0.1)	0.5 (0.0)	1.2 (0.2)	0.683	**0.007**	0.759	0.073
Sick^{v}	0.7 (0.2)	0.9 (0.3)	0.7 (0.1)	1.5 (0.3)	0.617	**0.010**	0.983	0.138

v indicates Visual Analog Scale;

* indicates peak change from baseline