Comprehensive Review

Reducing Opioid Analgesic Deaths in America: What Health Providers Can Do

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Background: Available data have shown steady increases of drug overdose deaths between 1992 and 2011. We review evidenced-based recommendations provided by a few prominent North American pain societies and suggest ways on how health providers might help reduce opioid analgesic deaths by implementing these practices.

Objective: To identify health care providers' roles in reducing opioid analgesic deaths.

Study Design: A comprehensive review of current literature.

Methods: The review included relevant literature identified through searches of MEDLINE, Cochran reviews, and Google Scholar, PubMed and EMBASE from January 1998 to January 2014. The level of evidence was classified as I (good), II (fair), and III (limited) based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).

Results: Several practices such as too high doses overall, giving too high doses to opioid naive patients, too fast opioid titration, insufficient use and knowledge of urine drug testing, not updating knowledge of drug metabolism/interactions, and inadequate patient monitoring are associated with higher risks of opioid analgesic deaths. Suboptimal risk stratification of patients, rotation practices, and use of opioids analgesics in chronic noncancer pain are also associated factors.

Limitations: There were a paucity of good evidence studies which show recommendations reduce death.

Conclusion: Providers should be aware of all associated factors with opiate analgesic deaths and apply the available evidence in reducing opioid analgesic deaths.

Key words: Opioid analgesic deaths, methadone deaths, opioid mortality, opioid guidelines, genetic testing for opioids, urine drug testing

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Nearly 2 decades of research pointed to undertreated pain in the nation's health system. In August of 1997, the Robert Wood Johnson Foundation, in response to this, provided support for a 3 year project to the Federation of State Medical Boards (FSMB) whose principal goal was to make pain assessment and treatment an integral part of the nation's health system (4). Pain assessment and management would be a standard for which all health care facilities would gain accreditation from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Pain control became useful criterion for which many health organizations were judged.

The FSMB undertook the development of model guidelines aimed at encouraging state medical boards, its licensees, and other health care regulatory agencies to adopt policies promoting adequate treatment of patients using opioids when appropriate.

The board held the view that pain management was important and integral to the practice of medicine; and that under-treatment of pain would be a deviation from the standard of care. Physicians were told to use opioid analgesics if necessary provided there was documented unrelieved pain for cancer and non-cancer pain (4). These policies may, in part, have resulted in an explosion of opioid analgesics use by physicians starting around 1997 and building up until today.

In October 2000, the 106th U.S Congress passed the Decade of Pain Control and Research into law which was duly signed by President Clinton to begin January 1, 2001 (5), the same day JCAHO standards came into effect. Professional bodies like the American Pain Society working in collaboration with partners like the American Academy of Pain Medicine, American Headache Society, and American Society of Anesthesiology advocated for the passage of the National Pain Care Policy Act (2009 H.R756/S.660) which would establish 6 regional pain centers. Other provisions of this act would establish an awareness of pain as a significant health problem; identify barriers to appropriate pain care; authorize a public awareness campaign to educate patients, families, and other caregivers on pain care; ensure veterans have appropriate pain care; and ensure patients enrolled in Medicare managed care plans receive appropriate pain care. Though it eventually passed the house in 2009, but did not pass the senate, the overall result was significant increased awareness about pain control (6,7). Other high-profile congressional pain initiatives included the Veterans Pain Care Act of 2008 (H.R. 6122) and Military Pain Care Act of 2008 (H.R. 5465), these, along with the National Pain Care Policy Act of 2009 (H.R. 756/S.660), were included in the Affordable Care Act (ACA) signed in to law by President Obama in March 2010 (8). All these events led to renewed clinical staff sensitivity to awareness of the control and treatment of pain.

While the awareness of pain assessment and control was a welcome development in many institutions, it led to an increased demand for opioids. To meet the demand, there was a 700% increase in the average supply of morphine equivalent per person between 1997 and 2007. However, as the availability and use of opioid analgesics increased, so did the fatalities (9,). By 2007, there were 27,000 drug overdose deaths, and by 2011, the number had ballooned to 41,340, with one occurring about every 13 minutes, with opioid analgesics playing a major role (1,10).

Discussion

Factors Associated with Opioid Analgesic Fatalities

The factors associated with opioid analgesic fatalities include use of initial doses too high for opioid naïve patients (11), too rapid titration of doses (12), too high doses overall (13,14) insufficient use and knowledge of UDT (15,16), not updating knowledge of drug metabolism/interactions (17), inadequate patient monitoring (18), suboptimal risk stratification of patients (18-20), rotation practices (21,22), and long-term use of opioids analgesics in chronic non-cancer pain (23).

Patient- or systems-related factors are also known to contribute to fatalities. Some patients display behaviors referred to as drug diversion and doctor shopping. There seems to be a lack of public awareness of the inherent dangers of taking another person's medication, including opioids (9,24,25). Poor safe keeping of these medications has also been implicated (9,25,26). Prescription drug monitoring programs (PDMPs) vary from state to state in data collection and sharing, creating loopholes for aberrant drug behavior (2). The Food and Drug Administration (FDA) in July 2012 approved a Risk Evaluation and Mitigation Strategy (REMS), for extended-release and long-acting opioid analgesics, which provides a platform for educating physicians on safe opioid use. A detailed discussion of all system, regulatory, or individual factors associated with opioid deaths is beyond the scope of this paper. We focus mainly on physician roles in reducing opioid deaths.

Possible Mechanisms of Deaths from Opioids

The primary mechanism of death from opioids is hypoxia due to apnea. The central apnea index (CAI) is the number of apneic episodes per hour. Walker et al (27,28) compared 60 patients taking chronic opioids matched for age, gender, and body mass index with 60 patients not taking opioids to determine the effect of dosage on breathing patterns and found increased central apneic episodes of 12.8/hour in the group of patients on chronic opioids vs. 2.1/hour in the control group ($P < .001$). They also observed that there was a dose-response relationship between the morphine equivalent dose (MED) and apnea-hypopnea ($P < .001$),

obstructive apnea ($P < .001$), hypopnea ($P < .001$), and CAI ($P < .001$) after controlling for body mass index, age, and sex. Seventy percent of chronic opioid users were noted in the study to have ataxic or irregular breathing versus 5% of controls ($P < .001$). Those who were taking MEDs of 200 mg or higher had an odds ratio greater than 15 for ataxic or irregular breathing (27,28).

The cause of death with methadone appears to be either via central depression of respiration or cardiac rhythmic abnormalities (11). Wang et al (29) randomized 2 groups of 50 patients on methadone maintenance treatment and 20 body-mass index matched controls. Both groups were exposed to polysomnography, blood toxicology tests, and ventilatory monitoring of responses to hypoxia and hypercapnia. They observed that 30% of the methadone patients had a CAI > 5, while all patients in the control group had CAI < 1.

Helpful Strategies for Reducing Opioid Deaths and Evidence from Published Studies

Primary care providers (PCPs) are the main prescribers of opioids in the US. In a five year retrospective study by Wu et al (30), 80% of all opioid prescriptions written in a Veteran Affairs facility were issued by PCPs, while only one percent was issued by pain specialists. Volkow et al (31), using data from a privately owned national-level prescription and patient tracking service, found that out of 79 million opioid prescriptions in 2009 (40% of all opioid prescriptions in the US), PCPs issued 43.4% of them. The majority of patients who died from opioid analgesic abuse did so when prescriptions were written within practice guidelines and not because patients were abusing them (2). We can deduce from the above that better guidelines and better provider training might be needed. This training might best be incorporated in medical school curriculums, featured in standard medical licensing exams, residencies in training examinations, upon receiving Drug Enforcement Agency (DEA) registration numbers, and during recertification exams.

At Initial Visit

Establish Medical Necessity for Opioid Use

In a retrospective study of 309,000 Canadians who underwent minor surgery, the likelihood for receiving an opioid one year after a minor surgery was 44% higher if opioids were given postoperatively (32). Patients who use opioids beyond 90 days are more likely to continue opioids several years later (33). One study found that the odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids (34). Clinicians need to examine the medical necessity of continuing treatment on opioids beyond 90 days following surgery (2).

In order to determine that opioid analgesic therapy is necessary, it is important to establish that the pain is moderate to severe, the patient has a physical diagnosis, and has exhausted multiple modalities of treatment, like non-opioid pharmacologic analgesic agents, adjuvants, behavioral interventions, physical therapy, osteopathic manipulation, structured exercises, interventional pain management techniques, and other alternatives.

Once the medical necessity is established, continued medical necessity should depend on whether opioids provide analgesia, presence and tolerability of adverse effects, continued physical activity, and absence of aberrant activity (2).

If a prescriber feels the use of opioid analgesics in a patient who is currently on an opioid is not warranted, the opioid analgesics could be discontinued by using a slow taper. The Agency Medical Directors Interagency Guidelines suggest that most patients are able to tolerate a decrease of 10% of the total dose every week (35).

In cases where opioid abstinence withdrawal symptoms occur, patients may have nausea, diarrhea, muscle pain, and myoclonus. These symptoms can be managed using a weekly clonidine patch at 0.1 mg every 24 hours or a scheduled dose of clonidine 0.1 – 0.2 mg orally every 6 hours (35). Clonidine may cause changes in blood pressure.

Some patients may experience mild psychological withdrawal symptoms for a few weeks to as long as 6 months, which could present as increased irritability, depression, and insomnia (35). These can be managed with antiepileptic medications like valproate, carbamazepine, and gabapentin (36). While valproate and carbamazepine are more effective than gabapentin in mood disorders, they often require some degree of monitoring and have worse side effect profiles compared to gabapentin (36). Gabapentin at doses of 1600 mg – 2400 mg/day has been shown to be a helpful adjuvant in improving opiate withdrawal symptoms (37-42), though one study reported it was not better than placebo (43).

An antidepressant like mirtazapine at bedtime can help with insomnia and depression that may be found during substance withdrawal (44). Increased appetite

and weight gain are common side effects with the use of mirtazapine.

In patients with significant behavioral symptoms, referral to addiction psychiatry is warranted. In patients who already show significant dependence to opioids, stabilization on buprenorphine/nalaxone for several weeks followed by a gradual tapering off of buprenorphine/naloxone has been shown to be helpful (45). One multi-site randomized study of 653 opioid prescription analgesic dependent patients on buprenorphine/naloxone and opioid dependence counseling showed that maintenance on buprenorphine/naloxone for patients dependent on opioid analgesics was associated with higher success rate (49.2%) when compared to stabilization and tapering off of buprenorphine/naloxone in 2 – 4 weeks (6.6 – 8.6%) (46). The key here may be that the taper speed was more aggressive than the 10% weekly reduction in total dose which most patients can often tolerate (35).

Use Opioid Agreements

There has been some controversy over the utility of opioid treatment agreements or contracts, and attempts have been made to demonstrate the evidence for the effectiveness of opioid agreements in reducing opioid misuse and aberrant drug behaviors. The issues of concern are having a universal definition of what constitutes an opioid agreement, the lack of standardized opioid agreements, and uneven application of consequences or alternative treatment steps in the event patients fail to abide by the agreement make it difficult to compare studies. Real assessments of the validity of the effectiveness of opioid agreements and utility of UDTs may be achieved when a standardized opioid agreement is used and treatment plan on failing the agreement are the same across the board (47). Such a scenario may only possible in a randomized blinded control study.

Some physicians have abandoned using opioid agreements and UDT because of these concerns.

There are many published articles on opioid treatment agreements most of which are low evidence observational studies (48). A recently conducted meta-analysis by Starrels and colleagues (48), published in 2010, showed weak evidence for opioid agreements. The authors themselves mentioned that most of these studies were mainly observational studies with poor to fair evidence, lacked homogeneity because the treatment agreements were very disparate in content, and studies had included patients who at least were prescribed opioids for 3 months, and excluded patients with substance abuse.

They reviewed 11 studies, 4 of which showed a 7% to 23% reduction in opioid misuse after opioid agreements with or without UDT was instituted.

In the other 7 studies between 3% and 43% of patients continued to misuse opioids despite treatment agreements with or without UDT (48). However physicians view opioid agreements, an opioid contract provides the opportunity to discuss the risks, benefits, and alternatives within the frame work of an informed consent and set up mutually agreed treatment goals and terms for continuing or discontinuing opioids (49).

Screen and Risk Stratify Patients

While there is insufficient evidence that screening tools will reduce deaths, it might help identify patients who are substance abusers. The concomitant use of benzodiazepines, illicit substances, unemployment status, psychiatric disorders, are the strongest risk factors for opioid analgesic overdoses and deaths (50). Since combined use of illicit substances such as alcohol and benzodiazepines increase the risk of fatal overdoses, risk stratifying patients, both during the initial assessment and in ongoing treatment, could help to reduce the problem of fatal overdoses. There are several screening tools that have been tried. Jones et al (51) did a comparative analysis of these tools and found that the psychologist clinical interview showed a sensitivity of 0.77 and the Screener and Opioid Assessment for Patients-Revised (SOAPP-R) a sensitivity of 0.72 for detecting aberrant behavior. The SOAPP-R is a 24 item questionnaire used by the clinician that takes 10 minutes to complete. The SOAPP-R was the most sensitive self-report measure, while the psychologist interview was the most sensitive predictor of detecting aberrant behavior.

Seghal et al (52) compared several screening instruments for opioid risk assessment and identified varying levels of sensitivity, specificity, and limitations. Knowledge and application of these screening tools in an appropriate patient setting may help identify aberrant drug behavior.

Modesto-Lowe et al (11), in their review paper, enumerated advancing age, medically compromised patients, liver or pulmonary pathology, sleep apnea, poly substance abuse, opioid naïve, high doses of methadone, and rapid titration of methadone as potential risk factors for respiratory depression leading to deaths. Identifying patients with high-risk potential may help

the provider minimize fatalities associated with the use of opioids.

Use of Urine Drug Testing Optimally

Combined use of illicit substances along with opioids poses an increased risk of fatalities (50). Not enough physicians use UDT and some evidence suggests many do not adequately interpret UDT results (16,17). One study showed only 8% of PCPs, who are the providers most likely to prescribe an opioid, used UDT (17).

The American Society of Interventional Pain Physicians (ASIPP) guidelines show fair to good evidence that UDT, especially when used in conjunction with subsequent adherence monitoring, is helpful in establishing drug noncompliance, decreasing prescription or illicit drug use in patients with chronic pain (2).

The interagency medical group published guidelines to help physicians determine frequency based on individual risk using the Opioid Risk Tool (ORT) (a 5 item questionnaire) (35).

They recommend once, twice, and 3 times a year, respectively, for patients with low, moderate, and high ORT risk profiles. For patients presenting with aberrant behaviors (lost prescriptions, multiple requests for early refill, opioids from multiple providers, unauthorized dose escalation, apparent intoxication) UDTs need to be done during the clinic visit.

Other pain experts have suggested practical algorithmic approaches to the appropriate use of UDT that are based on the risk profile of the patient (53,54).

Overall there is insufficient evidence to guide physicians on who should have UDT or how many times a year this should happen, but the ASIPP, Canadian, and ACOEM guidelines all agree that it is helpful in establishing baseline data at initiation of therapy and during maintenance therapy (2,50,55).

As will be discussed below, UDT may also offer insight into issues of poor analgesia. Dipstick or point-of-service (POS) testing utilizes immunoassays to provide a positive or negative assessment of licit and illicit medications. While this can provide important information affecting the practitioner's decision to prescribe (or continue to prescribe) opioids, there can be many false positives and false negatives. Additional confirmatory testing may be necessary, using methods such as gas chromatography, mass spectroscopy, and high performance liquid chromatography to identify specific medications, their quantitative levels, or their metabolites (56,57). The physician should assess the need for additional confirmatory tests as reports of misuse of UDT have occurred without corresponding increase in care (53).

In using UDT, it is important to know what to expect and how to interpret the results. Oxycodone is metabolized to oxymorphone (CYP2D6) and to noroxycodone (CYP3A4). Hydrocodone is metabolized to hydromorphone, and codeine is metabolized to morphine. Heroin may be metabolized to morphine, but it has an intermediate metabolite called 6 monoacetylmorphine (6-MAM). In high doses, morphine may be metabolized to small amounts of hydromorphone. The provider should expect to see both the parent compound and the metabolite in urine (56) (Fig. 1) if the medication has been absorbed and not just added to the urine.

There can be several different results for a UDT. The UDT may show a positive result for a prescribed drug, meaning the patient recently took the prescribed drug. The UDT might show a negative result for a prescribed drug; in this case, the patient may not be taking the prescribed opiate, as is possible in cases of drug diversion, could be taking it in an irregular fashion, or the UDT could have been done hours or days after the last pill so that residual metabolites are no longer present in urine. Sometimes the UDT may be positive for a nonprescribed drug. A patient taking codeine or heroin may have morphine in the urine because both codeine and heroin are metabolized to morphine. Sometimes certain foods like poppy seed bagels may show opiates in urine. A metabolite of the drug (e.g., norhydrocodone or noroxycodone) may be present even when the parent drug is absent, especially if the patient is an ultrarapid metabolizer of the drug. A false-positive opiates test can result from drug cross-reactivity with the urine enzyme immunoassay tests (EIA) as is seen with ingestion of quinolones and rifampin, which may give a false-positive opiate EIA test, whereas verapamil, quetiapine, diphenhydramine, and doxylamine may give false-positive results on methadone-specific EIA testing. Disease conditions where patients may be at risk for lactic acidosis (toxin ingestion, liver disease, diabetes) may also produce false-positive results on immunoassay which may require additional confirmatory testing (56-58).

Urine drug panels should therefore include metabolite panels; that way, it is possible to identify the drug, the metabolite, and a combination of the drug and the metabolite in varying percentages.

There are several clues that are used to detect adulteration of a urine sample. The temperature should fall between 90 degrees to 100 degrees F within 4 minutes

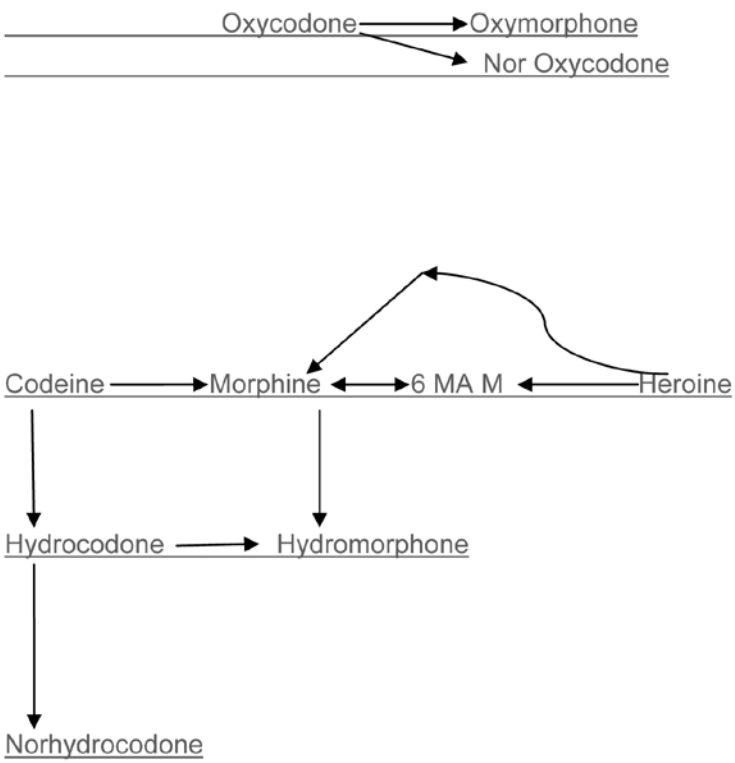

Fig. 1. *Simplified metabolic pathway of commonly known opiates in urine.*

of voiding. Normal urine pH should be between 4.5 and 8.0, with a specific gravity of 1.010 to 1.025. Urine creatinine should be more than 20 mg/dl in any urine sample. Values less than 5 mg/dl is inconsistent with human urine (56). Any aberrant behavior or suspect UDT should call for a discussion with the patient and documentation in the medical record.

Consider Use of Genetic Testing

Clinicians often walk a fine line between providing adequate pain relief and preventing unwanted side effects (including addiction and overdose) in their drug selection and dosing. Unfortunately, there can be dramatic inter-individual variations in pain relief with the same opioids and between different opioids. Pharmacogenetic factors can explain some of the variability. There are genetic polymorphisms in drug metabolizing enzymes, drug transporters, opioid receptors, cyclooxygenases, or in structures involved in the perception and processing of nociceptive information.

P-glycoprotein 1 (permeability glycoprotein, abbreviated as P-gp or Pgp), also known as multidrug resistance protein 1 (MDR1), is a glycoprotein that in humans is encoded by the ABCB1 gene. The ABCB1/MDR1 transporter gene is a major determinant of morphine bioavailability and the OPRM1 gene encodes for the opioid receptor, the primary site of the action of morphine. Mutations in either of these 2 genes affect the efficacy of morphine. Campa et al (59) genotyped 145 patients for the SNP C3435T of the ABCB1/MDR1 gene and the A80G SNP of the OPRM1 gene and observed statistically significant pain relief variability ($P < 0.00001$) allowing for the detection of 3 groups of patients: strong responders, intermediate responders, and nonresponders with close to 100% sensitivity and 70% specificity (Table 1) .

In a related study, Chou et al (60) examined a SNP involving position 118 at exon 1 of the mu opioid receptor gene (OPRM1 gene). In their study they examined 147 patients: 74 were A118 homozygous (AA), 33 were heterozygous (AG), and 13 were G118 homozygous (GG). The homozygous group GG consumed significantly more morphine (40.4 ± 22.0 mg) than group AA (25.3 ± 15.5 mg) and group AG (25.6 ± 11.7 mg) during the

first 48 hour postoperatively, pointing to pharmacogenetic factors in inter-individual variability in pain relief.

What could be an analgesic dose for some patients could cause fatal respiratory depression for others. Oertel et al (61) noted homozygous carriers of G118 needed 2 – 4 times the alfentanil concentrations to produce analgesia and 10 – 12 times the concentration to produce respiratory depression as those with the wild type (AA). The authors concluded that, for homozygous carriers, the therapeutic range was significantly broader than was standard.

Besides the OPRM1 gene, candidate genes for catechol-o-methyltransferase (COMT), melanocortin 1 receptor, and guanocine triphosphate cyclohydrase have been linked to analgesic sensitivity. For example, variations in the gene encoding COMT at codon 158 (val158met) have been associated with the human experience of pain. Diatchenko et al (62) found specific haplotypes (genes that tend to be inherited together) were associated with low, average, or high pain sensitivity.

The number of active alleles classifies patients into poor, intermediate, extensive, or ultrarapid metabolizers of a particular opioid. For instance, patients with 3 active alleles of CYP2D6 are classified as ultrarapid metabolizers (UM). Patients with 2 active alleles are classified as extensive metabolizers (EM), while heterozygous with one active allele and one deficient allele are termed intermediate metabolizers (IM). Those with 2 inactive alleles are poor metabolizers (PM). In general, PM will need a much smaller dose than rapid metabolizers, unless the opioid is a prodrug, in which case they need much more. For instance there have been reports of toxicity resulting in high levels of codeine when codeine was administered to CYP2D6 PM who were unable to form the morphine metabolite and morphine toxicity in rapid metabolizers who rapidly formed morphine from codeine (63). The FDA had recently placed alerts to warn physicians about deaths in pediatric patients who were administered codeine but suffered toxicity (63). Knowledge of these variations could be obtained by genetic testing, and PCPs who prescribe the majority of these opioids need to be aware of these variations.

Overall, there is insufficient evidence to guide physicians about whom should or should not get genetic testing. Trescot and Fayboym (64) outlined a few conditions when genetic testing might be considered: in improving the selection of some medications based on results from individualized genetic tests, as well as predicting efficacy, toxicity, and dosing of medications in individuals whose opioid requirements differ significantly from normal.

Table 1. *Detection times for opioids and their metabolites in urine.*

Parent Opioid	Urinary Analytes	Detection Time in Urine
Codeine	Codeine Morphine Hydrocodone	2 – 4 days 2 – 4 days
Morphine	Morphine 6 MAM Hydromorphone Codeine	 Up to 8 hours 2 – 4 days
Hydromorphone	Hydromorphone Hydrocodone 6-Hydrocodol	 2 – 4 days
Oxycodone	Oxycodone Oxymorphone Hydrocodone	2 – 4 days 2 – 4 days
Oxymorphone	Oxycodone Oxymorphone	 2 – 4 days
Fentanyl	Norfentanyl Fentanyl	 2 – 3 days
Methadone	Methadone 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)	Up to 14 days
Buprenorphine	Buprenorphine Norbuprenorphine	Up to 11 days
Meperidine	Meperidine Norpethidine	2 – 4 days
Tramadol	n-desmethyltramadol o-desmethyltramadol	2 – 4 days

Source: Urine Drug Monitoring: Opioids
Available at www.anesthesiologynews.com/download/PG0818_WM.pdf Accessed April 9, 2015 (59)

Use Prescription Drug Monitoring Programs

According to the National Alliance for Model State Drug Laws (NAMSDL), as of December 2014, 48 states now have operational PDMPs, while the state of New Hampshire and District Columbia have enacted pending legislation. The state of Missouri still has pending legislation (65).

There is evidence that use of these programs helps change prescribing behavior, and reduces doctor shopping and prescription abuse (66). There is also evidence that in states where PDMPs were operational there was

less increase in abuse of opioids, admission for opioid treatment, and opioid poisoning compared to states where they were not operational (67).

A pill chart showing pictures of the most commonly used opioids, a pain and pain medication diary, pill or patch count, and urine and genetic testing should be part of the physician evaluation.

Education about safely storing opioid prescriptions and the risk of sharing these medications with others should be part of the informed consent.

During Ongoing Treatment

Be Familiar with Appropriate Doses for Opioid Naive Patients

Careful attention must be given by providers who prescribe opioid analgesics.

According to the US FDA, a person may be considered opioid tolerant, if a minimum of any of the following or an equianalgesic dose of another opioid is ingested for a week or more: the ingestion of 60 mg oral morphine/day, 30 mg oral oxycodone/ day, 8 mg oral hydromorphone, 25 mg oral oxymorphone/ day, or 25 µg transdermal fentanyl/hour.

Opioid naive patients are those who do not meet the above definition of opioid tolerant and who have not taken opioid doses at least as much as those listed above for one week or longer (68). Health care providers need to know typical fatal doses of medication when given to opiate naïve patients. For instance fentanyl patches have caused repeated fatalities when given to opiate naïve patients and should be avoided in opioid-naive patients because of their time-release nature which means lethal overdose could occurs some hours after application (69). A dose of 40 mg of oxycodone or 30 mg of methadone could be lethal in opioid-naïve persons (70). Caplehorn (71) found that the relative risk of methadone deaths in the first 2 weeks of inducing treatment, versus much later in the treatment, was roughly 100 times more. Table 2 gives approximate starting doses of opioids in opioid-naive patients. This should be used as a rough guide. Physicians should use their judgment as individual patient characteristics differ and safe use in individual circumstances may warrant use of less medications.

Table 2. *Approximate starting doses of opioid analgesics for opioid naive individuals.*

Opiate	Approximate Starting Dose for Opioid Naive Individuals
Hydrocodone	5 – 10 mg q –4 – 6 hrs
Hydromorphone	2 mg q –4 – 6 hrs
Methadone	2.5 – 5 mg BID - TID
Morphine	IR 10 mg q 4 hrs (adjust for renal impairment)
	SR 15 mg q 12 hrs
Oxycodone	IR 5 mg q –4 – 6 hrs
	SR 10 mg q 12 hrs
Oxymorphone	IR 5 – 10 mg q 4 – 6 hrs (potential fatal interaction with alcohol)
	SR 10 mg q 12 hrs
Fentanyl	Not Recommended
Codeine	30 mg q 4 – 6 hrs

Adapted from the Agency Medical Directors Group Interagency Guideline on Opioid Dosing available at www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf
Accessed April 9, 2015 (35).

Be Cautious About Titrating Opioids Especially in the Beginning

Caplehorn and others found that most opioid-related deaths occur within the first 2 weeks of treatment or during the initial titration phase. Caplehorn (71) reviewed 13 fatal cases of methadone-related deaths that occurred in the first 2 weeks of 1994 in NSW, Australia. He found most of these patients had only taken about 30 – 40 mg of methadone daily for 3 days before they were found dead. They appeared over sedated, sleeping for many hours, and died in their sleep. Most had a prior exposure to heroin, but may not have used it recently. Four of the deaths occurred in people who had been released from prison a week earlier and may have lost tolerance (11,71,72). In methadone-naïve persons, it takes approximately 2 weeks for enzymatic systems to convert methadone into its inactive metabolites, so there is the potential for greatly increased plasma level with repeated dosing during the titration phase (11).

Avoid Too High Doses of Opioids If Possible (Trigger Re-evaluation after Reaching a Dose Threshold)

Improving health care provider dosing practices may help reduce opioid analgesic fatalities. According to the ASIPP guidelines, there is fair evidence about what is considered a fair, moderate, or high dose. Zero to forty mg of MED is considered low, 41 – 90 mg is medium dosing, while > 90 MED is considered high (2).

In a CDC analysis of patients and prescription drug overdoses by risk group, published in January of 2012,

it was observed that 80% of all fatalities occurred in the 20% of patients with high doses (> 100 mg of morphine equivalent/day) (10).

Dunn et al (13) followed 9,940 patients for 42 months who were taking varying doses of opioids. The hazards ratio for serious overdose events in the 0 – 20 mg group was 1.0, but 3.1 in the 50 – 100 mg group and 11.18 for the > 100 mg group. In a related study, Gomes et al (73) conducted a population-based case control study of 605,156 persons who received an opioid and found that an average daily dose of 200 mg or more of morphine, or its equivalent, was associated with a threefold increase in opioid-related mortality when compared to those with doses of 20 mg or less. Patients whose deaths were related to opioids were also more likely to have ingested a sedating drug, suffered alcoholism, or received prescriptions from multiple sources.

Most patients develop tolerance to opioids with time, so when the same dose does not produce the same amount of pain relief, providers might be inclined to continue to increase dosing until very high doses are reached. Certain strategies to limit excessive dosing have produced good results in Washington State. Their guidelines emphasize a dosing "yellow flag" at 120 mg/day MED for patients with chronic pain.

Following the introduction of dosing guidelines in Washington State's workers compensation system in 2007, which mandated PCPs to consult with pain specialists if prescribing greater than 120mg/day MED, the proportion of patients on doses greater than 120mg/day MED fell by 35% and the number of deaths decreased 50% between 2009 to 2010 (74).

Reduce Dose When Switching Between Opioids

Paternek (75) proposed a theoretical hypothesis on how drugs acting on the same receptors might be so different. Sometimes, the tolerance to the currently administered opioid may not extend to another opioid (incomplete cross tolerance). This difference exists among all opiates so when one uses the equianalgesic table, it is possible the same equianalgesic dose equivalent might be fatal to the same patient because the index patient might be tolerant to one medication while naïve to another medication of the same class. While there is insufficient evidence for this, most experts recommend that when switching or opioid rotation is done, there should be a 33 – 50% reduction in the dose of the new opioid to account for this difference (76). More so, conversion ratios of many equianalgesic tables may not apply to repeat dosing as some of these tables were based on single dose studies. Published equianalgesic ratios are considered crude estimates and cautious monitoring and titration should be done in an individualized manner (77) (Table 3).

Table 3. *Morphine equianalgesic dosing for selected opioids.*

Morphine	30 mg
Codeine	200 mg
Fentanyl Transdermal	12.5 mcg/hr
Hydrocodone	30 mg
Methadone	4 mg
Oxycodone	20 mg
Oxymorphone	10 mg

Adapted from the Agency Medical Directors Group Interagency Guideline on Opioid Dosing available at www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf
Accessed April 9, 2015 (35)

Be Cautious When Rotating to Methadone

Methadone has a half-life of about 17 – 128 hours (78). Time to peak plasma level is 2 – 4 hours. Methadone has a biphasic elimination pattern. An alpha elimination phase lasting for 8 – 12 hours and a beta elimination which last 30 – 60 hours (79). Dosing for effective pain control occurs every 8 – 12 hours, meaning several layers of repeated dosing occurs when much of the drug still remains in the system (11).

It is important to individualize treatment and titrate the medication, carefully balancing analgesic response and adverse effects. The clinician should monitor for over-sedation which may often be a precursor to respiratory depression, hold next dose, and decrease subsequent doses in cases where concerns of toxicity exist.

Methadone comprised 1.7% of all opioid prescriptions but accounted for a third of all opioid-related fatalities in 2009 and should be reserved for the experienced prescriber (80). Methadone can be fatal in 3 ways: a single overdose, as seen in accidental ingestion of 30 mg or more in an opiate naïve person, an accumulated toxicity over as little as 3 days, and when methadone is combined with sedatives or alcohol. Due to these factors, frequent follow-up visits are recommended during dosing titration (11,81). Physicians should avoid discharging patients home on long-acting opioids after acute surgery because of the risk of drug accumulation and possible toxicity (2).

Two approaches commonly used for rotation to methadone are the "stop and go" and the "3-day" phased conversions. Using the stop and go approach,

the initial opioid is discontinued and substituted with methadone at once. Several guidelines and expert opinion suggest a 75 – 95% reduction when switching to methadone, with the initial dose never exceeding 40 mg. Short-acting opioids are then used for breakthrough pain, while watching for sedation and respiratory depression (11,82). The "3-day" phased conversion approach involves a 30% reduction of the first opioid medication daily over 3 days (81,82).

There can be up to several fold inter-individual variability of methadone blood concentration for a given dosage of the medication (83-85). When co-administered medications were considered, the inter-individual blood methadone level variations were up to 42 fold for a given dosage of methadone in one study (85).These individual differences could be accounted for in part by variability in plasma clearance, P-glycoprotein activity, and Cytochrome P450 (CYP) 3A4 and 2D6 metabolism. For instance induction by CYP3A4 activity leads to a decrease in methadone concentration, when co-administered with rifampicin, phenobarbital, phenytoin, carbamazepine, nevirapine, and efavirenz. Inhibitors of CYP3A4 like fluconazole and the antidepressant paroxetine can lead to increased levels of methadone (85). Therefore the utility of methadone levels in assessing optimal dosing in chronic pain patients is suboptimal at best. However, in the methadone maintenance treatment population (methadone clinics), blood levels of at least 200 ng/ml is generally associated with optimal outcomes, less withdrawal, and less relapse to illicit substance use (86).

A safer strategy is to individualize dose, start slowly, and titrate upward slowly to effect watching for side effects and escalating doses no sooner than once weekly because of the long half-life and time to reach steady state (4 to 5 half-lives).

It is often safest for the nonexperienced clinician to defer prescribing methadone to others more experienced or trained in its use or seek guidance.

Reduce Doses if Loss of Tolerance Is Suspected

When patients who were previously using high doses of opioids either reduce their intake or discontinue use there is usually loss of tolerance over time (87). This has been observed in heroin addicts who were incarcerated for a period of months to years, were released, and attempted to use the same amount of heroin they used prior to their incarceration. There have been many fatal overdoses in similar circumstances (88). For instance if a patient who was placed on a total daily dose of 16 mg of hydromorphone 2 years prior for right knee surgery and had been maintained on a lower opioid dose or no doses since then is suddenly given 16 mg of hydromorphone on presentation 2 years later for left knee surgery, an overdose with life-threatening consequences could result.

Adopt Harm Reduction Principles for Patients on Opioids

When someone develops an apneic episode or stops breathing because of an opioid overdose, there is often only a few minutes to intervene. Following a pilot program in 2010 by the Quincy Police Department in Massachusetts, where Narcan was administered by police officers to 179 people who overdosed on opioids (170 of whom survived), there has been widespread encouragement to use the hand-held Narcan sprays by family members of opioid-dependent patients and by members of the community (89). There have been reports of children who took a single pill of their parent's oxycodone resulting in fatal overdoses (25). Providers should educate patients about safe storage of opioids and consider issuing a prescription of Narcan spray for family members to use in the event of an overdose, especially if opioids are prescribed for patients with a coexisting background of substance dependence. Death of opioid-dependent individuals could be prevented by use of Narcan sprays by their family members or community members who may otherwise not elicit help for fear of arrest (89).

Areas of Uncertainty

Currently about 44% of all opioids prescribed are by PCPs. What is uncertain is how physicians who prescribe opioids may respond to increasing regulatory burden. In one study of 259 physicians who prescribe opioids, 18.9% said they would stop prescribing opioids altogether if they were required to enter information in a registry every 6 months (90). Pain patients may become under-treated if doctors abandon prescribing opioids. Others fear reducing opioid analgesic prescriptions may increase addiction and deaths from heroin again as evidenced by data from cities which cracked down on opioid analgesic prescriptions in the past (91-95).

Guidelines by Professional Organizations

Between 2009 and 2015, the American Academy of Pain Medicine (AAPM), the British Pain Society, the Ca-

nadian National Opioid Use Guideline Group (NOUCG), the ACOEM, and ASIPP published recommendations for opioid use in chronic non-cancer patients which are, but for a few exceptions, similar. They uniformly recommend a comprehensive assessment, careful patient selection, addiction screening, UDT, discussion of treatment goals, considering the use of opioids as a trial, and cautious initiation and titration of opioids while monitoring patients (2,50,55,96,97).

The Canadian guidelines additionally call for a 3-prong approach to administering opioids in addicted patients: use of methadone or buprenorphine, structured opioid therapy, or abstinence therapy (55). The ACOEM does not recommend the use of opioids routinely for chronic non-cancer pain (50).

The British Pain Society guidelines emphasize an extensive non-opioid analgesic trial first before opioids are offered. They caution that totally eliminating pain may not be possible for everyone prescribed opioids, but functional recovery should be the therapeutic goal (97) (Table 4).

Summary of Provider Strategies to Reduce Opioid Analgesic Deaths

After surgery providers should be mindful of not exceeding certain doses in opioid naive patients (68-71). Providers should avoid discharging patients with acute pain home on long-acting opioids (2). For instance the use of fentanyl patches after acute surgery could increase the risk of toxicity and fatal overdoses. This is because some of these patches have a thin membrane protecting the drug reservoir, thus when the integrity of this membrane is broken by heat or by patients who suck on them, then a large dose of the drug may suddenly be introduced into the systemic circulation (18).

During the initial visit to a clinic for opioid therapy, providers should take a detailed history, do a comprehensive physical exam, and establish a diagnosis (2,50,55,96,97). They should use UDT (2,38,46,81), and PDMPs (2) to reduce the likelihood of opioid analgesic abuse. The use of genetic tests should be considered in certain circumstances (64).

During initiation of opioids and upward titration, physicians should watch out for signs of over sedation, excessive sleepiness, snoring, and apneic episodes which may be harbingers of fatal overdoses (71,72). When patients have been off a particular dose of opioid for a long time (months to years), it is safest to assume that they have lost some opioid tolerance and reduce their opioid dose from what they got previously. This concept has been observed in cases of previously incarcerated patients who after release died days to weeks

Table 4. *Evidence grading by professional societies*.

CANADIAN GRADING	
Grade A:	Recommendations are supported by evidence from RCT(s).
Grade B:	Recommendations are supported by:
	Evidence from controlled trial(s) without randomization, or,
	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group, or
	Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here.
Grade C:	Recommendations are supported by consensus opinion of the National Advisory Panel.
ASIPP	
Grade Definition	
Good (High-AAPM)	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality RCTs or studies of diagnostic test accuracy).
Fair (Moderate-AAPM)	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; 2 or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least 2 consistent, lower quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).
Limited, lack of evidence of poor (low-AAPM)	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important

Table 5. *Comparison of professional pain societies' recommendations for opioid use.*

Stage of Treatment	Professional Pain Society Recommendations for Opioid Use	Level of Evidence as Interpreted by Professional Societies		
		Canadian	ASIPP	AAPM
Prior to Initiating Treatment	Comprehensive Assessment	Good	Low	B
	Obtain Informed Consent		Low	B
	Use Treatment Agreements	Fair	Low	C
	Stratify Risk in Individualized Manner/ Screen	Limited	Low	B
	Use Urine Drug Screening	Good	Low	C
	Use Opioids for Acute; Subacute (< 90 days) Non Cancer Pain; Efficacy	Good		A
	Use of Opioids for Chronic (> 90 days) Non Cancer Pain, Efficacy	Limited	Low	Insufficent Data
	Taper off Benzo's if possible,especially in Elderly before starting	Fair		B
	Establish a Physical or Psychological Diagnosis	Good		A
	Establish Medical Necessity to Initiate or Continue Opioids	Good		A
During an Opioid Trial	During Opioid Titration, Advise Against Driving Until Stable Dose		Low	C
	During Opioid Titration, Advise Caution with alcohol, sedating drugs			B
	Use a Stepped Approach, Use Weaker Opioids first (codeine, tramadol)			C
	Use Methadone as third line agent	Limited		C
	For methadone obtain Ekg prior to, at 30 days, and yearly after	Fair		
	Start Low and Go Slow	Good	Low	B
	Most Patients Do well with < 200 mg a day of morphine equivalent			A
	Consult Pain Specialist for Doses >200 mg/day morphine equivalent	Fair		C
	Consider Pain Specialist or Clinician familiar with Methadone		Moderate	
	Switch a particular opioid, if ineffective and has high adverse effect		Low	B
	For Patients already on Opioids, Revaluate need for Continued Opioids			C
	Be Cautious with Elderly, Pregnant, Adolescent and Psychiatric Patients		Low	B
	Chronic Opioid Therapy should integrate Psychotherapeutic Interventions		Moderate	
	Seek Interdisciplinary Management or Consultation if needed		Moderate	
	For Addicted Patients Use Buprenorphine or Methadone,			A
	For Addicted Patients Use Structured Opioid Therapy			B
	Use Prescription Monitoring Programs or Methods	Fair	Low	C

when they used the same amount of heroin used prior to their incarceration because of this loss of tolerance (71,72,87,88).

Providers should wean patients off opioids within 30 – 90 days following surgery (32-34) if possible. They should wean patients off benzodiazepines if possible before starting opioid doses as most fatal cases of opioid poisoning have occurred in patients taking opioids together with benzodiazepines and or alcohol (55,73). Evaluation of continued need for opioids needs to be done on every outpatient visit. Providers should avoid using methadone as a first line agent (2,50,55). There have been fatalities from taking as little as 30 mg of methadone daily for 3 days (70-72).

Medical necessity for opioids should be based on patients exhausting other treatment modalities such as physical therapy and prior trial of non-opioid analgesics for their pain (2). Patients should be encouraged to do baseline UDT and screening for aberrant drug behavior (2,50,55,96). If aberrant drug behavior is detected this should be addressed and followed up with appropriate referral for addiction psychiatric help. If substance use disorder is an issue, methadone, buprenorphine, or structured opioid therapy is recommended (55).

Providers should take incomplete tolerance into consideration when switching from one opioid to another and initially reduce the dose of the new opioid by 33 – 50% (75,76). If opioids must be prescribed, avoid excessive doses or unwarranted dose escalations as fatalities are more likely at higher doses (11,74). They should refer patients on high doses of opioids to pain physicians or appropriate specialists who may have more experience with managing such cases. Providers should avoid prescribing tramadol to patients already taking selective serotonin reuptake inhibitors (SSRIs) because of the risk of serotonin syndrome (98). Caution should be exercised when prescribing opioids to high risk populations especially those with psychiatric illnesses, renal diseases, hepatic diseases, congestive heart failure, advancing age, chronic obstructive pulmonary disease, central apneic syndrome, and in cases of drug-drug interactions which inhibit opioid metabolism and may potentially lead to toxicity (11).

Finally for patients who are substance dependent and at risk for fatal opioid overdoses, supplying naloxone which is available for intranasal administration is an effective harm reduction model which has helped to reduce fatalities in many patients. This could be issued to patients' family members, friends, and members of the community to administer to the patient in the event of fatal overdoses (87,99).

Conclusion

Providers from all specialties are likely to encounter patients on opioids analgesics (whether they prescribe the opioids or not). Some of the recommendations discussed in this review have shown promise in reducing opioid analgesic deaths in population-based samples (50% decrease in deaths in Washington State following introduction of a policy of red flags after 120 mg of morphine equivalents are exceeded). Others show fair to good evidence that their use will reduce opioid analgesic deaths. Providers should be aware of all associated factors with opiate deaths and apply the available evidence in reducing opioid analgesic deaths.

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