

# Standardizing research methods for opioid dose comparison: the NIH HEAL morphine milligram equivalent calculator

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## Abstract

We developed the National Institutes of Health helping to end addiction long-term initiative morphine milligram equivalent (MME) calculator to standardize MME calculations across pain research studies, addressing a critical barrier to effective research synthesis and meta-analysis. The tool provides evidence-based mapping factors for 29 opioids through a research electronic data capture-based calculator and companion Web site ([research-mme.wakehealth.edu](http://research-mme.wakehealth.edu)). Development involved systematic evidence evaluation of literature from 1949 to March 2024, following PRISMA guidelines. From an initial screening of over 170,050 articles, we identified 24 studies providing evidence for conversion factors. The calculator incorporates 4 standardized time-window calculation methods aligned with current research approaches and includes traditional full agonists, partial agonists, and mixed-mechanism agents. Using modified GRADE methodology, we evaluated evidence quality for each conversion factor, documenting levels from high-quality randomized controlled trials to pharmacokinetic extrapolation. Our tool replicates most existing Centers for Disease Control and Prevention (CDC) conversion factors while expanding coverage to 7 additional opioids and 6 formulations not included in the 2022 CDC conversion table. The calculator features options to analyze results with or without buprenorphine, accommodating its emerging role in pain research. This standardized framework enables researchers to map opioid doses using consistent, evidence-based ratios and harmonize data collection across research networks. While the tool represents a significant advance in standardizing MME calculations for research, limitations in the underlying evidence base highlight the need for continued validation through clinical research.

**Keywords:** Opioid analgesia, FAIR (findable, accessible, interoperable, reusable), Morphine milligram equivalents (MMEs), Data calculator tool, NIH HEAL, Data harmonization

## 1. Introduction

Standardizing pain research data collection and analysis methodologies remains a critical challenge in the field of pain science. The National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) Initiative Common Data Elements (CDE) program addresses this need through harmonization of data collection across funded pain research studies.<sup>2,3,54</sup> Recognizing the importance of consistent opioid measurement, in 2023 the program mandated collection of morphine milligram equivalents (MME) data for all NIH HEAL-funded pain studies involving opioids.<sup>25</sup>

Pain research faces a fundamental methodological challenge: the lack of standardization in quantifying opioid doses across studies. While MMEs serve as a common metric for comparing different opioids, inconsistencies in calculation methods and mapping (or conversion) factors create significant barriers to research synthesis.<sup>20</sup> For example, 2 clinical trials evaluating identical opioid reduction strategies may yield discordant outcomes not because of true therapeutic differences but rather because of variability in the MME conversion factors or calculation methodologies used, even when analyzing identical opioid agents. When studies use different mapping factors or calculation

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approaches, their results cannot be directly compared without significant caveats. This heterogeneity complicates the interpretation of research findings and introduces additional uncertainty into literature comparisons, systematic reviews, and meta-analyses examining opioid-related outcomes.

The shortcomings in the development of current MME tools are thoroughly discussed in the literature.<sup>5,20,42</sup> Many commonly used factors derive from studies conducted in the 1940s and 1950s that compared analgesic efficacy in acute pain and cancer pain settings.<sup>8,13,14,18,19,27,29–31,33,35,53</sup> As acknowledged by investigators conducting these seminal studies, their methodological approaches and study populations may not adequately represent contemporary pain research paradigms.<sup>28</sup> Recent efforts to standardize MME calculations, such as the 2022 Centers for Disease Control and Prevention (CDC) guidelines, have helped establish common factors for frequently prescribed opioids.<sup>16</sup> However, these guidelines focus on MME primarily as a marker for opioid-related adverse drug events (ORADES) rather than pain equianalgesia.<sup>16,17</sup> The CDC excluded several opioids that may be important in pain research, including buprenorphine formulations indicated for pain management.<sup>51,55,57</sup> This creates a gap for researchers studying the full spectrum of available opioid analgesics.

To address these challenges, the NIH HEAL Initiative established required standards for the development of an MME calculator (tool) to be required for use by studies funded by the Initiative.<sup>25</sup> These 2 key design requirements were comprehensive inclusion of all opioids potentially used in pain research and incorporation of 4 predefined MME calculation methods. Through systematic evidence evaluation, we established consistent mapping factors and calculation approaches to enable reliable cross-study comparisons.

Building on our extensive experience developing research instruments in collaboration with the NIH HEAL Initiative CDE team,<sup>1–3</sup> we sought to develop a comprehensive tool incorporating evidence-based mapping factors derived from systematic literature review, standardized calculation methods for various MME/Day time-window definitions of additional opioids pertinent to pain research. This approach ensures transparent documentation of calculation methodology, facilitates cross-study comparisons using different calculation methods, and establishes a framework amenable to future updates of mapping factors. Through development of this standardized instrument for converting opioid doses to MMEs in research settings, we aim to advance pain research methodology by documenting the supporting literature for each mapping factor and enabling consistent MME/Day calculations across multiple pain-related definitions using time windows. This standardization will facilitate interstudy comparisons, trend identification, and ultimately strengthen the evidence base in pain research. Importantly, our work focuses exclusively on providing a research methodology tool and does not address clinical practice applications or prescribing guidance.

## 2. Methods

### 2.1. Tool development

The tool was then developed using the selected conversion factors to calculate the Total MME/Day. In addition, the tool incorporates 4 distinct MME/Day calculation methods selected by the NIH HEAL CDE program as defined by Dasgupta et al.<sup>10</sup> and Goud et al.,<sup>21</sup> allowing researchers to examine how different calculation approaches might affect their findings. We

developed pain-related use-case examples for each of the time windows (Supplement 1, <http://links.lww.com/PAIN/C213>). Research electronic data capture was selected as the primary research collection method because of its ability to collect metadata that aligns with the Findability, Accessibility, Interoperability, and Reuse (FAIR) data standards.<sup>32</sup>

### 2.2. Literature review and selection process

We conducted a comprehensive literature review from 1949 to March 1, 2024 using PubMed and Google Scholar as primary databases, with verification searches in MEDLINE(via OVID). The literature and extraction process followed PRISMA guidelines<sup>44</sup> (Supplement 2, <http://links.lww.com/PAIN/C213>).

We included peer-reviewed original research articles published in English or with accessible translations. Studies were required to include a morphine comparison and provide recommended conversion ratios between morphine and other opioids. We excluded conference proceedings, abstracts without full text, letters to the editor, commentaries, and editorials from our analysis. PubMed (search terms: “opioid name” AND morphine AND [conversion OR equianalgesic OR equivalent OR ratio]) and Google Scholar (search terms: “opioid name” morphine dose equivalence) yielded a total of 6124 and 263,210 titles, respectively. After duplicates and excluded literature types were removed from the PubMed and Google Scholar searches, the remaining 170,050 (2532 and 96,830, respectively) articles were screened by reviewing the title for relevance yielding 2640 articles. Abstracts of these articles were reviewed for relevance yielding 174 articles. Manual reference list search of the full-text articles identified an additional 28 articles for full-text review. The full text of 202 articles was assessed by 2 reviewers (R.W.H., M.C.B.A.). One hundred eighty-two papers were excluded for lack of conversion factors or ability to calculate a factor. We arranged group discussions for those articles marked as uncertain during the review of abstracts and extraction process of full articles, and all potential differences were resolved by consensus (R.W.H., M.C.B.A., L.W.). A total of 24 studies<sup>6,9,15–19,22,26,34,36,37,39,40,42,43,45–47,49,50,52,56,58</sup> were identified as potential sources for opioid conversion factors and were extracted (Supplement 2, <http://links.lww.com/PAIN/C213>). MEDLINE via OVID was then used as a confirmatory database. The same search terms were used; however, all target opioids were combined using the Boolean operator “OR” to reduce duplicates (tramadol OR tapentadol OR dihydrocodeine OR codeine OR oxymorphone OR hydrocodone OR hydromorphone OR methadone OR levorphanol OR oxycodone OR oxymorphone OR meperidine OR butorphanol OR buprenorphine OR pentazocine OR fentanyl) AND morphine AND (conversion OR equianalgesic OR equivalent OR ratio). This confirmatory search yielded 1700 manuscripts. These citations were downloaded, deduplicated, and compared to the initial searches. No additional papers were identified after application of inclusion/exclusion criteria.

### 2.3. Evidence evaluation and mapping (conversion) factor selection

We evaluated evidence quality using modified GRADE methodology, applying distinct assessment approaches for overall conversion factors and individual supporting studies.<sup>7,23,48</sup> Two reviewers (R.W.H., M.C.B.A.) independently assessed all quality evidence of the remaining 24 studies. In evaluating conversion

factors, opioids with multiple published mapping factors, we selected those with the highest level of evidence. In cases where reviewer consensus could not be reached through this process, NIH HEAL Initiative representative (L.W.) was consulted for final arbitration.

### 3. Results

We developed 2 implementations of the NIH HEAL Initiative MME calculator to maximize accessibility and utility for researchers. The primary version consists of a research electronic data capture (REDCap)-based calculator that enables simultaneous data collection and MME calculation.<sup>24</sup> Research electronic data capture has the NIH HEAL required capability to collect metadata that aligns with the Findability, Accessibility, Interoperability, and Reuse (FAIR) data standards.<sup>32</sup> To accommodate researchers using different data collection platforms, we also created a companion Web site (<https://research-mme.wakehealth.edu>) that provides identical calculations. The Web site provides an application programming interface (API) that enables automated data exchange with external Web sites and databases, thereby reducing researcher burden and potential manual data entry errors.<sup>41</sup> The tool's API enables automated data exchange between research databases and the calculator facilitating large-scale analysis across multiple studies.<sup>4</sup> This allows research teams to integrate standardized MME calculations directly into their existing data pipelines, supporting harmonization of opioid-related data across the NIH HEAL Initiative and broader research community.

The tool encompassed 29 opioids, including 7 opioids and 6 formulations not previously included in the 2022 CDC conversion table (Table 1). The literature evaluation largely replicated 15 existing conversion factors from CDC guidelines, with a modification to the tapentadol factor from 0.4 to 0.3, supported by new clinical evidence from Mercadante et al.<sup>39</sup> and updated ANZCA guidelines (Fig. 1).<sup>6</sup>

The evidence supporting conversion factors was systematically evaluated and stratified according to established GRADE criteria, encompassing randomized controlled trials, observational studies, systematic reviews, and expert consensus statements (Table 2). The most common level of evidence for mapping factors was GRADE B (moderate) followed by D (very low), then A (high), and C (low). The levels of evidence for mapping factors for various buprenorphine formulations were downgraded to D based on the lack of a secondary source meeting inclusion criteria: transdermal buprenorphine and buprenorphine opioid use disorder formulations used off-label for pain management factors rely on Nielsen et al.,<sup>42</sup> while buccal formulation conversions derive from pharmacokinetic studies referenced in earlier CDC guidelines.<sup>16</sup>

### 4. Discussion

The NIH HEAL Initiative MME Calculator fulfills a critical need for standardized opioid data collection in pain research. It aligns with the NIH HEAL Initiative Common Data Elements (CDE) program requirements, enabling precise calculation of total morphine milligram equivalents (Total MME) and daily MME (MME/Day). The tool captures essential data, including opioid name, formulation, dosage, administration frequency, quantity, and treatment duration, across various time windows to support rigorous and consistent pain research methodologies.

This research tool introduces several advances in opioid conversion methodology. An application programming interface enables automated data exchange between research databases and the calculator. The tool implements 4 distinct calculation methods for daily morphine milligram equivalents (MME). Although these temporal parameters were initially developed for adverse event (eg, ORADE) monitoring,<sup>10</sup> we adapted the intervals to reflect patterns of analgesic use<sup>21</sup> and designated them as Pain Morphine Milligram Equivalents per Day (Pain MME/Day). Research teams can thus select calculation approaches aligned with their specific outcomes and data requirements, including analyzing results using multiple definitions when appropriate. Given the documented impact of calculation methods on MME totals and research interpretation,<sup>10,21,25</sup> this approach provides methodological standardization while preserving analytical flexibility. The tool's evidence grading system allows investigators to evaluate the empirical foundation of their analyses.

Our evidence review largely replicated existing conversion factors while creating a standardized tool for calculating morphine milligram equivalents (MMEs) across the 29 opioids. This comprehensive coverage includes traditional full agonists, partial agonists, and mixed mechanism agents with potential use in NIH HEAL funded pain research. While our findings align with recent reviews of clinical conversion factors,<sup>12</sup> with 1 notable exception of tapentadol, our tool expands beyond earlier guidelines<sup>16,17,42</sup> to include the full potential range of opioid medications being investigated in NIH HEAL pain research. The analysis and documentation of evidence quality behind the selected conversion factors allows investigators to evaluate the empirical basis underlying them as they interpret future study results. The overwhelming similarity of the conversion factors likely reflects the limited underlying evidence base, although our findings are specifically intended for pain research rather than clinical use.<sup>16,17,20,38</sup> The calculator expands beyond traditional clinical tools by including medications potentially relevant to human analgesia research, such as partial agonists and mixed-mechanism opioids that have been debated in clinical calculators.<sup>17,20</sup>

Mapping factors for the included fentanyl formulations presented unique challenges because of their food and drug administration (FDA) indication for opioid-tolerant patients only. For transdermal fentanyl, we selected a mapping factor of 2.4 based on evidence from both Reddy et al.<sup>46</sup> and Nielsen et al.<sup>42</sup> The other fentanyl formulations lacked direct evidence; therefore, the methodology similar to that used in previous CDC guidelines was adopted.<sup>16,17</sup> A notable advancement is the inclusion of buprenorphine, which recent CDC guidelines omitted because of its historical use in treating opioid use disorder and its differential effects on analgesia and respiratory depression.<sup>5,20</sup> The incorporation of buprenorphine conversion factors is supported by emerging evidence in pain management research<sup>55,57</sup> and clinical practice,<sup>11,17,38</sup> the tool's focus on analgesic equivalence, and FDA approval of transdermal and buccal formulations for pain treatment. To maintain flexibility, buprenorphine calculations are optional, allowing researchers to analyze data with or without buprenorphine based on their study objectives.

The NIH HEAL MME Calculator faces several important constraints in its application. As with all MME conversion tools, it cannot account for individual patient variability in opioid metabolism and response,<sup>20</sup> while the underlying concept of equianalgesic dosing necessarily simplifies complex pharmacological interactions. The evidence base for most opioid

**Table 1****National Institutes of Health helping to end addiction long-term initiative morphine milligram equivalent mapping table.**

Medication (oral formulation unless otherwise specified)	Mapping factor*	Equianalgesic dose†	Mapping factor reference	Medication evidence level <sup>8,24</sup>
Buprenorphine tablet/film (mg) sublingual	38.8	0.26 mg	Nielsen, 2016 <sup>42</sup>	Very low (D)
Buprenorphine buccal film (mcg) buccal	0.039	263 mcg	CDC, 2016 <sup>16</sup>	Very low (D)
Buprenorphine patch (mcg/hr) transdermal	2.2	4.55 mcg/h	Nielsen, 2016 <sup>42</sup>	Very low (D)
Butorphanol (mg)	7	1.42 mg	Dobkin, 1974 <sup>15</sup> ; CDC, 2016 <sup>16</sup>	High (A)
Codeine (mg)	0.15	66.7 mg	CDC, 2022 <sup>17</sup> ; Himmelsbach 1941 <sup>26</sup>	Moderate (B)
Dihydrocodeine (mg)	0.25	40 mg	CDC, 2016 <sup>16</sup> ; Gravenstein 1956 <sup>22</sup>	Moderate (B)
Fentanyl buccal (mcg)	0.13	77 mcg	CDC, 2016 <sup>16</sup>	Very low (D)
Fentanyl oral lozenge (mcg)	0.18	55.6 mcg	CDC, 2016 <sup>16</sup>	Very low (D)
Fentanyl nasal (mcg)	0.16	62.5 mcg	CDC, 2016 <sup>16</sup>	Very low (D)
Fentanyl patch (mcg/h)	2.4	4.2 mcg/h	Nielsen, 2016 <sup>42</sup> ; Reddy, 2016 <sup>46</sup>	High (A)
Hydrocodone (mg)	1	10 mg	CDC, 2022 <sup>17</sup> ; Reddy, 2014 <sup>45</sup>	High (A)
Hydrocodone LA (mg)	1	10 mg	CDC, 2022 <sup>17</sup> ; Reddy, 2014 <sup>45</sup>	High (A)
Hydromorphone (mg)	5	2 mg	CDC, 2022 <sup>17</sup> ; Lawlor, 1997 <sup>37</sup>	Moderate (B)
Hydromorphone (mg) LA	5	2 mg	CDC, 2022 <sup>17</sup> ; Lawlor, 1997 <sup>37</sup>	Moderate (B)
Levorphanol tartrate (mg)	11	0.9 mg	Nielsen, 2016 <sup>42</sup> ; Reddy, 2023 <sup>47</sup>	Moderate (B)
Meperidine HCL (mg)	0.1	100 mg	CDC, 2016 <sup>16</sup> ; Lasagna and Beecher 1954 <sup>36</sup>	Moderate (B)
Methadone (mg)	4.7	2.1 mg	Nielsen, 2016 <sup>42</sup> , Walker, 2008 <sup>52</sup>	Low (C)
Morphine (mg)	1	10 mg	N/A	N/A
Morphine (mg) LA	1	10 mg	N/A	N/A
Opium (mg)	1	10 mg	10 mg of morphine is contained in each 1 mL of liquid opium	N/A
Oxycodone (mg)	1.5	6.7 mg	Zecca 2016 <sup>58</sup> , Mucci-LoRusso 1998 <sup>40</sup>	High (A)
Oxycodone (mg) LA	1.5	6.7 mg	Zecca 2016 <sup>58</sup> , Mucci-LoRusso 1998 <sup>40</sup>	High (A)
Oxymorphone (mg)	3	3.3 mg	CDC, 2022 <sup>17</sup> ; Nielsen, 2016 <sup>42</sup>	Moderate (B)
Oxymorphone (mg) LA	3	3.3 mg	CDC, 2022 <sup>17</sup> ; Nielsen, 2016 <sup>42</sup>	Moderate (B)
Pentazocine (mg)	0.37	27 mg	Paddock, 1969 <sup>43</sup> ; CDC, 2016 <sup>16</sup>	Low (C)
Tapentadol (mg)	0.3	33 mg	Mercadante, 2013 <sup>39</sup> ; ANZCA 2021 <sup>6</sup>	Moderate (B)
Tapentadol (mg) LA	0.3	33 mg	Mercadante, 2013 <sup>39</sup> ; ANZCA 2021 <sup>6</sup>	Moderate (B)
Tramadol (mg)	0.2	50 mg	CDC, 2022 <sup>17</sup> ; Nielsen, 2016 <sup>42</sup>	Moderate (B)
Tramadol (mg) LA	0.2	50 mg	CDC, 2022 <sup>17</sup> ; Nielsen, 2016 <sup>42</sup>	Moderate (B)

\* The MME conversion factor is intended only for research purposes where prescription data are used to calculate an equianalgesic MME. It is to be used in the formula: Strength per Unit × MME conversion factor = MME, eg, 5 mg (hydromorphone) × 5 = 25 mg MME. This value does not constitute clinical guidance or recommendations for converting patients from 1 form of opioid analgesic to another, nor does this allow for calculation from morphine to another opioid analgesic.

† Equianalgesic dose of an opioid as compared to 10 mg of oral morphine, eg, 2 mg (hydromorphone) × 5 = 10 mg.

Studies informing the NIH HEAL Initiative MME Calculator Tool were evaluated using modified GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology. GRADE provides a systematic approach for rating quality of evidence from high (A) to very low (D). High quality (A) indicates randomized controlled trials with consistent results and good methodology. Moderate quality (B) represents downgraded RCTs or upgraded observational studies. Low quality (C) typically indicates observational studies or RCTs with significant limitations. Very low quality (D) represents any evidence with serious limitations or indirect evidence.

CDC, centers for disease control and prevention; LA, long-acting formulation; mg, milligram; N/A, not applicable; Pk, Pharmacokinetic; po, per os (by mouth); µg, microgram; µg/h, micrograms per hour.

mapping factors remains limited, with factors often derived from pharmacologic principles and expert consensus because of insufficient empirical data.<sup>16,17,42</sup> The tool's focus remains exclusively on mapping opioid doses to morphine equivalents for research purposes, addressing only analgesic equivalence. This targeted scope means it does not account for other important aspects such as opioid-related adverse events, which may have different dose-response relationships.<sup>22</sup> The tool's current scope primarily covers nonintravenous formulations, reflecting NIH HEAL CDE priorities, although this may be expanded in future iterations.

The NIH HEAL Initiative MME Data Calculator represents a significant advancement in standardizing opioid data collection

and analysis for pain research. By providing consistent, unidirectional conversion ratios and standardized calculation methods, the tool enables more reliable synthesis and interpretation of opioid research findings. The tool was developed to incorporate the best available evidence on opioid mapping factors and multiple MME/day time-window calculation approaches. The inclusion of a broader set of opioids, including partial agonists like buprenorphine and mixed mechanism opioids like tapentadol, makes the tool particularly relevant for contemporary pain research, where understanding the analgesic comparisons between diverse opioids is crucial. While the tool advances the standardization of research MME data, the limitations of the underlying equianalgesic dosing concept and

Medication	CDC 2016 Conversion Ratio	CDC 2022 Conversion Ratio	NIH HEAL 2024 Conversion Ratio
Buprenorphine tablet/ film (mg) sublingual	30	—	38.8
Buprenorphine buccal film (mcg) buccal	0.03	—	0.039
Buprenorphine patch (mcg/hr) transdermal	12.6	—	2.2
Butorphanol (mg)	7	—	7
Codeine (mg)	0.15	0.15	0.15
Dihydrocodeine (mg)	0.25	—	0.25
Fentanyl buccal (mcg)	0.13	—	0.13
Fentanyl oral lozenge (mcg)	0.13	—	0.18
Fentanyl nasal (mcg)	0.16	—	0.16
Fentanyl patch (mcg/hr)	7.2	2.4	2.4
Hydrocodone (mg)	1	1	1
Hydrocodone LA (mg)	—	—	1
Hydromorphone (mg)	4	5	5
Hydromorphone (mg) LA	—	—	5
Levorphanol tartrate (mg)	11	—	11
Meperidine HCL (mg)	0.1	—	0.1
Methadone (mg)	Varies by dose (4 to 12)	4.7	4.7
Morphine (mg)	1	1	1
Morphine (mg) LA	—	—	1
Opium (mg)	1	—	1
Oxycodone (mg)	1.5	1.5	1.5
Oxycodone (mg) LA	—	—	1.5
Oxymorphone (mg)	3	3	3
Oxymorphone (mg) LA	—	—	3
Pentazocine (mg)	0.37	—	0.37
Tapentadol (mg)	0.4	0.4	0.3
Tapentadol (mg) LA	—	—	0.3
Tramadol (mg)	0.1	0.2	0.2
Tramadol (mg) LA	—	—	0.2

**Figure 1.** Comparison of morphine milligram equivalent (MME) conversion factors across CDC guidelines and NIH HEAL initiative calculator. This figure presents a comprehensive comparison of opioid conversion factors across 3 key reference sources: the 2016 CDC Guidelines, 2022 CDC Guidelines, and the newly developed NIH HEAL Initiative Calculator (2024). The conversion ratios represent the multiplication factor used to convert a given opioid dose to its morphine equivalent. Dashes (—) indicate that the specific formulation was not included in that guideline.

the need for ongoing validation of conversion ratios are acknowledged. As more standardized opioid data becomes available using this tool, it will enable further refinement and validation of the mapping ratios. Complementary mapping ratio tools to address other important aspects of opioid use, such as craving, withdrawal, and adverse events, will also be necessary to

provide a more comprehensive understanding of opioid therapy. Overall, the NIH HEAL Initiative MME Data Calculator represents a significant step forward in standardizing opioid research data, laying the foundation for standardized cross-study comparisons and meta-analyses to advance pain science and, ultimately, improve clinical outcomes.

**Table 2**

**GRADE evaluation of evidence supporting National Institutes of health helping to end addiction long-term initiative morphine milligram equivalent mapping table.**

Authors	Study title	Country	Study design	Population characteristics	Sample size	Route	Paper grade
Himmelsbach et al. 1941 <sup>26</sup>	The Effects of Certain Chemical Changes on the Addiction Characteristics of Drugs of the Morphine, Codeine Series	US	Preclinical and clinical addiction studies	Addiction treatment center patients	20 participants	Oral and parenteral	D
Lasagna and Beecher 1954 <sup>36</sup>	The Analgesic Effectiveness of Codeine and Meperidine	US	Controlled clinical trial with a crossover design	Adults with postoperative pain; includes healthy male volunteers aged 21–27 for side effects evaluation	23–34 patients per group	Subcutaneous (parenteral)	C
Gravenstein et al. 1956 <sup>22</sup>	Dihydrocodeine: Further Development in Measurement of Analgesic Power and Appraisal of Psychological Side Effects	US	Observational Study	Postoperative patients with moderate to severe pain	Varies, 20+ analyzed	Subcutaneous	C
Keats et al. 1957 <sup>34</sup>	Studies of Analgesic Drugs: Dihydrocodeine	US	Double-blind clinical study	Postoperative patients; healthy volunteers for respiratory analysis	Varies by group	Subcutaneous	C
Eddy et al. 1957 <sup>18</sup>	Synthetic Substances with Morphine-like Effect	US	Experimental and clinical studies	Early clinical evaluations on opioid-naïve patients	Varied by study arm	Parenteral and oral	C
Eddy 1959 <sup>19</sup>	<i>The Analgesic Equivalence to Morphine and Relative Side (oxymorphone)</i>	US	Experimental and clinical studies	Early clinical evaluations on opioid-naïve patients	Varied by study arm	Subcutaneous (parenteral)	C
Seed et al. 1958 <sup>49</sup>	A Comparison of the Analgesic and Respiratory Effects of Dihydrocodeine and Morphine in Man	US	Double-blind study	Cancer patients with chronic pain; normal volunteers for respiratory studies	Varies: ~7 for respiratory studies; terminally ill for analgesic study	Subcutaneous	C
Paddock et al. 1969 <sup>43</sup>	Analgesic and side effects of pentazocine and morphine in a large population of postoperative patients	US	Double-blind clinical study with three-point assay	Postoperative patients (1074 total, mostly male)	1074 patients	Intramuscular	B
Dobkin et al. 1974 <sup>15</sup>	Butorphanol: A Double-Blind Evaluation in Postoperative Patients with Moderate or Severe Pain	Canada	Randomized, double-blind study	Postoperative patients with moderate to severe pain	120 patients	Intramuscular	A
Wilder-Smith et al. 1994 <sup>56</sup>	Oral Tramadol and Morphine for Strong Cancer Pain	Switzerland	Randomized, double-blind, cross-over study	Cancer patients with severe pain	20 patients (25 initially enrolled)	Oral	C
Lawlor et al. 1997 <sup>37</sup>	Dose Ratio Between Morphine and Hydromorphone in Patients with Cancer Pain	Canada	Retrospective study	Cancer patients undergoing opioid rotation	91 rotations in 74 patients	Oral and subcutaneous	B
Mucci-LoRusso et al. 1998 <sup>40</sup>	Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain	US	Randomized, double-blind, parallel-group study	Patients with chronic cancer-related pain	100 patients (48 oxycodone, 52 morphine)	Oral	A
Coluzzi et al. 2001 <sup>9</sup>	Breakthrough Cancer Pain—Comparing OTFC and Morphine IR	US	Randomized, double-blind, cross-over study	Patients with breakthrough cancer pain	134 patients (93 completed titration)	Oral transmucosal (OTFC); oral (morphine)	C

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Table 2 (continued)

Authors	Study title	Country	Study design	Population characteristics	Sample size	Route	Paper grade
Sloan et al. 2005 <sup>50</sup>	Effectiveness and Safety of Oral Extended-Release Oxymorphone for the Treatment of Cancer Pain	US	Open-label sequential crossover pilot study	Cancer patients with moderate-severe pain	86 patients (59 completed)	Oral	C
Walker et al. 2008 <sup>52</sup>	Switching from Methadone to a Different Opioid: What Is the Equianalgesic Dose Ratio?	US	Retrospective cohort	Cancer patients switching from methadone	29 patients	Oral and intravenous	C
Mercadante et al. 2013 <sup>39</sup>	Opioid switching from and to tapentadol extended release in cancer patients	Italy	Prospective exploratory study	Advanced cancer patients requiring opioid switching	37 patients	Oral	B
Reddy et al. 2014 <sup>45</sup>	The Opioid Rotation Ratio of Hydrocodone to Strong Opioids in Cancer Patients	US	Retrospective cohort	Cancer outpatients undergoing opioid rotation	170 patients	Oral	A
Reddy et al. 2016 <sup>46</sup>	The Opioid Rotation Ratio From Transdermal Fentanyl to Strong Opioids in Patients With Cancer Pain	US	Retrospective cohort	Cancer patients undergoing opioid rotation	47 patients	Transdermal and oral	C
Zecca et al. 2016 <sup>58</sup>	Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment	Italy	Open-label randomized controlled trial	Cancer patients requiring opioid analgesia	200 patients	Oral	B
Nielsen et al. 2016 <sup>42</sup>	A Synthesis of Oral Morphine Equivalents (OME) for Opioid Utilisation	Australia	Guideline and literature synthesis	General populations using opioids	Not applicable		B
Dowell et al. 2016 <sup>16</sup>	CDC Opioid-Morphine Equivalent (OME) Conversion Factors	US	Conversion table and guideline development	Opioid-prescribed patients	Not applicable		B
ANZCA 2021 <sup>6</sup>	ANZCA Opioid Dose Equivalence Calculation Table	Australia and New Zealand	Dose equivalence and practical guideline	Patients using various opioids	Not applicable		C
Dowell et al. 2022 <sup>17</sup>	CDC Clinical Practice Guideline for Prescribing Opioids for Pain	US	Systematic review and evidence-based guideline	Adults with acute, subacute, or chronic pain	154 trials reviewed		B
Reddy et al. 2023 <sup>47</sup>	Levorphanol as a Second-Line Opioid in Cancer Patients	US	Open-label interventional study	Cancer patients requiring opioid rotation	40 patients	Oral	B

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