

## Critical Review

# Assay Sensitivity of Pain Intensity Versus Pain Relief in Acute Pain Clinical Trials: ACTION Systematic Review and Meta-Analysis

Neil Singla,<sup>\*</sup> Matthew Hunsinger,<sup>†</sup> Phoebe D. Chang,<sup>\*</sup> Michael P. McDermott,<sup>‡</sup>  
Amit K. Chowdhry,<sup>‡</sup> Paul J. Desjardins,<sup>§</sup> Dennis C. Turk,<sup>¶</sup> and Robert H. Dworkin<sup>||</sup>

<sup>\*</sup>Lotus Clinical Research, Huntington Hospital, Department of Anesthesiology, Pasadena, California.

<sup>†</sup>School of Professional Psychology, Pacific University, Hillsboro, Oregon.

Departments of <sup>‡</sup>Biostatistics and Computational Biology and <sup>||</sup>Anesthesiology, University of Rochester, Rochester, New York.

<sup>§</sup>Desjardins Associates, LLC, Maplewood, New Jersey.

<sup>¶</sup>Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington.

**Abstract:** The magnitude of the effect size of an analgesic intervention can be influenced by several factors, including research design. A key design component is the choice of the primary endpoint. The purpose of this meta-analysis was to compare the assay sensitivity of 2 efficacy paradigms: pain intensity (calculated using summed pain intensity difference [SPID]) and pain relief (calculated using total pain relief [TOTPAR]). A systematic review of the literature was performed to identify acute pain studies that calculated both SPIDs and TOTPARs within the same study. Studies were included in this review if they were randomized, double-blind, placebo-controlled investigations involving medications for post-surgical acute pain and if enough data were provided to calculate TOTPAR and SPID standardized effect sizes. Based on a meta-analysis of 45 studies, the mean standardized effect size for TOTPAR (1.13) was .11 higher than that for SPID (1.02;  $P = .01$ ). Mixed-effects meta-regression analyses found no significant associations between the TOTPAR – SPID difference in standardized effect size and trial design characteristics. Results from this review suggest that for acute pain studies, utilizing TOTPAR to assess pain relief may be more sensitive to treatment effects than utilizing SPID to assess pain intensity.

**Perspective:** The results of this meta-analysis suggest that TOTPAR may be more sensitive to treatment effects than SPIDs are in analgesic trials examining acute pain. We found that standardized effect sizes were higher for TOTPAR compared to SPIDs.

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**Key words:** Acute pain, postoperative pain, pain intensity, pain relief, summed pain intensity difference, total pain relief, methodology.

Over the past 20 years, many of the drugs that have progressed to late-phase development have been reformulations of opioids or other molecules

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Address reprint requests to Neil Singla, MD, Lotus Clinical Research, 100 W. California Blvd, Unit 25, Pasadena, CA 91105. E-mail: [neil@lotuscr.com](mailto:neil@lotuscr.com)  
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with known analgesic efficacy.<sup>32,36</sup> Since the mid-1990s, however, there has been a significant rise in the percentage of negative analgesic clinical investigations.<sup>16,17,35,64,65</sup> If one assumes that reformulated drugs should generally demonstrate efficacy in phase 3, then why should so many late-phase analgesic investigations have negative results? The precise answer is a matter of ongoing debate, but it is clear that in order for any analgesic investigation to yield a statistically significant treatment benefit, it must 1) test an efficacious product, 2) be properly designed, and 3) be conducted with minimal experimental error.

Acute pain analgesic clinical trials traditionally use 2 different efficacy paradigms, pain intensity and pain relief, to assess treatment effect. The results of a systematic review of acute pain clinical trial methods concluded

that summed pain intensity difference (SPID) and total pain relief (TOTPAR) scores<sup>74</sup> were comparable in their ability to detect analgesic treatment effects.<sup>4</sup> However, this study examined only trials of single doses of aspirin, paracetamol, and ibuprofen, and there were only 3 trials for which SPID and TOTPAR could be compared. It is, therefore, currently unclear whether these approaches to assessing efficacy in acute pain trials are generally comparable or whether one of them has greater assay sensitivity to detect treatment effects. For this reason, decisions about the use of these measures are generally made based on expert opinion rather than on empirical evidence (data).

Because of this uncertainty, many acute pain clinical trials utilize both TOTPAR and SPID. The availability of multiple studies that assessed pain outcomes utilizing different paradigms (TOTPAR and SPID) at the same time provides an opportunity to examine which paradigm (pain relief or pain intensity) is more sensitive to treatment effects.

## Methods

### Data Sources

A systematic electronic search of MEDLINE and the Cochrane Library database was performed by the first and third authors (N.S. and P.D.C.) to identify randomized, double-blind, placebo-controlled clinical trials of analgesics for treatment of acute postoperative pain. The detailed search strategy included the following subject headings and MeSH terms: "acute pain," "randomized," "placebo controlled," "postoperative," "analgesics in adults." The resulting list was intersected with the following group of terms: "pain intensity," "pain assessment," "SPID," "pain relief," and "TOTPAR." Reference lists, meta-analyses, U.S. Food and Drug Administration summary basis of approvals, and clinical trial register databases, including [ClinicalTrials.gov](http://ClinicalTrials.gov), of relevant studies were also manually screened for quantitative data. Titles and abstracts ranging from January 1999 to September 2013 were independently reviewed by the first and third authors (N.S. and P.D.C.) to determine whether each trial met eligibility criteria.

### Inclusion and Exclusion Criteria

For inclusion, trials had to be randomized and double-blind with a placebo control group; include participants who suffered from acute postoperative pain of moderate to severe intensity; and measure both pain relief and pain intensity, assessed by TOTPAR and SPID, respectively, at the same time point. The pain measurement scales accepted for the calculation of TOTPAR were an ordinal pain relief scale (eg, none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4) or a continuous visual analog scale with the ends labeled as "no relief" and "complete relief" and no intermediate divisions or descriptive terms. For SPID, the accepted scales were an ordinal pain intensity scale such as the numerical rating scale (eg, 0 = no pain; 10 = worst pain imaginable) or a visual analog scale with the ends labeled "no pain"

and "worst pain imaginable" and no intermediate divisions or descriptive terms. In almost all of the studies, the TOTPAR and SPID data used for our calculations were the prespecified primary or co-primary endpoints. In all cases, the TOTPAR and SPID data used to calculate standard effect sizes (SEs) were from time points after the first administration of study treatment but before the second administration (if multiple doses of study treatment were administered). Publications had to be written in English, subjects had to be 16 years of age or older, and each treatment group in the study had to include at least 10 subjects. Studies were excluded if insufficient information was presented to calculate effect sizes, that is, studies that provided only group means without providing standard deviations or quantities from which standard deviations could be derived (eg, confidence intervals or t-statistics). Other studies that were excluded were those that used active comparators as controls instead of placebos, those that used devices to treat pain, and those that did not examine postoperative acute pain. Even though we did not include the outcome of the trial as an inclusion criterion, our criteria resulted in a pool of articles that did not include any negative trials, possibly because of a bias toward publishing positive clinical trials in medical research.<sup>15,18,25,33,66,67</sup>

### Data Synthesis

Data from the original reports were extracted by the second and third authors (M.H. and P.D.C.), and the following information was coded: number of patients per treatment arm, means and standard deviations for SPID and TOTPAR in each study arm, total number of randomized patients in the trial, surgical procedure, methods of pain measurement, trial sponsor, drug type, number of doses, and time from randomization until the endpoint was measured.

Quantitative data from trials where TOTPAR and SPID data were collected at the same time points were used to calculate SEs. When there were multiple treatment groups with varying dose levels, we chose the treatment group with the highest dose. The SEs were defined as the ratio of the treatment effect (mean value in treatment group minus mean value in control group) to the pooled standard deviation of the outcome variable. For each study, a single time point after the administration of the first dose of study medication, but before the second dose of study medication, was selected. The earliest time point that contained both SPID and TOTPAR data was used. An SE was calculated at that time point for both SPID and TOTPAR.

For trials that met all eligibility criteria but did not include standard deviations for the treatment and control groups ( $n = 4$ ), standard deviations were calculated based on other information provided in the trial. In 3 trials, standard deviations were calculated for the treatment and control groups based on the standard errors reported for each group. For 1 trial, the pooled standard deviation was calculated based on the reported  $P$  value from an independent samples t-test along with the group means and group sample sizes.

## Statistical Analysis

The parameter of interest was the TOTPAR – SPID difference in SES. Because the data on the TOTPAR and the SPID were paired (measured in the same subjects), the standard error of the estimated TOTPAR – SPID difference in SES depends on the correlation between the TOTPAR and the SPID.<sup>27</sup> In the absence of the individual-level data from each trial, this correlation cannot be estimated. Therefore, formal analyses were performed separately for a range of plausible correlations between the TOTPAR and SPID, specifically, .35 to .65. Based on the estimates and standard errors of the TOTPAR – SPID difference in SES from each study, we performed a random-effects meta-analysis<sup>73</sup> using the “meta” package in R (R Foundation for Statistical Computing, Vienna, Austria), which employs the DerSimonian and Laird estimator of the between-study variance.<sup>10</sup>

Mixed effects meta-regression analyses<sup>73</sup> were performed to investigate whether the TOTPAR – SPID difference in SES was associated with selected trial characteristics. The trial characteristics investigated included procedure type (dental, nondental), the number of subjects randomized in the trial, number of doses planned (single, multiple), time from randomization until the endpoint was measured, and drug type (opioid/tramadol, acetaminophen/nonsteroidal anti-inflammatory drugs). These analyses were performed using the “rma.mv” function in the R package “metaphor,” with each trial characteristic as the independent variable and the TOTPAR – SPID difference in SES as the dependent variable.

## Results

Three hundred fifty-one reports were identified from our initial electronic search, of which 139 were excluded because they were duplicates or reviews of studies. Ninety-eight original articles were also excluded because they did not report both SPID and TOTPAR pain outcomes. After excluding studies that failed to meet other eligibility criteria, 45 studies were selected for the meta-analysis (Fig 1 and Table 1).

Of the 45 studies included in our review, 29 (64%) examined subjects having dental surgery, 7 (16%) examined subjects undergoing a bunionectomy, and 9 (20%) examined subjects undergoing other kinds of procedures. Thirty-three trials (73%) were sponsored by industry (eg, pharmaceutical companies), 2 trials (4%) had a nonindustry sponsor (eg, a government agency), and 10 trials (22%) did not report sponsorship of any kind. In terms of drug type, 29 trials (64%) administered acetaminophen or some type of nonsteroidal anti-inflammatory drug, and 16 trials (36%) administered an opioid or tramadol. Forty trials (89%) were single-dose studies, and 4 (9%) were multiple-dose studies (in one trial it was unclear whether only one or multiple doses were administered). The mean randomized sample size was 171 with a standard deviation of 94 (range = 36–540); and the mean time until endpoint was 11.8 hours with a standard deviation of 10.2 hours (range = 6–48 hours).

The primary results of the meta-analysis are presented in Table 2. The estimated mean SES was 1.13 for TOTPAR and 1.02 for SPID. The estimated mean difference between the TOTPAR and SPID SESs of .11 was statistically significant ( $P = .01$ ) regardless of the assumed value of the correlation between the TOTPAR and SPID (in the plausible range of .35–.65).

The mixed effects meta-regression analyses did not detect any significant associations between the TOTPAR – SPID difference in SES and any of the trial characteristics examined (Table 3). Although the estimated TOTPAR – SPID difference in SES was higher in studies with multiple doses (.32) than in single-dose studies (.08–.09), this subgroup difference was not statistically significant ( $P > .34$ ).

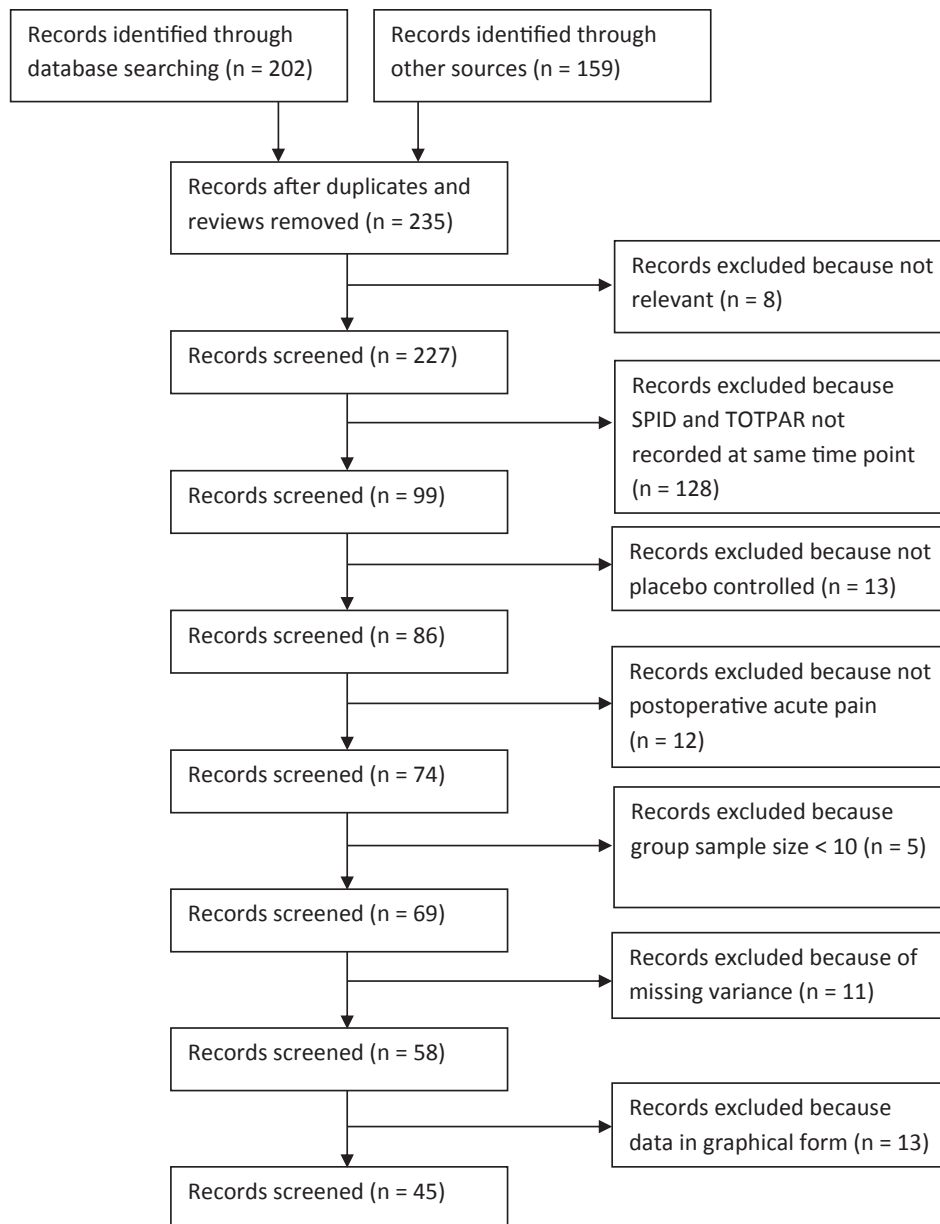
## Discussion

Pioneers in clinical trial design over the last century have established several reliable design elements that have allowed effective and informative evaluations of acute pain therapies, including randomization, blinding, placebo control, accounting for baseline pain, standardizing pain models (choice of surgery type), and the 2-stopwatch technique.<sup>19,30,29,47</sup> Published literature clearly demonstrates that the existing methodology of single-dose clinical trials has produced many successful studies.<sup>4,5,14</sup> Over the past 20 years, however, a surprising number of late-phase analgesic clinical trials have not demonstrated a statistically significant benefit of treatment.<sup>2,38,76</sup> This situation raises the question, Why are so many late-phase trials negative? Although the answer is a matter of some debate, it is likely that limitations in study design, nonoptimal study execution, chance, and lack of adequate sample size or statistical power<sup>51</sup> all play a role.

Several previous studies have compared SPID and TOTPAR measures in acute pain clinical trials. Moore et al<sup>52</sup> showed that using SPID and TOTPAR to derive dichotomous outcome measures produced very similar results. In subsequent studies, a significantly lower number needed to treat (ie, greater treatment effect) with TOTPAR than with SPID was found for 1 of 5 drug/dosage comparisons<sup>4</sup> and for 2 of 10 comparisons of minimum efficacy criteria,<sup>50</sup> and the investigators concluded that TOTPAR and SPID were comparable in their ability to discriminate between treatments. However, the overall pattern of these results favoring TOTPAR is not inconsistent with our data.

The present study extended previous results by focusing on clinical trials of a wide range of analgesics in which both TOTPAR and SPID had been calculated, using the SES as a measure of the assay sensitivity of these 2 different outcome measures, and finding a significant advantage for TOTPAR. It may be that the SES is a more sensitive index of assay sensitivity than the number needed to treat, which is based on categorizations of responders versus nonresponders.

Pain relief in acute pain clinical trials is generally assessed by TOTPAR, which is a time-weighted measure of total area under the pain relief curve that integrates serial assessments of a subject's pain over a prespecified



**Figure 1.** PRISMA chart for screened, excluded, and included studies.

time period during the trial. In this review, all assessments of TOTPAR were gathered through the use of a 5-point ordinal scale. The main advantage of the ordinal scale is its simplicity; there are only 5 categories from which subjects choose to indicate their pain relief at that current moment. A theoretical disadvantage of TOTPAR is that subjects have to recall their baseline pain intensity each time they are asked to assess their pain relief. Poor or inaccurate baseline pain recall can potentially render the trial data less dependable, particularly in cases where the times of assessments are farther away from the initial baseline. In the draft guidance for analgesic drug development released by the U.S. Food and Drug Administration in February 2014, this particular limitation of TOTPAR as an efficacy endpoint is mentioned.

Pain intensity in acute pain trials is generally assessed by SPID, a time-weighted sum of pain intensity differ-

ences from baseline. The advantage of SPID is that its accuracy does not rely on recall of baseline pain; the subject simply rates his or her pain intensity "at this current moment." Based on the characteristics of these different outcome measures, our hypothesis, contrary to our actual results, was that pain intensity would be the more sensitive efficacy paradigm. Theoretically, one would assume that reporting current pain intensity, without any recall of baseline pain that may have occurred hours earlier under the influence of residual postsurgical anesthesia, would allow the most accurate evaluation of treatment effect. Why, then, was TOTPAR more sensitive? Perhaps it is because when rating their pain relief, patients consider not only changes in their pain intensity but also any improvements in other domains such as physical functioning or sleep, and such a "composite" rating has greater assay sensitivity. We are

**Table 1. Summary Table of Studies Included in the Review**

REFERENCE	MODEL	TREATMENT	PIIPR SCALE
Ahdieh et al, 2004 <sup>1</sup>	Knee arthroplasty	Oxymorphone ER	Cat/Cat
Aqua et al, 2007 <sup>3</sup>	Abdominal surgery	Oxymorphone IR	Cat/Cat
Chang et al, 2004 <sup>6</sup>	Dental surgery	Rofecoxib	Cat/Cat
Chang et al, 2004 <sup>7</sup>	Dental surgery	Etoricoxib	Cat/Cat
Daniels et al, 2010 <sup>8</sup>	Dental surgery	Diclofenac	NPRS/Cat
Daniels et al, 2011 <sup>9</sup>	Bunionectomy	Oxycodone HCl/niacin*	VAS/Cat
Desjardins et al, 2000 <sup>12</sup>	Dental surgery	Butorphanol	Cat/Cat
Desjardins et al, 2004 <sup>11</sup>	Bunionectomy	Rofecoxib	Cat/Cat
Desjardins et al, 2007 <sup>13</sup>	Dental surgery	Rofecoxib	Cat/Cat
Fricke et al, 2002 <sup>21</sup>	Oral surgery	Tramadol/acetaminophen	Cat/Cat
Fricke et al, 2002 <sup>22</sup>	Oral surgery	Rofecoxib	Cat/Cat
Fricke et al, 2004 <sup>20</sup>	Dental surgery	Tramadol/acetaminophen	Cat/Cat
Gatoulis et al, 2012 <sup>23</sup>	Dental surgery	Acetaminophen/codeine*	Cat/Cat
Gimbel and Ahdieh, 2004 <sup>24</sup>	Abdominal or pelvic surgery	Oxymorphone IR	Cat/Cat
Haglund et al, 2006 <sup>26</sup>	Dental surgery	Cyclooxygenase-2 inhibitor	VAS/Cat
Hersh et al, 2004 <sup>28</sup>	Dental surgery	ProSorb DIC	Cat/Cat
Jackson et al, 2004 <sup>31</sup>	Dental surgery	Rofecoxib	Cat/Cat
Juhl et al, 2006 <sup>34</sup>	Dental surgery	IV paracetamol	Cat/Cat
Kleinert et al, 2008 <sup>37</sup>	Dental surgery	Tapentadol	Cat/Cat
Korn et al, 2004 <sup>39</sup>	Dental surgery	Rofecoxib	Cat/Cat
Kubitzeck, 2003 <sup>40</sup>	Dental surgery	Diclofenac	Cat/Cat
Litkowski et al, 2005 <sup>41</sup>	Dental surgery	Oxycodone/ibuprofen*	Cat/Cat
Malmstrom et al, 2002 <sup>43</sup>	Dental surgery	Rofecoxib	Cat/Cat
Malmstrom et al, 2004 <sup>44</sup>	Dental surgery	Etoricoxib	Cat/Cat
Malmstrom et al, 2004 <sup>45</sup>	Dental surgery	Etoricoxib	Cat/Cat
Malmstrom et al, 2005 <sup>42</sup>	Dental surgery	Etoricoxib	Cat/Cat
Mehlich, 1998 <sup>48</sup>	Oral surgery	Bromfenac sodium	Cat/Cat
Moller et al, 2005 <sup>49</sup>	Dental surgery	Paracetamol	Cat/Cat
Morrison et al, 1999 <sup>53</sup>	Dental surgery	Rofecoxib	Cat/Cat
Palangio et al, 2000 <sup>54</sup>	Dental surgery	Hydrocodone/ibuprofen*	Cat/Cat
Qi et al, 2012 <sup>55</sup>	Dental surgery	Acetaminophen	VAS/Cat
Rasmussen et al, 2005 <sup>56</sup>	Knee or hip Replacement	Etoricoxib	Cat/Cat
Reicin et al, 2001 <sup>57</sup>	Orthopedic surgery	Rofecoxib	Cat/Cat
Riff et al, 2009 <sup>58</sup>	Bunionectomy	Diclofenac	NPRS/Cat
Schwartz et al, 2007 <sup>59</sup>	Dental surgery	MK-0703	Cat/Cat
Sinatra et al, 2005 <sup>60</sup>	Orthopedic surgery	IV acetaminophen	Cat/Cat
Singla et al, 2005 <sup>61</sup>	Abdominal or pelvic surgery	Oxycodone/ibuprofen*	Cat/Cat
Stegmann et al, 2008 <sup>63</sup>	Bunionectomy	Tapentadol	Cat/Cat
U.S. Food and Drug Administration <sup>68</sup>	Dental surgery	Oxycodone/ibuprofen*	Cat/Cat
Van Aken et al, 2004 <sup>69</sup>	Dental surgery	Propacetamol	Cat/Cat
Van Dyke et al, 2004 <sup>70</sup>	Dental surgery	Oxycodone/ibuprofen*	Cat/Cat
Webster et al, 2010 <sup>71</sup>	Bunionectomy	Morphine/oxycodone	NPRS/Cat
Wermeling et al, 2005 <sup>72</sup>	Dental surgery	Butorphanol tartrate	Cat/Cat
Winingner et al, 2010 <sup>75</sup>	Abdominal surgery	IV acetaminophen	VAS/Cat
Zuniga et al, 2010 <sup>77</sup>	Dental surgery	Diclofenac	Cat/Cat

Abbreviations: ER, extended release; Cat, categorical scale; IR, immediate release; NPRS, numeric pain rating scale; VAS, visual analog scale; DIC, diclofenac; IV, intravenous.

NOTE. PIIPR scale indicates the scale with which pain intensity/pain relief was obtained.

\*Combination product.

not aware of any qualitative research in which patient interpretations of relief versus intensity scales have been compared. Such studies would be valuable in continuing to evaluate how these 2 different kinds of outcomes can best be used in acute pain trials.

It is important to emphasize that there are multiple considerations when selecting outcome measures for analgesic clinical trials. In the present article, we have emphasized assay sensitivity as measured by the SES, and our results show a statistically significant advantage of TOTPAR versus SPID. For truly efficacious treatments, the use of outcome measures with greater assay sensi-

tivity has the potential to reduce sample sizes and the likelihood of falsely negative results. In any clinical trial, however, it is important to consider the clinical meaningfulness of the estimated treatment effect in addition to its statistical significance for proper interpretation of the results, regardless of the outcome measure used.

### Limitations

Because the SPID and the TOTPAR are measured on different scales, the treatment effects were summarized using the SES, a scale-free, commonly used metric that is

**Table 2. Results of the Random Effects Meta-Analysis for Different Assumed Correlations Between TOTPAR and SPID**

ASSUMED CORRELATION BETWEEN TOTPAR AND SPID	DIFFERENCE IN SES (TOTPAR – SPID)	95% CONFIDENCE INTERVAL	P VALUE
.35	.11	.02, .19	.01
.45	.11	.02, .19	.01
.55	.11	.03, .20	.01
.65	.11	.03, .20	.01

particularly amenable to meta-analysis. However, there are important limitations of our analyses that need to be considered. First, the analyses assumed that the studies were large enough to permit the use of the asymptotic (large-sample) distribution of the estimator of the TOTPAR – SPID difference in SES. This assumption appeared to be reasonable given the sample sizes in the studies included in our review. Second, this large-sample distribution depends on the correlation between the TOTPAR and the SPID, and this value was not available from any of the studies we examined. Our meta-analyses, however, demonstrated that the results depended very little on the value of the correlation that was assumed within a plausible range from .35 to .65.

A third limitation is that the characteristics of the included studies were not homogeneous, which was addressed, in part, by the use of a random effects model in the meta-analysis. One important source of heterogeneity is the differences in the types of surgeries that were studied. Although our sample was too small to examine SES differences between SPID and TOTPAR as a function of type of surgery, previous reviews have found no differ-

ences in analgesic efficacy between dental and postsurgical pain<sup>4,46</sup>; such analyses, however, do not directly address whether the assay sensitivity of different outcome measures differs among these different conditions. Other important sources of heterogeneity among the trials are in dosing (ie, single vs multiple dose studies) and in the specific drugs studied. Moreover, several studies were omitted from the analysis that did not fulfill eligibility criteria, and there may have been others that were not published; it is not clear how representative the studies included in our analyses were of the intended population of studies. The inclusion of only trials that included both the TOTPAR and the SPID measures may have affected the nature of response on these measures. For example, it may be the case that completing both pain assessments in the same trial influences how patients respond on each measure such that they may respond differently if they had completed only one measure. Future research is needed to address this issue.

In addition, there were no clinical trials included in our analyses that calculated SPID and TOTPAR measures of movement-evoked pain. In a meta-analysis of trials examining acute postoperative pain, Srikandarajah and Gilron<sup>62</sup> found that patients reported higher levels of acute pain for movement-evoked pain compared to resting pain. Given the important differences between these 2 types of pain, research is needed on differences in assay sensitivity between SPID and TOTPAR measures of evoked pain. It would also be important to systematically examine whether the assay sensitivity of evoked and resting pain outcome measures differs.

Finally, the power of the meta-regression analyses may have been limited because of the relatively small number

**Table 3. Results of the Mixed Effects Meta-Regression Analyses of Trial Characteristics for Different Assumed Correlations Between TOTPAR and SPID**

VARIABLE	ASSUMED CORRELATION	SUBGROUP	TOTPAR – SPID DIFFERENCE IN SES (95% CI)	SUBGROUP DIFFERENCE OR COEFFICIENT (95% CI)*	P VALUE†
Procedure type	.35	Dental	.12 (.03, .21)	.03 (–.17, .24)	.70
		Nondental	.09 (–.10, .27)		
	.65	Dental	.12 (.04, .20)	.03 (–.17, .23)	.69
		Nondental	.09 (–.10, .27)		
Drug class	.35	Opioid/tramadol	.16 (–.04, .36)	.09 (–.12, .31)	.34
		Acet/NSAID	.06 (–.02, .15)		
	.65	Opioid/tramadol	.15 (–.05, .35)	.08 (–.14, .29)	.45
		Acet/NSAID	.07 (–.00, .15)		
Number of doses	.35	Single	.08 (.01, .15)	–.24 (–.91, .43)	.08
		Multiple	.32 (–.35, .99)		
	.65	Single	.09 (.03, .15)	–.23 (–.90, .44)	.11
		Multiple	.32 (–.35, .99)		
Time endpoint measured (h)	.35	N/A	N/A	–.01 (–.09, .08)	.89
	.65	N/A	N/A	–.01 (–.09, .08)	.86
Sample size	.35	N/A	N/A	–.02 (–.11, .07)	.65
	.65	N/A	N/A	–.03 (–.12, .07)	.56

Abbreviations: CI, confidence interval; Acet, acetaminophen; NSAID, nonsteroidal anti-inflammatory drug; N/A, not applicable.

\*For categorical variables, this is the subgroup difference in the TOTPAR – SPID difference in SES. For quantitative variables (time endpoint measured and sample size), this is the change in the TOTPAR – SPID difference associated with a 10-hour increase in the time the endpoint was measured or a 100-subject increase in the sample size, as appropriate.

†P value from a meta-regression analysis testing the null hypothesis that the subgroup difference or coefficient is equal to zero.

of studies in some of the subgroups examined. The finding that there were no trial characteristics that were statistically significantly associated with the TOTPAR – SPID difference in SES does not completely rule out such associations, as indicated by the widths of the confidence intervals in Table 3.

## Conclusions

Thoughtful analysis and exploration of analgesic clinical trial design elements have been spearheaded by groups such as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), a public-private partnership with the U.S. Food

and Drug Administration. Many recent publications have focused on methodological concerns relevant to the assay sensitivity of chronic pain studies.<sup>16,17,19,35</sup> However, the concerns are analogous for acute pain, and the reevaluation of methodologies used in acute pain trials would seem to be valuable. Our results suggest an important avenue for future research in terms of the need to prospectively examine the assay sensitivity of pain relief versus pain intensity in clinical trials. Additionally, future research should address whether differences in assay sensitivity between these 2 types of measures are present for chronic pain trials and for pain treatments other than analgesics (eg, nerve blocks, physical therapy, acupuncture, cognitive-behavioral therapy).

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