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LETTER TO THE EDITOR

Use of Opioids for Chronic Noncancer Pain. A Recapitulation of the Science

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Introduction

Last year, the *New England Journal of Medicine* (NEJM) published an editorial by Andrew Kolodny and Robert Bohler[1] that sought to reinforce the central premise of the CDC Guideline of 2016,[2] updated in 2022.[3] This premise, now long disproven,[4,5] is that the primary cause of the opioid crisis and its continuation has been overprescribing of opioids by clinicians. We asked the editors of NEJM if they would consider an op-ed that presented the relevant science. They would not. This explicit editorial support by what is arguably the most prestigious journal of clinical science in the world indicated a strong need to recapitulate all of the scientific evidence bearing on the use of opioids in medicine. We summarize that evidence below.

Summary of the Science

- OPIOID EFFICACY.

Vast clinical experience testifies to the high efficacy of opioids for treatment of chronic pain, provided such important comorbidities as depression have also been effectively treated.[6] The closest anyone has come to a true study of opioid efficacy is a prospective single group open trial of opioids in a palliative care setting (mean dose 351 MMED, median 151, range 0-2355).[7] Kollas et al. report a mean 4.8/10 point reduction in pain, defined by a 0-10 point numerical pain rating scale, that was sustained over four years.[7] However, in excess of 100 prospective, randomized controlled trials (RCTs) have not provided compelling evidence of opioid efficacy.[4,6] The Center for Disease Control and Prevention (CDC) has interpreted this lack of evidence of efficacy as proof of inefficacy. However, we have argued that the problem lies with inadequate trial design and we have proposed an alternative, the enriched enrollment randomized *gradual* withdraw (EEGRW) design.[8]

- OPIOID SAFETY.

Retrospective cohort studies published 10 years ago established that annual opioid-associated mortality among clinic populations was approximately 0.25% with dosage greater than 100 mg morphine equivalent/day (MMED).[4] Oliva et al.,[9] in a large retrospective cohort study of Veterans Administration hospitals demonstrated that this risk was not evenly distributed: it mainly accrued to patients with severe psychiatric disease, defined by multiple inpatient psychiatric admissions and multiple overdoses/ suicide attempts, and severe physical pain (hence the opioids). Previously documented opioid use disorder (OUD) did make a substantial contribution to the odds ratio of a morbid outcome. However, the DSM-5 scale defining OUD is fraught with largely unrecognized problems[4], not the least being that any patient with severe, inadequately treated chronic moderate to severe pain seeking relief would qualify as having at least moderate OUD. In addition, the discriminant value of the scale has never been determined. In the Oliva et al. study, higher opioid dosage explained very little additional variance. Thus, one could reasonably interpret the results of this study as showing that opioids have been incriminated as innocent bystanders.

Other studies have demonstrated a number of potentially serious adverse effects of opioids short of death.[6] However, these studies did not establish to what extent such effects were due to opioids *per se* versus severe chronic pain and its comorbidities.

- USE OF OPIOIDS FOR POST-SURGICAL ANALGESIA.

The incidence of opioid "misuse" during the 2.5 years after surgery is 0.6%[10](see also prospective study[11]). Misuse was defined on the basis of 14 ICD codes, the top three, opioid type dependence, unspecified; opioid type dependence, continuous; and opioid abuse unspecified, accounted for 75% of patients (supplemental table e1A). These are all clinical diagnoses based upon variable and uncertain clinician-specific criteria. Longer term opioid use after surgery is mainly associated with operations that are commonly complicated by long-term residual pain, such as total knee arthroplasty.[12]

- ACUTE SIDE EFFECTS OF OPIOIDS.

Clinical experience indicates a high incidence of idiosyncratic side effects of opioids and the almost

universal potential for avoiding these side effects merely by switching to a different opioid. Few practitioners seem to be aware of this, even as the observation is implicit in the design of enriched enrollment randomized withdrawal trials.[8]

- HAVE PRESCRIPTION OPIOIDS CONTRIBUTED TO THE NATIONAL OPIOID OVERDOSE CRISIS?

The answer is yes and no. Between 1999 and approximately 2011, pill mills, supplied by major drug distribution firms, distributed vast quantities of pharmaceutical grade opioids to vulnerable populations, thereby creating a large population of people with drug addiction.[4,6,13,14] Between 2010 and 2012, the states shut down the pill mills through direct legal action and, most importantly, by expansion of use of Prescription Drug Monitoring Plans (PDMPs) to 49 states (now 50). PDMPs rendered and still do render pill mill operations transparent. People with addiction had to turn to Mexican heroin and Chinese fentanyl. There is robust evidence derived from the CDC database that since 2011, there has been no statistical correlation between clinician prescribed opioids and annual US opioid associated mortality.[4,5]

- CDC OPIOID GUIDELINES.

The CDC guidelines of 2016 and 2022[1-3] are premised upon the assumption that over-prescribing by clinicians started and is responsible for sustaining the national opioid crisis. Between 2016 and 2022, the annual opioid-associated mortality doubled notwithstanding enormous success by the CDC in reducing prescriptions.

- ALTERNATIVE OPIOID GUIDELINES.

In lieu of the demonstrable failure of the CDC 2016 and 2022 guidelines to curb national opioid associated mortality, we have provided a detailed, evidence-based guide for chronic pain management.[6]

- OPIOID DOSAGE.

The CDC guidelines recommend a one size fits all approach to opioid dosage in all patients in chronic pain. Data from studies of post-operative treatment of pain and from studies of long-term administration of opioids are in agreement in suggesting a 13-15 fold variability in individual patient dosing requirements.[4] This is likely related primarily to variability in individual pain severity, patient resilience in dealing with pain, and major differences in first pass hepatic metabolism of opioids.[4]

- CONSEQUENCES OF INADEQUATE TREATMENT OF CHRONIC PAIN.

"Inadequate treatment of chronic pain is associated with increased functional limitations, reduced employment, increased absence from work, disability retirement, reduced household income, poor global recovery from surgery, worsened mental health, increased use of health care resources, increased mortality, and impaired cognitive function. Chronic pain is associated with increased risk of suicidal ideation, planning, and attempts"[4](see also[15,16]).

- DEPRESSION.

Clinical experience suggests that depression is nearly ubiquitous among patients with chronic moderate to severe pain. Depression is readily treatable if one is willing to use an aggressive pharmaceutical approach. The vast reduction of suffering that results can significantly reduce the opioid dosage needed to achieve control of pain.[4,6] However, depression is typically detected and diagnosed in only 12.9% to 32% of patients in studies of opioids[6] and treatment, guided by today's psychiatric authorities,[17] tends to be very conservative. EERGW designs would be capable of detecting the effects of aggressive treatment of depression.[8]

- COMBINED USE OF OPIOIDS AND BENZODIAZEPINES.

Multiple studies have demonstrated that the risk of co-administration of opioids and benzodiazepines (e.g., for anxiety or insomnia) is extremely low and that reduction of benzodiazepine dosage, ostensibly to reduce this risk, may cause significant harm.[4,18]

- PROBABILITY OF OPIOID ADDICTION IN CLINIC POPULATIONS.

The universal adoption of OUD as a diagnostic entity has made it impossible to determine the incidence

of true addiction in clinic populations with any degree of accuracy. Clinical experience suggests that opioid addiction does occur but that its incidence is extremely low — too low to justify policy making to prevent it. We have suggested that a person's motivation for taking opioids is an important factor to consider when we deal with opioid use by various populations.[19] There is RCT evidence that the sole motivation for seeking opioid treatment by patients in pain is to achieve analgesia.[20-22] This finding is entirely consistent with clinical experience. There is suggestive evidence that people with drug addiction use opioids and other drugs to achieve temporary oblivion to the conditions of their destitute and hopeless lives.[14,19]

Conclusion

A vast body of scientific evidence now provides a more than adequate basis for evidence-based and safe prescription of opioids. There are some important gaps, most crucially the need to employ better clinical trial designs to test the efficacy of opioids over the long run and the drugs and alternative treatments that might enhance efficacy to the point of enabling reduction in opioid dosage. The EERGW design would serve this purpose. Before 2008, the major impediment to optimal use of opioids was the seriously inadequate training of physicians. This impediment persists.

The position maintained by the CDC and just this year supported by NEJM[1] is highly inconsistent with a very large body of scientific evidence. The harm rendered is very large: in 2023, 8.5% of Americans (28.46 million) experienced high-impact chronic pain.[23] The comparable figure in 2019 was 7.4%.[24] Our current regulatory framework condemns these people to lives of suffering and dysfunctionality.

Author Contributions:

SEN was primarily responsible for the literature review, the analyses, and writing this paper. RAL critiqued the various drafts of the paper and contributed to interpreting data published by CDC.

RAL and SEN have engaged in an intensive collaborative effort since 2016 to define the scientific evidence bearing on the prescription opioid crisis, to provide a clinical guideline for management of chronic pain, to understand the fundamental causes of the current crises in clinical pain management and illicit opioid use, and to propose solutions to these crises. The current manuscript represents a summary of this work.

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Data Availability:

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