Nonconsensual Dose Reduction Mandates are Not Justified Clinically or Ethically: An Analysis

Stefan G. Kertesz, Ajay Manhapra, and Adam J. Gordon

Introduction: An Evolving Crisis

The context driving an ongoing recalibration of opioid prescriptions is a North American crisis of addiction in which opioids are prominent. There were an estimated 46,802 overdose/poisoning deaths involving opioids in 2018.[1] National data using rigorous clinical surveys indicate that the prevalence of opioid use disorder — the diagnostic term indicating addiction to opioids — doubled from 2003 to 2013, both for heroin,[2] and for prescription opioids.[3] Across communities, countless children now lack parents or grandparents. Estimated economic damages for a single year vary from $78.5 billion to $431.7 billion.[4]

Most accounts for this crisis affirm a causal role in the surge of opioid prescribing that took place from the late 1990s until it crested, in 2012.[5] Explanations for the rise in prescribing typically invoke one or more actors or agencies, including the pharmaceutical industry, federal regulators, professional societies, and quality of care arbiters such as the Joint Commission. The ease with which opioids were embraced, however, also reflected a collective failure on the part of health care payers, educators, and credentialing boards to foster expertise and services for the comprehensive care of two conditions in particular: pain and addiction. With neither form of expertise taken seriously by professional schools, regulators, or payers, the table was set for marketing a seemingly simple solution to pain, while disregarding the inevitable downstream risks. Opioids were embraced as the ever-appropriate response to perturbations of the fifth vital sign, pain.[6]

While opioid prescribing likely contributed to the incidence of opioid use disorder, presumably by making opioids more accessible,[7] data do not demonstrate that most people with this condition began in a doctor's office. Among respondents to a national survey designed to identify heroin use disorder, 53% of Whites and 26% of African-Americans reported beginning "with pills."[8] The misused pain reliever pills, according to the National Survey on Drug Use and Health, were obtained "from one doctor" by 22.1% of individuals reporting such misuse in its 2014 survey (a major

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redefinition of pain reliever misuse, to encompass their use to treat pain in the prescription recipient, makes the post 2015-figures less applicable).[9] Excess prescriptions nevertheless presented an ample market for diversion, theft, and drug initiation by individuals who were young, or troubled, or seeking substances for other reasons.[10]

Opioid prescribing in the US began to fall in 2012, presumably as negative effects of opioids were publicized and as clinicians realized that opioids — and the physical dependence they engender — are often not benign. The decline in prescribing seems to have accelerated in response to early reports from the US Centers for Disease Control and Prevention (CDC) and others.[11] In tandem with declines in prescriptions, interdictions of heroin and fentanyl rose precipitously,[12] implying a shift in the illicit market from diverted prescriptions to illicit opioids.

The decline in opioid prescribing accelerated after the release of a consensus Guideline from the CDC in 2016.[13] By that point, the opioid crisis had the full attention of governments and the population at large. The Guideline's text disavowed presenting a new standard of care or the basis for law. Its major provisions focused on restraint, but not prohibition, in the use of opioids. It urged caution in dose escalation. Doses of 50 and 90 morphine milligram equivalents (MME) were flagged as points of caution. The Guideline suggested that patients already receiving over 90 MME "should be offered the opportunity to reevaluate their continued use of opioids at high dosages…For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan."[14] Thus, as written, the Guideline urged decisions be made collaboratively with patients and providers through assessment of risks and benefits of continuing opioids at current doses.

In addition, the Guideline lacked evidence that tapering a long-term recipient to lower doses reduces his or her personal risk. Accordingly, the CDC appropriately avoided asserting that lowering doses reliably delivers a personal (or societal) health benefit. As a result, the 2016 Guideline was relatively restrained on how to manage patients already above dose thresholds.

In contrast to the Guideline's restraint, effective mandates and powerful incentives were introduced by many policy actors.[15] These included insurers, health care employers, pharmacies, quality metric agencies, contractors to the US Centers for Medicare and Medicaid Services, and sometimes state legislators or Medicaid authorities.[16] Often the 90-milligram threshold (or 120 MME, with the National Committee for Quality Assurance[17]) was flagged as the basis for distinguishing care as safe versus dangerous, payable versus not payable, or professional versus grounds for suspicion. Most, if not all, of these policy actors invoked the CDC's Guideline as justification, effectively "weaponizing" that document.[18] The decline in prescriptions that began before 2012, accelerated.[19] By 2017, US opioid prescriptions per capita had fallen 28% from their 2012 peak, and sat well below the levels seen in 2006.[20] Initial opioid prescriptions fell by 54% from 2012 to 2017.[21] When counted in MME per capita, the US continued to receive prescribed opioids at levels far above other countries.[22] This statistic primarily reflected a smaller group of longer-term and higher-dose patients, since 5% of US opioid recipients accounted for 59% of MME consumed.[23] In short, only the acceleration of stoppages among this smaller group of long-term and higher-dose patients could ever bring US consumption in MME in line with other countries.

The impact of the "effective mandate" to reduce prescribing is not fully known, and not all achieved reductions can be attributed to pressure on prescribers. Some long-term recipients of opioids have no desire to continue opioid medications, and they taper off successfully. However, other long-term recipients of opioids were affected adversely as clinicians responded to mandates and incentives. Prior to 2019,

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their stories had emerged primarily in public reporting by news outlets,[24] in experiences told by patients in the comments sections to editorials,[25] reports of medical deterioration or suicides shared privately among colleagues or, occasionally, described by health professionals.[26] For example, one late-2018 Fox News story profiling suicides after forced opioid taper received over 5,000 online comments, many from patients and their families.[27]

By late 2018, professionals and organizations began to issue formal statements of concern. An International Stakeholder Letter of Concern appeared in the journal Pain Medicine, signed by over 100 professionals.[28] Human Rights Watch issued a report, "Not Allowed to Be Compassionate."[29] One month later, an academic consensus paper was published on "challenges" with implementation of the CDC Guideline of 2016, focusing in part on issues related to taper.[30] By spring of 2019, government agencies began to respond. Key authors of the 2016 CDC Guideline wrote in the *New England Journal of Medicine* that their Guideline had been misapplied, to the detriment of patients.[31]

The eventual pushback emerged in part because patients, clinicians, and a human rights organization observed harms, before scientific reports emerged that tended to substantiate their concerns. Most often, the patients suffering were people with long-term and often complex pain and mental health conditions who, as they saw it, had derived functional benefit and sustained relief from opioids over years. As health care providers tapered, discontinued, or bowed out of opioid prescribing altogether, not all patients could survive. Before touching on the conflicting and limited evidence regarding the benefits and harms of opioid stoppage or taper, we should summarize the underlying scientific challenge that renders tapering a clinical conundrum.

Why Tapering Presents a Conundrum

A recent article by Manhapra et al. highlights challenges related to the mechanism of opioids' benefit for pain, and from the neuroplastic and behavioral adaptations that emerge, to varying degrees across patients, as a result of long-term opioid therapy.[32] The briefest possible summary takes note of the following. Pain is not just a nociceptive experience, but an affective state in which pain and its relief are modified by learning, memory and behavior. Each of these, one might add, are influenced by life history, the clinical care context, and, in ways that are still subject to debate, the perpetuation of whatever injuries generated the pain in the first place.

Opioids' admittedly uneven benefit in long-term pain depends not just on interrupting pain signals (antinociception) impacts but on affective and emotional relief (i.e. interaction with brain reward systems), as well as expectancies associated with taking medicine. Evidence on opioid utility is mixed. Opioids show small benefits compared to placebo in studies of three to six months' duration,[33] and similar (and small) average benefits as non-opioid treatments.[34] A one-year trial compared aggressive opioid dose escalation to a stepwise series of non-opioid therapies, with a low-potency opioid being the final step (and required by only a small number of patients). Both trial arms obtained similarly good outcomes.[35] Long-term con-

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tinuation at low dose without obvious adverse effect is observed in some selected adult populations.[36] However, the downside of repeated opioid use is, crucially, not limited to physiologic tolerance or the potential for acute opioid withdrawal syndrome, which manifests with a myriad of symptoms (i.e. diarrhea, sweats, anxiety) when opioid medications are stopped quickly.

A greater challenge is physical and psychologic dependence on the opioid. Dependence is a complex neuro-adaptive change involving multiple neurologic substrates and mechanisms, not all of which are covered here. One of cardinal interest, however, is the "opponent process," which derives from psychological literature.[38] An opponent process is a normal psychological phenomenon that tends to "push back" against reward or relief experiences.

The power of this opponent process is likely to differ greatly across situations and people. But we reason that it tends to grow more pronounced after repeated exposure to a rewarding/relieving stimulus, such as pain relief from an opioid dose. As a result, net relief tends to diminish over time and the overall pain experience can worsen, independent of the primary pathology that created the pain, even if each dose is still experienced as helpful to the individual.

The term "dependence" indicates that the patient reaches a new steady-state (termed "allostatic reset"). On its face, that steady-state may look good (i.e. patient takes medication and functions well in life), or it may look bad (in the extreme, addiction). Somewhere between these poles, some patients have formed a dependence in which the pain, emotions and energy levels are volatile, but the opioids are experienced as helpful anyway. The heuristic expression "complex persistent dependence" has been applied to this situation.[38] Opioid discontinuation and dose reduction among patients with complex persistent opioid dependence can cause several effects beyond the acute physical withdrawal that most people know about. After dose reduction, a more protracted opioid withdrawal syndrome can transpire, with a complex presentation, of which many clinicians are unaware. This more complex clinical presentation may include sustained worsening of pain (i.e. rebound) and function, psychiatric instability, aberrant behaviors in relation to the prescribers and clinical caregivers, emergence of new substance use disorder, and medical destabilization.[39]

A taper of dose (MME) for a prescription opioid seems intuitively appealing from a clinical perspective, especially in the setting of problematic opioid dependence, save for two underestimated issues:

First, opioids may still represent the only operational, effective treatment for assuring reasonable function among those with severe long-term pain. Many alternatives pose less risk, to be sure. The one-year trial, mentioned above, found that aggressive use of opioids was not superior to a careful and systematic opioid-avoidant strategy in which a low-potency opioid (tramadol) was held in reserve, for a few.[40] But that trial did not purport to represent the full spectrum of human conditions involving severe pain, and it relied on people who volunteered to be randomized. Additionally, among non-opioid treatments, a summary by the US Agency for Healthcare Research and Quality found that most showed small average benefits, in trials of short duration, demonstrating efficacy for only some patients, not all.[41] Finally, many helpful behavioral interventions, such as yoga, are not easily accessed by people contending with geographic distance, payment barriers, and full time jobs.[42]

The second issue is the as-yet unresolved evidentiary debate on taper, which governs the following two sections.

Tapering: Introducing the Arguments

In considering taper, a metric of success is required. In understanding the conflict between institutional actors (e.g. regulators, payers) and patients, it is crucial to describe the difference between regulatory definitions of success and clinical definitions of success.

For institutional voices such as the Office of the Inspector General for the US Department of Health and Human Services,[43] the National Committee for Quality Assurance,[44] and other actors, reducing the number of persons at "high amounts" of opioids (i.e. >90 or >120 MME) defines success. That reduction alone permits institutions to document good faith in confronting a societal crisis, and also to contain political or legal vulnerability.

For clinicians, however, success has to involve patient well-being. In general, an opioid taper can be considered successful only if the probable risk improvement with dose reduction can be balanced with the degree of achievement of goals that are important to patient, namely, stability or improvement in pain and function, avoiding instability and harm related to medical, psychiatric, and psychological conditions.[45] And, with the recognition of protracted opioid withdrawal syndrome as a serious adverse effect, successful taper should also avoid significant protracted abstinence syndrome.

Thus, the evidentiary argument reviewed here will focus on success and failure from a clinical perspective, returning to the issue of ethical imperatives only in closing.

Taper: Evidence For Benefit

Evidence arguing for taper as a clinically helpful undertaking comes in three categories. First, there is

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an association between overdose risk and the dose prescribed on a chronic basis, across multiple cohorts.[46] As a matter of common sense, a correlation between prescribed dose and "overdose" suggests that the event termed "overdose" can be seen as an iatrogenic pharmacologic excess, correctable through dose reduction.

Second, there have been a number of trials and observational studies regarding dose reduction or discontinuation. A literature review published in 2017 identified 11 randomized trials and 56 observational studies, rating study quality as "good" for three studies, "fair" for 13, and "poor" for 51.[47] More studies focused on discontinuation than dose reduction. Most appeared to involve voluntary patients, and most entailed formal assistance programs for achieving taper (often multi-disciplinary). The authors rated the overall quality of the evidence "very low". Among eight fair-quality observational studies, there were improvements in pain severity, function, and quality of life (in three of three studies measuring those particular outcomes) after opioid dose reduction.

The review's authors did mention limitations to their review. For example, just five of 67 studies assessed primary care, where pace of work tends to be higher and accessibility of taper supports low.

Third, in favor of taper, there have been a range of observational studies to suggest other downsides to opioids. These may include, but are not limited to: depression,[48] bacterial infectious risk,[49] and changes in sexual hormones. A formal debate on the degree to which each association may be seen as causal sits outside this paper's purview. However, as with almost any medication, there are risks associated with administration of opioids. Elimination of these risks should reduce potential morbidity.

Taper: Data Against

Evidentiary arguments "against" tapering come in three broad categories.

The first evidentiary argument notes the limitations of the data "for" taper, and thus draws on the same evidence. The aforementioned review declared the quality of evidence to be low, and cautioned on the lack of evidence regarding mandates such as are now in play:

> In the context of ongoing health system and population-level efforts to reduce opioid use and prevent opioid-related harms, we identified no prospective studies of mandatory, involuntary opioid dose reduction among otherwise stable patients. Finally, this review found insufficient evidence on adverse events related to opioid tapering, such as accidental overdose if patients resume use of high-dose opioids or switch to illicit opioid sources or onset of suicidality or other mental health symptoms. [50]

The second evidentiary argument provides a different account for why the poisoning event termed "opioid overdose" occurs, one that greatly de-emphasizes prescription dose per se. Namely, in prescription-opioid receiving populations, a majority of overdose events seem to occur among individuals receiving low prescribed doses,[51] or who had no recent prescription. For example, in Washington State's Medicaid program, close to half the opioid prescription recipients suffering overdose had no prescription that could have covered the time when opioid poisoning transpired.[52]

Prescribed dose could still *be associated with* relative risk, but the degree to which the prescribed dose *caused* that risk is less certain due to the challenges inherent in the retrospective statistical modeling exercises in research studies that gave opioid dose its prominence. While dose is easily gleaned from large retrospective databases, other factors connoting life instability, emotional chaos, and the propensity or risk factors that lead to overdose are less discernible. Some data suggest that dose escalation itself is correlated with distress indicators such as depression.[53] There is reason to suspect that prior to 2012, primary care providers prescribed opioids (and escalated doses) without assiduously querying all the forms of distress in their patents. For such patients, the operational "cause" of a poisoning event may not be the dose on the bottle so much as the distress that leads to ingesting an extra pill, borrowing some sleeping pills, and downing a few shots of whiskey, causing catastrophe. This would explain the predominance of *low* prescribed doses in prescription recipients who "overdose."

In fact, the notion that "most overdose is underdose" was first articulated in historic analyses of heroin-related deaths.[54] Prior to the influx of fentanyl in the US,[55] most heroin overdose decedents had low heroin metabolite levels, not high. Most appeared to have used in unfamiliar settings (suggesting life chaos), with combinations of other psychoactive substances, in the context of medical illness. This combination of risks approximates the deaths seen among prescription recipients today, and suggests a need to address polypharmacy, life chaos, and consistent therapeutic relationships, potentially more intensely than dose reduction per se.

The third evidentiary argument against opioid taper takes note that whatever benefits might be conferred in clinical trials of taper conducted by experts with voluntary patients, observational reports suggest risk under ordinary conditions of practice. Sequential papers in 2019 showed: (a) that most discontinuation

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among high dose Medicaid patients in Vermont was rapid, and often followed by hospital care;[56] (b) that cessation was associated with increased risk of death from overdose in one health system,[57] and termination of care relationships in another;[58] (c) that upward and downward dose variations were associated with elevated overdose risk in Colorado;[59] (d) that physicians reduce doses rapidly in ways that exceed CDC Guidelines among one in four patients;[60] (e) that prescription opioid cessation among veterans was followed by elevated risk of death from both overdose and suicide, in analyses that controlled for a range of patient characteristics.[61] Finally, a Michigan study found that 41% of primary care physicians refuse to see patients already receiving opioids,[62] a situation that limits the opportunities to protect the same patients.

The third evidentiary argument against pushing opioid taper in long-term pain patients takes note that the spectrum of dependence includes a considerable "grey zone" (characterized above as complex persistent dependence[63]) between benign dependence and diagnosable opioid use disorder). For the opioid use disorder group, taper is usually ineffective or dangerous. In a large randomized controlled trial for patients with prescription opioid use disorder, taper failed among 91.5% of participants (manifested by return to compulsive use of opioids), regardless of how the taper was conducted.[64] If a treatment fails for 90% of people at one end of the spectrum of dependence, and its success is mostly untested for the rest, that alone justifies caution in pushing taper as a general safety measure.

A summary, in regard to the case for and against opioid taper, could be as follows: there is evidence that under some conditions, often in clinical trials with voluntary patients, some number of patients benefit from opioid taper. Under conditions of a major social crisis brought on in good part by excess prescribing of opioids in general, taper of opioid-receiving patients holds natural appeal, if not to the patients, then to other interested parties. However, other evidence suggests that in regular practice, poor outcomes often follow opioid dose variation or stoppage, although the cause-and-effect relationship is not proven by such observational data.

Ethical Considerations

The push to taper opioids in patients who receive these medicines long-term for care of pain occurs in the context of a complex a social tragedy of addiction. In that context, institutional actors, leaders and clinicians are under pressure to show evidence of good faith in attempting to correct prescribing practices that contributed to the genesis of the crisis itself. In turn, payers, regulators, lawmakers, and others have created strong incentives or mandates on prescribers and patients in the form of payment policies, legal restrictions, and quality of care metrics that treat the opioid dose received as bad if it sits above a given level. Such policy initiatives incentivize taper and discontinuation, with or without the patient's consent.

And yet the evidence to favor forced or mandated dose reduction remains weak since existing studies favorable to taper involve voluntary patients working with experts, and a body of observational data has emerged to suggest that outcomes after opioid stoppage are often poor.

For institutions tracking prescription changes, however, the metrics of achievement are aggregate in nature and focused on patient panels (i.e. "percentage of patients receiving high dose"), and appear to be in serious tension with metrics focused on individual well-being and health. This emphasis on the aggregate tends to be the case for institutional actors regardless of whether their leaders are motivated by altruism or simple desire to reduce adverse attention. An emphasis on maximizing a perceived aggregate good for the most persons is, traditionally, aligned with utilitarianism.[64] However, we have not seen health care institutions declare a willingness to harm some patients in order to advance a perceived health care benefit for others. Thus, even if some quality metrics and strategies appear utilitarian on their face, underlying commitments of institutional leaders in health care, quality measurement or regulatory offices are not likely to be entirely so.

The ethical situation for prescribers is clearer. A doctor is expected to focus on optimizing benefit for each patient as an individual. In that fiduciary relationship, the provider is trained never to treat a patient merely as a means to an end (and in this situation, optimizing a population metric would be one example), but as an end in himself or herself, an echo of one of the categorical imperatives first laid out by Kant.[65] If a prescriber adheres to institutional pressure to reduce dose despite sincere concern that doing so harms the patient, it is clearly unethical for the provider.

When these conflicts emerge in health care, they have been termed a problem of a dual agency.[66] To uphold the interests of institutions (many of which have power over the physician's livelihood, at least indirectly), prescribers should cut prescriptions, effectively acting as agent for those institutions. Certainly, they are under forms of pressure to do so, most notably through payment controls, quality metrics, risk of legal investigation, and governmental rules. Perspectives on how physicians should generally handle dual agency have often arisen in the context of whether to offer potentially costly services to an individual, when

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doing so might affect the fiscal stability of the payer. In that context, there is ample room for dispute.

In this case, however, one cardinal principle can guide us. A general injunction against harming patients makes a generalized policy of forced opioid taper problematic, if death or debility number among the potential outcomes. Naturally, a principle of "do no harm" could also justify scrutinizing ongoing prescriptions with a level of concern, given that such data as exist for opioid-related benefit cannot be divorced from consideration of opioid-related harm. That may justify attempted taper, if the clinician can assure a level of support and follow-up that would allow protection against harm and reversal of course if harm emerges. However, actions that risk grievous harm to patients, including death, in favor of institutional perceptions of an "aggregate good" are hard to justify.

In sum, clinicians who care for patients receiving opioids face an ethical problem in regard to tapering incentivized or mandated by agencies that deliver, regulate and otherwise govern health care. It is a problem of dual agency, of being pulled between a regulatory definition of success in addressing a national opioid crisis and a clinical definition of success in caring for patients. For institutional actors, reducing high-dose prescriptions has proven a compelling objective, despite warnings from several federal agencies that not all opioid reductions are necessary or protective. Clinicians seeking to uphold a primary fiduciary duty to each patient as an individual are likely to find that their actions are often in tension with the agencies that pay, regulate, measure, and govern them, until there is greater agreement about how success is defined in the care of a vulnerable patient population.

Note

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