ASCO Policy Statement on Opioid Therapy: Protecting Access to Treatment for Cancer-Related Pain

Background

The escalation of abuse, addiction and diversion of opioids—both prescription pain medications and illicit drugs—has led to declaration of an "opioid epidemic" in the United States. Congress, the Administration, and multiple federal agencies are involved in efforts aimed at preventing and responding to prescription drug abuse; many states and local agencies are examining different approaches to stem the tide of abuse and deaths and many have already implemented new laws and programs around opioid prescribing.

Much of this increased legislative and regulatory activity is aimed at tighter controls and increased education in the use of drugs. While ASCO fully supports efforts to address the issues surrounding opioid misuse and abuse, we are concerned that some of these initiatives could have the unintended consequence of limiting access to treatment of pain for cancer patients.

It is already widely acknowledged that too much pain goes untreated, and while not all patients with untreated pain require opioids, these agents remain an essential part of many pain treatment plans, especially among patients with cancer. On a global scale, there is mass unavailability of opioids, leading to untold amounts of needless suffering; world bodies have issued analyses and recommendations intended to balance the need for medical opioids with efforts to combat diversion.[1,2] While overall the US consumes the vast majority of the world's opioids, access even in this country is unbalanced and may present an issue for certain populations.[3,4,5] Large-scale proposals currently being considered in the US could likely exacerbate this problem, and have adverse consequences on patient in need of medically indicated treatments.

Already, there are multiple barriers to access and appropriate use,[6,7] even in the absence of additional proposed restrictions. Such barriers include constraints on access to prescriptions and lack of availability of opioids at pharmacies, as well as insurance and reimbursement limitations. Specific access examples reported by oncology providers caring for patients in active cancer treatment include: partial filling of opioid prescriptions by pharmacies lacking a fully supply, requiring the patient to obtain a new prescription for the remaining supply; refusals by pharmacies to fill prescriptions even when the diagnosis is included but ICD10 code is omitted; and refusals of pharmacies to honor three-day emergency supply allowed in state regulations. Specific restrictions set by insurance companies or limits on reimbursement include: limits on the number of pills (or patches) dispensed per fill, which requires more refills with additional copays; limits on the mix of opioids dispensed every 30 days, so that patients requiring an additional opioid due to poor pain control may wait many days for prior authorization approval; the need to wait 30 days or obtain prior authorization when dose is titrated upwards; and the

need to obtain prior authorization for a refill when the original prescription is used sooner than originally planned (due to prescriber instructions to patient to increase dose for better pain control). In general, the requirements for prior authorizations for all types of opioids is increasing, including low-dose and inexpensive agents. Prior authorizations often take 72 hours (business days only) or longer to obtain, with even expedited review taking 24 to 48 hours. This leads to a situation where patients go without medication or pay out of pocket for a few days' supply, then must obtain a new prescription. In addition, weekend hospital discharges are complicated by the fact that insurance company access is very limited on Friday afternoons and usually not available over the weekends.

Combatting the Problem: Federal and State Initiatives

The White House Office of National Drug Control (ONDCP) coordinates the efforts of the multiple federal agencies attempting to address this issue. These agencies include the Food and Drug Administration (FDA), the Drug Enforcement Agency (DEA), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Centers for Disease Control and Prevention (CDC).

The FDA has a special unit focused on controlled substances within the Center for Drug Evaluation and Research. Its responsibilities include oversight of abuse liability and risk management requirements, both during the review process and post-marketing. In February of 2016, the FDA announced an opioid action plan focused on labeling, post-market data collection, updated Risk Evaluation and Mitigation Strategies (REMS), prescribing guidelines and new guidance on approval standards for abuse-deterrent formulations. Other recent changes include the rescheduling of hydrocodone from Schedule III to the more restrictive Schedule II, and the addition of expanded safety information to the labels of all immediate-release opioids.

The FDA has also instituted a REMS program for prescription extended release/long acting (ER/LA) opioids, which has been in existence for approximately two years; a more restrictive REMS (i.e. physician registration and other requirements) exists for transmucosal immediate release fentanyl formulations. The continuing education provided under the current ER/LA opioid REMs is voluntary, although providers are "strongly encouraged" by FDA to participate. This education is provided by CE/CME providers who have submitted successful applications to the FDA, and is funded through the drug manufacturers. Providers receive this education free or at a "nominal" charge. Current providers include universities, non-profit associations, and for-profit entities.[8] At a joint meeting of FDA Advisory Panels in May 2016, despite many Panel members noting that the evidence to date for impact of the REMS on prescribers and patients was very weak, the joint Panel voted to essentially strengthen the REMS by including IR/SA opioids and requiring mandatory prescriber education.

Inadequate treatment of pain is a very real concern. In March of 2016, the Centers for Disease Control and Prevention (CDC) released guidelines[9] on the prescription of opioids for chronic pain. The guidelines apply to individuals eighteen or older who are experiencing chronic pain unrelated to active cancer treatment and are not receiving palliative or end-of-life care. (It is important to note, however, that these differences are often fluid: the definition of active cancer treatment may not be clear and some

patients may not be under active treatment but have active disease and some are at high risk of recurrence; some patients have pain as a consequence of specific, highly effective cancer treatments; palliative care is an evolving set of service delivery models that may be started at the time of diagnosis and there is no standard definition of end-of-life care.) The guidance aims to improve communication between providers and patients about the risks and benefits of opioid use, improve safety of pain treatment and reduce risks of abuse, dependence, overdose and death. Adherence to the guideline is currently voluntary.

Currently, there are at least a dozen bills in Congress related to the control of opioid abuse. In brief, the legislation would:

- Expand prevention and educational efforts
- Expand the availability of naloxone
- Expand resources to identify and treat incarcerated individuals suffering from addiction
- Expand disposal sites for unwanted prescription medications
- Launch an evidence-based opioid and heroin treatment and interventions program
- Strengthen prescription drug monitoring programs

States have broad authority to regulate prescribing and dispensing of prescription drugs and have implemented a wide range of programs and policies. State-regulated Prescription Drug Monitoring Program (PDMPs) contain electronically transmitted prescribing and dispensing data submitted by pharmacies and dispensing practitioners. They are managed under the authority of a state, commonwealth, or territory of the United States. Currently, PDMP programs exist in 49 states and Guam.

Many states are also currently considering strengthening their own laws related to the prescribing and dispensing of prescription opioids. A recently enacted Massachusetts law may serve as a model for other states, and contains the following provisions:

- First in the nation to limit an opioid prescription to a 7-day supply for a first time adult prescription and a 7-day limit on every opiate prescription for minors, with certain[1] exceptions.[10,11]
- All opioid prescriptions (Schedule II or III) are accompanied by the requirement that both the physician and pharmacist check the state's PDMP on issuance of the prescription.
- A requirement for continuing education, including training on effective pain management and the risks of abuse and addiction associated with opioid medications.

[1] The practitioner may prescribe a larger supply as long as there is appropriate documentation in the medical record. (i.e. the condition triggering the prescription, explanation of why a non-opiate alternative was not appropriate). The conditions meeting this exception are listed in the statute as "…acute medical condition or…the treatment of chronic pain management, pain associated with a cancer diagnoses or for palliative care."

- PDMP data will be used on an annual basis to determine "the mean and median quantity and volume of prescriptions for opioids…issued by practitioners…the mean and median prescription quantities and volumes shall be determined within categories of practitioners of a similar specialty or practice type as determined by the department." The practitioner will then be sent a confidential percentile ranking within their category, and resources will be made available to prescribers regarding ways to change prescribing practices and incorporate alternative pain management options.

Pending or recently passed state and federal legislation, in combination with ongoing federal agency initiatives, aims to curb the incidence of opioid misuse and abuse in the US. However, these well-intentioned proposals may also very well serve to limit access to opioids for patients with cancer, thus challenging the mandate of oncologists to provide compassionate care in the form of pain control. Taken together, the proposed restrictions place burdens on cancer patients and oncologists with limited evidence as to their potential impact.

ASCO Principles for Balancing Opioid Access With the Need to Curb Misuse and Abuse

This policy statement lays out principles that we believe would balance the public health need to mitigate the abuse and misuse of prescription opioids with continued access to appropriate pain management for cancer patients and survivors.

Cancer Patients: A Special Population

Cancer patients represent a special population that should be largely exempt from regulations intended to restrict access or limit doses, in recognition of the unique nature of the disease, its treatment, and potentially life-long sequelae. Cancer is very heterogeneous, with some diseases experiencing high rates of cure and others having an indolent biology extending over many years. Cure and prolonged remission represent trajectories that raise varying concerns and complexities, including the problem of chronic pain in survivors. Both solid tumors (with the exception of non-invasive skin cancers) and hematological neoplasms represent serious and potentially life-limiting illnesses, even if the course is relatively prolonged. This complexity in the presentation and course of cancer must be appreciated, as it has implications for practices and policies related to opioid therapy. From the clinical perspective, there is broad agreement that opioid therapy is generally the first-line approach for moderate to severe chronic pain associated with active cancer, whether or not the patient is receiving anti-neoplastic therapy; for this group of patients, access to opioids must be assured, and laws and regulations intended to address abuse and overdose should be crafted to avoid creating impediments to this treatment—particularly as there is no evidence that the treatment of cancer pain has in any way contributed to these problems.

We are encouraged to see that many of the new laws, guidelines, and regulations limiting opioid prescribing specifically exempt cancer patients under active treatment, as this reflects the recognition

that cancer patients represent a special population undergoing often drastic treatment for severe, often life-threatening diseases. As noted, however, active treatment does not fully represent the universe of clinical conditions associated with active disease, or the potential for severe chronic pain associated with the disease itself or the powerful treatments used to manage it. We are concerned about the potential for reduced access if the definition of "patients under active treatment" is misinterpreted.

In addition, cancer survivors often suffer recognized post-cancer or treatment syndromes, and others present with less common, potentially unique, but nevertheless very real post-treatment pain syndromes. More commonly recognized post-cancer pain syndromes may include chemotherapy induced peripheral neuropathy, lymphedema, post-surgical pain syndromes such as phantom limb pain, graft versus host disease after transplant, or post-radiation therapy syndromes. The approximately 12 million cancer survivors in the US represent a heterogeneous population that may suffer pain related or unrelated to previous cancer diagnoses, and may be considered similar to other populations with chronic pain. Opioid therapy may be appropriate for a carefully selected subgroup, as long as benefits clearly outweigh the risks over time and treatment can be monitored. Providers caring for such patients may want to consider referral to a specialist; additionally, ASCO has developed guidelines on pain management in cancer survivors.[12]

Provider Education

Providers should have a choice of sources and materials for education in opioid prescribing, and mandated education in particular should be provided by entities other than manufacturers.

Given the ever-growing sub-specialization of medicine, provider education should be tailored to the special needs of professionals practicing in those areas, and as such, we believe that such education is best provided by bodies such as medical professional societies or other organizations that understand the specific needs of their audience. Education provided by ASCO is developed by professionals, peer-reviewed, and carefully tailored to meet the needs of oncology professionals; the ASCO faculty developing these materials additionally provide published conflicts of interest statements.

Any mandated provider education should not present an additional hurdle to those who prescribe opioids, but should be associated with existing requirements such as renewal of DEA licensure, Board examinations, or state licensure. Finally, any mandated education should be associated with evidence of outcomes.

The basis for mandatory prescriber education is the expectation that such education will lead to more appropriate prescribing, likely more limited prescribing, and heightened awareness of the risk for patient misuse and abuse, ultimately resulting in a decrease in overdose and overdose deaths. Therefore, in assessing the impact of provider education, the most relevant and valuable endpoint would be overdose and overdose death statistics; intermediate outcomes could include patient awareness of risks and benefits, maintenance of access for appropriate patients, and provider prescribing patterns.

Initial Prescription Limits (Total Supply, Dose, or Time)

Patients with cancer and cancer survivors should not be subject to arbitrary prescription limits that artificially limit access to medically necessary treatment. Arbitrary restrictions that have the effect of limiting access to a medical treatment--in the absence of evidence that this approach can reduce harms without compromising care--is inconsistent with a balanced policy and should not be implemented, especially for patients with active cancer. If such limits are instituted, mechanisms should be established which enable ease of patient access to the supply deemed appropriate by the treating physician in consultation with the patient.

As stated earlier, we are pleased to see and support the exemptions to prescribing limits and timing that have been put into place for cancer patients. We hope that these exemptions will remain widespread; however, if prescribing limits do affect cancer patients or survivors, there should be mechanisms in place for a patient or their caregiver to easily access needed medications without additional barriers. Some patients may benefit from another face-to-face encounter with their physician prior to extending an initially limited prescription, while for others this may not be necessary or even desirable, depending on clinical circumstances, prior exposure to opioids, and other factors. For the latter group, an additional trip to the physician office and subsequently to the pharmacy is likely unnecessary or even a hardship--for example, those who live in rural areas and must drive significant distances for a physician office or pharmacy visit.

Therefore, in situations where a patient with cancer is impacted by initial prescription limits, we would encourage the use of alternative mechanisms not necessarily requiring an additional physician visit, such as the availability of the "balance" of a full prescription at a patient's local pharmacy. Clearly, any decision regarding prescribing amounts and frequency of patient assessment is related to clinical and patient-specific factors and, as in all areas of medicine, requires a careful risk-benefit analysis.

In addition, existing communication methods such as telephone, e-mail, and—in select circumstances—more sophisticated electronic methods of communication, allow for follow up discussion between the patient and physician office.

Patient Education

Patient education on the correct medical use of opioids is best provided by a health professional with the addition of supplementary materials as appropriate. Broader public awareness campaigns that target the public at large and are not tailored to patient educational needs should present a balanced picture of the risks and benefits of use. Given that opioid misuse includes improper access to legitimately prescribed opioids by other than the patient, much more emphasis needs to be placed on awareness of safe storage. A variety of useful resources exist for patient education on topics such as safe storage and

disposal of unused or unwanted medications[13]; however, dissemination of these materials needs significant enhancement.

A health care professional is the best source of education for the patient, regardless of the drug being prescribed. Publicly available materials from professional societies, government sources (e.g. medication guides), and patient advocacy groups may also play a valuable supplemental role.

Patient education should also be available from a variety of sources, especially professional medical societies. Such education should be balanced, comprehensive, and clear to patients of all types. Patients are best served with the comprehension that opioid drugs, when appropriately prescribed and used, may provide relief from severe pain, but that like most drugs, there can be serious side effects if the drugs are not used as prescribed.

Prescription Drug Monitoring Programs (PDMPs)

Individual state PDMPs should be accessible through a single portal or interoperable in a way that is seamless to the end-user. Health care providers or their designees should have equal access to both query and enter information into PDMPs. Any efforts by regulators or those in law enforcement to to identify "aberrant" patterns of prescribing for any individual provider must consider the provider specialty and any further sub-specialization, population of patients treated, and other factors that may legitimately influence prescribing patterns. Those who treat cancer pain may prescribe opioids to relatively large numbers of patients and may provide some with multiple controlled drugs at relatively high doses; these providers should not repeatedly trigger review by regulators or law enforcement.

PDMPs can provide valuable information to prescribers and dispensers regarding the prior or current use of opioids by individual patients. Policymakers also find the aggregate information useful in order to track overall opioid prescriptions and patterns of use. However, physicians and health care professionals are often hampered in their use of PDMPs due to lack of interoperability and the need to check multiple databases for one patient.

Interoperability of these systems, or some form of single-portal entry, should be a priority for states, and we support the additional funding being proposed by Congress for these programs. In addition, elective or mandated queries of or reporting into these databases should not be limited only to prescribers. As the checking of these databases is largely an administrative activity, we feel that it is appropriate for a clinician to delegate authority for such activities, while the clinician is responsible for interpreting the results contextually for each patient. We would also encourage more "real-time" reporting into these databases in order to make them more useful to practicing clinicians; currently, the average required reporting time is weekly, although some states require more frequent reporting.[14]

With growing widespread use of PDMPs, it is appealing to different entities to use this data for many forms of research, which can help inform physicians, policymakers and others on the use of opioids. However, we caution against the superficial use of this data in order to identify physicians that are

prescribing "inappropriately" (e.g. are "outliers" in the PDMP database). If the data is used in such a way, the physician should be given every opportunity to explain why they believe their prescribing is appropriate.
We are therefore pleased to see efforts, as exemplified by a new Massachusetts law, which recognize that different physicians legitimately have different prescribing habits. It should be noted, however, that even amongst physicians judged to be in the same "category" (e.g. oncologists) there will likely be quite wide variation in prescribing habits due to further sub-specialization and type of patient population treated.

Patient Screening & Assessment Prior to and During Opioid Treatment; Patient Adherence: Provider-Patient "Treatment Agreements" and Urine Testing

After initial screening and assessment of cancer patients, the timing and form of subsequent assessments should be left to the judgment of the treating physician, based on clinical and patient-specific circumstances; however, reassessment tailored to individual patients on a regular basis is considered one reasonable approach.

Compliance tools such as treatment agreements and urine testing subsequent to an initial prescription may prove valuable for some patients, and their use should be tailored to individual patients and clinical circumstances. We do not believe that these tools should be made mandatory for all patients receiving opioid therapy.

In the initial screening of all patients, it may be considered a reasonable approach to include urine testing. For some patients, tools to encourage compliance with correct prescription medication use after the initial prescription can be very helpful. However, the routine institution of such practices with every patient may not be constructive and can present an unnecessary burden to both physician and patient; therefore, these interventions should be tailored based on clinical and patient circumstances and ongoing monitoring.

While certain patient circumstances and medical history (for example, prior substance abuse, data obtained from a PDMP) lend themselves to more intense follow up and monitoring in the setting of medically necessary opioid use, it has been documented that certain conscious or unconscious biases, sometimes related to ethnicity or racial group, may also play a role in the intensity of providers' monitoring of patients on opioid treatment.[15]

Abuse Deterrent Formulations

We support efforts to develop abuse deterrent formulations as one approach to mitigating abuse, but note that most prescription drug abuse and overdose occur via the oral route, and are not likely to be positively impacted by the currently available formulations. We also caution that the costs of these newer formulations may present a barrier to access if they are not covered by payers to the same extent

that non-abuse-deterrent formulations are. Accordingly, non-abuse deterrent formulations should remain available to patients with clinical or other factors where they would be an appropriate option.

We support FDA's efforts to encourage new formulations of opioids that include abuse deterrent properties, recognizing that it is part of a multi-faceted effort to decrease the availability of opioid use for non-prescription purposes, whether those opioids are prescription or "street" drugs. Studies have shown that abuse of Oxycontin®, for example, decreased after introduction of the abuse deterrent formulation to the market.[16,17]

While results from these and other studies are encouraging, in a more global picture of drug misuse and abuse it should be noted that there may be a caveat to the success in curbing abuse through market introduction of abuse deterrent opioids. For example, one study pointed out that while Oxycontin abuse decreased subsequent to the introduction of reformulated Oxycontin, it appeared that those individuals with a prior history of abuse simply turned to other drugs, most frequently heroin.[18]

Because these drugs are more expensive to manufacture and represent new formulations, the cost to the patient can be significantly higher than the older, non-abuse deterrent formulations. One US state that investigated the status of abuse deterrent formulations found that all three of these drugs approved for coverage in public health plans were classed as "Tier 3" drugs, with corresponding higher co-pays and co-insurance.[17]

Depending on the clinical situation, there are times when either an abuse deterrent formulation or non-abuse deterrent formulation may be perfectly appropriate. The prescribing physician, in consultation with the patient, should decide which is preferred based on clinical and patient-specific circumstances. Cost should not be a barrier to obtaining treatment with either type of opioid, and we urge policymakers to avoid the understandable inclination to potentially shift—through reformulation--many medically necessary opioids into a more expensive category which may or may not be appropriate for any given patient.

Treatment for Misuse, Abuse, or Addiction

All individuals with an opioid-related disorder should have rapid access to appropriate assessment, diagnosis, and treatment, regardless of payer or geographic setting.

We fully support the expanded availability of medication-assisted treatment (MAT) currently being championed by Congress and the Administration. To that end, we also applaud efforts to expand Medicaid coverage of such treatment, and efforts to ensure its coverage in all Medicare Managed Care and Part D plans.[19]

Prescription "Take-Back" Programs

In order to decrease the availability of unused or unwanted opioid drugs, authorized collection sites should be readily available to patients.

We strongly support efforts to rid our communities of unused and unneeded prescription drugs, and are pleased to see additional funding going towards these programs, as well as pending bills in Congress[20] appropriating additional funding to communities to expand access to such programs. There are currently areas of the country where there is not realistic access to DEA-authorized collection sites, and consumers are advised to flush certain medications, including opioids, down the toilet. Collaboration between the DEA, FDA, and EPA in developing consistent guidelines for situations where authorized collection sites are not available would greatly help patients and others to dispose of their medications responsibly.

Modifications to the existing Controlled Substances Act (CSA) would allow patients to return opioids and other controlled substances (e.g. benzodiazepines) to the pharmacy at which they were obtained. This modification, in addition to expanding existing approved drug-disposal mechanisms, could reduce the availability of unused opioids potentially available for abuse.

Wider Availability of Naloxone

ASCO supports increasing the ease of access to naloxone, as it plays a life-saving role in cases of opioid overdose.

We agree with ongoing efforts to increase the availability of naloxone, whether at the first-responder level, availability at pharmacies without an individual prescription ("standing orders"), or co-prescribing by health professionals. It is important to note that family and caregivers should be instructed in the correct use of any overdose antidotes prescribed, as they will most likely be the individuals administering the drug in a case of potential opioid overdose. Such education should pay careful attention to the timing of any potential administration of naloxone by a caregiver, especially in those cases, for example, where it may not be unusual for a patient to have symptoms consistent with an opioid overdose but rather are declining due to their advanced disease.

Summary

The issue of opioid misuse, abuse, and overdose presents a complex problem with multiple contributing factors. The compelling needs of the cancer population underscore the importance of an approach to these problems based on a critical understanding of the extent to which the problem relates to the management of pain, particularly chronic pain in the medically ill. Although greater access to prescription opioids may be a factor in unmasking addiction and abuse, there is no evidence that treatment of cancer pain has substantially contributed to the problem, and the adverse consequences of abuse and overdose appear to be much more highly related to polysubstance abuse in those without

pain than to the use of opioid drugs to manage pain in medically ill patients in a manner consistent with best clinical practices. Opioid overdose is a major problem, but what remains to be clarified is to what extent the initiatives to address it should focus on patients who are prescribed these drugs for a legitimate medical condition and in the usual course of practice.

The numbers of people dying from opioid overdoses or suffering misuse and abuse disorders in the US is alarming, with the magnitude of the problem sharply increasing in the past few years. Federal and state initiatives are legitimately concerned with reining in the problem and protecting the public health.[2] ASCO is supportive of efforts to address issues of opioid abuse and its related consequences; however, some elements of both state and federal tightening of controls could introduce barriers to appropriate treatment of pain related to cancer and its treatment, thereby harming a vulnerable population. There is already strong evidence of under treatment of cancer-related pain and new barriers would serve to worsen this situation. Patient advocates are deeply concerned that appropriate management of pain will be compromised if controls become overly restrictive.

ASCO is also concerned about the myriad requirements potentially being placed upon oncology care providers (physicians, nurse practitioners, physician assistants, others with prescribing privileges) in order for them to be able to continue to provide appropriate pain management for their patients. Overly prescriptive demands for patient screening, use of administratively burdensome PDMPs, mandatory education, linking of prescribing rights to certain mandated activities, and the identification and subsequent education of physicians who prescribe in a way that deviates from their "peers" could all erect barriers to appropriate access, if not carefully considered and implemented.

Despite the existence of multiple guidelines or recommendations on pain management and opioid use,[21,22] it is widely acknowledged that evidence is lacking in many aspects of opioid use. Studies on long-term effects are sorely lacking, as is research on clinical activities providers may perform regularly, such as tapering of opioid doses. ASCO strongly supports the furtherance of this and additional research, and stands ready to work with policy makers and others to achieve a safe, equitable, and reasonable balance of opioid access and the public health.

Appendix

Opioid Abuse and Overdose Deaths: Scope of the Problem

Opioids were involved in 28,648 deaths in 2014[9], and it has been estimated that some 4.3 million people abuse prescription painkillers.[23] As noted in a recent statement from the Administration and as

[2] Because heroin and illicit fentanyl (along with other miscellaneous opioid-based "street drugs") are considered part of the overall opioid epidemic, federal and state/local entities that are engaged in criminal investigation and law enforcement (e.g., DOJ, DEA) are also playing a large role. In the context of an ASCO policy statement, however, we will limit ourselves largely to those programs and proposals that bear upon control of and access to prescription opioids.

reported by the Drug Enforcement Agency, four in five heroin users start out by misusing prescription drugs.

The problem of opioid misuse and abuse has been escalating in the past few years. Rates of opioid overdose deaths have increased significantly, from 7.9 per 100,000 in 2013 to 9.0 per 100,000 in 2014, a 14% increase. With the exception of methadone, the rates of overdose deaths for all classes of opioids have increased[9] (Table 1). Natural and semisynthetic opioids (all considered prescription drugs; see Table 2) are responsible for more overdose deaths than any other opioid type. (Note that this class of opioids includes the most commonly prescribed pain relievers—oxycodone and hydrocodone.) Many more people have access to prescription opioids than to other types of opioids, with more than 75% of recreational opioid users receiving the drugs from non-medical sources[24]; a small percentage only of patients with emergency department visits for opioid overdose actually have a pain diagnosis.[25] Most overdose deaths involve polysubstance abuse.

Table 1. Age-Adjusted Rates of Death from Opioid Overdose, 2013-2014

CDC Classification[9]	***Opioid Type****	***Age-adjusted Rate of Death (per 100,000)***		***Percent Increase***
		2013	***2014***	
Prescription Opioids	Natural and semisynthetic (morphine, oxycodone, hydrocodone)	3.5	3.8	9%
	Synthetic opioids (fentanyl, tramadol)	1.0	1.8	80%
	Methadone (synthetic)	N/R	N/R	0
Heroin	Heroin	1.0 (2010)	3.4	26% (2013-2014)
All Combined		7.9	9.0	14%

*Deaths involving more than one drug were counted in each type.

A Note on Data Reporting and Limitations

If broad and sweeping restrictions on access to certain drugs are being contemplated, it is important to have a critical understanding of the data underlying the drive for such restrictions. In the case of opioid drugs particularly, the data limitations should give pause to the specific conclusion that the problem of opioid abuse relates to the use of opioids in patients with acute and chronic pain, and instead should encourage a more nuanced understanding of the problem along with caution in drawing potential conclusions between pain management and adverse outcomes.

Overall. Studies investigating deaths due to overdoses, including prescription- and non-prescription-related opioid deaths, are somewhat hampered by the fact that there is no standardized system for reporting drug-related deaths in the US. Data collection and reporting varies with each medical

examiner and coroner, and the substances tested for and the toxicological laboratory tests used vary by jurisdiction.[9,23] Furthermore, the percent of overdose deaths with specific drugs identified on the death certificate varies widely by state. According to the CDC MMWR report, in 2013 and 2014, 22% and 19% of drug overdose deaths, respectively, did not include information on the death certificate about the specific types of drugs involved.

The Contribution of Illicit Fentanyl to Fatal Prescription Overdose Statistics. The CDC synthetic opioid category includes both prescription synthetic opioids (e.g., fentanyl and tramadol) and non-pharmaceutical fentanyl manufactured in illegal laboratories (illicit fentanyl). Toxicology tests used by coroners and medical examiners cannot distinguish between prescription and illicit fentanyl[9]; therefore, overdose deaths from either substance are counted as pharmaceutical fentanyl and reported as a synthetic (prescription) opioid death.[23] The amount of illicit fentanyl available seems to be increasing at an alarming pace: in 2013, the number of fentanyl-related seizures in the US was 942; in 2014 it was 3,344. According to the DEA, only a tiny percent of fentanyl-related overdose deaths are related to pharmaceutical fentanyl; the majority may be assumed to come from illicit fentanyl. The CDC has also stated that, based on reports from states and drug seizure data, a substantial portion of the increase in synthetic opioid deaths appears to be related to increased availability of illicit fentanyl.

Under-reporting of Heroin Deaths. Because heroin and morphine are metabolized similarly, it is possible for heroin-related overdose deaths to be reported after toxicology tests as morphine-related overdose deaths. The CDC expressed concern that this could lead to under-reporting of heroin deaths. The converse of this, of course, is that morphine-related deaths are over-reported. According to the DEA, it is possible that "many" deaths due to heroin are in fact misclassified as morphine-related deaths.[23] Also according to the DEA, the population that abuses prescription opioids was 15 times higher than the population of heroin users in 2013, but prescription abusers experienced 2 times as many deaths as heroin users. See Table 2 for a summary of potential misattribution in opioid-related deaths.

Table 2. Potential Misattribution in Opioid-Related Deaths

Attribution	***Actual Source***	***Drug Reported As***	***CDC Classification***
Correct	Pharmaceutical/Prescription Fentanyl	Fentanyl	Prescription (synthetic)
	Heroin	Heroin	Heroin
Potentially Incorrect	Illicit Fentanyl	Fentanyl	Prescription (synthetic)
	Heroin	Morphine	Prescription (natural and semisynthetic)
	Illicit Fentanyl/Heroin Combination	Fentanyl AND	Prescription (synthetic)
		Morphine	Prescription (natural and semisynthetic)

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