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Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence

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Introduction

The opioid crisis, already of staggering proportions, continues to grow despite many years of effort within the field of medicine, the issuance of treatment guidelines, and substantial legislative action across the nation. At the same time, we find ourselves at an impasse. On the one hand, we have the scientific knowledge to substantially address the crisis. On the other hand, the combination of efforts by physicians concerned with rising opioid mortality, the issuance of a national guideline by the Centres for Disease Control and Prevention (CDC), and legislative action has not had a measurable impact on the crisis. Worse, it has spawned a second crisis, this one involving Americans who have relied for years on opioid treatment to manage chronic pain and enable them to contribute to society and enjoy some quality of life. Epidemiologic studies suggest that 22% of U.S. adults (55 million) experience chronic pain and 7% (18 million) moderate to severe pain [1]. These patients now face disability, inordinate suffering, and excess mortality. Given these two crises, it seems timely to re-assess the scientific evidence and examine its implications for medical practice, public policy, and further research.

Our particular focus will be on issues relevant to clinical decision making by the practitioner; clarification of the research questions that need to be addressed; and clinical trial experimental designs that may be able to address questions in this field that have stymied conventional designs. Our review involved particularly careful analysis of study methodology and data with an attempt to incorporate the full dimensionality of chronic pain and its treatment in each assessment. Some perspectives on the opioid crisis have been substantially influenced by misperceptions [reviewed by Oliver and Carlson [2].

This analysis is based almost entirely on American literature. There may be much for other countries to learn from the American experience. However, the particular characteristics of the opioid crisis in America reflect cultural influences, the extraordinary heterogeneity of American society, the existence of large pockets of poverty, the absence of comprehensive health care for every citizen, an American approach to opioid abuse that has emphasized interdiction and incarceration over mental health treatment, the availability of licit and illicit opioids, laissez faire approaches to business regulation (hence pill mills), and long-standing ambivalence among physicians to treatment of pain. They also reflect the prevalence of the particular hopelessness that comes from denial of opportunity to people living in a country founded on hope [3].

All clinical studies of opioids inevitably reflect the fact that opioid treatment may not be sustained and that it may be discontinued for a variety of reasons, including lack of efficacy, adverse effects, comorbidities, drug abuse, and lack of access to alternative treatments. From an analytic point of view, these factors contribute to unexplained statistical variance.

Meta-analyses have become the generally accepted means for evaluating the large clinical trial literature, even as such analyses often do not adequately consider the scientific strengths and weaknesses of individual trials, instead focusing almost entirely on the quantitative outcomes and their susceptibility to meta-analysis. Most critically, intention to treat designs (the gold standard for RCTs) involving patients with more severe pain are either seriously undermined or precluded by high drop-out rates in placebo groups. Avoidance of these high drop-out rates requires inclusion of only patients with modest pain, who are less likely to benefit, while accommodating the limited dose titration that is possible in short duration trials. The particular focus on patients with modest pain is reflected in the modest doses of opioids typically employed. Of the 96 trials reviewed by Busse et al. 35% involved tramadol and in the 87 RCTs for which dosing data were quantified, median milligrams morphine equivalent/day (MMED) was 45 (interquartile interval 28.2–78.3).

The Efficacy of Opioids in Treatment of Chronic Pain

A large number of randomized placebo-controlled trials (RCTs) have been conducted to test the efficacy of opioids in treatment of chronic non-cancer pain [4]. Taken together; they provide evidence of modest opioid efficacy in relief of pain and improvement of physical functioning but also significant opioid side effects. Unfortunately, by and large, these trials have been marked by failure to accommodate the enormous patient to patient variability in necessary opioid dosage (see below), failure to titrate opioids to achieve adequate control of pain, over-rapid drug titration (which magnifies side effects and renders achievement and assessment of dosage adequacy difficult), and lack of recognition of the high prevalence of idiosyncratic side effects .It may take many months to identify an opioid that is well-tolerated by a given patient, gradually titrate dosage to the point of effective control of pain, and effectively treat important comorbidities such as depression. However, among the 62 trials reviewed by Furlan et al, 51% were one month or less, 39% were 5–12 weeks in duration, and the remaining 9% were 13–24 weeks in duration. There are several reports of open trials, non-randomized, involving large numbers of patients treated with either transdermal fentanyl or oxycodone continuous release that have demonstrated the ability to achieve sustained relief of pain for years. Although these trials provide some evidence of long-term efficacy and low incidence of tolerance, they cannot substitute for RCTs. In sum, few trials employing rigorous scientific methods have tested opioids as they are best used in clinical practice

The challenges of testing opioid effectiveness in a way that can translate readily to clinical use can be addressed by employing an Enriched Enrolment Randomized Withdrawal (EERW) design. A 3-month trial of extended release oxymorphone for chronic moderate to severe low back pain, conducted by Hale et al , involving 250 patients,

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is representative. During the first phase of the trial, oxymorphone was titrated to clinically optimal dosage and participants intolerant of the drug dropped out. Those stabilized on oxymorphone (N = 143) were then randomized to drug continuation or placebo. Physical withdrawal symptoms in those randomized to placebo were mitigated with supplementary oxycodone. By 3 months, 75% of patients in the placebo group had dropped out (53% from lack of efficacy; 11% from side effects; 11% other), compared with 30% of the oxymorphone group (11% for lack of efficacy; 10% from side effects; 9% other), thereby providing substantial evidence of efficacy. However, the high placebo drop-out rate obviated intention to treat statistical analysis of pain scores. At the end of the titration phase, 72% of patients rated their experience with the oxymorphone as good or excellent. Other EERW trials have achieved comparable results and meta-analysis . This said, EERW trial results, in aggregate, suggest the possibilities rather than proving the case.

In addition to addressing the challenges of emulating opioid prescription in good clinical practice, EERW trials have analytic advantages and achieve greater statistical power. Visual analogy pain scales (VAPS), the typical primary outcome measure in opioid RCTs, may be, like subjective measures in general, susceptible to anchor point drift over time . They also correlate poorly with more objective measures of pain, such as the McGill Pain Questionnaire With an EERW design, efficacy can be established with a logistic outcome measure—participant drop-out, thereby turning to advantage the dropout problem that plagues trials of conventional design. Drop-out may occur because of inadequate control of pain or because of opioid side effects. Scant data are available on the distribution of opioid dosage typically needed to achieve adequate control of pain. In an EERW trial of oxymorphone for treatment of chronic low back pain involving 325 participants, Katz et al. reported that 76.8% of those who successfully completed the oxymorphone titration phase (N = 205) achieved ≥ 30% pain reduction and 67.4% experienced a > 50% decrease in pain; 97% rated the treatment as good, very good, or excellent. Among participants, 53% had been titrated to ≤ 90 mg morphine equivalent/day (MMED), 81% to ≤ 150 MMED, and 93% to ≤ 240 MMED. Maximum dose in the trial was 420 MMED.The RCT conducted by Krebs et al. which involved 240 patients treated for chronic pain in VA hospitals, has been widely cited as proof that opioids are no more effective than non-opioid pharmacologic treatments for chronic pain. However, the mean dose of opioid was 21 MMED and only 12.6% of patients randomized to the opioid group were taking >50 MMED. Furthermore, antidepressants were among the treatment options in the non-opioid group. These study details suggest that the results of this trial may be best construed as: patients whose pain is not sufficiently severe to warrant opioid treatment do not particularly benefit from opioids; or opioids are not of benefit to patients with moderate to severe chronic pain when opioid dosage is not sufficiently titrated; or the optional use of antidepressants in the non-opioid group substantially mitigated the inadequacy of other non-opioid therapy.

Given that further clinical trials are needed, we propose a variation on the EERW design in which initial dose is very gradually titrated and participants, rather than being randomized to drug continuation or placebo, are randomized to continuation of their opioid regimen without change or to gradual tapering, e.g., by 10%/month, utilizing control tablets containing less and less opioid—an enriched enrolment, randomized gradual withdrawal design (EERGW). The statistical method would be survival analysis based upon time to trial drop-out . This design would likely be more successful than EERW designs in sustaining participant blinding. It would enable trials extended over almost arbitrarily long periods of time and the use of Cox proportional hazards analysis to identify potential predictors of outcomes.

Risk of Death from Opioid Treatment

The rise in prescription opioid-associated mortality from ~6,500/year in 1999 to 17,500/year in 2011 generated widespread concern about the risks of opioid use and paved the way for the idea that opioid over-prescribing was responsible for the opioid crisis. However, two things have been missing from this conversation: the statistical contribution of increasing numbers of patients being prescribed opioids; and (2) the number of annual deaths related to prescribing by pill mills, in which opioid use is not adequately medically supervised.

Conclusions

This analysis of the clinical scientific literature on opioids suggests that many of the conventional assumptions about opioids, including safe opioid dosage, opioid efficacy, the factors that lead to opioid use and abuse, and the risks associated with opioid use, are not supported and in many cases, are refuted by existing scientific data. Conclusions about opioid efficacy, or the lack thereof, have been drawn from seriously flawed RCTs characterized by inadequate experimental designs. Data on the high variability in opioid dosage requirements and the high frequency of idiosyncratic side effects have been overlooked. Estimates of the risk of death from prescription opioids have been largely predicated on the national increase in total opioid mortality from all sources, legal and illegal. Well-designed studies have demonstrated estimated annual case fatality rates for >100 MMED regimens in the vicinity of 0.25%/year—a level of risk comparable to that associated with chronic anticoagulation for prophylaxis of stroke due to atrial fibrillation. Excess risk of death associated with opioid use conflates risks attributable to opioids and risks related to being in chronic pain, with its associated comorbidities. Risks of the development of OUD have commonly been overestimated, even as the operational definition of OUD requires further research. State legislatures are passing laws based on the gateway theory even as scientific evidence has demonstrated that this theory has little merit.

Strong measures are being taken to restrict prescription opioid use without consideration of the vast cost of inadequately treated chronic pain, whether measured in terms of human suffering and degraded quality of life or in terms of the literal costs of health care and lost productivity ($600 billion/year). Ideas about the potential value of alternative non-pharmacologic therapies have flourished despite the lack of comparative effectiveness studies. Absolute proscription of co-prescription of opioids and benzodiazepines appears to have effectively become the law of the land, even as studies supporting this concept have yielded data that are at best suggestive. These studies have also revealed the complexity of this issue [5]. The relative effectiveness and risks of alternatives to benzodiazepines for treatment of idiopathic insomnia and anxiety have received no consideration. The potential role of depression in contributing to the adverse effects of chronic pain and its treatment and the potential value of aggressive treatment of depression in chronic pain patients has scarcely been considered.

The causes of the opioid crisis are now coming to light and a coherent narrative can be constructed. It seems that the CDC, in attempting to deal with a crisis in the streets by restricting treatment of pain in clinics, has created a second very serious crisis, this one involving 18 million patients in moderate to severe chronic pain. These CDC efforts have not addressed the crisis in the streets, one now accounting for nearly 3/4 of opioid deaths This is a crisis of community economic failure, poverty, social isolation, hopelessness, and serious mental health problems [6].

Clearly it is time to return to the scientific evidence bearing on these issues, of which there is a considerable body. We now have a fairly clear picture of what needs further study. Innovative RCT designs have been proposed, e.g., EERGW, to test opioid efficacy and dosage variability, to conduct comparative effectiveness studies, and to assess the impact of comorbidities such as depression. Much is known about how to treat opioid addiction. What is lacking is adequate funding and implementation of treatment programs. Management of chronic pain is complex, labor intensive, requires considerable investment of health care resources, and entails significant risk. Major improvements in training of physicians , health care infrastructure, and re-imbursement policies are needed to optimize care and minimize risk.

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Conflict of Interest

None

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