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Original Research Articles

Durations of Opioid, Nonopioid Drug, and Behavioral Clinical Trials for Chronic Pain: Adequate or Inadequate?

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Abstract

Objectives. A recent US federal review and clinical guideline on opioids for chronic pain asserted that the literature contributes no evidence on efficacy because all trials had "inadequate duration." To explore the evidence, we examined durations of studies on opioid, nonopioid drug, and behavioral therapies for chronic pain.

Methods. We retrieved Cochrane reviews of anticonvulsants, antidepressants, NSAIDs, opioids, or behavioral interventions for chronic pain. We also examined all opioid treatment studies retrieved for the federal evidence report but excluded due to "inadequate duration."

Results. Of 378 Cochrane reviews retrieved, 72 evaluated one of the five therapies. Six of these 72 were excluded because they were proposals without data or investigated acute pain. Fourteen addressed multiple interventions, leaving 52 for analysis. We graphed numbers of trials vs duration for the five treatments reviewed in the Cochrane Library, compared with durations of opioid trials dropped from the federal evidence report. Most graphs were overdispersed Poisson distributions. Nearly all trials had active treatment durations of 12 weeks or less.

Conclusions. No common nonopioid treatment for chronic pain has been studied in aggregate over longer intervals of active treatment than opioids. To dismiss trials as "inadequate" if their observation period is a year or less is inconsistent with current regulatory standards. The literature on major drug and nondrug treatments for chronic pain reveals similarly shaped distributions across modalities. Considering only duration of active treatment in efficacy or effectiveness trials, published evidence is no stronger for any major drug category or behavioral therapy than for opioids.

Key Words. Chronic Pain; Anticonvulsants; Antidepressants; NSAIDs; Opioids; Behavioral

Introduction

The use of opioids began in prehistory [1] and is now standard practice in much of the world for the management of acute, chronic, and cancer-related pain. Concerns related to long-term effectiveness, safety, and

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abuse liability of prescription opioids have increased in recent decades, particularly in the United States, as both the numbers of prescriptions for and total doses of opioids have increased markedly [2,3]. Balancing the legitimate medical use of opioids for analgesia vs society-wide abuse, misuse, diversion, addiction, and mortality has become a major public health theme [4].

In March 2016, the US Centers for Disease Control and Prevention (CDC) published a guideline for prescribing opioids for chronic pain on the CDC website [5]. The guideline's intent is "to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy." An important message communicated in the CDC guideline and related press releases is that the body of evidence addressing the effectiveness or efficacy of opioid therapy for outcomes of pain, function, or quality of life was insufficient to contribute any studies for their analyses. In reaching this conclusion, the minimal duration for inclusion of a long-term study was set by the authors as ">1 year," the same threshold employed by a 2014 evidence report [6] that informed the 2016 CDC guideline. The same consultant was the lead methodologist for both the 2014 evidence report and the 2016 CDC guideline. However, earlier systematic reviews of the effectiveness or efficacy of opioids for chronic noncancer pain [7,8], co-authored by the same consultant and based upon the best available evidence, had identified dozens of clinical trials and systematic reviews of this topic. Although their conclusions were guarded due to the poor overall quality of the literature, both earlier reviews concluded that selected, carefully monitored patients might benefit from such therapy. Because the 2016 CDC literature review may be viewed as an update of the earlier reviews, it was striking that the 2016 review reached far more negative conclusions about the risk-benefit ratio for long-term opioid therapy than did the 2009 and 2010 reviews.

The 2014 evidence report and the 2016 CDC guideline relied upon the absence of studies of a year or greater duration to advance recommendations reflecting a low perceived benefit-to-risk ratio of opioid use for chronic pain. We wondered whether a more standard approach to study retrieval and inclusion would confirm or refute this perception. Issues related to study inclusion also have implications for switching from or preferring one therapy to another. If the clinical trial literature supporting one or the other therapy had equivalent distributions of duration and their risk-to-benefit assessments were equivalent, the evidence to support recommending such a switch would be very weak. We therefore sought to characterize the clinical trial literature for chronic pain treatment with an opioid, based upon the literature retrieved for the 2014 Agency for Healthcare Research and Quality (AHRQ) review but excluded by the authors of that review because of "inadequate duration." In addition, we examined studies cited in in the Cochrane Library of Systematic Reviews addressing opioids, antidepressants, anticonvulsants, NSAIDs, and behavioral treatments. Our objective was to assess whether differences exist between the duration of treatment trials for chronic pain using each of these modalities, if analyzed without applying the one-year minimum threshold for inclusion newly introduced in the 2014 AHRQ and 2016 CDC reports.

Methods

To prepare a profile of the numbers of studies of various treatments for chronic pain vs the duration of active treatment in each study, we examined each of the clinical trials tabulated in Appendix D ("Excluded Studies") of the AHRQ 2014 evidence review [6]. Data extraction was carried out independently using Microsoft Excel by two authors (AEB, BOT), who cross-checked each other's extraction. Two other authors (YSB, DBC) conferred as needed to confirm and clarify specifics. A focused third check of study duration and number of participants was performed by (BT) after data entry into Excel; any disagreement was resolved by discussion.

The number of days of observation during active treatment included only the interval during which participants received the opioid or other treatment and a measure of effectiveness was captured. For example, we did not include open-label, safety extension phases during which no data on effectiveness was gathered. When the duration of monitored active treatment was not reported in days, we applied the conventions that one week equals seven days, one month equals four weeks, and one year equals 12 months. The number of patients was defined as the total number of actual randomized patients for randomized controlled trials (i.e., not the intent-to-treat population) or the number of patients entering the initial observation period for nonrandomized experimental and observation studies.

Data were extracted from tables of included studies within each review. When such data was lacking or unclear, we retrieved the full text of the original study to verify or complete any missing data. When the above data was not readily available or not clearly defined, we designated the entry as "unclear."

To explore the distributions of active treatment duration in the published literature on opioid therapy for chronic pain, as assessed in separate systematic reviews published independently of the 2014 AHRQ evidence review, we searched the Cochrane Library [9] for all systematic reviews retrieved in response to the single search term "chronic pain." We also consulted the Cochrane Library for systematic reviews addressing the literature on other major modalities for chronic pain: anticonvulsants, antidepressants, NSAIDs, and nondrug behavioral therapies. We did not assess other broad categories of analgesic therapies other than those featured in the CDC opioid guideline (e.g., we did not assess interventional pain management or complementary and alternative practices). When an individual study within a Cochrane review did not meet our overall

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inclusion criteria described above, that study was excluded. Most commonly, such excluded studies were acute pain trials of interventions whose acute and chronic effects were pooled within a single Cochrane review, e.g., "gabapentin for pain." We checked for duplicate studies presented within the different Cochrane reviews in each intervention category and removed such duplicates.

Statistical analysis was conducted in three stages. First, we derived descriptive statistics for trial length for each intervention. Then, we visualized the distributions as histograms. Finally, to formally compare the differences between the time frames, we conducted a negative binomial regression using the active treatment duration of each trial as the dependent variable and modality as the categorical independent variable. We selected negative binomial regression over Poisson regression due to the data being overdispersed. Results are reported as risk ratios, each indicating the ratio of mean duration of active treatment in trials of nonopioid therapies compared with the duration of active treatment in opioid trials excluded for "inadequate duration" from the 2014 AHRQ review. Stata 14 (College Station, TX, USA) was used for data visualization and analysis. Statistically significant differences were based on the threshold of $P < 0.05$.

Results

The numbers of articles and systematic reviews retrieved, along with numbers of patients enrolled and the ranges of study durations, are presented in Table 1. The greatest number of included studies was in the category of behavioral interventions, with 269 articles. The next highest number of included articles was 141 for antidepressants and 148 for the long-term opioids, each approximately half the number for behavioral interventions. The fewest number of articles was for NSAIDS, with 102 articles covering over 34,500 patients. The number of patients included in studies for a specific intervention ranged from over 45,000 for the long-term opioids category in the 2014 AHRQ evidence review to as few as approximately 18,000 patients in the Cochrane reviews of opioids and antidepressants. At the middle range of numbers of patients studied, behavioral interventions and NSAIDS each had approximately 28,000 and 34,000 participants, respectively. Anticonvulsant studies enrolled nearly 22,000 and antidepressants over 17,000 patients. Additional descriptive statistics for each therapeutic modality, including durations of observation (means, standard deviations modes, and medians), are also presented in Table 1.

Of the retrieved trials in the 2014 AHRQ evidence review, 627 presented in Appendix D of that report did not meet that review's inclusion criteria; of these, 168 were excluded specifically due to their "inadequate duration." We retrieved and reviewed all seven abstracts and 161 complete publications deemed of "inadequate duration" and then excluded those studies that did not examine opioid effectiveness (e.g., that compared one NSAID with another in patients receiving opioids) or were reviews rather than primary studies. This process resulted in 148 publications enrolling 45,504 patients.

Our search of the Cochrane Library identified 378 reviews, of which 72 met inclusion criteria. Nine of these reviews were excluded for the following reasons: had no included studies (one study); were of a different class of medication (antipsychotic, one study), were an overview of other already-included Cochrane reviews (one study), or were proposals for future reviews (six "protocols"). After correcting for duplications (i.e., when a single review presented information on more than one intervention), the end result was 52 reviews comprising 871 individual studies (see Table 2). Details about the 871 individual included studies are presented in a supplemental file.

To explore differences or similarities between the duration profiles of the opioid trial literature retrieved for but excluded from analysis in the 2014 AHRQ report and Cochrane reviews of opioids and other typical pain treatments, we prepared histograms showing the number of retrieved studies of a given duration of active treatment (Figure 1). To avoid compressing the

Table 1 Articles, systematic reviews, enrolled patients, duration (range in days), and other descriptive statistics for publications cited in 2014 AHRQ review and Cochrane Library, on treatments for chronic pain

	Articles	Reviews	Patients	Duration (range, d)	Mean duration (SD)	Mode	Median
Opioids (AHRQ 2014)	148	–	45,504	1 to 2,352	76 (220)	7	28
Opioids (Cochrane)	101	9	17,796	1 to 1,344	178 (301)	1	52.5
Anticonvulsants	108	13	22,064	5 to 1,176	62 (114)	56	56
Antidepressants	141	13	17,872	2 to 189	58 (37)	56	56
NSAIDS	102	6	34,531	4 to 364	37 (49)	42	28
Behavioral	269	14	28,309	1 to 756	66 (70)	56	56
Total	869	55	166,076	–	–	–	–

See text for full explanation of retrieval process. Note that several reviews contributed to more than one therapeutic category; removal of multiple citations of the same review (e.g., Chaparro 2012 [10] cited under opioids as well as anticonvulsants and antidepressants) reduces the actual total of distinct retrieved reviews to 52 instead of 55.

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Table 2 Cochrane systematic reviews of drug and nondrug modalities to treat chronic pain

Modality	Included reviews
Opioids	Chaparro 2012 [10], Chaparro 2013 [11], Gaskell 2014 [12], Haroutounian 2012 [13], McNicol 2013 [14], Noble 2010 [8], Quigley 2002 [15], Santos 2015 [16], Wrzosek 2014 [17]
Anticonvulsants	Aboumarzouk 2012 [18], Chaparro 2012 [10], Gurusamy 2016 [19], Gill 2011 [20], Hearn 2012 [21], Moore 2009 [22], Moore 2014 [23], Moore 2015 [24], Mujakperuo 2010 [25], Üçeyler 2013 [26], Wiffen 2013 [27], Wiffen 2013 [28], Wiffen 2014 [29]
Antidepressants	Chaparro 2012 [10], Cording 2015 [30], Derry 2015 [31], Derry 2015 [32], Gallagher 2015 [33], Hauser 2013 [34], Hearn 2014 [35], Lunn 2014 [36], Moore 2015 [37], Saarto 2007 [38], Tort 2012 [39], Urquhart 2008 [40], Walitt 2015 [41]
NSAIDs	Garner 2005 [42], Moore 2015 [43], Mujakperuo 2010 [25], Roelofs 2008 [44], Derry 2012 [45], Derry 2014 [46]
Behavioral	Anie 2015 [47], Bernardy 2013 [48], Boldt 2014 [49], Eccleston 2014 [50], Eccleston 2014 [51], Fisher 2015 [52], Henschke 2010 [53], Kamper 2014 [54], Karjalainen 1999 [55], Karjalainen 2003 [56], Monticone 2015 [57], Price 2008 [58], Theadom 2015 [59], Williams 2012 [60]

See text for full explanation of retrieval process. Note that Chapparo 2012 [11] is cited under opioids as well as anticonvulsants and antidepressants, and Mujakperuo 2010 [25] is cited under NSAIDs as well as anticonvulsants.

histograms by virtue of lengthening the x-axis in order to capture the very few trials in which active treatment extended beyond a year, we truncated the x-axes in Figure 1 at 15 months.

We noted that the distribution of the opioid trials excluded from the 2014 AHRQ report appeared to be an overdispersed Poisson distribution. We therefore fitted the plots of active treatment durations vs number of trials using binomial distributions so as to smooth the curves and facilitate visual comparisons with the reference distribution, i.e., the opioid studies retrieved for the 2014 AHRQ opioid evidence report but not selected due to their "inadequate duration." Comparisons of the 2014 AHRQ opioid trial number-vs-duration distribution with the other modalities commonly employed to treat chronic pain are displayed in Figure 2.

Table 3 provides quantitative comparisons of the data presented visually in Figures 1 and 2. The results presented in Table 3 indicate that the durations of the active interventions in trials of anticonvulsants and behavioral therapies, although numerically shorter than those for opioid trials excluded from the 2014 AHRQ review, are not statistically significantly shorter. On the other hand, the duration of NSAID active exposure is less than half of those in the excluded opioid studies in the 2014 AHRQ review ($P < 0.001$), while the duration of active opioid treatment in the reports included in the Cochrane opioid review is 2.4 times longer than the opioid trials identified but excluded from the 2014 AHRQ review ($P < 0.001$). Thus, the durations of active treatment in efficacy or effectiveness trials for chronic pain are shorter, although not always statistically so, for any of the nonopioid modalities (including behavioral treatments) than for the opioid trials identified but not utilized in the 2014 AHRQ evidence review. In turn, the opioid treatment trials retrieved for the latter review are shorter as a group than those in the aggregated literature on opioids for chronic pain cited in Cochrane systematic reviews of that topic.

Discussion

We conducted an investigation of the nature of the evidence for five frequently used interventions for chronic pain recommended in the 2016 CDC guideline [5] for opioids in chronic pain: pharmacotherapies (anticonvulsants, antidepressants, NSAIDs, and opioids) and nondrug, behavioral interventions. Our motivation for doing so was curiosity as to why the 2014 AHRQ evidence review [6] and 2016 CDC guideline for the use of opioids in chronic pain [5] declared that no suitable studies of opioid therapy qualified for inclusion. Earlier systematic reviews [7,8] in which one or more coauthors of the 2014 AHRQ evidence review [6] and 2016 CDC guideline [5] had participated, had identified sufficient studies to conclude, albeit guardedly, that selected patients carefully followed might benefit from such therapy. Because the principal reason for the 2014 and 2016 documents' exclusion of all retrieved effectiveness and efficacy trials was stated as "inadequate duration," we focused our analysis upon the durations of active treatment in published clinical trials of all six modalities for chronic pain. We did not attempt a reanalysis of the published evidence in favor of or against the use of opioids or any other modality for chronic pain. To reach such an overall conclusion was the task of the systematic reviews themselves, and the fact that none of the reviews of opioids for chronic pain reached an unequivocal conclusion speaks to the difficulty of synthesizing this literature. For example, even the assignment of a binary rating of effective/ineffective to each study was precluded by the heterogeneity of study protocols, participants enrolled, outcomes measured, and differing results at some time points vs others. Had a

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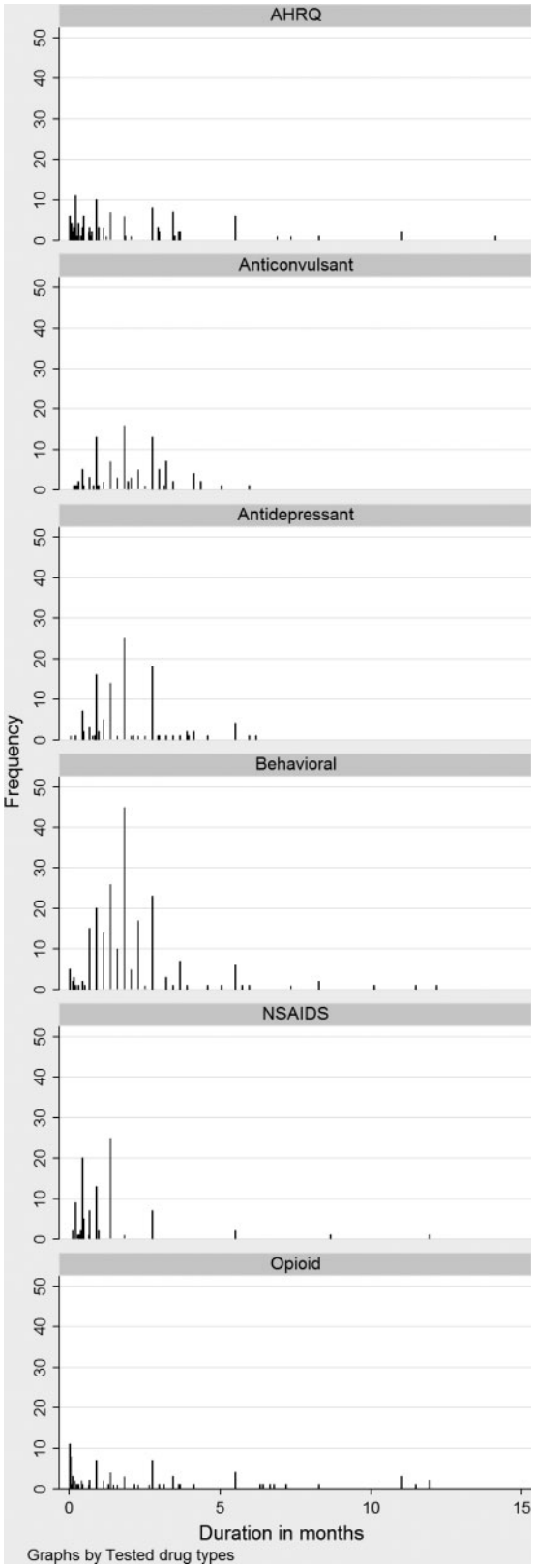

Figure 1 Durations of active treatment in trials of typical treatments for chronic pain (x-axis) vs numbers of trials with each duration (y-axis). The treatments evaluated were opioids as described in the 2014 AHRQ review (top graph) and the following modalities as described in Cochrane systematic reviews (second from top, proceeding downwards): anticonvulsants, antidepressants, behavioral, NSAIDs, and opioids. To enhance legibility (i.e., to avoid compressing these graphs horizontally), the x-axes were truncated at 15 months; a negligible number of studies exceeded that active treatment duration.

straightforward synthesis of the literature on opioids for chronic pain been possible, it would already have been published; hence the tentative and conditional language of the 2009 [7] and 2010 [8] systematic reviews.

Focusing upon study duration, we used the best available evidence and tabulated the number of studies of each modality vs the duration of exposure to active treatment in all included studies. We included opioid treatment studies that were identified for the 2014 AHRQ and 2016 CDC reports but discarded due to their having durations of active treatment of less than a year. We separately gathered studies of opioid treatment that were reported upon in nine Cochrane systematic reviews [8,10–17]. The methods employed to prepare Cochrane reviews are widely accepted as likely to minimize bias in their assessment of treatment effectiveness and efficacy [61].

We formally compared the distributions of the lengths of trials using negative binomial regression and found that the lengths of anticonvulsants, behavioral drugs, and antidepressants were about 95%, 87%, and 79%, respectively, of those of the AHRQ-selected studies. NSAID trials tend to be shorter, while opioid trails tend to be longer.

The distribution of active treatment duration in the 148 opioid studies retrieved for but not used in the 2014 AHRQ evidence review showed a shorter duration than the 101 opioid studies examined to support nine Cochrane systematic reviews of the same therapy. Nonetheless, in both groups nearly all trials had a duration of 100 days or shorter. The shape of the distribution for the opioid trials retrieved for but not used in the 2014 AHRQ report displays a clustering at the low range and a tapering off toward the high range, i.e., an apparent Poisson distribution [62]. The qualitative overdispersed Poisson distribution shape was less evident in the Cochrane opioid trials, which had a greater duration of active treatment than the 2014 AHRQ trials. Similar distribution shapes were evident in the graphical summaries of anticonvulsants, antidepressants, NSAIDs, and nondrug behavioral therapies; as a group, these four modalities had equivalent durations, all of which were shorter than the 2014 opioid trials. In summary,

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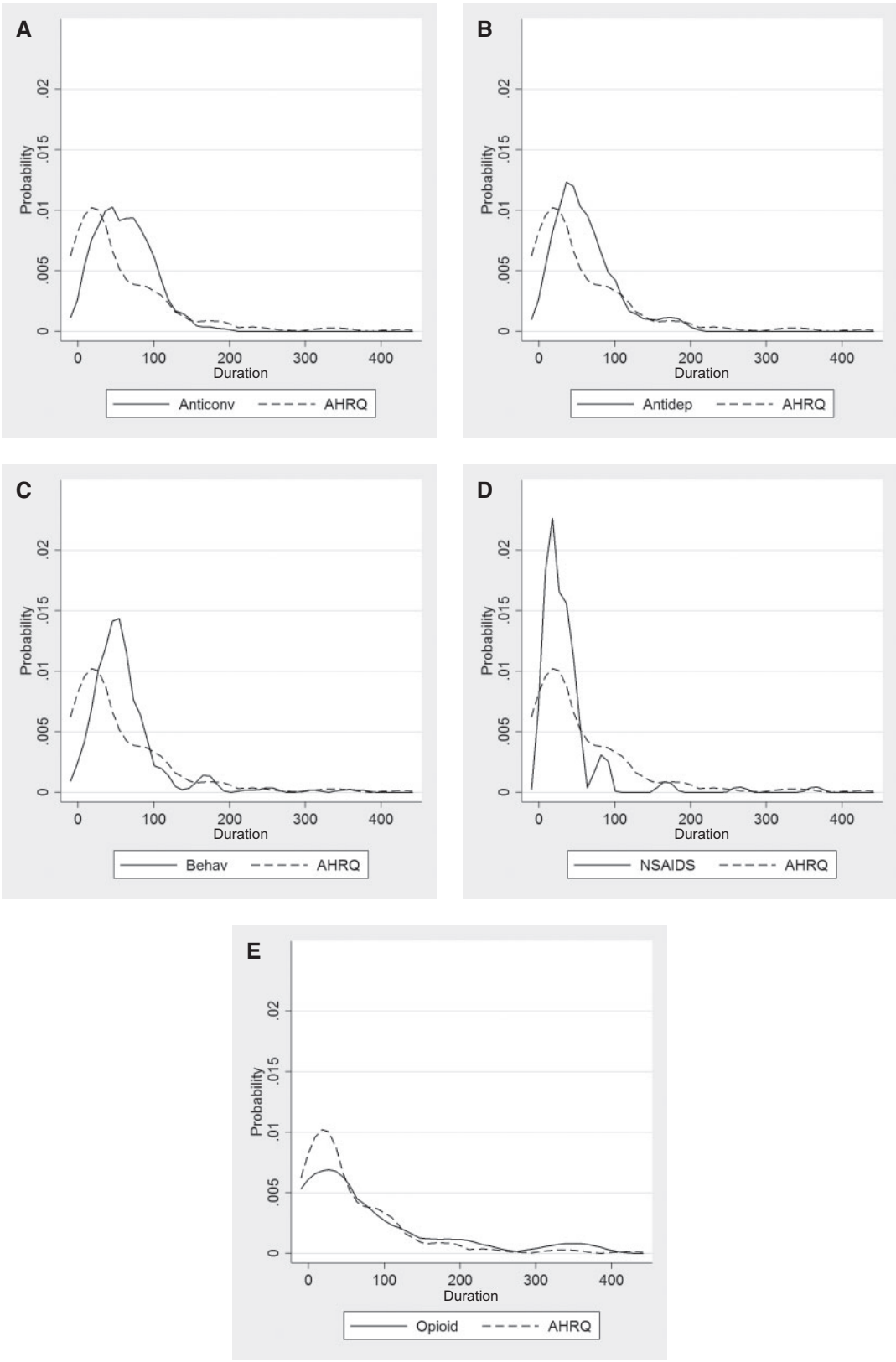

Figure 2 Pairwise comparisons of curves fitted (i.e., smoothed) to the distributions of active treatment duration vs numbers of trials with that duration, and those of the opioid trials retrieved for 2014 AHRQ opioid evidence review

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Table 3 Comparisons of trial duration for varied analgesic interventions for chronic pain

	Ratio	95% CI	*P*
Intervention			
AHRQ opioid	Reference	–	–
Anticonvulsant	0.95	(0.81–1.13)	0.565
Antidepressant	0.79	(0.67–0.94)	0.008
Behavioral	0.87	(0.76–1.01)	0.066
NSAIDS	0.49	(0.40–0.60)	<0.001
Cochrane opioid	2.36	(2.06–2.72)	<0.001

Data comparison using negative binomial regression reveals that the average durations of exposure to the active intervention for anticonvulsants and behavioral modalities do not differ from those in the opioid studies screened for inclusion in, but subsequently excluded from, the 2014 AHRQ review. The duration of active treatment with antidepressants is over 20% shorter than the excluded opioid studies in the 2014 AHRQ review ($P = 0.008$). The duration of NSAID active exposure is less than half of those in the excluded opioid studies in the 2014 AHRQ review ($P < 0.001$), while the duration of active opioid treatment in the reports included in the Cochrane opioid review is 2.4 times longer than the opioid trials identified but in, but subsequently excluded from, the 2014 AHRQ review ($P < 0.001$). Except for "AHRQ opioid," all tabulated data is from the Cochrane Database of Systematic Reviews (see Table 2).

the distribution of active treatment durations in the opioid trials retrieved for but not used in the 2014 AHRQ evidence report and 2016 CDC guideline lay between those for the anticonvulsant/antidepressant/NSAID/behavioral trials and the Cochrane reviews of opioid therapy.

Is it justified to state, as did the 2014 AHRQ evidence report and the 2016 CDC guideline, that there are no trials of opioid therapy whose duration is adequate to inform clinical guidelines on chronic pain treatment? Based upon the above analysis, the opioid literature retrieved for but not included in the 2014 AHRQ evidence report and 2016 CDC guideline has a shorter duration of exposure to active treatment than the studies of opioid therapy included in the nine aggregated Cochrane systematic reviews. Both the AHRQ and Cochrane opioid literatures have longer durations than corresponding literatures for anticonvulsant, antidepressant, NSAID, and behavioral therapies. Thus we found no evidence for the statement that currently available literature on opioid efficacy and effectiveness are inadequate to provide clinical guidance. Further, if a one-year minimum threshold for duration of active treatment were required to justify using any of the major typical therapies for chronic pain, then none of these nonopioid therapies could be recommended. Insofar as strength of the recommendation to switch from an opioid to a nonopioid therapy was based upon the durations of active treatment in the corresponding clinical trials, the published literature is insufficient to recommend any switch from one modality to another.

The similarities between the graphs of numbers of studies vs duration of active treatment in each study suggest that the clinical trial literature concerning therapy for any chronic pain condition represents a balance between its expected target population, ease of recruitment, the anticipated dose and duration of therapy, and its expected effects and adverse effects—all of which may be similar across trials of different types of interventions [63]. Overall trial duration also reflects, for analgesic trials, the feasibility of designing and executing trials in patient cohorts in whom ethical and practical considerations preclude very long exposures to active or placebo treatments [64]. Academics, regulatory bodies, and commercial sponsors have worked for decades to establish and update guidances in the United States [65] and abroad, e.g., Europe [66], to advise investigators about all aspects of clinical analgesic trials, including their duration. Presently, international harmonized standards adopted by the United States and Europe recommend that for approval to treat chronic pain, registration trials must show efficacy and acceptable safety in replicate trials of a duration of 12 weeks in a cohort of at least 1,000 patients, with safety data continued for a year in at least 500 patients [67]. More prolonged periods of observation were not recommended by those crafting such guidance [65–67], given (for example) their tendency to accrue an enriched population of placebo responders, increasingly greater likelihood of confounding intercurrent conditions or other morbidity, and the tendency for adverse drug reactions to occur early during prolonged exposure [65–67]. Therefore, regardless of the specific modality studied, analgesic trials of therapies for chronic pain generally adhere to

Figure 2. Continued
but excluded because of "inadequate" duration (the reference distribution). In each figure, the AHRQ opioid reference distribution is shown as a solid line and the comparison treatment (from the Cochrane reviews) as a dashed line. To normalize results and thereby facilitate visual comparisons, the y-axis presents the probability that a clinical trial, or trials, having an active duration of the number of days shown on the x-axis contributes to the areas under the entire curve for that intervention. Hence the summed total area under each curve by definition is set at 1. See text for full explanation of statistical analysis. Figure 2A shows anticonvulsants, 2B shows antidepressants, 2C shows behavioral interventions, 2D shows NSAIDs, and 2E shows the Cochrane opioid reviews.

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prevailing regulatory standards and hence rarely exceed 12 weeks of efficacy or effectiveness assessment.

Our focus in the present analysis on duration of active treatment reflects our observation that raising the threshold of this inclusion criterion to become greater than a year was responsible for disqualification of an entire literature. That disqualification led to negative conclusions about the efficacy and effectiveness of opioid therapy in the AHRQ 2014 evidence review and the 2016 CDC guideline that it informed, as well as other related publications involving one or more authors of these reports and including the same threshold of one year for inclusion of efficacy or effectiveness trials [68]. These negative conclusions were in contrast to two guardedly positive earlier systematic reviews by the same methodologist, who led the 2009 American Pain Society/American Academy of Pain Medicine guidelines [7] and contributed to a 2010 Cochrane review [8] of the same topic. Of course, duration of active treatment is only one of many dimensions of evidence-based medicine that must be considered when evaluating and synthesizing the published literature to inform medical practice [69], and many approaches have been applied to rate the strength of scientific evidence [70].

Conclusion

To categorize analgesic trials as of "inadequate duration" if their observation period is a year or less is a major departure from existing standards for the duration of published treatment trials for chronic pain, the vast majority of which are 12 weeks or less. The published literature on major drug and nondrug treatments for chronic pain reveals similar profiles across modalities for numbers of studies vs duration of active treatment.

The risks of substance misuse and abuse posed by prescriptions of opioids at high doses for long durations—leading to more prolonged periods of opportunity for their diversion and diffusion into the community at large—have appropriately led to numerous efforts to curtail this public health problem. However, basing therapeutic decision-making upon durations of published clinical efficacy or effectiveness trials does not support choosing any drug or nondrug therapy over another. In fact, the opening words of the first recommendation of the CDC guideline [5] ("Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain") and the rationale presented directly below it make no mention of the overwhelmingly strong evidence for significant morbidity and mortality risk from the most likely nonopioid alternatives to opioid therapy for chronic pain: NSAIDs, coxibs, and acetaminophen [71–73]. The morbidity and mortality likely to result from an increased population-wide consumption as a consequence of following this recommendation are difficult to estimate [74] but likely to be of the same magnitude as from opioids. Safety concerns about these nonopioid alternatives are sufficiently compelling as to have prompted the US FDA to issue its latest of many NSAID safety warnings in a 2015 "Drug Safety Communication" [75]. In the future, as more population-based information becomes available to fill existing research gaps [76], clarifying the selection and maintenance of patients who may benefit from opioid therapy or other drug or nondrug interventions to control chronic pain must be a high priority.

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Supplementary Data

Supplementary Data can be found online at http://painmedicine.oxfordjournals.org.

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