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Comprehensive review

# A comparison of the clinical and experimental characteristics of four acute surgical pain models: Dental extraction, bunionectomy, joint replacement, and soft tissue surgery

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ABSTRACT

When a clinical trial of an analgesic produces a negative finding, it is important to consider the influence (if any) of experimental error on the validity of that result. Although efforts to identify and minimize experimental error in chronic pain investigations have begun in earnest, less work has been performed on the optimization of acute pain methodology. Of the acute surgical pain methodology articles that have been published over the last decade, almost all focus on either the dental or bunion model. Analgesics are typically evaluated in a variety of surgical models that eventually include hospital-based models (eg, joint replacement and soft tissue surgery). Every surgical procedure has unique clinical characteristics that must be considered to optimize study design and conduct. Much of the methodological knowledge garnered from bunion and dental studies is applicable to other surgical models, but some extrapolations are hazardous. The purposes of this review were (1) to qualitatively describe the clinical and experimental characteristics of the 4 classic surgical models: dental extraction, bunionectomy, joint replacement, and soft tissue surgery; and (2) to quantitatively compare the models by analyzing 3 factors: effect size, enrollment rate, and demographics. We found that the dental extraction and bunionectomy models had higher assay sensitivity than the joint replacement and soft tissue surgery models. It is probable that this finding is secondary to the superior experimental conditions under which the dental and bunion models are executed (utilization of few centers that have the ability to reduce surgical, anesthetic, and postoperative confounders).

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## 1. Introduction

The high incidence of false-negative findings in analgesic investigations hinders the process of molecular discovery, increases the cost of pharmaceutical development programs, and unnecessarily burdens study participants by subjecting them to the dangers of nonproductive research. Although several groups have initiated efforts to identify factors that contribute to false-negative results in chronic pain investigations [35–37,60], less attention has been focused on optimizing acute pain methodology. Over the past 20 years, most drug candidates indicated for the treatment of acute pain have been opioid reformulations or reformulations of other molecules with known analgesic efficacy [62]. If one assumes that reformulated drugs should generally demonstrate efficacy in phase 3, why are a significant number of late-phase acute pain studies negative [112–114]? When considering this question, it is important to remember that drug efficacy is not the only prerequisite for a positive acute surgical analgesic trial; choice of surgical model, minimization of perioperative confounders, and control of surgical/anesthetic variability also impact the likelihood of trial success.

To test a drug in acute surgical pain, one must first decide what type of surgery will be utilized as a pain generator against which the efficacy of an investigational product will be measured. The ideal surgical research model would have the following characteristics: (1) produce a homogeneous and predictable pattern of pain in a diverse population, (2) allow a range of experimental manipulations that reliably alter the postoperative pain experience in order to meet the needs of the experiment, (3) closely match the clinical environment in which the agent will ultimately be administered, (4) include volunteers whose demographics are a representative sample of the target clinical population, (5) produce pain via a well-understood physiological process, (6) be common enough so

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that recruitment can be achieved in a reasonable time frame, and (7) allow state-of-the-art care to be provided in a manner that minimizes analgesic confounders. The clinical realities of a specific surgical procedure and the degree to which these realities can be ethically manipulated determine the potential of that procedure to serve as an ideal research model.

Considering the variety and frequency of painful surgical interventions, one might imagine that there are many well-described, high-quality surgical research models available to an investigator. However, models that appear to be ideal but have not been scrutinized over time may have characteristics that are not yet understood. Therefore, researchers generally make what they consider to be a safe choice by selecting a classic surgical model that has been widely utilized in previous analgesic investigations. The 4 classic surgical models are: dental impaction, bunionectomy, joint replacement surgery (JRS), and soft tissue surgery (STS). Unfortunately, most of the published literature on the methodology of acute pain focuses either on the dental or the bunion model [20,22,69,93], forcing design considerations in JRS and STS to be based on extrapolation. Because JRS and STS are clinically distinct from both dental and bunion surgery, these models have unique experimental characteristics, which as of yet are not well understood.

The purposes of this review were (1) to qualitatively describe the clinical and experimental characteristics of the 4 classic surgical models and (2) to quantitatively examine each model in order to make objective comparisons. The discussion of each of the 4 models is divided into 5 sections: (1) introduction, (2) surgical and anesthesia protocol, (3) enrollment rate, (4) assay sensitivity, and (5) model limitations. The first 2 sections contain qualitative data only. Sections 3, 4, and 5 present quantitative results and relevant conclusions.

## 2. Methods

The procedures utilized to evaluate the investigation's 3 quantitative endpoints (standardized effect size [SES], enrollment rate, and demographic characteristics) are described. All quantitative endpoints were first subjected to a common primary set of inclusion/exclusion (I/E) criteria. Subsequently, each of these 3 endpoints was subjected to a unique set of secondary I/E criteria (Fig. 1).

### 2.1. Data sources

A systematic review of the literature using MEDLINE, PubMed, the Cochrane library, and manual search techniques was performed to identify prospective, double-blind, randomized, and controlled clinical trials using analgesics for treatment of acute postoperative pain. The detailed search strategy included subject headings and MeSH terms 'acute pain', 'randomized', 'placebo controlled', 'postoperative', and 'analgesics in adults'. The resulting list was intersected with a group of terms relating to 'bunionectomy', 'foot surgery', 'abdominal surgery', 'hysterectomy', 'hernia repair', 'total knee arthroplasty', 'total hip replacement', and 'dental surgery'. Reference lists, meta-analyses, US Food and Drug Administration summary basis of approvals, and clinical trial register databases (clinicaltrial.gov) also were manually screened for relevant data. Titles and abstracts ranging from 1998 to the present were reviewed and independently read by the authors (N.S. and P.D.C.) for eligibility according to predefined criteria.

### 2.2. Primary I/E criteria

Studies were included if they were: (1) primarily concerned with the evaluation of acute surgical pain, (2) double-blind, (3) placebo- or active-controlled, (4) randomized, (5) industry-sponsored, (6) written in English, (7) nonpediatric (defined as age >16 years), (8) of sufficient size (defined as at least 10 patients per study arm), and (9) performed in 1 of the 4 surgical models relevant to this investigation.

### 2.3. Secondary I/E criteria

For the SES endpoint, studies were included if they: (1) presented a continuous prespecified analgesic endpoint and (2) measured the effect of an active product against placebo. Studies were excluded if they: (1) used only active comparators as controls, (2) used devices to treat pain, (3) did not include sample size, (4) did not explicitly provide treatment means (eg, provided data only in graphical form), or (5) did not provide variance (eg, standard deviation, standard error, or confidence interval). The prespecified primary endpoint was used for the SES calculation preferentially. If the primary endpoint was not one for which an SES could be calculated, a secondary endpoint pertaining to the assessment of pain was utilized. If more than one secondary endpoint was provided, the first complete endpoint presented in the results section of the article was selected. In studies in which various doses were examined, the effect size of the largest dose (vs placebo) was utilized.

For the enrollment rate endpoint, studies were included if they disclosed: (1) the total number of enrolled subjects, (2) the number

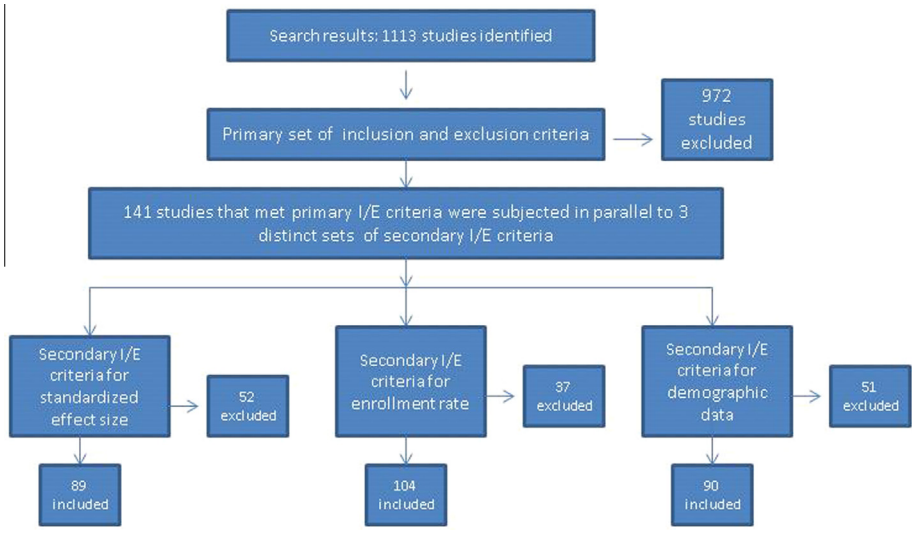


**Fig. 1.** Study selection process for quantitative endpoints. I/E = inclusion/exclusion.

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of participating sites, and (3) the investigation's start and completion dates. The date of study completion was defined either as the date that the final subject received a perioperative intervention or as the final date on which data were collected. The former definition was used preferentially. For the demographic endpoint, any study that presented quantifiable demographic data was included.

### 2.4. Data synthesis

The SES for an individual study was determined by calculating the ratio of the selected endpoint's treatment effect to its pooled standard deviation. Because SES can be positive or negative depending on the nature of the endpoint, we assigned a positive value to the SES when treatment outperformed placebo and a negative value when placebo outperformed treatment. SES was selected as the critical outcome measure for this analysis because it is a simple scale-free metric that is an accepted measure of an investigation's assay sensitivity (a numeric representation of an experiment's signal-to-noise ratio). Assay sensitivity is defined as the ability of a research study to detect a treatment difference when the molecule being tested is in fact efficacious.

$$\mathrm{SES} = \frac{(\text{Mean of treatment group} - \text{Mean of placebo group})}{\text{Pooled standard deviation}}$$

Recruitment rates were calculated by dividing the total number of subjects enrolled in a particular study by both the number of months it took for study completion and the number of participating sites (enrolled subjects/center/month).

## 3. Results

### 3.1. Dental surgical model

#### 3.1.1. Introduction

The dental impaction model relies on postsurgical pain generated via the prophylactic or therapeutic extraction of third molars. The model has been in widespread use for over 50 years, is well characterized, and is frequently used to investigate the pharmacodynamic properties of analgesic molecules (onset/offset, dose-response, and potency) [20–22,26]. Because third molar surgery is generally performed on an outpatient basis, there is a common misperception that the postoperative pain course is mild, and as such, the experimental model is appropriate only for low-potency oral analgesics [21]. In fact, surgical protocols can be modified so that the postoperative pain experience is severe enough to (1) allow discrimination of strong intravenous analgesics vs placebo on a multiple-dose basis for up to 24 hours after surgery [34,63,115] or (2) mild enough to evaluate weak oral analgesics [17,81,84]. Efficacy in the dental model is highly predictive of efficacy in later stage models. Barden et al., comparing dental with nondental analgesic data available through the Cochrane Collaboration, concluded that "a drug, which is an analgesic in one pain context, will also be an analgesic in other contexts" [4].

#### 3.1.2. Surgical and anesthetic protocol

Because the dental model has been well characterized, the relationship between initial surgical trauma and resultant acute postoperative pain is understood. By varying the number (1 to 4), location (mandibular vs maxillary) and impaction grade (erupted, impacted by soft tissue, bony impaction) of protocol mandated extractions, the researcher can match the postoperative pain trajectory to the needs of the experiment ([22]) (Fig. 2).

The anesthetic protocol for third molar extraction is straightforward, requiring primarily short-acting local anesthetics [16,31,40,58,80]. The use of systemic medications that have central nervous system depressant activity can largely be avoided. The ideal experimental condition allows subjects to experience moderate to severe postoperative pain at a time when intraoperatively administered agents are no longer influencing pain perception [22]. Although this experimental ideal is achievable in the dental model, anesthetic regimens for bunion surgery, JRS, and STS all require administration of at least some systemic concomitant medication [94,104,118]. Carryover effects of central nervous system depressants into the postoperative efficacy evaluation period may reduce the assay sensitivity of the 3 nondental models [22].

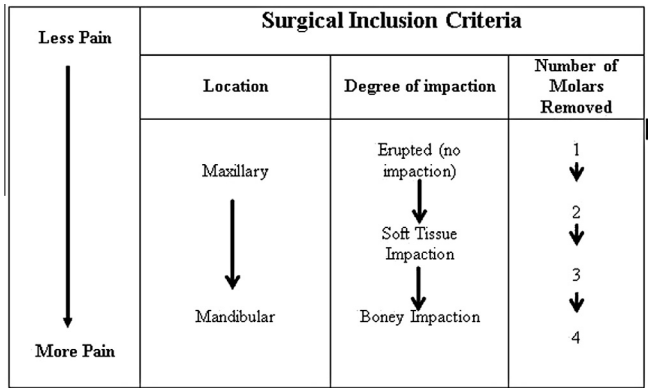


**Fig. 2.** Depiction of surgical characteristics within the dental model that can be manipulated to alter the subject's postoperative pain trajectory.

#### 3.1.3. Enrollment rate

Enrollment into dental studies was the most rapid of all models analyzed, averaging 63 subjects per center per month (Fig. 3). This rate illustrates that dental recruitment is on average 3.2 times faster than bunionectomy, 16.2 times faster than JRS, and 26.4 times faster than STS. To understand the dental model, one needs to appreciate its financial and logistical underpinnings. In most circumstances, the dental surgery fee is paid for by the research grant. Although this point may seem at first to have little influence over the scientific merit of the model, in fact there are important implications. Remuneration of surgical fees provides an easily understood benefit for the subject and greatly facilitates subject accrual. Consequently, subjects do not need to be pooled from various institutions to meet enrollment timelines. Each dental study in our review required an average of only 2.2 centers to complete enrollment, in contrast to 4.5, 10.9, and 18.4 centers for bunionectomy, JRS, and STS, respectively (Tables 1–4).

#### 3.1.4. Assay sensitivity

The average SES in the dental model was 1.51; 64%, 122%, and 202% higher than bunionectomy, JRS, and STS, respectively (Fig. 4). The high assay sensitivity demonstrated in the dental model is likely the result of the experimental conditions in which the protocol is carried out. In general, these studies are performed within standalone research units where attempts are made to control standard of care confounders (perioperative ice, use of adjuncts, time to oral intake) [22]. Utilizing few centers reduces the number of surgeons and anesthesiologists involved with the clinical trial, each of whom introduces variability.

The dental extraction itself is predicated on the subject consenting to clinical trial participation. This is in contrast to the JRS and STS models, in which the study protocol is an add-on feature of the surgery that would have proceeded in a clinical environment (eg, hospital) whether or not the subject had been enrolled in a research study. The quid pro quo established by subsidizing the cost of the dental surgery may lead to a more objective research rela-

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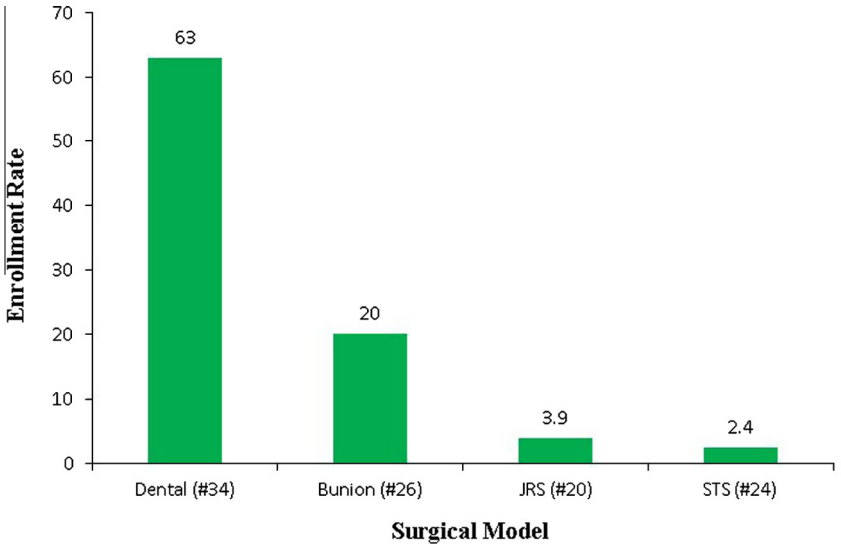


**Fig. 3.** Enrollment rate by surgical model. Enrollment rate was determined as the number of subjects enrolled in an investigation per study center per month (subjects enrolled/center/month). # = Number of studies used in the analysis. SES = standardized effect size; JRS = joint replacement surgery; STS = soft tissue surgery.

tionship between investigator and subject. In JRS and STS, extensive preoperative interaction fosters a classic therapeutic relationship between doctor and patient, which postoperatively may hinder their ability to establish an objective relationship.

*3.1.5. Model limitations*

The primary limitation of the dental model is lack of generalizability. Positive results in the dental model have significance in the proof-of-concept sphere, but for most acute analgesics, regulators and prescribing physicians will demand proof of efficacy in scenarios that more closely resemble those in which the drug will ultimately be prescribed. Although when manipulated the model may be painful enough to discriminate intravenous opioids, these medications are not a standard of care for acute dental pain. When performed in a clinical setting (not for research purposes), dental surgery is an outpatient procedure involving predominantly healthy, young adult subjects (Table 5). Copious local anesthetic infiltration, nerve blocks, and adjunctive therapy (eg, ice and nonsteroidal anti-inflammatory drugs) minimize the perioperative pain experience so that patients can be adequately treated with outpatient oral analgesics [50].

*3.2. Bunionectomy model*

*3.2.1. Introduction*

The bunionectomy model relies on surgical pain generated from the correction of hallux valgus deformities of the first metatarsal [69]. The pain is a result of the procedure's requisite osteotomy and less so secondary to soft tissue damage required to gain appropriate surgical exposure. As such, it is generally classified as a bone pain model and has been frequently used to evaluate drugs that reduce the inflammatory response involved with periosteal disruption [29,32]. The model was developed in the early 2000s primarily as a solution to a significant shortcoming in the dental model—the need for pain of an adequate duration to measure multiple-day efficacy [9,109].

The model has good assay sensitivity for approximately 72 hours after the surgical insult [32,33,111], with mixed results

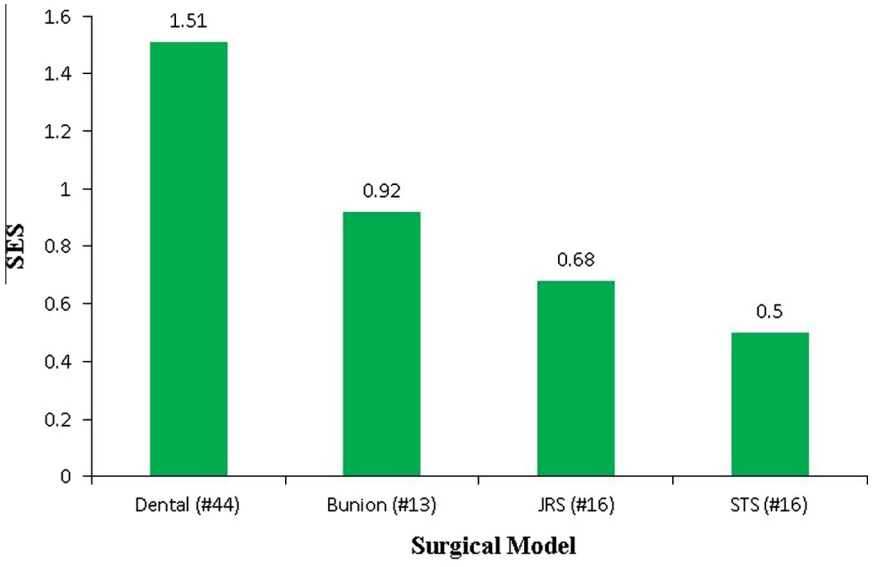


**Fig. 4.** Standardized effect size by model. Numbers above bars represent the average SES for each surgical model. # = Number of studies used in the analysis. SES = standardized effect size; JRS = joint replacement surgery; STS = soft tissue surgery.

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**Table 1**
Dental surgery standardized effect size and enrollment rate summary.

| Sponsor | Source | Trial identification | Drug | Drug type | N | Primary endpoint | Standardized effect size | Number of sites | Duration of study (months) | Enrollment rate (subjects/center/month) |
|---|---|---|---|---|---|---|---|---|---|---|
| AstraZeneca | Hill 2006 [82] | | AZD3582 | NSAID | 356 | MPID 8 | 1.5293 | 1 | – | – |
| AstraZeneca | Hill 2006 [82] | | AZD3582 | NSAID | 341 | MPID 8 | 0.5892 | 4 | – | – |
| Bayer | | NCT01495858 | BAY98-7111 | NSAID | 267 | Wake time after sleep onset 10 | – | 2 | 2 | 66.75 |
| Iroko Pharmaceuticals | | NCT00964431 | Celecoxib | NSAID | 203 | TOTPAR 8 | 1.2282 | 1 | 4 | 50.75 |
| Daiichi Sankyo Pharma | Moberly 2007 [83] | | Celecoxib | NSAID | 304 | TOTPAR 4 | – | 2 | 3 | 50.67 |
| Pfizer | Cheung 2007 [17] | | Celecoxib | NSAID | 171 | TOTPAR 24† | 1.285 | 2 | 2 | 42.75 |
| Pfizer | Saito 2012 [96] | NCT01062113 | Celecoxib | NSAID | 255 | Efficacy rate (5) of patient impression | – | 22 | 4 | 2.90 |
| Merck | Gottesdiener 1999 [49] | | [5,5-dimethyl-3-(2-isopropoxy)-4-(4-methanesulfonylphenyl)-2(5*H*)-furanone] | NSAID | 196 | TOTPAR 8* | 1.634 | 1 | – | – |
| Merck | Chang 2004 [15] | | Etoricoxib | NSAID | 225 | TOTPAR 6 | 1.7992 | 1 | – | – |
| Merck | Malmstrom 2005 [72] | | Etoricoxib | NSAID | 302 | TOTPAR 6 | 1.7933 | 1 | 1 | 302.00 |
| Merck | | NCT00694369 | Etoricoxib | NSAID | 588 | TOTPAR 6 | 1.8435 | – | 6 | – |
| Merck | Malmstrom 2004 [76] | | Etoricoxib | NSAID | 398 | TOTPAR 8 | 1.9501 | 1 | 5 | 79.60 |
| Merck | Malmstrom 2004 [75] | | Etoricoxib | NSAID | 201 | TOTPAR 8 | 1.7901 | 1 | – | – |
| King Pharmaceuticals and GlaxoSmithKline | Varner 2009 [117] | NCT00114049 | GW406381 | NSAID | 300 | SPID 8† | 0.9524 | 1 | 4 | 75.00 |
| Iroko Pharmaceuticals | | NCT00985439 | Diclofenac | NSAID | 202 | TOTPAR 12 | 0.8505 | 1 | 3 | 67.33 |
| Novartis | Kubitzek 2003 [66] | | Diclofenac | NSAID | 245 | Average pain relief 1 | 1.2354 | – | – | – |
| Forest Laboratories | Hersh 2004 [53] | | ProSorb diclofenac | NSAID | 265 | SPID 3 | 1.9382 | 6 | – | – |
| Xanodyne Pharmaceuticals | Zuniga 2010 [125] | | Diclofenac | NSAID | 249 | SPID 6 | – | 7 | – | – |
| Javelin Pharmaceuticals | Leeson 2007 [67] | | Diclofenac | NSAID | 155 | TOTPAR 4 | 3.0049 | 1 | – | – |
| Javelin Pharmaceuticals | Christensen 2011 [18] | | Diclofenac | NSAID | 353 | TOTPAR 6 | 1.8559 | 3 | – | – |
| Pfizer | | NCT00913627 | Ibuprofen | NSAID | 196 | SPID 12 | – | 1 | 3 | 65.33 |
| SCOLR Pharma | | NCT00707057 | Ibuprofen Extended-release | NSAID | 256 | SPID 12 | 0.9608 | 1 | 4 | 64.00 |
| Lutipold Pharma | | NCT01356225 | Intranasal ketorolac | NSAID | 80 | SPID 8 | – | 1 | 1 | 80.00 |
| Merck | Schwartz 2007 [98] | | MK-0703 | NSAID | 121 | TOTPAR 8 | 1.3353 | 1 | 5 | 24.20 |
| Bayer | | NCT00720057 | Naproxen sodium Extended-release | NSAID | 312 | SPID 24 | 1.296 | 3 | 2 | 52.00 |
| Bayer | | NCT01389284 | Naproxen sodium Extended-release | NSAID | 300 | SPID 24 | 1.086 | 1 | 3 | 100.00 |
| Merck | Daniels 2006 [25] | NCT00092300 | Rofecoxib | NSAID | 450 | TOTPAR 12 | 1.9896 | – | 4 | – |
| Merck | Chang 2001 [16] | | Rofecoxib | NSAID | 393 | TOTPAR 6 | 1.3093 | 1 | – | – |
| Merck | Chang 2004 [13] | NCT00092313 | Rofecoxib | NSAID | 271 | TOTPAR 6 | 1.4959 | 2 | 3 | 45.17 |
| Merck | Desjardin 2007 [30] | NCT00092326 | Rofecoxib | NSAID | 270 | TOTPAR 6 | 1.6662 | 2 | 3 | 45.00 |
| Merck | Daniels 2006 | NCT00092339 | Rofecoxib | NSAID | 125 | TOTPAR 12 | 1.4159 | 1 | 4 | 31.25 |

(*continued on next page*)

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**Table 1** (*continued*)

| Sponsor | Source | Trial identification | Drug | Drug type | N | Primary endpoint | Standardized effect size | Number of sites | Duration of study (months) | Enrollment rate (subjects/center/month) |
|---|---|---|---|---|---|---|---|---|---|---|
| | [25] | | | | | | | | | |
| Merck | Malmstrom 2002 [74] | | Rofecoxib | NSAID | 482 | TOTPAR 8 | 1.6824 | 1 | – | – |
| Merck | Korn 2004 [64] | | Rofecoxib | NSAID | 212 | TOTPAR 6 | 1.276 | 1 | 2 | 106.00 |
| Merck | Malmstrom 1999 [73] | | Rofecoxib | NSAID | 272 | TOTPAR 8 | 1.5525 | 1 | – | – |
| Merck | Chang 2002 [14] | | Rofecoxib | NSAID | 305 | TOTPAR 8* | 1.63 | 4 | – | – |
| Reckitt Benckiser Healthcare | | NCT01229449 | Ibuprofen/acetaminophen | NSAID/ other | 678 | SPRID 12 | – | 1 | 8 | 84.75 |
| Reckitt Benckiser Healthcare | Mehlisch 2010 [80] | | Ibuprofen+paracetamol | NSAID/ other | 234 | SPRID 8 | 2.1402 | 2 | 2 | 58.50 |
| Reckitt Benckiser Healthcare | Mehlisch 2010 [81] | | Ibuprofen+paracetamol | NSAID/ other | 735 | SPRID 8 | – | 3 | 11 | 22.27 |
| Reckitt Benckiser Healthcare | Daniels 2011 [26] | | Ibuprofen+paracetamol | NSAID/ other | 678 | SPRID 12 | 4.6 | 3 | 7 | 32.29 |
| Bristol-Myer Squibb | Desjardin 2000 [31] | | Butorphanol | Opioid | 151 | SPID 6* | 0.7578 | 2 | – | – |
| Intranasal Technology | Wermeling 2005 [122] | | Butorphanol | Opioid | 60 | SPID 6* | 0.6784 | 1 | – | – |
| Javelin Pharmaceuticals | Christensen 2008 [19] | NCT00390312 | Intranasal morphine | Opioid | 225 | TOTPAR 2 | – | 2 | 2 | 56.25 |
| Grunenthal | Kleinert 2008 [63] | | Tapentadol | Opioid | 400 | TOTPAR 8 | 1.4325 | 2 | – | – |
| Forest Laboratories | Litkowski 2005 [68] | | Combo oxycodone/ibuprofen | Opioid/ NSAID | 249 | TOTPAR 6* | 1.6659 | 3 | – | – |
| Forest Laboratories | van Dyke 2004 [116] | OXY-MD-05 | Combo oxycodone/ibuprofen | Opioid/ NSAID | 498 | TOTPAR 6* | 1.3129 | 3 | – | – |
| Forest Laboratories | | OXY-MD-06 | Combo oxycodone/ibuprofen | Opioid/ NSAID | 676 | TOTPAR 6* | 1.6986 | – | – | – |
| Ortho-McNeil Pharmaceuticals | Fricke 2002 [41] | | Tramadol/acetaminophen | Opioid/ other | 200 | TOTPAR 4* | 0.9693 | 1 | – | – |
| Ortho-McNeil Pharmaceuticals | Fricke 2004 [40] | NCT00236483 | Tramadol/acetaminophen | Opioid/ other | 456 | TOTPAR 3* | 1.3776 | 1 | 3 | 152.00 |
| Bayer Health Care | Gatoulis 2012 [44] | | Acetaminophen with codeine | Opioid/ other | 302 | SPID 6 | 0.7328 | – | – | – |
| McNeil PPC | | NCT01115673 | Acetaminophen | Other | 540 | SPRID 6 | 1.3656 | 1 | 7 | 77.14 |
| Array BioPharma | | NCT00663767 | ARRY-371797 | Other | 250 | TOTPAR 6 | – | 2 | 2 | 62.50 |
| GlaxoSmithKline | | NCT01082081 | Paracetamol | Other | 350 | SPRID 6 | – | 2 | 5 | 35.00 |
| Bristol-Myer Squibb | Moller 2005 [84] | | Paracetamol | Other | 152 | TOTPAR 6† | 1.0772 | 1 | 3 | 50.67 |
| Baxter Healthcare Corp | | NCT00406679 | Paracetamol | Other | 135 | Unknown | – | 2 | 11 | 6.14 |
| GlaxoSmithKline | Qi 2012 [89] | NCT01075243 | Paracetamol | Other | 440 | SPRID 6 | – | 1 | 4 | 110.00 |
| Bristol-Myer Squibb | Juhl 2006 [58] | | Paracetamol | Other | 297 | TOTPAR 6 | 1.414 | 1 | 10 | 29.70 |
| Pfizer | | NCT01529346 | PF-05089771 | Other | 235 | TOTPAR 6 | – | 2 | 6 | 19.58 |
| Bristol-Myer Squibb | Van Aken 2004 [115] | | Propacetamol | Other | 99 | TOTPAR 5* | 1.0671 | 1 | 22 | 4.50 |
| Average | | | | | 304.5 | | 1.51 | 2.2 | | 63.29 |

MPID = mean pain intensity difference; TOTPAR = total pain relief; SPID = sum pain intensity difference; SPRID = sum of pain intensity difference and total pain relief; PR = pain relief.

* Study presented multiple primary endpoints.

† Not primary endpoint.

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**Table 2**
Bunionectomy standardized effect size and enrollment rate summary.

| Sponsor | Source | Trial identification | Drug | Drug type | N | Primary endpoint | Standardized effect size | Number of sites | Duration of study (months) | Enrollment rate (subjects/center/month) |
|---|---|---|---|---|---|---|---|---|---|---|
| Pharmacia Corp | Gimbel 2001 [46] | | Celecoxib | NSAID | 418 | SPID 8* | – | 24 | 5 | 3.48 |
| Iroko Pharmaceuticals | | NCT01543685 | Indomethacin | NSAID | 460 | SPID 48 | – | 4 | 4 | 28.75 |
| Iroko Pharmaceuticals | | NCT01462435 | Diclofenac | NSAID | 424 | SPID 48 | – | 4 | 4 | 26.50 |
| Xanodyne | Daniels 2010 [24] | NCT00375934 | Diclofenac gel caps | NSAID | 200 | SPID 48† | 1.2263 | 4 | 4 | 12.50 |
| Xanodyne | Zuniga 2010 [125] | | Diclofenac gel caps | NSAID | – | SPID 3* | 1.7048 | – | – | – |
| Xanodyne | Riff 2009 [94] | NCT00366444 | Diclofenac XP21L | NSAID | 201 | Mean NPRS 48 | 1.1162 | 6 | 2 | 16.80 |
| Merck | Desjardins 2004 [29] | NCT00092378 | Rofecoxib | NSAID | 252 | TOTPAR 8 | 0.7789 | 2 | 3 | 42.00 |
| Pharmacia Corporation | Desjardins 2002 [32] | | Valdecoxib | NSAID | 223 | Median time to rescue | 0.4418 | 2 | – | – |
| Acura Pharma | Daniels 2011 [27] | NCT00654069 | Acurox | Opioid | 405 | SPID 48 | 0.5526 | 6 | 5 | 13.50 |
| J&J | | NCT00609466 | CG5503 IR | Opioid | 291 | SPID 48 | 0.5245 | 6 | 5 | 9.70 |
| Aradigm Corp | Thipphawong 2003 [111] | | Inhaled morphine | Opioid | 89 | SPID 1 | 0.9017 | 2 | 2 | 22.25 |
| Javelin Pharmaceuticals | Stoker 2008 [110] | | Intranasal morphine | Opioid | 187 | TOTPAR 4 | – | – | – | – |
| QRxPharma | | NCT01280331 | MoxDuo | Opioid | 375 | Difference in desaturation events 48 | – | 4 | 3 | 31.25 |
| QRxPharma | Richards 2011 [92] | | MoxDuo | Opioid | 197 | SPID 24 | – | 6 | 2 | 16.42 |
| QRxPharma | | NCT00831051 | Q8003 (MoxDuo) | Opioid | 197 | PID 48 | – | 6 | 5 | 32.83 |
| QRxPharma | | NCT01016808 | Q8003 (MoxDuo) | Opioid | 522 | PID 48 | – | 5 | 3 | 34.80 |
| Grunenthal GmbH | | NCT00806247 | Tapentadol | Opioid | 480 | SPRID 12 | – | – | 7 | – |
| Grunenthal GmbH | | NCT01435577 | Tapentadol | Opioid | 177 | SPID 24 | – | 1 | 5 | 35.40 |
| J&J | Weber poster 2006 | | Tapentadol | Opioid | – | TOTPAR 8 | 1.2592 | – | – | – |
| J&J | Daniels 2009 [28] | NCT00364247 | Tapentadol | Opioid | 602 | SPID 48 | 1.2903 | 5 | 9 | 13.40 |
| J&J | Daniels 2009 [23] | NCT00613938 | Tapentadol | Opioid | 901 | SPID 48 | 0.9105 | 3 | 8 | 37.50 |
| J&J | Stegmann 2008 [109] | | Tapentadol IR | Opioid | 269 | SPI 24 (day 3) | 0.7703 | 3 | – | – |
| AbbVie | | NCT01333722 | Hydrocodone/Ace ER | Opioid/other | 99 | SPID 12 | – | 3 | 2 | 16.50 |
| Abbott Laboratories | | NCT00402792 | Hydrocodone/Ace ER | Opioid/other | 150 | SPID 12 | – | 5 | 4 | 7.50 |
| Abbott Laboratories | | NCT00404222 | Hydrocodone/Ace ER | Opioid/other | 90 | SPID 12 | – | 3 | 3 | 10.00 |
| Abbott Laboratories | | NCT00404391 | Hydrocodone/Ace ER | Opioid/other | 210 | TOTPAR 12 | – | 4 | 5 | 10.50 |
| AbbVie | | NCT01038609 | Hydrocodone/Ace ER | Opioid/other | 250 | SPID 48 | – | 4 | 5 | 12.50 |
| Mallinckrodt | | NCT01484652 | Cov795 | Opioid/other | 329 | SPID 48 | – | 5 | 9 | 7.31 |
| Pacira Pharmaceuticals | Golf 2011 [47] | NCT00890682 | DepoBupivacaine | Other | 193 | AUC NPRS 24 | 0.4705 | 4 | 5 | 9.70 |
| AbbVie | | NCT00872885 | GRT6005 | Other | 258 | SPID 2 to 10 | – | 1 | 5 | 51.60 |
| Merck | Wang 2010 [121] | NCT00601458 | Pregabalin | Other | 256 | PCA hydromorphone use 24 | – | 1 | 6 | 16.67 |
| QRxPharma | | NCT01206595 | SKY0402 | Other | 58 | Time to first use of supplemental medication 96 | – | 4 | 12 | 1.21 |
| Average | | | | | 292.1 | | 0.92 | 4.5 | | 20.0 |

NPRS = numerical pain rating scale; TOTPAR = total pain relief; PID = pain intensity difference; SPI = sum of pain intensity; SPID = sum pain intensity difference; SPRID = sum of pain intensity difference and total pain relief; PR = pain relief; PCA = patient-controlled analgesia; AUC = area under the curve.

* Study presented multiple primary endpoints.

† Denotes not primary endpoint.

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**Table 3**
Joint replacement surgery standardized effect size and enrollment rate summary.

| Sponsor | Source | Surgery type | Trial identification | Drug | Drug type | N | Primary endpoint | Standardized effect size | Number of sites | Duration of study (months) | Enrollment rate (subject/center/months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pfizer | | TKA | NCT00633386 | Celecoxib | NSAID | 200 | Analgesic use 24 | – | 9 | 6 | 3.70 |
| Pfizer | | TKA | NCT00633438 | Celecoxib | NSAID | 204 | Analgesic use 24 | – | 18 | 5 | 2.27 |
| Merck | Rasmussen 2005 [90] | TKA/THA | | Etoricoxib | NSAID | 228 | TOTPAR 8 | 0.5348 | 8 | – | – |
| Merck | | TKA | NCT00820027 | Etoricoxib | NSAID | 776 | Average PID at rest 3 days | – | – | 24 | – |
| Cumberland Pharmaceuticals | Singla 2010 [104] | TKA/THA | NCT00470600 | Ibuprofen | NSAID | 185 | AUC Visual analog scale upon movement 6 to 28 | 0.8298 | 8 | 16 | 1.45 |
| Javelin Pharmaceuticals | | Orthopedic | NCT00507026 | Intravenous diclofenac | NSAID | 277 | SPID 24 | – | 8 | 5 | 6.93 |
| Novartis | Chan 2005 [12] | TKA/THA | | Lumiracoxib | NSAID | 180 | SPID 8 | 0.5072 | 14 | – | – |
| Pharmacia Corporation | Hubbard 2003 [54] | TKA | | Parecoxib | NSAID | 195 | Analgesic consumption 24* | – | 10 | 8 | 2.44 |
| Merck | Reicin 2001 [91] | TKA/THA | | Rofecoxib | NSAID | 218 | TOTPAR 8 | 0.5673 | 9 | – | – |
| Pharmacia/Pfizer | Camu 2002 [10] | THA | | Valdecoxib | NSAID | 217 | Morphine consumption until 2nd dose* | 0.6819 | 12 | – | – |
| QRxPharma | | TKA | NCT01055015 | Q8003 | Opioid | 141 | PID 48 | – | 10 | 10 | 1.41 |
| AcelRx Pharmaceuticals | | TKA | NCT00612534 | Oral sufentanil | Opioid | 188 | PID 12 | – | 1 | 7 | 26.86 |
| Endo Pharmaceuticals | Gimbel 2004 [45] | TKA/THA | Opana 3203-04 | Oxymorphone | Opioid | 300 | TOTPAR 8* | 0.72 | 29 | – | – |
| Endo Pharmaceuticals | | TKA/THA | Opana 3203-05 | Oxymorphone | Opioid | 324 | TOTPAR 8 | 0.6081 | 9 | – | – |
| Endo Pharmaceuticals | Ahdieh 2004 [1] | TKA | 2102-012 | Oxymorphone | Opioid | 126 | TOTPAR 12 | 0.4125 | – | – | – |
| QRxPharma | | TKA/THA | NCT00818493 | Q8003 | Opioid | 44 | PID 48 | – | 4 | 5 | 2.20 |
| AcelRx Pharmaceuticals | | TKA | NCT00859313 | Sufentanil NanoTab | Opioid | 30 | Percent of patients without device failure 12 | – | 3 | 4 | 2.50 |
| J&J | Hartrick 2009 [51] | TKA/THA | NCT00361582 | Tapentadol | Opioid | 666 | SPID 5 days | 0.464 | – | 10 | – |
| QRx Pharma | Joppich 2012 [57] | THA | Eudra CT-No.2008-008527-14 | Intravenous morphine + oxycodone | Opioid | 41 | SPID 65 minutes | 0.5458 | 2 | 10 | 2.05 |
| Forest Laboratories | | TKA/THA | OXY-MD-07 | Combunox | Opioid/ NSAID | | TOTPAR 6 | 0.9186 | – | – | – |
| Anesiva Inc.; Arcion Therapeutics | | TKA | 114-01P | 4974 Capsaicin | Other | 217 | AUC 48 | 0.2914 | 24 | – | – |
| Anesiva Inc. | | THA | NCT00683267 | 4975 Capsaicin | Other | 118 | PI (NRS) 2 days | – | 14 | 10 | 0.84 |
| Skye Pharma | Viscusi 2005 [119] | THA | SKY0401-011 | DepoDur | Other | 200 | Total fentanyl use 48 | 1.2586 | 23 | – | – |
| Skye Pharma | Martin 2006 [78] | THA | | DepoDur | Other | 126 | Total fentanyl use 48 | 1.4734 | 16 | – | – |
| Javelin Pharmaceuticals | | Orthopedic | NCT00709436 | Intranasal ketamine | Other | 250 | SPID 6 | – | 16 | 38 | 0.41 |
| Cadence Pharmaceuticals | Sinatra 2005 [100] | TKA/THA | RC2103-002 | Paracetamol | Other | 156 | TOTPAR 6 | 0.8923 | 7 | 9 | 2.48 |
| Bristol-Myers Squibb | | THA | NCT00344045 | Paracetamol | Other | 86 | Total tramadol consumption 24 | – | 5 | 22 | 0.78 |
| Baxter Healthcare Corp | | THA | NCT00508495 | Paracetamol | Other | 148 | PCA-morphine 6 | – | 8 | 7 | 2.64 |
| Orthopaedic Research & Innovation Foundation | | THA | NCT01106001 | Periarticular Levo Bupivicaine | Other | 91 | Difference in morphine consumption | – | 2 | 12 | 3.79 |
| Pfizer | Unpublished data | TKA | NCT00442546 | Pregabalin | Other | 307 | Mean worst pain 24 | 0.1379 | 28 | 19 | 0.58 |
| Pacira Pharmaceuticals | Bramlett 2012 [8] | TKA | NCT00485693 | SKY0402 | Other | 138 | AUC NRS-A 4 days | – | 10 | 26 | 5.31 |
| Pacira Pharmaceuticals | | TKA | NCT00745290 | SKY0402 | Other | 251 | AUC NRS-A 72 | – | 19 | 5 | 2.64 |
| KAI Pharmaceuticals | | TKA/THA | NCT01015235 | KAI-1678 | Other | 90 | SPID 4 | – | 1 | 14 | 6.43 |
| Average | | | | | | 209.9 | | 0.68 | 10.9 | | 3.9 |

TKA = Total Knee Arthroplasty; THA = Total Hip Arthroplasty; NSAID = nonsteroidal anti-inflammatory drug; TOTPAR = total pain relief; PID = pain intensity difference; SPI = sum of pain intensity; SPID = sum pain intensity difference; AUC = area under the curve; NRS = numerical rating scale.

* Study presented multiple primary endpoints.

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**Table 4**
Soft tissue surgery standardized effect size and enrollment rate summary.

| Sponsor | Source | Surgery type | Trial identification | Drug | Drug type | N | Primary endpoint | Standardized effect size | Number of sites | Duration of study (months) | Enrollment rate (subjects/center/month) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cumberland Pharmaceuticals | Kroll 2011 [65] | Hysterectomy | NCT00225732 | IV ibuprofen | NSAID | 319 | Mean morphine consumption 24† | 0.2807 | 10 | 36 | 0.89 |
| Javelin Pharmaceuticals | Gan 2012 [43] | Abdominal | NCT00448110 | IV diclofenac | NSAID | 331 | SPID 48 | – | 16 | 18 | 1.15 |
| Merck | Fleckenstein 2010 [39] | Abdominal | NCT00716833 | Etoricoxib | NSAID | 87‡ | Morphine use 48 | – | 2 | 58 | 0.75 |
| Merck | Viscusi 2012 [118] | Hysterectomy | NCT00788710 | Etoricoxib | NSAID | 430 | Average PI 3 days | 0.4971 | 39 | 21 | 0.53 |
| Merck | Sinatra 2006 [99] | Gynecological | | Rofecoxib | NSAID | 164 | Average total dose of opioid 5 days | 0.4467 | 7 | – | – |
| Pfizer | | Cholecystectomy | NCT00661635 | Valdecoxib | NSAID | 490 | SPI 24 | – | 65 | 8 | 0.94 |
| Pfizer | | Prostatectomy | NCT00346268 | Parecoxib | NSAID | 105 | Cumulative morphine consumption 24‡ | 0.4155 | 4 | 45 | 0.58 |
| Pfizer | Malan 2005 [71] | Gynecological | | Paracoxib | NSAID | 264 | TOTPAR 8 | 1.2529 | – | – | – |
| ROXRO Pharma | Singla 2010 [105] | Abdominal | NCT00266786 | Ketorolac | NSAID | 321 | SPID 1 day | 0.2471 | 6 | 14 | 3.82 |
| Endo Pharmaceuticals | Aqua 2007 [3] | Abdominal | NCT00226395 | Oxymorphone | Opioid | 320 | TOTPAR 6* | 0.5338 | 21 | 11 | 1.39 |
| J&J/Grunenthal GmbH | | Hysterectomy | NCT00478023 | Tapentadol | Opioid | 854 | SPID 24 | 0.5561 | 52 | 9 | 0.68 |
| Cara Therapeutics | | Hysterectomy | NCT00877799 | CR845 | Opioid | 114 | PI at rest after surgery | – | 12 | 10 | 0.95 |
| Forest Pharmaceuticals | Singla 2005 [103] | Abdominal | OXY-MD-10 | Combination Oxycodone/ ibuprofen | Opioid/ NSAID | 456 | TOTPAR 6 | 0.7933 | 26 | – | – |
| Knoll Pharmaceuticals | Palangio 2000 [88] | Gynecological | | Hydrocodone with ibuprofen | Opioid/ NSAID | 180 | Mean TOTPAR 8† | 1.4821 | 1 | – | – |
| Cadence Pharmaceuticals | | Gynecological | NCT00399568 | IV acetaminophen | Other | 331 | SPI 24 | 0.115 | 27 | 10 | 1.23 |
| Cadence Pharmaceuticals | Wininger 2010 [123] | Abdominal | NCT00564486 | IV acetaminophen | Other | 244 | SPID 24 | 0.2699 | 17 | 10 | 1.44 |
| DURECT Corp | | Hysterectomy | NCT00993226 | SABER-bupivacaine | Other | 115 | PI 3 days | – | 14 | 7 | 1.17 |
| Endo Pharmaceuticals | Carvalho 2005 [11] | Cesarean delivery | | DepoDur | Other | 79 | Total opioid use 48 | – | 8 | – | – |
| SkyePharma | Gambling 2005 [42] | Abdominal | | DepoDur | Other | 541 | Total IV fentanyl 48 | – | 55 | – | – |
| Innocoll Technologies | | Hysterectomy | NCT00624910 | CollaRx bupivacaine | Other | 54 | Opioid rescue 24 | – | 1 | 9 | 6.00 |
| Innocoll Technologies | | Hysterectomy | NCT00749749 | CollaRx bupivacaine | Other | 27 | Opioid rescue 24 | – | 1 | 3 | 9.00 |
| Pacira Pharmaceuticals | | Herniorrhaphy | NCT00485433 | DepoBupivacaine | Other | 98 | AUC NRS-A 72 | – | 7 | 6 | 2.33 |
| Pacira Pharmaceuticals | | Herniorrhaphy | NCT01203644 | DepoBupivacaine | Other | 76 | Time to 1st supplemental pain medication 96 | – | 16 | 13 | 0.37 |
| Pacira Pharmaceuticals | Gorfine 2011 [48] | Hemorrhoidectomy | NCT00890721 | DepoBupivacaine | Other | 189 | AUC 72 | 0.5867 | 13 | 8 | 1.90 |
| Pacira Pharmaceuticals | | Hemorrhoidectomy | NCT00529126 | DepoBupivacaine | Other | 100 | AUC 72 | – | 7 | 3 | 4.76 |
| Pacira Pharmaceuticals | | Hemorrhoidectomy | NCT00744848 | DepoBupivacaine | Other | 220 | AUC 96 | – | 20 | 6 | 1.83 |
| Pfizer | Mathiesen 2009 [79] | Hysterectomy | NCT00209495 | Pregabalin | Other | 130 | Morphine consumption 24* | – | 2 | 29 | 2.24 |
| Pfizer | Paech 2007 [87] | Gynecologic | | Pregabalin | Other | 99 | Predischarge pain | 0.0952 | 1 | 7 | 12.86 |
| Pfizer | Unpublished data | Hysterectomy | NCT00468845 | Pregabalin | Other | 501 | Mean worst pain 24 | 0.0902 | 42 | 35 | 0.34 |
| Pfizer | Unpublished data | Herniorrhaphy | NCT00551135 | Pregabalin | Other | 425 | Mean worst pain 24 | 0.2078 | 42 | 20 | 0.51 |
| Average | | | | | | 261.3 | | 0.50 | 18.4 | | 2.4 |

PI = pain intensity; TOTPAR = total pain relief; SPID = sum pain intensity difference; SPI = summed pain intensity; AUC = area under the curve; IV = intravenous.
* Multiple primary endpoints.
† Not primary endpoint.
‡ Study was terminated.

**Table 5**
Demographics by surgical model.

| | Dental | Bunion | JRS | STS |
|---|---|---|---|---|
| Total subjects | 13,875 | 5073 | 3116 | 4357 |
| Average age (years) | 22.2 | 43.4 | 59.2 | 44.6 |
| Sex (%) | | | | |
| Male | 40 | 16 | 45 | 22 |
| Female | 60 | 84 | 55 | 78 |
| Race | | | | |
| White | 77 | 63 | 91 | 69 |
| Hispanic | 9 | 15 | 1 | 4 |
| African American | 5 | 16 | 6 | 17 |
| Other | 9 | 6 | 2 | 10 |
| Baseline pain (%) | | | | |
| Moderate | 65 | 46 | 49 | 78 |
| Severe | 35 | 54 | 51 | 22 |
| Average duration of surgery (minutes) | 17.7 | 29.8 | 70.9 | 82.3 |

JRS = joint replacement surgery; STS = soft tissue surgery.

from hours 72 to 120 [94]. After hour 120, measuring treatment effect is challenging because a significant portion of patients no longer require analgesic therapy [9,94]. Bunionectomy is typically an outpatient procedure. Therefore a common misperception is that the surgery is not painful, and as such is ill-suited to the evaluation of intravenous analgesics. In fact, when performed under experimental conditions, the anesthesia protocol for bunionectomy can be manipulated so that subjects experience the amount of pain requisite for multiple-day experiments, but not so much pain that the postoperative course becomes unethical or below a reasonable standard of care.

#### 3.2.2. Surgical and anesthetic protocol

Surgical inclusion criteria in bunion models are relatively homogeneous and are not purposefully manipulated to affect the postoperative pain trajectory (in contrast to the manipulations utilized in the dental model that are described in Fig. 2). Generally, only subjects with type 2 hallux valgus deformity requiring first unilateral metatarsal head osteotomies are enrolled. Subjects with a type 3 deformity requiring a base wedge osteotomy (a more extensive procedure) or those requiring concomitant surgery such as hammertoe repair are excluded [29,94].

Alterations in the anesthetic protocol are the main experimental manipulation utilized in the model primarily because the intraoperative infiltration of local anesthetics and performance of any concomitant nerve block can predictably alter the postoperative pain course. That being the case, the anesthetic regimen dictated by each protocol is distinct and is specifically designed to optimize the pain trajectory required for the experiment. Once selected, anesthetic protocols tend to be prescriptive and allow few discretionary modifications based on local practice.

Duration and density of postoperative analgesia secondary to local anesthetic infiltration are influenced by altering the type and volume of intraoperative infiltration (ie, 20 mL of long-acting bupivacaine vs 10 mL of shorter-acting lidocaine) [2,47,94]. In some instances, popliteal catheters are utilized to continuously infuse local anesthetic near the sciatic nerve to provide dense anesthesia over a prolonged period of time [55,95,102]. These catheters are used when there is a desire to delay the onset of postoperative pain until 18 or 24 hours after the initial surgical insult. A delayed pain trajectory is desirable when there is concern that the otherwise unfettered pain intensity from bunionectomy in the early postoperative hours (0 to 24 hours after surgery) will overwhelm the experimental agent, and as such the 24+ hour pain trajectory is preferred. In these circumstances, randomization is delayed until after the nerve block catheter is removed and the patient subsequently develops moderate or severe pain intensity.

#### 3.2.3. Enrollment rate

Similar to the dental model, the bunionectomy model generally relies on the research grant to subsidize the cost of the surgical procedure. As such, the 2 models share several characteristics: rapid subject acquisition (20 bunion subjects/center/month) at a few centers (average 4.5) that primarily focus on analgesic research (Fig. 3, Table 2).

#### 3.2.4. Assay sensitivity

Average bunion SES was 0.92; 39% less than dental, 35% greater than JRS, and 84% greater than STS (Fig. 4). Bunionectomy and JRS share a similar pathophysiology, yet SES in bunionectomy is significantly higher. The pain response in both surgical models emanates primarily from bony injury, and JRS is the more painful of the two. Why then is the SES in bunionectomy greater? We speculate that the conditions under which bunionectomy studies are performed (few centers, trained staff, control of standard of care confounders) reduce experimental error.

#### 3.2.5. Model limitations

Similar to the dental model, the main criticism of the bunion model is its lack of clinical relevance. In contrast to STS or JRS, bunionectomy performed in clinical practice (outside of research settings) is an outpatient procedure performed primarily on young (mean age 43.4) women (84%; Table 5), that can be managed with copious intraoperative local infiltration and oral analgesics [77,97]. If one is investigating a potent intravenous analgesic meant primarily for relief of pain in elderly hospitalized subjects, clinicians and regulators have argued that efficacy and safety findings in the bunionectomy model are not generalizable.

### 3.3. Joint replacement surgery model

#### 3.3.1. Introduction

Over 1 million patients undergo joint replacement surgery (total knee or total hip arthroplasty) annually [108]. These surgeries are generally performed on older (mean age 70.9) [56,120] individuals who have significant concomitant pathologies and are preoperatively on several prescription drugs [38]. Postoperatively, patients are hospitalized with an average length of stay of 5 days [7,52]. During this inpatient stay, multiple drugs and techniques are used to ameliorate postsurgical pain [101]. After approval, potent analgesics intended for inpatient use will frequently be administered (1) to subjects who match the demographics of those included in the JRS model and (2) in institutions similar to those in which JRS subjects have surgery and convalesce. Therefore, the model is regarded as clinically relevant by regulators and prescribing physicians.

#### 3.3.2. Surgical and anesthetic protocol

Because of their frequency, joint replacements represent an important service line in most multispecialty hospital environments. Local standards are agreed upon and protocolized by a diverse care team, with significant attention focused on improving the patient's postoperative pain experience. Every local standard is unique because the standard depends heavily on the human and technical resources available at the institution that creates it. Therefore, perioperative analgesic management of joint replacement subjects between institutions is variable, and within institutions, dogmatic. Research protocols that attempt to control analgesic confounders are in many instances in conflict with institutional practices.

There is significant heterogeneity in the surgical techniques used to accomplish joint replacement [86]. For hip replacement

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specifically, minimally invasive surgery and an anterior surgical approach reduce tissue damage, postoperative pain, and length of hospital stay [61,106]. Standard of care anesthetic techniques are also heterogeneous. The availability of ultrasound guidance is increasing the popularity of femoral nerve blocks in total knee replacement surgery. In both knee and hip arthroplasty, multimodal analgesic therapy and neuraxial anesthesia are in common use [70,101].

Successful JRS studies generally attempt to control surgical and anesthetic confounders by disallowing subjects scheduled to receive minimally invasive surgeries, bilateral joint replacement, revision arthroplasties, nerve blocks, epidural analgesia, and analgesic adjuncts (eg, nonsteroidal anti-inflammatory drugs, pregabalin, acetaminophen) [1,10,90,119]. Protocols also attempt to minimize variability by standardizing institutional confounders such as (1) use of perioperative ice and cooling devices, (2) timing and frequency of physical therapy, and (3) use of continuous passive range of motion devices [45,91].

#### 3.3.3. Enrollment rate

Enrollment into JRS studies is slower than enrollment into dental impaction or bunionectomy studies. Only 3.9 subjects per center per month were recruited into JRS protocols, necessitating a large number of centers (average 11) to accrue subjects in a timely fashion (Fig. 3). Dental and bunion enrollment is faster than JRS for the following reasons: (1) JRS is an expensive inpatient surgery that cannot practically be subsidized by the research grant, (2) JRS patients identified for the study are otherwise scheduled for elective surgery at participating institutions, performance of the surgery is not predicated on study participation, (3) therefore, subjects in JRS protocols must be garnered from hospital databases or physician offices (not recruited via advertisement as with bunion and dental subjects), and consequently (4) funneling subjects into nonhospital-based standalone research institutions is impractical.

#### 3.3.4. Assay sensitivity

Although in our review the average SES for JRS was 0.68 (Fig. 4), the true value is probably significantly lower and has been inflated here secondary to publication bias (see Section 4 for details). The average sample size for JRS studies reviewed was 209. In a 2-arm study with a total enrollment of 209, if one desires 90% power to detect an alpha of 0.05, an SES of at least 0.45 is required. When average SES values near 0.45 in studies with 209 subjects, the risk of trial failure is high. If our reported average JRS SES of 0.68 is in fact inflated, the high frequency of late-phase JRS failures is an unfortunate but predictable consequence.

#### 3.3.5. Model limitations

To adequately care for postsurgical patients, hospitals have protocols and norms outside the research study that dictate standard of care perioperative treatment [6,70,124]. These institutional norms, although clinically useful, often introduce analgesic confounders. The problem is compounded when multiple research centers are involved with a single project. Slow recruitment rates force programs to adopt a multicenter approach in order to complete enrollment in a reasonable timeframe. As a result, the study protocol is forced to accommodate a range of local practices and to allow some degree of surgical and anesthetic variation. These compromises increase variability, in turn reducing SES.

### 3.4. Soft tissue surgery model

#### 3.4.1. Introduction

STS represents a diverse group of surgical procedures that are generally performed on an inpatient basis. As a group, they are common and as such are of significant clinical interest to regulators and prescribing physicians. Within most studies, the specific procedure type was not homogenized, forcing us to categorize disparate surgeries into this model. Our a priori definition of STS was abdominal or pelvic surgeries not involving significant bony injury. Hysterectomy, cholecystectomy, cesarean section, herniorrhaphy, hemorrhoidectomy, and prostatectomy were all represented. The surgical insult and recovery from this incongruent group of procedures is heterogeneous, confounding our analysis.

#### 3.4.2. Surgical and anesthetic protocol

In the discussion of previous surgical models, specific surgical and anesthetic comparisons were possible because the surgery types were relatively homogeneous. In STS, the surgical and anesthetic paradigms are so variable [48,87,99] that meaningful comparisons could not be made. One consistent feature throughout most STS studies was that an attempt was made to control for laparoscopic vs open approaches [3,65,71,118]; either only laparoscopic or only open procedures were allowed. Although the dental and bunion models altered surgical and anesthetic management to optimize experimental conditions, precise manipulations of this sort were not attempted in STS. Instead of optimization, focus was placed on surgical standardization and the avoidance of obvious perioperative confounders such as epidural analgesia, neuraxial opioids, adjuvant medications, nerve blocks, and infiltration analgesia (both single-dose and via continuous infusion) [39,65,103,105].

#### 3.4.3. Enrollment rate

STS has the slowest enrollment rate of all models considered (Fig. 3). It suffers from the same logistical problems as JRS, inability to subsidize procedural costs and therefore funnel patients into select units. The problem for STS is compounded by the fact that recent advances in laparoscopic surgery have divided the already thin field of potential candidates into 2 categories: laparoscopic and open.

#### 3.4.4. Assay sensitivity

Of all 4 models, STS had the lowest SES values (74%, 54%, and 33% of JRS, bunionectomy, and dental, respectively; Fig. 4). Low SES values in STS are difficult to attribute squarely to experimental error because STS is the only soft tissue model examined; dental, bunion, and JRS are all regarded as bony models. Perhaps the pathophysiology of STS is unique, such that our current spectrum of analgesics is actually, not artificially, less effective against soft tissue pain. In STS, pain results not only from soft tissue trauma, but also from ileus, bloating, cramping, and insufflation-related diaphragmatic irritation [5,85].

#### 3.4.5. Model limitations

Although low SES values in STS may be attributable to unique pathophysiology, STS is subject to the same institutional confounders as JRS. Both models generally must be performed inside multispecialty hospitals and cannot be executed within controlled research-centric units. Like JRS, slow recruitment in STS necessitates a multicenter approach. Often, investigators within an institution are compelled to pool their resources and enroll subjects emanating from several surgical practices. Although this process can be positive and collaborative, it increases variability. Finally, the episodic nature of cramps and gas pain in STS may lead to spurious analgesic measurements [85].

## 4. Discussion

Our conclusions have relied heavily on SES data. Although study design and conduct impact SES, the inherent efficacy of the study

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| Molecule (dose/route) | Dental | Bunion | JRS | ASTS |
|---|---|---|---|---|
| Rofecoxib (50mg/PO) | 1.45* | 0.78 | 0.57 | 0.45 |
| Tapentadol (75mg/PO) | 0.63 | 0.80* | 0.46 | 0.54 |
| Combunox (5mg/400mg/PO) | 1.51* | -- | 0.74 | 0.79 |
| Etoricoxib (120mg/PO) | 1.87* | -- | 0.53 | 0.50 |
| Ibuprofen (800mg/IV) | 0.96 | -- | 0.65 | 0.22* |
| Paracetamol (1000mg/PO) | 0.98* | -- | 0.89 | 0.19* |

*Average SES based on more than one study performed in the model.

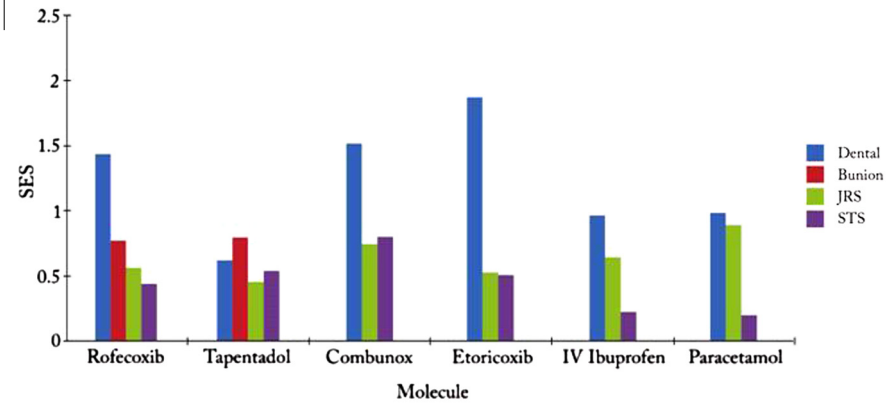


**Fig. 5.** Standardized effect size in specific surgical models with molecule, dose, and route held constant. Combunox (oxycodone HCl/ibuprofen), etoricoxib, intravenous ibuprofen, and paracetamol were not studied in the bunionectomy model. *Average of multiple SES values if more than 1 study was conducted utilizing a particular model. JRS = joint replacement surgery; STS = soft tissue surgery; PO = oral; IV = intravenous; SES = standardized effect size.

molecule exerts a significant influence. To address this issue, we rearranged a subset of our data to control for molecule, dose, and route of administration (Fig. 5). We found 2 molecules that have been studied in all 4 surgical models and 4 molecules that have been studied in at least 3 models. We made no statistical comparisons, but the numerical trend is apparent; a significant decrease in assay sensitivity from the dental and bunion models (well-controlled investigations performed at few centers) to the JRS and STS models (clinically confounded investigations performed at many centers).

In our primary analysis, SES values were averaged, not weighted based on study enrollment. Meta-analytical techniques that attempt to estimate the true treatment effect of a drug in a population must consider how many patients were enrolled in each study because there is an assumption that all experiments are subject to the same degree of experimental error. Variations in SES values between studies are assumed to be random. Therefore, studies with higher sample sizes are considered to be more reliable (less random) and given more weight. Our premise was the opposite; we assumed that SES variations were not random but could in fact be systematically predicted. Here, each study SES represented a best-effort scenario within each surgical model, and an averaging of all of these best-effort attempts without regard to sample size was therefore considered to be a more accurate way to evaluate experimental error.

The SES analysis did not attempt to control for number of centers, randomization schemes, endpoint characteristics, imputation methods, or rescue paradigms. If the purpose of the systematic review had been to quantitatively measure the confounding characteristics of specific study features, a multivariate analysis would have been appropriate. Here, an attempt was made to compare surgical models, not specific study features, with the important output being SES trends rather than absolute values.

We chose to limit our review to data published or presented after 1998. Numerous acute pain studies with valuable information were performed before this date. However, the surgical approach, anesthetic management, and perioperative care of patients undergoing JRS and STS have evolved significantly over the past 15 years. The models are inherently different than they once were; therefore, inclusion of studies performed before this date would have confounded our analysis. Additionally, we chose to include only industry-sponsored studies because a priori we hypothesized that sponsorship status would affect study methodology and SES trends. Post-hoc, we reanalyzed our data and found that the inclusion of nonindustry-sponsored studies did not materially change our results (data on file).

It is likely that publication bias inflated our SES results. Studies that report positive findings tend to be published more frequently than studies that report negative findings [107]. Negative studies have SES values that fall short of predictions made during the design phase. Our investigation relied heavily on published studies. Of 89 studies that met SES criteria, 86 (97%) were positive. The specific percentage of acute pain investigations that yield positive results is unknown, but 97% is clearly an overestimation.

It is probable that recruitment data presented are also inflated. The subject per center per month calculation is predicated on the number of centers that were reported in the relevant data source. In late-phase studies, approximately 27% of centers fail to enroll any patients [59]. Nonenrolling centers are generally not included in the final tally when total number of centers is disclosed. If true, our subject/center/month quotient would have been artificially increased. Similar to the SES analysis, trends are the reliable output.

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### 4.1. Conclusions

Surgical procedures have unique clinical characteristics that influence the degree to which their experimental properties can be idealized. We found that the dental impaction and bunionectomy models had higher assay sensitivity than the JRS and STS models. It is probable that this finding is secondary to the superior experimental conditions under which the dental and bunion models are executed (utilization of few centers that have the ability to limit surgical, anesthetic, and postoperative variability). Joint replacement and soft tissue surgery are, in general, complex procedures that require inpatient care. From an experimental standpoint the hospital is a nonideal environment because it is confounded by the effects of multispecialty care.

Over the past 60 years, pioneers in acute pain research have posed, debated, and resolved several key methodological questions. The knowledge garnered through their purposeful study has been successfully applied to the dental and bunion models. However, a significant gap exists in the application of these principles to the JRS and STS models. Certain groups are experimenting with techniques that may improve the assay sensitivity of JRS and STS.

Specifically, an outpatient model for STS that mirrors the experimental conditions of the dental and bunion models is being developed (subjects recruited through advertisement, cost of surgical care subsidized with subsequent funneling of participants into research-centric units). Herniorrhaphy, abdominoplasty, and laparoscopic cholecystectomy are outpatient soft tissue procedures that are candidates for model development. If one of these models consistently demonstrates adequate assay sensitivity, it could be utilized to generate drug efficacy data in soft tissue on an outpatient basis, avoiding the confounding effects of multispecialty inpatient care.

There are circumstances in which an inpatient environment should not or cannot be avoided (eg, a new drug administered via a patient-controlled analgesic device). In these situations we theorize that several modifications can be made to hospital-based experiments that have the potential to improve their assay sensitivity: (1) reducing the number of research centers participating in a single study, (2) limiting the surgical variance by including only specific surgeries performed utilizing a consistent technique, (3) controlling anesthetic management and perioperative care, (4) training subjects on placebo response and completion of protocol-mandated analgesic scales, and (5) education of investigators and study staff on bias reduction and uniform data gathering techniques.

Further study will be required to correlate and quantify the specific design features that are responsible for degrading assay sensitivity in the JRS and STS models. By implementing and critically evaluating new techniques, the knowledge garnered from the work of previous analgesic methodologists may be expanded.

## Conflict of interest statement

Potential Conflicts of Interest: Dr. Singla currently serves as CEO for Lotus Clinical Research, LLC, which received research grants for its participation in some of the studies cited in this review. Dr. Singla has served as a consultant for the following companies: Cumberland Pharmaceuticals, Cadence Pharmaceuticals, AcelRx, Astellas Pharma Europe B.V., Imprimus Pharmaceuticals Inc, Revogenex, Theravance Inc, ProFibrix, Inc, Mallinckrodt Inc, Pacira, PPD Development, LLC, CARA and others. Dr. Desjardins served as Sr. Vice President for Scirex Corporation, which received research grants for some of the studies cited in this review. He was an employee of Wyeth Consumer Healthcare and Pfizer Consumer Healthcare from 2005 until 2011. He is currently President of Desjardins Associates, LLC. Dr. Desjardins has served as a consultant for the following companies: Pfizer, Grunenthal USA, Novartis Consumer Healthcare, Adynxx, Regenesis Biomedical, Dental Leaning Systems, CRO Analytics, Medtronics, Proctor & Gamble and Reckitt Benckiser.

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