

The Proliferation of Dosage Thresholds in Opioid Prescribing Policies and Their Potential to Increase Pain and Opioid-Related Mortality

Introduction

The past two decades have witnessed increases in opioid-related morbidity and mortality concomitant with increases in the prescribing of opioids to treat chronic pain. State policy-makers, under pressure to do something about the overdose rate, have intervened. One such intervention involves the adoption of daily opioid thresholds in state prescribing policies that, once reached, will trigger specific actions or recommendations. Although dosage threshold models continue to spread across the United States, these governmental interventions could have serious unintended outcomes in terms of increased pain and opioid-related injury and mortality. The following commentary highlights the evolution of dosage thresholds, their potential for unintended outcomes, and advocates for the evaluation of these models and the adoption of mandatory education-based alternatives, alternatives that would provide a balanced approach to the treatment of pain and the prevention of harm without interfering with the physician-patient relationship.

Background

An estimated 100 million Americans suffer from chronic pain [1]. Whether nociceptive or neuropathic, treatments and outcomes can vary depending on individual patient characteristics [2]. Notwithstanding these variations, and the challenges associated with measuring the efficacy of long-term opioid therapy [3], prescription opioids have been used to help reduce pain and improve function for millions of people [4]. At the same time, however, the use of prescription opioids has been associated with an alarming increase in substance abuse, injury, and death [5]. Increased media

attention on one side of the equation (overdose), has translated into increased involvement by drug policy entrepreneurs in the form of congressional inquiries, new laws [6], and even a petition to the U.S. Food & Drug Administration that sought a labeling change and limits on opioids [7].

The state of Washington, however, took a different approach to reducing overdose. In 2007, Washington was the first to experiment with the use of total daily dosage in their state prescribing guidelines as a trigger to recommend further action or consideration by the health care provider.¹ At their inception, these advisory guidelines were “part of a year-long educational pilot to improve care and safety when treating chronic non-cancer pain with opioids,” and did “not apply to the treatment of acute pain, cancer pain, or end-of-life (hospice) care” [8]. At that time, Washington prescribers were asked to calculate the dosage that their chronic non-cancer pain patients were receiving each day, convert that dosage to morphine equivalency, and if the total daily dose exceeded 120 mg, the guidelines recommend a pain consultation [9]. Washington characterized this 120 mg threshold as a “yellow flag [10],” a precautionary signal to get the prescriber to press pause before moving forward with dose escalation. In a 2009 editorial, Fishman and Webster raised a variety of concerns with the Washington model and its potential to spread to other states [11]. Six years later, the Washington dosage threshold model has not only changed from a recommendation to a requirement, it has indeed spread to other states and continues to proliferate across the United States and varies in terms of regulatory approaches, dosages, triggers, patient conditions, and insurance coverage. A table summarizing that proliferation appears immediately below, followed by a discussion focusing on the many serious concerns raised by these models.

Ziegler

State dosage thresholds across six states²

State	WA ^a -1	WA ^a -2	MA ^b	OH ^c	IN ^d	CO ^e	MN ^f
Year effective	2007	2012	2012	2013	2014	2014	2015
Total daily MED	120	120	120	80	15, 60	120	120(Limit)
Rule/Guideline	Guideline	Rule	Guideline	Guideline	Rule	Guideline	Rule/Policy
Limited to non-cancer pain only	YES	YES	YES	YES	YES	YES	NO
Patient population impacted	ALL	ALL	Workmens Comp	ALL	ALL	ALL	MHCP only (Medicaid, MnCare)

^a WA: [8].

^b MA: <http://www.mass.gov/lwd/workers-compensation/hcsb/tg/treatment-guidelines-as-of-10-27-2014.pdf> (accessed May 15, 2015).

^c OH: <http://med.ohio.gov/PrescriberResources.aspx#514113-opioid-prescribing> (80 MED Guidelines, last accessed May 15, 2015);

^d IN: <http://www.ismanet.org/pdf/legal/FinalRule93014.pdf> (last accessed May 15, 2015).

^e CO: Board Adopts New Opioid Policy, <http://cdn.colorado.gov/cs/Satellite?c=Page&childpagename=DORA-Reg/DORALayout&cid=1251632324357&pagename=CBONWrapper> (last accessed May 15, 2015).

^f MN: http://www.dhs.state.mn.us/main/idcplg?IdcService=GET_DYNAMIC_CONVERSION&RevisionSelectionMethod=LatestReleased&dDocName=dhs16_190131 (last accessed May 15, 2015).

Concerns Related to Dosage Thresholds and Triggers

Although states continue to adopt dosage thresholds, there is a paucity of research focusing on the actual efficacy of these models and their impacts on overdose reduction and the treatment of pain. Consequently, in an effort to encourage research evaluating the effectiveness of public policy initiatives aimed at improving public health (National Pain Strategy) [12], and to alert policy-makers about the serious unintended outcomes that these models could produce, the following criticisms of dosage threshold models are offered.

Overdose Can Occur at any Dosage Level

One state policy official remarked that one reason dosage thresholds and triggers have become so popular is because they are so easy to create. While it may be “easy” to establish a 120 mg dosage threshold, such decisions ignore the reality that injury and overdose can occur well below the popular 120 or 80 mg morphine equivalent dose (MED) threshold [11]. In fact, a Washington study found that 72% of poisonings and 70% of adverse effects from opioids were at prescribed dosages well below the state’s 120 mg MED “yellow flag” threshold. The authors admitted that:

opioid dosing and duration guidelines that focus primarily on higher dose use may not be sufficient to achieve a substantial reduction in morbidity related to prescription opioid use. Even at modest dosing levels over short time intervals, prescription opioid use can have serious health consequences [13].

Moreover, even in the Dunn study, a study often cited to support dosage thresholds, researchers found that “most overdoses occurred in patients receiving low-to-moderate-dose regimens” [14].

Fixating on Dosage Levels Ignores or Subordinates the Many Other Factors that can Contribute to Opioid-Related Morbidity and Mortality

Factors relating to individual patient characteristics, non-therapeutic use, drug formulation, mental health, nonadherence, prescriber error, suicide, poly-substance, poly-pharmacy, and pharmacokinetics can all play a role in opioid-related injury and death [16–21].

Association Is Not the Same as Causation

Dosage threshold advocates continue to cite studies that they claim support dosage thresholds and the relationship between dosage and overdose. However, a recent systematic review of the very studies proponents rely on undermines these assertions [22]. Indeed, high dosage has been associated with overdose [15,23], but association is not causation [24], and high therapeutic dosage by itself is not the singular cause of unintentional overdose.

State Variation in Dosage Threshold Models Seem More like Experimentation with Increased Risk Rather than Informed Policymaking

The lack of dosage uniformity and regulatory approaches across the United States raises the concern that dosage

The Proliferation of Dosage Thresholds

levels are not informed by high-quality evidence, are arbitrary, and may amount to experimentation with increased risk to patients. For example, Washington, Massachusetts, and Colorado all have a dosage thresholds of 120 mg MED, and some states use mandatory rules while others rely on advisory guidelines. Second, Minnesota's approach is not just a 120 mg MED dosage threshold, it is actually a limit; a limit that applies to all chronic pain patients, new and existing—even those who are terminally ill. While exceptions can be made to Minnesota's 120 mg MED/day limit, those exceptions can only be granted through prior authorization, and only through a private company retained by the state whose stated mission was to "improve care and contain costs." [25]. While state policy experimentation should be encouraged, such experimentation must not come at the expense of patient welfare. Moreover, policies must be evaluated for their impact, and consistent with the Colorado guidelines, respond "to any unintended consequences" the prescribing policies may create [26].

The Increased Necessity of Calculating Morphine Equivalency Could in Turn Increase the Rate of Unintentional Overdose and Incidence of Under-Treated Pain

Dosage threshold models have the potential to increase the risk of unintentional overdose by virtue of the necessity to determine morphine equivalency, an error prone process [27]. Following calculation of a patient's total daily dosage, dosage threshold models suggest the prescriber first convert that daily dose into a morphine equivalent. But the conversion process itself is fraught with many dangers. First, published conversion tables have been found to vary significantly between each other and "recent evidence suggests that the use of dose conversion ratios published in equianalgesic tables may lead to fatal or near-fatal opioid overdoses" [27]. Second, while on line opioid conversion calculators can help facilitate the conversion process, and some states encourage their use to help prevent overdose [28], a recent study revealed substantial differences among them. For example, one study found a (-) 55% to (+) 242% difference between online opioid calculators when comparing them to each other, significantly increasing the likelihood of unintentional overdose [29]. While Washington posts its own online conversion calculator on their prescribing website, they nevertheless recognize some of the dangers that online calculators and the conversion process poses:

CAUTION: This calculator should NOT be used to determine doses when converting a patient from one opioid to another. This is especially important for fentanyl and methadone conversions. Equianalgesic dose ratios are only approximations and do not account for genetic factors, incomplete cross-tolerance, and pharmacokinetics [30]. [Emphasis in original]

Consequently, increased frequency and reliance on these calculators in turn increases the potential for error

in terms of overdosing unless warnings about the conversion process and the variation in on line calculators are made clear. Moreover, the problems associated with the calculation and conversion process are not limited to overdose; errors in conversion can also result in the under-treatment of pain through under-dosing and concomitant increased risk of withdrawal [29] and perhaps pseudoaddiction [31].

Concerns Related to Dosage Triggers (Post-Threshold Recommendations or Requirements)

At first blush, many of the post-threshold actions appear consistent with good medical practice and the current Federation of State Medical Board guidelines. For example, some recommendations or requirements address the need to obtain informed consent, consider risks and benefits, alternatives and treatment plans, patient history, periodic visits, or to make appropriate use of the state's prescription monitoring program. And since some patients may have or develop a substance abuse problem, drug monitoring may also be indicated. Nevertheless, several concerns still exist. For example, dosage thresholds and their post-threshold requirements may be difficult to interpret or may send the message that what they require or recommend can wait until after the threshold is reached. Second, some state post-threshold requirements may amount to unfunded mandates by requiring a pain consultation but failing to provide the means by which those consultants would be compensated. Washington recognized this problem early on [32], and there is evidence that many prescribers who treat pain on the east side of the state are not getting the consults they need ("45% reported very low capacity to access pain specialty consultation") [33].

Do Balanced Alternatives to Dosage Thresholds Exist?

Although it is often easier to criticize than create, balanced alternatives to dosage thresholds currently exist, and none of them rely on dosage thresholds. Project Lazarus, for instance, is an educational and community intervention that has shown promise in reducing unintentional overdose and treating pain [34]. What started out as a community-based educational intervention in a single North Carolina county has now expanded state-wide and continues to be adopted throughout the United States. Unlike governmental interventions that focus primarily on one side of the issue (preventing harm), Project Lazarus seeks to achieve two goals simultaneously: reducing the overdose rate in communities and to "help deliver better pain relief" [35].

In addition to Project Lazarus, another promising approach to achieving balance is being used in New Mexico, a state that has one of the highest overdose rates in the nation. In brief, New Mexico has adopted a continuing medical education requirement that addresses both overdose prevention and pain treatment

Ziegler

[36]. They recognized from the start that rule-based solutions could have the “unintended consequence of interfering with the physician-patient relationship.” Like Project Lazarus, New Mexico’s approach is balanced; it seeks to reduce the potential harm associated with opioids and actively improve the treatment of pain.

Conclusion

The use of daily dosage thresholds in prescribing policies represents an innovation to reduce the incidence of unintentional overdose. Indeed, high dosage levels can be a concern. But the reliance on dosage in these models as the factor, instead of a factor in preventing overdose is not supported by evidence [13,22], raises multiple concerns, and has the potential to increase the incidence of pain and opioid-related morbidity and mortality. In light of the paucity of empirical research evaluating the efficacy of threshold models and their outcomes, coupled with the realization that politics has been known to trump science [37], perhaps the current political solution is somewhere in the middle where thresholds are placed in advisory guidelines instead of mandatory rules, the concerns are addressed, and the actual impacts of these models are determined. In the interim, however, educational interventions to reduce pain and unintentional overdose currently exist [36] and can be effective [38]. After all, prescriber education remains a key component in federal efforts [39], and even the Washington model recognizes the value of education by exempting physicians from the mandatory pain consult requirement if the prescriber has taken continuing medical education (CME) in pain management [40]. Pain treatment and preventing overdose are not zero sum games, and solutions which focus predominantly on one problem while neglecting the other are doomed to fail [41]. While long-term studies about the effectiveness of opioids may be lacking [3], absence of evidence is not evidence of absence [22]. Opioids may not be the panacea, but they have helped reduce pain and improve function for millions of people. Future efforts and reforms should continue to focus on balance and the need to ensure access while preventing harm [12], rather than advocating for only one solution to a very complex problem or engaging in opioid-McCarthyism [42]. The Washington model started out as an educational pilot and asked prescribers to press pause before going further. Today, in light of the concerns articulated above, perhaps now is the time for policymakers to press pause and reconsider the adoption of dosage thresholds in their states.

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Notes

1. Technically, there are critical distinctions between policies, rules, regulations, and guidelines. Rules and regulations are administrative law terms that involve an administrative procedure that parallels the legislative process. Rules are proposed, an open period of comment follows, and once adopted carry the force and effect of law. In contrast, guidelines are primarily advisory and by definition not mandatory.
2. The 2007 Washington guideline was replaced by the 2012 rules but appears twice to illustrate the progression from voluntary guideline to mandatory rule.

References

- 1 Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies Press; 2011.
- 2 Turk DC. Customizing pain treatment for chronic pain patients: who, what, and why? *Clin J Pain* 1990;6:255–70.
- 3 Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a national institutes of health pathways to prevention workshop. *Ann Intern Med* 2015;162:276–86.
- 4 Reuben DB, Alvanzo AAH, Ashikaga T, et al. National institutes of health pathways to prevention workshop: The role of opioids in the treatment of chronic pain. *Ann Intern Med* 2015;162:295–300.
- 5 Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med* 2006; 31:506–11.
- 6 Ziegler SJ. Patient abandonment in the name of opioid safety. *Pain Med* 2013; 14:323–4.

The Proliferation of Dosage Thresholds

- 7 Fine P, Webster L, Argoff C. American academy of pain medicine response to PROP petition to the FDA that seeks to limit pain medications for legitimate noncancer pain sufferers. *Pain Med* 2012;13:1259–64.
- 8 Agency Medical Directors' Group. 2007 Opioid Dosing Guideline, available at: <http://www.agencymed-directors.wa.gov/opioiddosing.asp> (last accessed May 15, 2015).
- 9 Franklin GM. Opioids for chronic noncancer pain: A position paper of the American academy of neurology. *Neurology* 2014; 83:1277–84.
- 10 Franklin GM, Mai J, Turner J, et al. Bending the prescription opioid dosing and mortality curves: Impact of the Washington State opioid dosing guideline. *Am J Indus Med* 2012;55:325–31.
- 11 Fishman SM, Webster LR. Unintended harm from opioid prescribing guidelines. *Pain Med* 2009;10:285–6.
- 12 National Pain Strategy (Draft), Population Research, Objective 3, at 19, available at: http://prcc.nih.gov/National_Pain_Strategy/NPS_Main.htm (last accessed May 15, 2015).
- 13 Fulton-Kehoe D, Garg RK, Turner JA, et al. Opioid poisonings and opioid adverse effects in workers in Washington State. *Am J Ind Med* 2013; 56:1452–62.
- 14 Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med* 2010;152:85–92, at 90.
- 15 Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med* 2011;171:686–91.
- 16 Fishbain DA, Lewis JE, Gao J. The pain suicidality association: A narrative review. *Pain Med* 2014; 15:1835–49.
- 17 Cheatle MD. Pain & suicide: A hidden epidemic. *PWJ* 2014;2:30–5.
- 18 Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related deaths in the United States. *Pain Med* 2011;12:S26–35.
- 19 Shah NG, Lathrop SL, Reichard RR, Landen MG. Unintentional drug overdose death trends in New Mexico, USA 1990–2005: Combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction* 2008;103:126–36.
- 20 Johnson EM, Lanier WA, Merrill RM, et al. Unintentional prescription opioid-related overdose deaths: Description of decedents by next of kin or best contact, Utah, 2008–2009. *J Gen Intern Med* 2013;28:522–9.
- 21 Centers for Disease Control and Prevention, "Prescription Painkiller Overdoses: Use and Abuse of Methadone as a Painkiller" (2012), available at: <http://www.cdc.gov/VitalSigns/methadoneoverdoses/index.html> (accessed January 4, 2015).
- 22 King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: A systematic review. *Am J Pub Health* 2014;104:e32–42.
- 23 Hirsch A, Proescholdbell SK, Bronson W, Dasgupta N. Prescription histories and dose strengths associated with overdose deaths. *Pain Med* 2014;15:1187–95.
- 24 Neuman WL. *Social Science Research Methods: Qualitative and Quantitative Approaches* (6th ed). Boston, MA: Pearson Education; 2006.
- 25 North Dakota Medicaid Pharmacy Program Quarterly News (published by Health Information Designs, LLC). http://www.hidesigns.com/assets/files/ndmedicaid/newsletters/ND_Summer_2014_newsletter.pdf (last accessed May 15, 2015).
- 26 Colorado Department of Regulatory Agencies, Board Adopts New Opioid Policy, <http://cdn.colorado.gov/cs/Satellite?c=Page&childpagename=DORA-Reg/DORALayout&cid=1251632324357&pagename=CBONWrapper> (last accessed May 15, 2015).
- 27 Webster LR, Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. *Pain Med* 2012;13:562–70.
- 28 Kattan J, Amirfar VA. OpioidCalc: A tool to address the opioid analgesic overdose epidemic (December 1, 2014). American Pharmacists' Association, available at: <http://www.pharmacist.com/opioidcalc-tool-address-opioid-analgesic-overdose-epidemic> (last accessed May 15, 2015).
- 29 Shaw K, Fudin J. Evaluation and comparison of online equianalgesic opioid dose conversion calculators. *PPM* 2013; 13:61–6. Also available at: <http://www.practicalpainmanagement.com/treatments/pharmacological/opioids/evaluation-comparison-online-equianalgesic-opioid-dose-conversion> (last accessed May 15, 2015).
- 30 Opioid Dose Calculator, Agency Medical Directors' Group, available at: <http://agencymeddirectors.wa.gov/mobile.html> (last accessed May 15, 2015).

Ziegler

- 31 Martel MO, Dolman AJ, Edwards RR, Jamison RN, Wasan AD. The association between negative affect and prescription opioid misuse in patients with chronic pain: The mediating role of opioid craving. *J Pain* 2014;15:90–100.
- 32 Fishman SM, Webster LR. Unintended harm from opioid prescribing guidelines. *Pain Med* 2009;10: 285–6.
- 33 Franklin GM, Fulton-Kehoe D, Turner JA, Sullivan MD, Wickizer TM. Changes in opioid prescribing for chronic pain in Washington State. *JABFM* 2013;26: 394–400.
- 34 Albert S, Brason FW 2nd, Sanford CK, et al. Project Lazarus: Community-based overdose prevention in rural North Carolina. *Pain Med* 2011;12(suppl 2):S77–85.
- 35 Project Lazarus, available at: <http://projectlazarus.org/about-project-lazarus> (last accessed May 15, 2015).
- 36 Katzman JG, Comerci GD, Landen M, et al. Rules and values: A coordinated regulatory and educational approach to the public health crises of chronic pain and addiction. *Am J Pub Health* 2014;104: 1356–62.
- 37 Bernier NF, Clavier C. Public health policy research: Making the case for a political science approach. *Health Prom Intl* 2011; 26:109–114.
- 38 Wakeland W, Nielsen A, Schmidt TD, et al. Modeling the impact of simulated educational interventions on the use and abuse of pharmaceutical opioids in the United States: A report on initial efforts. *Health Ed Behav* 2013; 40:74S–86S.
- 39 Ziegler SJ. Governmental intervention in prescribing: Preventing harm and Medico-legal iatrogenesis. *PWJ* 2013;1:35–40.
- 40 WAC 246-919-862. Available at: <http://apps.leg.wa.gov/wac/default.aspx?cite=246-919-862> (last accessed May 15, 2015).
- 41 Ziegler SJ. Patient abandonment in the name of opioid safety. *Pain Med* 2013;14:323–324.
- 42 Ziegler SJ. Pain and the politics of hydrocodone. *Painview* 2014;10:13–16.