

Special Edition 2016

ADDRESSING THE CHALLENGES OF PRESCRIBING CONTROLLED DRUGS



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THE JOURNAL OF THE SOUTH DAKOTA STATE MEDICAL ASSOCIATION

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"Healing" across all cultures comes in many different ways to help the mind, body and spirit. Health care and medical practice often utilize medications and drugs as key to healing and promoting health.

Scientific knowledge of those medications and their clinical applications helps provide the highest quality and best evidence-based care for our patients as we strive to lead our health teams in providing care. Our knowledge and experience make physicians uniquely qualified to guide and educate regarding issues of prescription drug use and abuse.

The public's knowledge of, opinions about, and accepted uses of medications and drugs also are key to our cultural health. Society often has an ebb and flow regarding what is perceived as acceptable use or misuse of drugs and medications. Our governmental bodies with our laws, rules, regulations and enforcement agencies serve to protect the public and promote public health. Licensure to practice medicine is dependent on those regulations, interpretations and judicial decisions.

Medications that are used to promote quality and compassion in care for our patients may unfortunately also lead to dependence and abuse. That leads to more specialty care and more societal commitments to protect and serve our people.

On behalf of the South Dakota State Medical Association, I wish to thank all the physicians and educators for their contributions to this special issue of *South Dakota Medicine* on prescription drug abuse. I encourage you to read this issue in its entirety as it is an invaluable resource for promoting the best care for all our people.



H. Thomas Hermann, Jr., MD
SDSMA President



Today's society is one of immediate access – whether that be the internet, food or drugs. Our "take a pill for what ails you" culture and the perception that prescription drugs are *less* harmful than illicit drugs likely contribute to the problem.

According to the Centers for Disease Control and Prevention, drug overdose was the leading cause of injury death in 2013, surpassing automobile accidents. The abuse of certain prescription drugs – opioids, depressants and stimulants – can lead to a variety of adverse health effects, including addiction.

As the Comprehensive Addiction and Recovery Act progresses in Washington, DC, we look forward to supporting programs in South Dakota that strengthen prescription drug monitoring, improving treatment for addicts and expanding prevention and education initiatives. Congress has provided emergency funding for Ebola and the swine flu epidemic – prescription drug abuse is a national epidemic! Since the inception of South Dakota's Prescription Drug Monitoring Program in 2011, there have been 5.2 million prescriptions recorded into the system, raising the awareness and identifying patterns of concern to address this issue.

The South Dakota Association of Healthcare Organizations is pleased to be a part of this special issue of *South Dakota Medicine*. We trust this will be a valuable resource for physicians in your efforts to educate patients about the dangers of prescription drug abuse and lifestyle choices that can help them lead healthier lives. Thank you for your continued commitment to improve the health of our state's residents and the communities we serve.



Timothy J. Tracy
SDAHO Chairperson
CEO
Sanford Vermillion Medical Center



Opioid Overview

By Laura C. Fox; and Steven Waller, PhD

Abstract

Opioids are an important component of pain management strategies for many patients, but their use is associated with serious life-threatening adverse drug responses, such as respiratory depression, as well as a potential for abuse and dependence. This paper presents an overview of opioid pharmacology, pharmacokinetics and toxicology, as well as approaches to maintain or treat opioid dependence.

In recent years, much has been written and spoken about the increased misuse, abuse, and deaths associated with opioid analgesics.^{1,2} In a recent report detailing controlled substance prescribing patterns in eight states, higher prescribing rates for opioids paralleled self-reported rates of chronic pain but that a relatively small number of prescribers provided a majority of opioid orders.¹ In response to this trend, many states have deployed a prescription drug monitoring program that helps identify patients that may be misusing or abusing opioids. Unfortunately, there are concerns that as providers restrict patient access to the opioids, abusers switch to illicit forms of opioids, including heroin. Restriction of patient access to opioids also creates the risk that a highly effective form of pain relief will become increasingly difficult to provide to those who truly need opioid analgesia. Discussed here is a synopsis of opioid pharmacology and toxicology, as well as factors to consider in the management of opioid addiction.

The term “opioid” refers to any compound that works at one of three receptors, members of the rhodopsin family of G-protein coupled receptors.^{3,4} The mu (μ) receptor, the primary receptor governing opiate pharmacodynamics, is associated with supraspinal and spinal analgesia, sedation, inhibition of respiration, slowed gastrointestinal transit, and modulation of hormone and neurotransmitter release.^{3,5} In general, the Mu1 subtype receptor is associated with analgesia, while the Mu2 subtype is associated with most other actions. All currently used opiates (often referred to as narcotics) are considered mu agonists.

Additionally, there are delta (δ) receptors, which are associated with supraspinal and spinal analgesia and modulation of hormone and neurotransmitter release.^{3,5} Of currently available opioids, sufentanil, codeine, oxymorphone, and meperidine are also delta agonists. Finally, kappa (κ) receptors mediate supraspinal and spinal analgesia and slow gastrointestinal transit, but also produce psychomimetic effects.^{3,4} Morphine and oxycodone are also agonists at this receptor. In addition to opioid receptor binding, many agonists activate presynaptic GABA receptors that trigger dopaminergic neurons, ultimately contributing to the feeling of pleasure and euphoria.

Most opioids have favorable bioavailability by a variety of routes of administration, including subcutaneous, intramuscular, rectal, and oral delivery.^{3,4} Highly lipid soluble opioids such as fentanyl are available for transdermal delivery. Regarding oral administration, morphine, hydro-morphine, and oxymorphone undergo extensive first-pass biotransformation that necessitate oral doses higher than parenteral doses, and account for additional variability of drug response in some patients. In contrast, codeine and oxycodone have less first-pass biotransformation and may provide more reliable and stable blood levels.

Opioids distribute throughout tissue based on their lipid solubility.^{3,4} In general, opioids demonstrate some protein binding and tend to localize in highly perfused tissues such as the brain, liver, kidneys and lungs. With time, accumulation of opioids in skeletal muscle and adipose tissues will occur and may create a reservoir of drug,

especially for highly lipid soluble agonists like fentanyl.

The activity of opioids is largely terminated by biotransformation (mostly conjugation) followed by renal excretion.^{3,4} Morphine is conjugated with glucuronic acid to form morphine-6-glucuronide, an analgesic with twice the potency of morphine, and morphine-3-glucuronide, a non-analgesic metabolite with some excitatory activity. Meperidine is *N*-demethylated to normeperidine, a metabolite with a longer half-life than meperidine (15 to 20 hours compared to three hours) whose accumulation may result in an excitatory syndrome that includes hallucination, tremors, muscle twitches, dilated pupils, hyperactive reflexes, and convulsions. These stimulatory effects of normeperidine may be seen in patients taking meperidine for long periods, or in users tolerant to the opioid-like depressant effects of meperidine. Codeine, oxycodone, and hydrocodone are metabolized by CYP 2D6, a cytochrome isozyme exhibiting genotypic variability. For codeine, CYP 2D6 is responsible for conversion to morphine. The CYP 2D6 genotypic variability may explain the variability noted in analgesic responses to codeine. Hydrocodone is biotransformed by CYP 2D6 to hydromorphone, which is then conjugated to hydromorphone-3-glucuronide, which has central excitatory activity. Oxycodone is converted by CYP 2D6 to oxymorphone, which is further conjugated to the analgesic oxymorphone-3-glucuronide. Two opioids, heroin and remifentanyl, are hydrolyzed by plasma and tissue esterases and have short biological half-lives. In the case of heroin (diacetylmorphine), hydrolysis leads to biologically active 6-monoacetylmorphine and, ultimately, morphine. For all clinically used opioid analgesics, hepatic impairment will necessitate dosing adjustments.

Renal excretion is the final elimination process for opioids and their biotransformation products.^{3,4} For opioid analgesics clinically employed, renal impairment may require dosing adjustments. This may be especially true for morphine, codeine, and meperidine, where the potential accumulation of active biotransformation products increases the risk of adverse drug responses.

The pharmacodynamics of opioids, and tolerance to these effects, are well known.^{3,5} Euphoria shows very rapid tolerance. Tolerance to analgesia, respiratory depression, mental clouding, cough suppression, antidiuresis, emesis, and sedation develop more slowly and may be highly variable. Tolerance to opioid-associated bradycardia occurs but is slow. There is little to no tolerance observed

to pupillary miosis, seizures, or the constipating actions of opioids. Seizures are uncommon but have been noted in infants and children following opioid administration. The presumed mechanisms for these seizures may be the inhibition of GABA interneurons in the hippocampus, direct stimulatory effects mediated by G-protein receptors, and actions mediated by metabolites of opioids on other receptor systems.^{3,4} Opioids, especially morphine and codeine, cause histamine release that can potentially trigger bronchoconstriction, especially in individuals with hyperreactive airways, and vasodilation leading to hypotension. Fentanyl induces a lesser histamine release, and may be a better choice for patients sensitive to histamine's actions. The clinical use of opioids ranges from analgesia, cough suppression, treatment of diarrhea, management of acute pulmonary edema, anesthesia, and therapy for opioid dependence. Meperidine hydrochloride is used off-label for obstetric anesthesia and postoperative shivering/shaking chills, although use must be carefully limited in dosage and duration of use, because of possible consequences of its previously mentioned pro-convulsant metabolite.⁵

Respiratory depression is the principle cause of morbidity and mortality associated with the use of opioids.^{3,5} Opioids depress all aspects of respiration (rate, rhythm, minute volume, tidal exchange, etc.) and complications are largely the consequence of slower breathing and occur in a dose-dependent manner. Instructing the patient to consciously breathe can at times overcome respiratory depression, and this may be necessary in the acute use of high doses of opioids. Patients with known or suspected respiratory problems such as asthma, chronic obstructive pulmonary disease, cor pulmonale, hypoxia, concurrent use of depressant drugs, or who are vulnerable to respiratory depression because of age or general health status should be carefully monitored. Opioids are not recommended for use in patients with head injuries, as the depressed respiration leads to carbon dioxide retention resulting in cerebral vasodilation, which in combination with elevated intracranial pressures may be lethal. In addition, methadone use has been associated with prolonged QT interval and linked with serious cardiac arrhythmias, and should be used with caution in patients with a history of cardiac conduction abnormalities, those who are taking drugs that cause prolonged QT interval, or who are at risk for cardiac arrhythmias.

Constipation is a frequently mentioned problem with opioid use.^{3,6} Several strategies can be used proactively if

the patient requires an opioid therapy.⁷ All patients should be encouraged to consider incorporating lifestyle changes such as increased fluids, fiber, and physical activities. In addition, benefit may be realized by the early and regular use of an over-the-counter osmotic laxative containing polyethylene glycol, stimulant laxatives such as bisacodyl, or when these strategies prove inadequate, the addition of the more expensive opioid antagonists such as oral naloxegol (Movantik) or injectable methylnaltrexone (Relistor).

Physical dependence to opioids should be expected in patients presenting with signs of tolerance resulting from repeated use of any mu agonist.^{3,4} The time to emergence and severity of the abstinence syndrome are dependent on the specific agent used and its dosage. Comparing similar degrees of analgesia, opioids with shorter durations will present withdrawal symptoms earlier and with more intense signs, while opioids with longer durations will present later and with less intense signs. The abstinence syndrome generally is characterized by rhinorrhea, lacrimation, chills, piloerection (gooseflesh), muscle aches, diarrhea, yawning, anxiety, increased touch and pain sensitivity, and excessive aggression. The administration of an antagonist such as naloxone or naltrexone can result in a chemically triggered abstinence. Mixed mu receptor agonists/antagonists (buprenorphine, butorphanol, nalbuphine, or pentazocine) used with full agonists may trigger an abstinence syndrome, increasing the risk of respiratory depression and reducing the analgesic effects of the full agonists.^{3,4} It is important to note that while abstinence from opioids is unpleasant, it is seldom life threatening. This is in stark contrast to depressants such as alcohol and benzodiazepines.

Antagonists to opioids such as naloxone are available to treat opioid overdose or provide opioid reversal.^{3,4} Naloxone can be administered parenterally (SC, IM, IV), and soon intranasally.⁸ Naloxone administered to a person dependent on opioids can trigger abstinence and must be used cautiously in persons of unknown dependence status. Naloxone blocks the activity at all opioid receptor subtypes. Naltrexone, a longer-duration orally available opioid antagonist, is used to treat opioid and alcohol dependence, and appears to block opioid activity at all receptor subtypes.

Dependence usually arises concurrent with tolerance – as the body adapts to the presence of the drug, higher and higher doses are needed each time to achieve the desired

effect, whether that be euphoria or analgesia.³⁻⁵ Once receptor populations have adjusted to expect the presence of opiates, the departure of their ligand produces an increasingly agonizing abstinence syndrome the longer the person has used the drugs. This leads to both a psychological and physiological addiction. Opiates are particularly dangerous because their addictive components involve more than merely pursuing a high; this is coupled with the added complication of avoiding intense withdrawal pain. While a plethora of treatment approaches have arisen in the past several decades, additional research and resources are needed for an optimal therapy that successfully weans addicts from their narcotic habits.

In an effort to emphasize the dependence liability of certain opioids, several were recently reclassified from Schedule 3 to Schedule 2 status, including the rescheduling of the commonly abused hydrocodone products. While rescheduling provides additional controls, it is unclear if this really addresses the problem of abuse.

Considerable effort has been directed at development of abuse-deterrent opioid formulations, as recently summarized in *The Medical Letter*.⁹ The intent of these formulations is to make nontherapeutic use more difficult and less rewarding. Strategies include gelling agents to reduce the potential for injection, addition of nasal irritants to reduce inhalation of crushed drug, and chemical additives that prevent extraction from dissolved drug. Early postmarketing studies have been encouraging, but are not yet convincing that these strategies will truly solve the problem, as no abuse-deterrent formulation prevents taking more drug by the intended route of administration.

Treatments for opiate dependence vary in their mechanisms of action and success rates alike. The competitive antagonist naltrexone, which acts most strongly at the mu receptor, can be used in opioid agonist dependence.¹⁰ Blocking the mu receptor prevents the euphoric effect of opioids, presumably decreasing the desire to use opioids. However, as a competitive blocker, its effects can be overcome by high doses of opioids and, if given to an opioid-dependent patient, could chemically trigger withdrawal. A long-acting version of the medication (Vivitrol), which was first approved to treat alcoholism, has been approved for narcotic addiction. Patient compliance with naltrexone remains poor.¹⁰ Naloxone, a weaker blocker of the mu receptor, has a shorter half-life and is used mainly to treat opioid overdose.

Maintenance of opioid dependence is a common strategy

used in the step-wise treatment of dependent persons. Methadone is currently the most utilized treatment as it is relatively inexpensive. It acts upon mu receptors directly as an agonist, to maintain dependence or prevent/relieve symptoms of withdrawal. When used to manage opioid withdrawal, methadone's dosage is matched to maintain the dependence of the original opioid. Taking advantage of its long half-life, the dose of methadone is reduced slowly enough to allow some withdrawal symptoms but no signs of sedation or intoxication. The drug's primary benefit is that withdrawal symptoms are slow to begin, and less acute than withdrawal from heroin.¹⁰ For patients in opioid maintenance treatment, appropriate social and medical services are required. Compliance is fairly good. Stable methadone doses are noted to not cause euphoria or subjective pleasurable effects, and achieving this delicate balance in dosing is quite tricky. Only select clinics are authorized to offer methadone, and must do so according to strict federal standards. Access to these clinics is rapidly expanding, but this comes at a price, predominantly to taxpayers. Many addicts live too far away from an authorized clinic to maintain the frequency of appointments necessary for facilitating recovery.

Buprenorphine is a mixed agonist/antagonist utilized in some cases to curb opiate dependency and to treat opioid withdrawal symptoms. It is a partial agonist at the mu and delta receptors and an antagonist at the kappa receptor. The kappa blockade may be important to buprenorphine's actions, as it may explain why buprenorphine does not seem to produce the reinforcing and subjective effects characteristic of other opioids.⁶ Buprenorphine, available in injectable, sublingual and buccal delivery systems, is chosen less frequently than methadone for long-term withdrawal therapy and requires providers to be certified. It also interacts with many other medications American adults frequently take, including benzodiazepines and common antifungals.¹¹

Buprenorphine's greatest use in narcotic addiction treatment may be in partnership with another drug, naloxone.⁶ The abuse-deterrent combinations are marketed as generic (SL tab) and under the tradenames of Bunavail (buccal strip), Suboxone (SL strip), and Zubsolv (SL tab). All are restricted distribution drugs. Taken by the appropriate route, buprenorphine is adequately absorbed and will maintain opioid dependence. Taken orally, neither component has adequate bioavailability so symptoms of withdrawal may occur before the next scheduled dose. Taken by injection, both components are adequately

absorbed. Naloxone antagonizes mu receptors to prevent any sort of high and may trigger a short-lived chemically-induced withdrawal; while buprenorphine's partial agonism limits the withdrawal symptoms and persists longer than naloxone. If taken intranasally, the buprenorphine effects seem to be dominant, with only a small amount of withdrawal triggered by naloxone. Buprenorphine/naloxone seems a good method with which to assist patients toward recovery.¹¹ However, in the realm of successful therapeutic agents, novelty frequently accompanies expense. Buprenorphine/naloxone treatment is not nearly as affordable as methadone, and specific training in its appropriate use is required.

The aforementioned drugs are certainly making a dent in the issue of narcotic addiction, but only a small one thus far. There is still extensive work needed in the field. A fundamental insufficiency exists in basic research on novel treatment paths for painkiller dependency. Every remedy mentioned above targets just one of many known opiate receptors. Further exploration into additional mechanisms may reveal that the optimal cure has not been discovered yet, as it could lie outside the mu receptor pathway.

The most critical hurdles to treatment of opiate addiction include identifying those who need assistance, creating an effective support network to ensure they receive it, and funding for both basic research and health care provider training in the subject.¹² The long-term Monitoring the Future study, conducted at the University of Michigan, is tracking factors for narcotic use and dependency amongst young people in an attempt to find budding users before they become dependent.¹² Some ways the health care team might identify a patient with a painkiller addiction include noting when they refill their prescriptions late, or when they request a specific type of drug from a wide variety of options the physician might recommend.⁶ The Kaiser Health Tracking Poll reports that 40 percent of Americans know someone who is addicted to opiates, with most saying it is a close friend or family member and up to 2 percent admitting they themselves have a problem.¹³ Members of Congress are claiming narcotic dependence is a "crisis that is spiraling out of control."¹⁴ A call for support has begun across the U.S. for a better understanding of the problem through research, greater public and professional awareness, and for additional treatment facilities.

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The South Dakota State Medical Association Foundation, the philanthropic arm of the South Dakota State Medical Association, is a tax-exempt 501(C)(3) non-profit corporation, was established to assist and support medical research, medical teaching and medical education at the Sanford School of Medicine.

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Basics of Opioid Pharmacology

By John Hansen, MD

Abstract

The use of opioids in the treatment of chronic nonmalignant pain is neither endorsed nor proscribed by evidence-based medicine, except for the finding that opioids have certain risks.

Also challenging for clinicians are consensus definitions for opioid pharmacology which are poorly chosen, changing, or euphemistic. This paper collects opioid consensus definitions for addiction, physical dependence, tolerance, and withdrawal, and offers practical discussion of the concepts they address.

Addiction is a short-circuiting or overdrive of the mesocorticolimbic system of the brain.

Physical dependence on opioids means that after chronic opioid dosing an abrupt cessation or marked dose decrease causes an opioid withdrawal syndrome.

Physical dependence and addiction are unrelated neuroplastic phenomena which occur in different parts of the brain.

Tolerance means a decreasing drug effect for a given dose over time. This applies to desired drug effects and to drug side-effects.

Introduction

The use of opioids in the treatment of chronic nonmalignant pain is neither endorsed nor proscribed by evidence-based medicine, except for the finding that opioids have certain risks.^{1,2}

Also challenging for clinicians are consensus definitions for opioid pharmacology which are poorly chosen, changing, or euphemistic. This paper collects opioid consensus definitions for addiction, physical dependence, tolerance, and withdrawal, and offers practical discussion of the concepts they address.

Addiction

Addiction is a short-circuiting or overdrive of the mesocorticolimbic system of the brain. The mesocorticolimbic system includes the nucleus accumbens and the ventral tegmental area. It controls negative reinforcement and pain avoidance as well as positive reinforcement and pleasure seeking.

For healthy people, family relationships, career, physical fitness, a full emotional life, religious interests, avocations

and grooming result in changes in mesocorticolimbic neurotransmitter concentrations, including dopamine, opioids, serotonin, cannabinoids, glutamate and oxytocin.³⁻⁶ We feel good. We feel good about ourselves and about other people.

In addition, these domains of healthy living are eschewed, in measure, for the enhanced neurotransmitter effects of a drug, a solvent, or a habitual behavior. Behavioral addictions can include sex, gambling, eating, and risk-for-thrill.

There is a continuum of mesocorticolimbic behavioral health upon which any person may be located as part of their “check-up from the neck-up.”

Evidence-based medicine has not found addiction as a necessary concomitant of chronic opioid use in the treatment of chronic pain.⁷ In my own experience, highly-structured opioid prescribing tends to be effective in preventing de novo addiction; only one case comes to mind from the last 11 years of full-time chronic pain practice. Appropriate prescribing structure includes having

Table 1. Consensus Definitions for Addiction

I. American Academy of Pain Medicine/American Pain Society/American Society of Addiction Medicine, 2001.¹²

Definitions Related to the Use of Opioids for the Treatment of Pain

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

II. *Diagnostic and Statistical Manual of Mental Disorders, edition 5.*¹¹

Diagnostic Criteria for Opioid Substance Use Disorder

At least two criteria must be present in any 12-month period, not including tolerance or physical dependence in the case of receiving opioids from appropriate medical supervision.

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
 - A. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
 - B. A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by either of the following:
 - A. The characteristic opioid withdrawal syndrome.
 - B. Opioids are taken to relieve or avoid withdrawal symptoms.

III. International Classification of Diseases, edition 10.¹⁰

Dependence Syndrome

A cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals.

Diagnostic Guidelines

A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year: (a) a strong desire or sense of compulsion to take the substance; (b) difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use; (c) a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms; (d) evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users); (e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects; (f) persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm. Narrowing of the personal repertoire of patterns of psychoactive substance use has also been described as a characteristic feature (e.g. a tendency to drink alcoholic drinks in the same way on weekdays and weekends, regardless of social constraints that determine appropriate drinking behavior). It is an essential characteristic of the dependence syndrome that either psychoactive substance taking or a desire to take a particular substance should be present; the subjective awareness of compulsion to use drugs is most commonly seen during attempts to stop or control substance use. This diagnostic requirement would exclude, for instance, surgical patients given opioid drugs for the relief of pain, who may show signs of an opioid withdrawal state when drugs are not given but who have no desire to continue taking drugs. The dependence syndrome may be present for a specific substance (e.g. tobacco or diazepam), for a class of substances (e.g., opioid drugs), or for a wider range of different substances (as for those individuals who feel a sense of compulsion regularly to use whatever drugs are available and who show distress, agitation, and/or physical signs of a withdrawal state upon abstinence).

an active professional relationship with the patient and monitoring pill counts and the calendar to guarantee no dose-escalation by the patient. Opioids then become a prosaic factor for the mesocorticolimbic system.

Not all chronic nociceptive or chronic neuropathic pain patients are candidates for opioid therapy.

Patients with uncontrolled addiction and uncontrolled psychiatric presentations tend to do poorly as multidisciplinary chronic pain treatment participants, with or without opioids, and are not opioid candidates.

People who are recurrently unable to meet the guidelines of a Controlled Substance Treatment Agreement are not opioid candidates, regardless of the cause or explanation. They can be offered chronic pain treatment without opioids. Those with aberrant behavior with respect to a Controlled Substance Treatment Agreement may require an addiction assessment from a licensed addiction counselor. These should have corroborating information from a household or family member, and a clinical narrative report. Checklist assessments and reports are inadequate.

Consensus definitions of addiction are in Table 1.

Physical Dependence and Opioid Withdrawal Syndrome

Physical dependence on opioids means that after chronic opioid dosing an abrupt cessation or marked dose decrease causes an opioid withdrawal syndrome. Opioid withdrawal syndrome is the sine qua non of opioid physical dependence.

Of course, many drug classes besides opioids can produce a physical dependence, including benzodiazepines, antidepressants, anti-seizure medications, corticosteroids and adrenergic blockers.

Opioid withdrawal syndrome is highly variable between patients. As with other drug classes, it can be routinely prevented by dose taper-down.

Physical dependence and addiction are unrelated neuroplastic phenomena which occur in different parts of the brain. Opioid withdrawal syndrome involves the locus coeruleus.⁸

Consensus definitions of addiction and physical dependence have fostered confusion by referring to addiction as “dependence.”

- *The Diagnostic and Statistical Manual of Mental Disorders edition IV (DSM-IV)* did this.⁹
- The International Classification of Diseases edition 10 (ICD-10) still does it.¹⁰

Table 2. Consensus Definitions for Physical Dependence

- I. American Academy of Pain Medicine/American Pain Society/American Society of Addiction Medicine, 2001.¹²
Definitions Related to the Use of Opioids for the Treatment of Pain
Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- II. *The Diagnostic and Statistical Manual of Mental Disorders, edition 5.*¹¹
No definition of physical dependence.
- III. The International Classification of Diseases, edition 10.¹⁰
No definition of physical dependence.

Table 3. Consensus definitions for Opioid Withdrawal Syndrome

- I. American Academy of Pain Medicine/American Pain Society/American Society of Addiction Medicine, 2001.¹²
No definition of opioid withdrawal syndrome.
- II. *Diagnostic and Statistical Manual of Mental Disorders, edition 5.*¹¹
Diagnostic Criteria for Opioid Withdrawal
 - A. Presence of either of the following:
 1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer).
 2. Administration of an opioid antagonist after a period of opioid use.
 - B. Three (or more) of the following developing within minutes to several days after Criterion A:
 1. Dysphoric mood
 2. Nausea or vomiting
 3. Muscle aches
 4. Lacrimation or rhinorrhea
 5. Pupillary dilation, piloerection, or sweating
 6. Diarrhea
 7. Yawning
 8. Fever
 9. Insomnia
 - C. The signs and symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 - D. The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.
- III. International Classification of Diseases, edition 10.¹⁰
A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms.

- The *Diagnostic and Statistical Manual for Mental Disorders edition 5 (DSM-5)* adds a novel term to the jumble: substance use disorder.¹¹

Consensus definitions for physical dependence are in Table 2.

Consensus definitions for opioid withdrawal syndrome are in Table 3.

Tolerance

Tolerance means a decreasing drug effect for a given dose over time. This applies to desired drug effects and to drug side-effects.

Rarely, people who have become tolerant to opioid side-effects will not be physically dependent on opioids. That is, they will not have an opioid withdrawal syndrome with abrupt cessation of opioid use.

A degree of opioid tolerance can usually be established for nausea, cognitive impairment, and fatigue by several weeks of routine exposure to a very low dose. Judicious titration against pain can then proceed.

When pain control has been achieved by opioid titration, tolerance to the pain-relieving action of the opioid dosage may or may not develop over time.

Tolerance does not occur for the dose-related opioid side-effects of constipation, pituitary suppression, and sleep apnea.

In otherwise healthy patients, the side-effect of respiratory depression can be avoided by avoiding cognitive impairment. In patients with either pulmonary compromise or drug-drug interactions, this is more complicated, especially at high opioid doses.

Consensus definitions of tolerance are in Table 4.

Conclusion

Addiction is a short-circuiting or overdrive of the mesocorticolimbic system of the brain.

Physical dependence on opioids means that after chronic opioid dosing an abrupt cessation or marked dose decrease causes an opioid withdrawal syndrome.

Physical dependence and addiction are unrelated neuroplastic phenomena which occur in different parts of the brain.

Tolerance means a decreasing drug effect for a given dose over time. This applies to desired drug effects and to drug side-effects.

Table 4. Consensus Definitions of Tolerance

- I. American Academy of Pain Medicine/American Pain Society/American Society of Addiction Medicine, 2001.¹²
Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
- II. *Diagnostic and Statistical Manual of Mental Disorders, edition 5.*¹¹
Tolerance, as defined by either or the following:
 - A. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
 - B. A markedly diminished effect with continued use of the same amount of an opioid.
- III. International Classification of Diseases, edition 10.¹⁰
...evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users)...

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Trends in Substance Use Across the Nation and South Dakota

By Jeremy Daniel, PharmD, BCPS, BCPP; and Amanda Owen, PharmD

Abstract

With the discovery of morphine in the early 1800s, substance abuse quickly followed. Next came the production of heroin and other synthetic opioids, along with increases in nonmedical use of prescription medications. In the 21st century, drug abuse and addiction continues to rise nationwide with the three most common drugs abused in adolescents being marijuana, synthetic marijuana, and hallucinogens. Among adolescents and adults nationwide, rates of alcohol, opioids, and amphetamine use have increased over the last decade. In South Dakota, the most prevalent drugs consist of alcohol, methamphetamine, heroin, and prescription opioids. Through the implementation and use of the Prescription Drug Monitoring Program (PDMP) by the South Dakota Board of Pharmacy (SDBOP), hydrocodone/acetaminophen has been identified as the most dispensed controlled substance in the state with roughly 21,000 prescriptions dispensed last November alone. While the PDMP does not necessarily encompass all controlled substances used by the patient (e.g., those purchased from illicit sources), the generation of PDMP reports by physicians and pharmacists is still beneficial. With increased use of the PDMP along with urine drug screens and patient interviews, health care professionals can continue to work collaboratively to help curb the growing epidemic of substance use.

Introduction

A recent report released on Dec. 18, 2015 by the Centers for Disease Control and Prevention (CDC) revealed that drug overdose deaths hit record numbers in 2014.¹ Per the report, of the 47,000 people who overdosed, the majority

occurred with the use of prescription opioids and heroin – a 14 percent increase from 2013. Recently in October 2015, the *Chicago Tribune* reported that police responded to over 70 overdoses of heroin laced with fentanyl.² The most shocking piece of this statistic is that all of these

overdoses were isolated only on the west side of the city. The selection of drugs of abuse continues to change, but the need for understanding them and reducing the abuse continues to remain the same.

History of Opioids

The opium poppy, *Papaver somniferum*, is the only species used to produce opium. The majority of opium poppy is grown in a 4,500-mile stretch of mountains extending across southern Asia.³ It is believed opium was first described in the ninth century B.C. in Homer's *The Odyssey* as a drug to take away all pain. The first citation of opium was discovered on Egyptian papyrus around 1550 B.C. used by Sumerians in Mesopotamia, but it was not until eighth century A.D. that opium had begun to spread throughout Europe and Asia.^{4,5} In 1806, the German pharmacist Friedrich Sertürner successfully isolated the substance within opium and called it morphine after Morpheus, the Greek god of dreams.³ With the discovery of morphine, substance abuse quickly followed suit and ultimately altered the practice of medication use. Other landmarks during the 19th century included the invention of the hypodermic needle to inject morphine and the synthesis of heroin. Throughout the 20th century, the use of morphine and its derivatives continued to increase for not only medical utility but for nonmedical uses as well, and continues to be a significant issue into the 21st century.⁶

Definitions

As a general term, opioid often refers to all substances that bind to opiate receptors. Opioids are classified as either semi-synthetic opioids (heroin developed from morphine and oxycodone developed from thebaine) or synthetic opioids (methadone, fentanyl, and propoxyphene). In a narrower sense, the term opiate pertains to substances that are derived directly from the opium poppy (codeine and morphine). Opioids bind to specific opioid receptors in the central nervous system (CNS) that aid in pain modulation consisting of mu, delta, and kappa opioid receptors. In turn, stimulating these receptors, specifically the mu-opioid receptor, produces an analgesic effect.⁶

Process of Dependence and Addiction

Addiction to morphine was first described by the German physician Dr. Eduard Livenstein during the 19th century who argued that the craving for morphine was a physiologic response. Centuries later, there is more evidence to support this theory pertaining to addiction. When an individual ingests an opioid, the medication binds to the mu-opioid receptors in the CNS to produce an analgesic effect while simultaneously stimulating the mesolimbic

dopaminergic reward pathway. The mesolimbic dopaminergic reward pathway mediates reward through the increase in extracellular concentrations of mesolimbic dopamine that occurs with natural substances (i.e., food, sex, alcohol, cocaine, marijuana). The increase in dopamine with mesolimbic activation results in feelings of pleasure. This process increases the drive for continuous use of a substance in order to achieve higher concentrations of dopamine, thus, more pleasurable feelings. When these substances are used repeatedly, the reward processes in the brain motivates the individual to continue using the drug, leading to addiction.^{7,8}

Addiction is a complex brain disease that is considered a lifelong illness. Despite having a motivated patient, biochemical changes within the brain make it particularly challenging to “break” an addiction. The ultimate hurdle to overcome addiction is conquering the disequilibrium between dopamine and glutamate in the CNS. The normal release of dopamine during pleasurable experiences is disrupted in addiction, resulting in lower levels of dopamine. Over time, in order to overcome the reduced dopamine response, addicts require higher amounts of opioids to achieve that same pleasurable response. Compared to dopamine, the excitatory neurotransmitter glutamate is seen in higher amounts in the CNS and is the key component for driving addiction. In periods of drug abstinence, glutamate levels increase dramatically in the CNS, triggering a further increase in the release of dopamine. This surge in dopamine produces withdrawal symptoms, further increasing cravings and ultimately leading to relapse. Opioid dependence may cause slight acute changes in dopamine levels within the brain, but addiction leads to chronic chemical changes that create a cycle of cravings, drug use, withdrawal, and relapse.⁷

Nationwide Trends

To predict trends in substance use in adults, we must first look at trends in children and adolescents. It is well known that substance use disorders do not suddenly arise in adulthood. There are many developmental precursors that lead to adult substance dependence.^{9,10} A recent 405 participant study from 2010 further illustrates this fact.¹¹

The National Institute of Drug Abuse (NIDA), a subset of the National Institutes of Health, conducts a yearly survey in children and adolescents titled “Monitoring the Future.” The 2015 survey includes information from 44,892 students from 382 public and private schools across the U.S.¹² The trends are favorable for cigarettes and alcohol as a decline in use has been seen over the past two

decades. The rate of illicit substance use among school-aged children has remained fairly consistent over the past five years, though there is still a slight decline. A summary of rates of use for cigarettes, electronic cigarettes (e-cigarettes), alcohol, and illicit substances for eighth, 10th, and 12th graders within the past month is illustrated in Table 1.¹²

Table 1. Rate of Substance Use Within One Month¹²

	8th Grade	10th Grade	12th Grade
Cigarettes	3.6%	6.3%	11.4%
E-cigarettes	9.5%	14.0%	16.2%
Alcohol	9.7%	21.5%	35.3%
Illicit Substances	8.1%	16.5%	23.6%

E-cigarettes pose a potential issue for illicit substance use. Because the e-cigarette is refillable with liquid, any volatile or vaporizable liquid can be placed inside and inhaled. 6.1 percent of 12th graders who use e-cigarettes report using marijuana or hash oil within the device instead of the flavored or nicotine-containing liquid.¹² This is seen as an advantage over traditional methods by users because the vaporizing device does not yield the typical odor that may alert authorities or nearby persons of illegal substances. Additionally, 68.1 percent of 12th graders surveyed do not view regular marijuana smoking as harmful.¹² This is increased from 64 percent in the 2014 survey.¹³ This perception will likely lead to increased use, especially with the national push for marijuana legalization and successful results in a number of states.

While marijuana, synthetic marijuana, and hallucinogens remain the top illicit drugs used among adolescents, prescription and over-the-counter medications are also commonly abused.¹² The reports of past year misuse among 12th graders illustrate 7.7 percent misused amphetamines, 5.4 percent misused opioids (other than heroin), 4.7 percent misused tranquilizers, and 4.6 percent misused cough medicine. This is fairly consistent with 2014 numbers.¹³

Within the adult population, the trends show much of the same information. Overall, rates of alcohol, opioid, and amphetamine, and other illicit substance use has increased since 2002, according to the 2014 National Survey on Drug Use and Health (NSDUH) from the Substance Abuse and Mental Health Services Administration (SAMHSA).¹⁴ Two-thirds of the U.S. population age 12 and over drank alcohol at some point during the year with 10 percent of those subjects qualifying for a diagnosis of an alcohol use disorder. Illicit substance use in the same population has increased from 8.3 percent using in the past month in 2002 to 10.2 percent using in the past

month in 2014. Of those subjects, 26 percent qualify for a substance use disorder diagnosis.

However, novel agents are starting to be seen more often in the adult population. They are also likely used by children and adolescents, but a literature search found no strong articles detailing rates of use of these agents in the younger population. The most common novel agents of abuse are synthetic cannabinoids, commonly referred to as spice, K2, and many other street names. These agents do not show up as positive on traditional urine drug screens. Per the American Association of Poison Control Center's (AAPCC) November 2015 report, there have been 7,369 cases of synthetic cannabinoid use reported to the organization.¹⁵ This is increased from 3,682 cases in 2014. This clearly does not include usage not reported to AAPCC, though the increase in reporting does illustrate usage of higher doses leading to more deleterious effects.

Synthetic cathinones, also known as bath salts, are still used in some areas of the country. Per the NIDA, a new form of bath salt nicknamed "flakka" is being reported in Florida and is expected to spread across the U.S.¹⁶ Unfortunately, it is not easy to determine which specific substance an intoxicated patient has used as most agents present with symptoms of either psychosis and mood elevation or extreme sedation. They do not respond to standard reversal agents – only symptomatic management is indicated.

Though standard urine drug screens are ineffective in determining the agent, special labs are generally available, though may not have clinical utility. As most facilities do not have the equipment to conduct the test, the specimen must be sent to a specialized location. This takes several days to receive the results. The patient has most likely been treated within this timeframe and knowing the specific agent of use, if not disclosed by the patient, will not often alter the course of treatment.

The University of Maryland has developed a National Drug Early Warning System (NDEWS) that reviews drug use trends in 12 "sentinel community sites" to determine national trends.¹⁷ The closest sites to South Dakota are Chicago and Denver. Trends cited in the 2015 report demonstrate an increase in synthetic marijuana use, a surge of fentanyl abuse, and continued increasing abuse of methamphetamine across the nation.

South Dakota Trends

Within the state of South Dakota, alcohol abuse and methamphetamine use is still very prevalent, as well as

heroin and prescription opioids. At Avera Behavioral Health Center in Sioux Falls, the most common substances yielding a substance use disorder diagnosis during admission (excluding cannabis) are alcohol, opioids, and amphetamines. A large percentage of the opioid abuse is not heroin use; it is prescription drug abuse.

Since the initiation of the Prescription Drug Monitoring Program (PDMP) by the South Dakota Board of Pharmacy (SDBOP) in 2012, hydrocodone/acetaminophen has been the most dispensed controlled substance in the state. Table 2 shows a summary of the number of tablets dispensed and prescriptions written for hydrocodone/acetaminophen since the inception of the PDMP, data courtesy of internal reports from the SDBOP. It is noteworthy that the SDBOP changed vendors for the PDMP starting with the June 2015 report. There was initially an error in reporting leading to a concern of overprescribing, though this is not seen in updated data. The number of prescriptions and tablets dispensed have remained fairly consistent.

Table 2. Hydrocodone/Acetaminophen Prescribing in South Dakota

Month	Number of Prescriptions	Number of Tablets Dispensed
2013 Average	24,703	1,427,023
2014 Average	24,483	1,456,926
January 2015	22,164	1,500,526
February 2015	20,964	1,459,620
March 2015	22,896	1,585,232
April 2015	22,514	1,543,029
May 2015	16,423	1,141,759
June 2015	23,123	1,575,808
July 2015	24,545	1,672,951
August 2015	23,215	1,568,980
September 2015	22,713	1,515,039
October 2015	22,861	1,540,199
November 2015	22,667	1,545,232
December 2015	25,126	1,746,933
January 2016	21,078	1,408,892
February 2016	19,996	1,351,465
March 2016	23,421	1,584,474
April 2016	20,338	1,367,662

It is noteworthy that hydrocodone-containing products became Schedule II substances under the Controlled Substance Act on Oct. 6, 2014.¹⁸ Upon review of dispensing data from Table 2, there is no reduction in prescribing of hydrocodone/acetaminophen from the 2014 average

through the first portion of 2015. For 2015, the top five dispensed controlled substances have been hydrocodone/acetaminophen, tramadol, zolpidem, lorazepam, and clonazepam in order with the exception of August 2015 when zolpidem and lorazepam changed places in dispensing order.

One particularly positive trend in South Dakota is the generation of PDMP reports by both prescribers and pharmacists. Since its inception, 84 percent of pharmacists, 25 percent of physicians, 52 percent of physician assistants, 43 percent of nurse practitioners, and 20 percent of dentists are approved for access to the PDMP per SDBOP data. Registration has few steps and takes minimal time on the SDBOP website. Registration is just one tool in a provider's arsenal, along with urine drug screens and patient interviews, to help curb the growing epidemic of substance use.

Conclusion

Since the development of opioids, misuse of the chemicals have been evident in society. Currently nationwide, trends in substance use center around not only alcohol, opioids, and amphetamines, but also include newer, synthetic substances. These habits of misuse leading to dependence and addiction begin in childhood and adolescence, and are influenced by a number of factors. However, in the state of South Dakota, we do not have the increased incidence of newer agents, though they are making their way into the state slowly. Providers should use all tools available to monitor their patients and refer for treatment when necessary. For more information on urine drug screens, see the Pharmacology Focus article from the June 2015 edition of *South Dakota Medicine*.

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+Anthrax (<i>Bacillus anthracis</i>★) Anaplasmosis (<i>Anaplasma phagocytophilum</i>) Arboviral encephalitis, meningitis and infection (West Nile, St. Louis, Eastern equine, Western equine, Chikungunya, California, Japanese, Powassan, LaCrosse, Colorado tick fever) Babesiosis (<i>Babesia</i> spp) +Botulism (<i>Clostridium botulinum</i>) +Brucellosis (<i>Brucella</i> spp★) Campylobacteriosis (<i>Campylobacter</i> spp) Carbon monoxide poisoning Chancroid (<i>Haemophilus ducreyi</i>) Chicken pox / Varicella (<i>Herpesvirus</i>) Chlamydia infections (<i>Chlamydia trachomatis</i>) Cholera (<i>Vibrio cholerae</i>) Coccidioidomycosis (<i>Coccidioides</i> spp) +Coronavirus respiratory syndromes, such as MERS (Middle East respiratory syndrome) and SARS (Severe acute respiratory syndrome) Cryptosporidiosis (<i>Cryptosporidium</i> spp) Cyclosporiasis (<i>Cyclospora cayentanensis</i>) Dengue viral infection (<i>Flavivirus</i>) +Diphtheria (<i>Corynebacterium diphtheriae</i>★) Drug resistant organisms: - Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE) - Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), invasive - Vancomycin-resistant <i>Staphylococcus aureus</i> (VRSA)★ +E. coli, shiga toxin-producing (<i>Escherichia coli</i>★), includes <i>E. coli</i> O157:H7, O26, O111, O103 and others Ehrlichiosis (<i>Ehrlichia</i> spp) +Influenza, novel strains★ Influenza: including hospitalizations, deaths, lab confirmed cases (culture, DFA, PCR), weekly aggregate totals of rapid antigen positive (A and B) and total tested Giardiasis (<i>Giardia lamblia</i> / <i>intestinalis</i>) Gonorrhea (<i>Neisseria gonorrhoeae</i>) Haemophilus influenzae★, invasive disease	Hantavirus pulmonary syndrome and Hantavirus pulmonary infection (<i>Hantavirus</i>) Hemolytic uremic syndrome Hepatitis, viral, acute A, B and C; chronic B and C; and perinatal B Human immunodeficiency virus (HIV) infection, also including: - Stage III, Acquired immunodeficiency syndrome, (AIDS) - CD4 counts in HIV infected persons - HIV viral loads, and - pregnancy in HIV infected females Lead, elevated blood levels Legionellosis (<i>Legionella</i> spp) Leprosy / Hansen's disease (<i>Mycobacterium leprae</i>) Leptospirosis (<i>Leptospira</i>) Listeriosis (<i>Listeria monocytogenes</i>★) Lyme disease (<i>Borrelia burgdorferi</i>) Malaria (<i>Plasmodium</i> spp) +Measles (<i>Paramyxovirus</i>) +Meningococcal disease, invasive (<i>Neisseria meningitidis</i>★) Mumps (<i>Paramyxovirus</i>) Pertussis / Whooping cough (<i>Bordetella pertussis</i>) Pesticide-related illness and injury, acute +Plague (<i>Yersinia pestis</i>★) +Poliomyelitis, paralytic and nonparalytic (<i>Poliovirus</i>) Psittacosis (<i>Chlamydophila psittaci</i>) Q fever (<i>Coxiella burnetii</i>) +Rabies, human and animal (<i>Rhabdovirus</i>) +Rubella and congenital rubella syndrome (<i>Togavirus</i>) Salmonellosis (<i>Salmonella</i> spp★) Shigellosis (<i>Shigella</i> spp★) Silicosis +Smallpox (<i>Variola</i>★)	Spotted fever rickettsiosis (<i>Rickettsia</i> spp) Streptococcus pneumoniae, invasive Syphilis (<i>Treponema pallidum</i>) including primary, secondary, latent, early latent, late latent, neurosyphilis, late non-neurological, stillbirth, and congenital Tetanus (<i>Clostridium tetani</i>) Toxic shock syndrome (Streptococcal and non-Streptococcal) Transmissible spongiform encephalopathies, such as Creutzfeldt-Jakob disease Trichinosis (<i>Trichinella spiralis</i>) +Tuberculosis, active disease (<i>Mycobacterium tuberculosis</i>★ or <i>Mycobacterium bovis</i>★) Tuberculosis, latent infection (only in certain high risk persons: foreign-born <5 yrs in US, close contacts, diabetes, renal dialysis, children <5 yrs, and certain medical conditions) +Tularemia (<i>Francisella tularensis</i>★) Typhoid (<i>Salmonella typhi</i>★) Vaccine Adverse Events +Viral Hemorrhagic Fevers (Crimean-Congo Hemorrhagic Fever virus, Ebola virus, Lassa virus, Lujo virus, Marburg virus, New World Arenavirus – Guanarito virus, Junin virus, Machupo virus, Sabia virus) Vibriosis (<i>Vibrionaceae</i>) +Yellow fever (<i>Flavivirus</i>) ----- +Outbreaks of: +Acute upper respiratory illness +Diarrheal disease +Foodborne disease +Healthcare-associated infections +Illnesses in child care setting +Rash illness +Waterborne disease +Syndromes suggestive of bioterrorism and other public health threats +Unexplained illnesses or deaths in human or animal
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The South Dakota Department of Health is authorized by SDCL 34-22-12 and ARSD 44:20 to collect and process mandatory reports of diseases and conditions by physicians, hospitals, laboratories, and other institutions.

How to report:

Secure website: sd.gov/diseasereport

Telephone: 605-773-3737 or 800-592-1861 during business hours, or 800-592-1804 confidential answering device,

After hours emergency Category I diseases, call 605-773-3737 or 800-592-1861

Fax: 605-773-5509

Mail or courier to: Infectious Disease Surveillance, Department of Health, 615 East 4th Street, Pierre, SD 57501; marked "Confidential Disease Report"

What to report: Reports must include as much of the following as known:

- Disease or condition
- Date of disease onset
- Relevant lab results and specimen collect date
- Case name, age, birth date, sex, race, address, occupation
- Attending physician's name, address, phone number
- Name and phone number of person making report

CANCER (SDCL 1-43-14) Report to SD Cancer Registry, call 800-738-2301



Opioid Analgesics for Chronic Non-Cancer Pain: A Guideline on Opioid Prescribing

By Robert Van Demark, Jr., MD; Peter Chang, MS IV; and
Daniel Heinemann, MD, FAAFP

Abstract

Introduction: Over the past decade, the use of opioid analgesics has risen dramatically both in the U.S. and South Dakota. Opioids have been increasingly used to treat chronic non-cancer pain; however, the utilization of opioids for this role has limited and questionable utility. The U.S. has also seen a rise of opioid abuse, addiction, misuse, and overdose. The various pharmacological and non-pharmacological strategies to help physicians manage chronic non-cancer pain and a guideline on appropriate opioid prescribing are presented.

Discussion: Before the decision is made to begin opioid therapy for chronic non-cancer pain, other pharmacological and non-pharmacological therapeutic strategies should be explored. The schema for responsible opioid prescribing can be divided into the following: the initial assessment, initiating opioid therapy, maintenance therapy, and the discontinuation of opioid treatment. These categories are explored, and a general approach to prescribing opioids for chronic non-cancer pain is presented.

Conclusion: The Centers for Disease Control and Prevention (CDC) has declared opioid prescription abuse an “epidemic.” There are a variety of methods clinicians can utilize to relieve chronic non-cancer pain. If opioid therapy is sought, clinicians should be mindful of the current state of opioid abuse and misuse. This guideline may aid clinicians in appropriate opioid prescribing.

Introduction

When the use of opioid analgesics is appropriate, these drugs can serve as important tools for the relief of moderate to severe pain arising from a wide variety of illnesses, medical conditions, and medical procedures.¹ However, in the past two decades, the use of opioid analgesics has risen dramatically both in the U.S. and South Dakota.¹ Opioids have been increasingly prescribed for chronic non-cancer conditions including back pain, osteoarthritis, fibromyalgia, and headache.^{1,2} This nationwide revolution in opioid prescribing may be related to several factors: the 1995 national campaign to address the perceived under-treatment of pain by the American Pain Society in conjunction with the American Society of Anesthesiologists, the 1998 “Pain as the 5th Vital Sign” initiative from the Department of Veteran Affairs, and the 2001 implementation of new pain management standards by the Joint Commission.³ Since this time, opioid prescription sales to hospitals, pharmacies, and doctors increased four-fold from 2010 as compared to 1999.³ The U.S. represents less than

5 percent of the world’s population yet consumes 80 percent of the global opioid supply including 99 percent of the world’s hydrocodone supply.⁴ The implications of the widespread use of opioid prescribing can be seen with rising rates of opioid abuse, addiction, and diversion of opioids for non-medical uses.¹ In addition, deaths due to opioid related causes are now more prevalent than deaths due to suicide or motor vehicle crashes.⁵ Nontherapeutic opioid use in the U.S. has caused a substantial financial burden of over \$50 billion annually, 94 percent of which is due to lost productivity and criminal justice costs.⁴ The pendulum has swung to what the Centers for Disease Control and Prevention (CDC) now deems an “epidemic” of prescription opioid abuse.⁶ Physicians are called to be vigilant of the ongoing problem of opioid over-prescription while maintaining the balance of adequately relieving their patients’ pain.¹ Various pharmacologic and non-pharmacologic strategies to manage chronic non-cancer pain as well as a guideline for responsible opioid prescribing are presented.

Discussion

Key Concepts in Pain Medicine

Pain is the most common reason people seek health care;^{1,7} in the U.S., the incidence of chronic pain is estimated to be greater than that of diabetes, heart disease, and cancer combined.^{1,8,9} Unmanaged pain can affect quality of life, depression, anxiety, and result in a wide gamut of adverse consequences.¹⁰ Therefore, the complaint of pain should be fully explored. However, physicians must balance the role of relieving pain while remaining cognizant of the current problem of opioid abuse and misuse.¹ Pain can be classified by its duration, pathophysiology, and association with cancer. Acute pain is characteristically short in duration (days to a few weeks), caused by tissue injury, and resolves as the injury heals.² Chronic pain, on the other hand, is defined by the International Association for the Study of Pain as pain lasting for three months or longer.¹¹ The biological and pathophysiological nature of pain can be divided into nociceptive and neuropathic pain. Nociceptive pain is a physiological response to injurious stimuli and tissue damage with subsequent stimulation of nociceptors, or pain receptors.¹ Nociceptive pain is generally short in duration and secondary to an underlying medical condition.¹ Conversely, neuropathic pain is caused by aberrant neuronal firing without any underlying tissue damage and is an abnormal response from injury to the nervous system or from inadequately treated nociceptive pain.¹ Sensitization may occur in either nociceptive or neuropathic pain, and is a phenomenon in which hyperexcitability develops in peripheral nociceptors or neurons of the central nervous system due to increased stimulation of nociceptors or compounds released by the body from tissue damage and inflammation.^{1,12} Sensitization can lead to hyperalgesia or allodynia, complicating the management of chronic pain.¹³ Cancer pain is pain resulting either from the cancer disease process itself or related to the treatment of the disease.¹ Chronic non-cancer pain is defined as pain lasting longer than three months that is not associated with cancer or, for our purposes, end of life pain.^{2,14} Musculoskeletal pain, neuropathic pain, fibromyalgia, osteoarthritis, and rheumatoid arthritis can be included in the realm of chronic non-cancer pain.¹⁴ Chronic non-cancer pain has garnered national attention due to its association with prescription analgesia.

Management of Chronic Non-Cancer Pain

Chronic non-cancer pain can be managed with both non-pharmacologic and pharmacologic modalities.¹ In treating chronic non-cancer pain, it is imperative to identify

the source of chronic pain and target therapies towards the source.¹ Physicians must also select the most clinically appropriate approach to chronic pain management.¹ In general, this means frequent utilization of non-pharmacological approaches and/or choosing pharmacological therapy with the most benign side-effect profile at the lowest effective dose.¹ A function based long-term management plan must also be established early. Non-pharmacological therapies include cognitive-behavioral approaches, rehabilitative approaches, complementary and alternative therapies, and interventional approaches. Cognitive-behavioral approaches include individual, group, or family psychotherapy which help patients alter negative thoughts and beliefs about their pain and address comorbid anxiety or depression.¹ Rehabilitation therapies seek to alleviate pain, improve physical functioning, reduce anxiety and fear, and alter physiological responses to pain.¹ Examples of rehabilitation therapies include exercises to improve strength, mobility, and endurance.¹ Other treatments may include use of thermotherapy, cryotherapy, counter-irritation, and electroanalgesia.¹ The complementary and alternative therapies of meditation, acupuncture, relaxation, imagery, biofeedback, and hypnosis may also be helpful to some patients.¹ Interventional approaches, both surgical and non-surgical, tend to be based on patient-specific conditions and include trigger point injections, epidural injections, facet blocks, spinal cord stimulators, laminectomy, spinal fusion, and deep brain implants.¹ Pharmacotherapy includes non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, topical agents, antidepressants, anticonvulsants, and opioids. NSAIDs (aspirin and other salicylic acid derivatives) relieve pain via cyclooxygenase inhibition and can be used to manage acute and chronic pain as well as acetaminophen. Unlike opioids, NSAIDs and acetaminophen do not produce tolerance, physical dependence, or addiction; however, these agents have lower pain-reducing capabilities than opioids.¹ Since they use different mechanisms to relieve pain, a combination of opioids and NSAIDs and/or acetaminophen can be used to spare opioids and achieve improved pain relief.¹ Topical capsaicin, salicylates, NSAIDs, and lidocaine can be used to achieve short-term pain relief with relatively few side effects.¹ Some antidepressants, particularly tricyclics, SNRIs, and SSRIs have analgesic properties and are especially helpful in treating neuropathic type pain.¹ The analgesic qualities of antidepressants do not depend on the antidepressant activity.¹⁵ Antiepileptic drugs, gabapentin and pregabalin, can be used for the treatment of neuropathic type pain.³ Mechanistically, these drugs

bind the Alpha 2 Delta subunit of N-type voltage-gated calcium channels which inhibits the release of neurotransmitters and reduces neuronal excitability.³

Opioids for Chronic Non-Cancer Pain

Although opioid therapy is necessary for the relief of acute pain (post-operatively) and can be acceptably used in palliative care and cancer pain, opioid use in the management of chronic non-cancer pain is a source of controversy.¹⁶ The role of opioids in chronic non-cancer pain is being questioned, and a broad consensus is developing that opioids are not proper for this type of pain.¹ Very little evidence exists supporting the notion that long-term opioid use results in a clinically significant reduction in pain, better quality of life, or improved functioning.¹⁷ According to a Cochrane review by Noble et al., many patients on opioid therapy for non-cancer pain actually discontinued long-term opioid therapy due to adverse effects or inadequate pain relief.¹⁷ Additionally, a random sample of 705 patients undergoing long-term opioid therapy for non-cancer pain in a 2011 study by Boscarino et al. found that the lifetime prevalence rate of DSM-5 defined opioid-use disorder was 35 percent.¹⁸ In a study by Fleming et al., 801 patients receiving long-term opioid therapy were interviewed and maladaptive patterns of opioid abuse were elucidated.¹⁹ It was found that 39 percent of patients increased their dose without health care direction, and 26 percent of patients engaged in purposeful over-sedation.¹⁹ Both the dose and duration of opioid use are associated with opioid overdose, abuse, and dependence.²⁰ Opioids carry the potential for misuse, addiction, and life-threatening overdose and exert a side effect profile including somnolence, dizziness, hypogonadism, nausea, vomiting, constipation, erectile dysfunction, pruritus, and respiratory depression.¹

Guidelines for Responsible Opioid Prescribing

A guideline for responsible opioid prescribing will be presented to help South Dakota clinicians minimize the risks associated with opioid prescribing. Before going forth with prescribing opioids for chronic non-cancer pain, physicians should carefully evaluate the patient and the circumstance.¹ Situations when opioid therapy may be amenable include severe pain refractory to other treatment modalities, pain adversely impacting function or quality of life, and when the potential benefits outweigh the potential harms.^{1,2} The schema for responsible opioid prescribing can be divided into the realms of: the initial assessment, initiating opioid therapy, maintenance therapy, and the discontinuation of opioid treatment.

Initial Assessment

Before the decision is reached to engage in opioid therapy for chronic non-cancer pain, an initial assessment taking into account patient characteristics and pain assessment should be performed.¹ The initial assessment should begin with a thorough history and physical examination, appropriate testing, and an assessment of a patient's risk of substance abuse, misuse, or addiction.^{1,2} Patients who are not likely to benefit from opioid therapy include patients with poorly-defined pain conditions, daily headaches, fibromyalgia, somatoform disorder, and unresolved worker's compensation claims or legal issues related to the pain or injury.^{1,2} During the patient assessment, it is imperative to assess the patient's psychosocial functioning in terms of function at work and home, and how their pain affects their relationships, activities of daily living, sexual functioning, and recreational activities.¹ Additionally, clinicians should assess for depression, anxiety, and suicidality.¹ If any of these are uncovered, physicians may choose to pursue further questioning, a course of treatment, or referral to a mental health professional.¹ Patients should also be evaluated for risk of opioid dependence or abuse.¹ A personal or family history of alcohol or drug abuse has been a predictive factor of potential opioid abuse or misuse.^{1,2} Additionally, younger age and presence of psychiatric conditions have been associated with aberrant drug-related behaviors.^{1,2} Although some particular patient characteristics are associated with opioid abuse and misuse, it may be beneficial to use a "universal precautions" approach and administer the same screenings and diagnostic procedures to all patients.²¹ The Diagnosis, Intractability, Risk Efficacy (DIRE), Opioid Risk Tool (ORT), and Screener and Opioid Assessment for Patients with Pain, Version 1 and Revised (SOAPP and SOAPP-R) are relatively short, validated tools that can be used by physicians to quantify patient's risk of having a substance misuse problem.¹ Pain may be difficult to quantify and is challenging because no physical instruments exist to measure its intensity.¹⁶ Pain is reported directly by the patient, and patient reports may be ambiguous.¹⁶ In the assessment of pain, one-dimensional pain scales, such as numeric or faces scales, are highly subjective and have little use in guiding management of chronic pain.¹ Multidimensional tools such as the Initial Pain Assessment Tool,²² Brief Pain Inventory,²³ and McGill Pain Questionnaire²⁴ can provide an in-depth assessment of a patient's pain and can be administered in the office, examination room, or other clinical setting.¹

Initiating Opioid Therapy

After the decision is made to initiate opioid therapy, a

function-based opioid management plan or opioid medication agreement should be made and informed consent obtained before the patient is ever given the initial prescription. A “medication agreement” or “management plan” is a contract between the physician and patient. It can be useful for patient education, clarification of expectations, and goal setting.^{1,2} These agreements can help a patient adhere to a regimen of opioid pain medication.^{1,2} The components of an opioid medication agreement should include the rationale of treatment, risk of the drug, treatment goals (pain level, improvement of function), monitoring plan, refill policy, action plan for aberrant behavior, and conditions for discontinuation of opioids.¹ A sample agreement can be referenced in Appendix I of *Opioid Analgesics for Chronic Non-Cancer Pain* by the South Dakota State Medical Association (SDSMA) available at www.sdsma.org located under the Advocacy: Current Topics tab.¹ When crafting management plans, clinicians should avoid using punishing or stigmatizing language, and agreements should be written at a sixth to seventh grade level.¹ Agreements should be written in terms of functional goals as well as in terms of pain relief. Since chronic pain often impairs daily function, even modest reduction in pain level can result in functional improvements in physical activity, mental focus, and rest.¹ Treatment goals should be framed towards improved functioning such as having the ability to walk a designated number of steps.¹ Functional treatment goals should be realistic and patient-specific, and goals should be set slightly too low rather than slightly too high.¹ Informed consent should also be included as a part of the opioid management plan. Informed consent is a required component of any medical treatment plan but becomes paramount in long-term opioid use.¹ The components of the informed consent in regards to long-term opioid use can be found on page 19 of *Opioid Analgesics for Chronic Non-Cancer Pain* by the SDSMA.¹ After other treatment options are sought, a clinician may decide to initiate opioid therapy; however, before an opioid is prescribed, all of the schema described above should be performed in some manner. Opioid selection, initial dose, and titration must be individualized to the patient’s health status, previous opioid exposure, and overall treatment plan.^{1,2} A wide array of opioid drugs and formularies is available. Since there is little evidence that specific analgesic formulations affect efficacy or addiction risk, the choice of opioid agent should be individualized based on lifestyle, pain complaint, and preference.²⁵ Generally, a short-acting opioid at a low dose used on an as-needed basis should be initially tried with gradual upward titration to avoid

adverse effects.² Extended-release (ER) or long-acting (LA) opioids produce a more steady-state analgesia and may be useful in some patients.¹ However, ER/LA agents may result in using more drug than needed and pose a higher risk of being abused.^{1,26} Physicians should educate themselves about the general characteristics, toxicities, and drug interactions for both short-acting and ER/LA opioid agents. It is of note that caution should be taken when initiating opioid therapy in frail elderly patients or patients with comorbid conditions.¹ It is imperative to educate patients about safe usage, storage, and proper disposal of opioid medications.¹ Safe use education should include clinician instructions on dosing, side-effect profile, potential drug interactions, and proper consumption or application of opioids.¹ Opioids should be stored in a locked storage unit and should not be kept in an easily viewed or accessible location.¹ Proper disposal includes following specific disposal instructions on the drug labeling or patient information, returning medications to a pharmacy, health center, or other organization with a take-back program, or mixing the medication with an undesirable substance such as kitty litter.¹

Opioid Maintenance Therapy

Therapy should be regularly reviewed to ensure that opioid treatment is aiding the patient in meeting their functional goals and management plan. Clinicians should assess for progress towards prior agreed-upon treatment goals for pain relief and function, adverse effects, and confirm adherence to the prescription regimen.¹ Evidence-based strategies to reduce opioid-related adverse effects from the Veterans Administration/Department of Defense clinical practice are summarized in Figure 1.²⁷ If an unacceptable adverse effect is encountered or one particular opioid does not result in adequate analgesia, a different opioid may be tried.¹ This must be done cautiously with the use of an equianalgesic chart due to many pharmacokinetic and pharmacodynamic variables involved.¹ If pain flare-ups or inadequate analgesia are encountered, patients can create pain diaries to help them alter variables correlated to their pain flare-ups.¹ Non-opioid modalities previously discussed such as cold, warmth, acupuncture, or combination therapy of an opioid and non-opioid pharmacotherapy should be tried before the dose of opioid is increased.¹ It is of note that the escalation of opioid dosing has not been proven to reduce pain or increase function but can increase risks.²⁸ If it is suspected that a patient is non-adherent to their prescription, clinicians should thoroughly investigate the situation. Physicians should discuss the situation with the patient,

clarify expectations, review the existing patient/provider agreement, increase the intensity of patient monitoring, and establish a limit on refills or lost medications.¹ A urine drug screen may be conducted at every follow-up visit as a part of the agreed-upon management plan or may be used to investigate opioid non-adherence.¹ The appearance of metabolites in a urine drug screen may be misleading, and clinicians should familiarize themselves with metabolites associated with each opioid therapy.¹ If persistent non-compliance is encountered, drugs may be tapered down over several weeks, and patients can be referred to a pain specialist or addiction management program.¹

Discontinuation of Opioid Therapy

Opioid therapy may be discontinued if the injury or condition has healed, proper analgesia or functional outcomes cannot be attained, intolerable side-effects are experienced, or continued non-adherence, abuse, or addiction is apparent.¹ When discontinuing opioid therapy, for most patients, the dose should be tapered by 20 to 50 percent of the current dose each week.¹ In general, a slower taper should be used if a patient has been on the opioid long term or at a high initial dose.²⁷

Special Considerations

Clinicians should avoid prescribing opioids during pregnancy unless the potential benefits outweigh the risks.² Opioid overdose can be rapidly reversed by the timely administration of naloxone (trade name Narcan) which was authorized to be carried by medical first responders in South Dakota as of July 1, 2015.¹ Naloxone is an opioid antagonist that can rapidly reverse the respiratory depression from an opioid or heroin overdose.¹ Emergency room physicians are among the higher prescribers of opioids to patients ages 10 to 40.^{1,29} The SDSMA recommendations for patients presenting to the emergency room with acute or chronic non-cancer pain can be found on page 37 of *Opioid Analgesics for Chronic Non-Cancer Pain*.¹

Conclusion

The incidence of opioid related abuse, addiction, and overdose has been steadily increasing to the point of an “epidemic” of opioid abuse. A number of different therapeutic strategies can be used to address chronic non-cancer pain. Clinicians must be aware of abuse and misuse problems when using opioids for chronic non-cancer pain. These guidelines present an evidence-based strategy to aid South Dakota clinicians in safely prescribing opioids for chronic non-cancer pain. Appropriate prescribing of opioids is challenging but quintessential. The SDSMA

Committee on Pain Management and Prescription Drug Abuse published a comprehensive guideline on opioid prescribing in September of 2015 based on the current literature and existing clinical guidelines. The guideline is entitled *Opioid Analgesic for Chronic Non-Cancer Pain* and is a comprehensive approach to opioid prescribing for South Dakota clinicians.¹ This paper is meant to summarize the SDSMA’s guidelines, and for an extensive reference please defer to the SDSMA guidelines.

Figure 1. Recommendations for Preventing or Treating Opioid Induced Side Effects^{1,27}

Side Effect	Recommendations
Constipation	• Prophylactic mild peristaltic stimulant in all patients. • If no bowel movement in 48 hours, increase dose of peristaltic stimulant. • If no bowel movement in 72 hours, perform rectal exam. • If no fecal impaction, provide additional therapy such as suppository, enema, magnesium citrate.
Nausea and vomiting	• May consider a prophylactic antiemetic. • Add or increase a non-opioid pharmacologic pain adjuvant (acetaminophen, NSAID). • If analgesia is satisfactory, may decrease dose by 25 percent. • May add dopamine or serotonin antagonist, metoclopramide, dimenhydrinate or scopolamine depending on cause.
Sedation	• Attempt to identify cause of sedation. • Eliminate nonessential CNS depressants. • If analgesia is satisfactory, may decrease dose by 10 to 15 percent. • Add or increase a non-opioid or non-sedating pharmacologic pain adjuvant (acetaminophen, NSAID) in order to decrease opioid dose. • May add a stimulant during the day such as caffeine.
Itching	• Consider antihistamine treatment. • Change opioid.
Hallucination/dysphoria	• Attempt to identify cause. • Eliminate non-essential CNS medications such as steroids.
Sexual dysfunction	• Reduce dose of opioid. • Erection-enhancing medications such as sildenafil. • Testosterone replacement may be helpful.

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Appendix 1.

Checklist for Prescribing Opiates for Chronic, Non-Cancer Pain

The following checklist is designed to aid primary care providers who use opiates to improve function in patients with chronic pain. Specifically, this checklist is for treating adults (18+) with chronic pain > 3 months, excluding cancer, palliative, and end-of-life care.

CHECKLIST

When CONSIDERING long-term opiate therapy

- ☐ Review patient's medical and psychosocial history.
- ☐ Review results of all physical examinations and laboratory tests, including screening assessments.
- ☐ Check that non-opiate therapies tried and optimized.
- ☐ Evaluate risk of harm or misuse.
 - Confirm that the appropriate state prescription drug monitoring program (PDMP) has been accessed.
 - Check urine drug screen.
- ☐ Obtain an informed consent.
 - Discuss benefits and risks (eg, addiction, overdose) with patient.
- ☐ Assess baseline pain and function (eg, PEG scale).
- ☐ Set realistic goals for pain and function based on diagnosis (eg, walk around the block).
- ☐ Prescribe short-acting opiates using lowest dosage on product labeling; match duration to scheduled reassessment.
- ☐ Set criteria for stopping or continuing opiates.
- ☐ Schedule initial reassessment within 1-4 weeks.

If RENEWING without a patient visit

- ☐ Check that return visit is scheduled ≤ 3 months from last visit. Schedule visit earlier than 3 months if patient is requesting a prescription refill earlier than prescription instruction/dosage.

Continuation versus Initiation - REASSESSING at return visit

- ☐ Check that non-opiate therapies optimized.
- ☐ Assess pain and function (eg, PEG); compare results to baseline.
- ☐ Evaluate progress against agreed-upon treatment for pain relief and function.
 - Continue opiates only after confirming clinically meaningful improvements in pain and function without significant risks or harm.
- ☐ Evaluate risk of harm or misuse:
 - Observe patients for signs of over-sedation or overdose risk. If yes – taper dose.
 - Check PDMP.
 - Check for opiate use disorder if indicated (eg, difficulty controlling use). If yes – refer for treatment.
- ☐ Determine whether to continue, adjust, taper, or stop opiates, and document reasoning in clinic record.
- ☐ Calculate opiate dosage morphine milligram equivalent (MME).
 - If ≥ 50 MME/day total (≥ 50 mg hydrocodone; ≥ 33 mg oxycodone), increase frequency of follow-up; consider offering naloxone.
 - Avoid ≥ 100 MME/day total (≥ 100 mg hydrocodone; ≥ 66 mg oxycodone), or carefully justify; consider specialist referral.
- ☐ Schedule reassessment at regular intervals (< 3 months).
- ☐ Patients who may need more frequent or intense monitoring include:
 - Those with a prior history of an addictive disorder or past substance abuse;
 - Those in occupations demanding mental acuity;
 - Older adults;
 - Patients with an unstable or dysfunctional social environment;
 - Those with comorbid psychiatric or medical conditions;
 - Those who are taking benzodiazepines; and
 - Those who are taking other medications that may interact with an opiate – to include at-risk alcohol consumers.

REFERENCE

EVIDENCE ABOUT OPIATE THERAPY

- Benefits of long-term therapy for chronic, non-cancer pain is not well supported by evidence.
- Short-term benefits small to moderate for pain; inconsistent for function.
- Insufficient evidence for long-term benefits in low back pain, headache, and fibromyalgia.

NON-OPIATE THERAPIES

- Use alone or combined with opiates as indicated:
- Non-opiate medications (eg, NSAIDs, TCAs, SNRIs, anti-convulsants).
- Physical treatments (eg, exercise therapy, weight loss).
- Behavioral treatment (eg, CBT).
- Procedures (eg, intra-articular corticosteroids).

EVALUATING RISK OF HARM OR MISUSE

Known risk factors include:

- Illegal drug use; prescription drug use for nonmedical reasons.
- History of substance use disorder or overdose.
- Mental health conditions (eg, depression, anxiety).
- Sleep-disordered breathing.
- Concurrent benzodiazepine use.
- At-risk alcohol consumption (eg, binge drinking).

ASSESSING PAIN AND FUNCTION USING PEG SCALE

- PEG score = average 3 individual question scores
- 30% improvement from baseline is clinically meaningful

Q1: What number from 0 - 10 best describes your pain in the last week?

0 = "no pain," 10 = "worst you can imagine"

Q2: What number from 0 - 10 describes how during the past week, pain has interfered with your enjoyment of life?

0 = "not at all," 10 = "complete interference"

Q3: What number from 0 - 10 describes how, during the past week, pain has interfered with your general activity?

0 = "not at all," 10 = "complete interference"

NOTE: Always document assessments as required by applicable law, including any applicable administrative rules or regulations.

Prescription Drug Abuse – A Law Enforcement Perspective

By Marty Jackley

Law enforcement agencies across the nation are placing significant resources toward battling the rise in prescription drug abuse. This epidemic reaches and affects a broad spectrum of individuals, including ordinary citizens with legitimate pain reduction needs.

Prescription drug abuse has proven to be very difficult to tackle, particularly due to its diverse impact. Every single economic level is at risk. It does not target a particular gender or specific age group. Easy access to these drugs remains an ongoing concern. It may be as easy as hitting mom's medicine cabinet or taking a few pills from a friend's purse. The Division of Criminal Investigation (DCI) drug diversion agents also routinely encounter the all too common practice of doctor shopping. An individual begins with a legitimate pain prescription prescribed after an accident or in relation to a chronic pain issue, but then becomes addicted to the medication. In one example, a 28-year-old single mother of three "doctor shopping" for opioids (oxycodone, hydrocodone) while pregnant, deceived medical providers, urgent care doctors and dentists into giving her pain medication because of a toothache and other injuries. She continued to use multiple locations to avoid detection. She neglected to let her obstetrics doctor know that she was using opioids during her pregnancy and failed to list these prescriptions on her disclosure forms. After delivery, her baby tested positive for opiates and was subjected to withdrawal symptoms. After her actions were reported to Child Protection, she faced allegations of obtaining controlled Drugs by deception and child abuse. This is a pattern of abuse that drug diversion agents see every day.

Health care professions are also at risk with their accessibility to these drugs while caring and administering prescribed drugs to patients. As described by a DCI drug diversion agent, "I worked a case that involved a registered nurse, who was providing liquid fentanyl for a patient using a specific dosage on a doctor ordered time schedule. The typical protocol is to have a different nurse witness the 'wasting or destruction' of the remaining liquid per hospital policy. This particular nurse 'wasted' without a witness and diverted the leftover fentanyl and injected it in her arm with a needle at home."

Hospitals, clinics and home health agencies put safeguards in place, but access to prescription drugs will always be an issue in the health care field. The pervasive nature of these drugs makes this addiction so dangerous.

Like other drug addictions, prescription drug abusers can cause pain and suffering to those around them. Maintaining the habit becomes priority in their world and their families, friends and work commitments all fall behind or can even be forgotten. In addition, the abuser's health and well-being may well be the most obvious negative effect on society. Personality changes may be the first sign that this addictive behavior is affecting the mental health and eventually impacting the brain. Opioid pain medications are often assumed to be safer than illicit drugs because they are being prescribed by a physician, but when taken in the wrong doses or for the wrong reasons, medications can be harmful to an individual's overall health.

Research suggests that prescription drug abuse can lead to even more serious drug addictions, including involving heroin. South Dakota has been fortunate that we have not experienced a large number of heroin cases thus far, unlike other areas of the nation. As President of the National Association of Attorneys General, I have had the opportunity to talk with several of my counterparts across the nation who are dealing first hand with the effects of heroin. Our statewide drug task forces are closely watching activities that might indicate an increase in heroin use. Wisconsin and Ohio have described the heroin resurgence as epidemic. As much as 75 percent of those using heroin claimed to have been addicted to an opioid pain medication prior to their heroin use. The correlation between prescription drug abuse and heroin is alarming. In 2013, 32 people died in South Dakota of accidental overdoses and 42 died in 2014. The Attorney General's Office sponsored legislation in 2015 that would enable all first responders to carry naloxone, a medicine to reverse the effects of opioid overdoses. South Dakota has not experienced as many opioid overdoses as other states, but having the naloxone available is a cost-effective way to save lives, especially to our rural first responders.

So how do we, as law enforcement, deal with these addiction issues? In 2010, the Prescription Drug

Monitoring Program (PDMP) was passed into law at the request of the attorney general. The purpose of this voluntary program was to improve patient care by providing physicians and pharmacists with a controlled substance dispensing history for their patients. Pharmacists' and physicians' voluntary participation is helping prevent and reduce prescription abuses and enhance public health and safety. Online profile queries have steadily increased since the program's implementation in July 2011. The first full year in 2012 saw 14,689 queries, followed by 40,165 queries in 2013, 59,557 queries in 2014 and 78,588 queries through November 2015. These numbers indicate that the PDMP is being utilized as anticipated and each year we are seeing greater participation amongst pharmacists and prescribers.

In addition to the PDMP, several law enforcement agencies across the state have helped reduce drug diversion by offering prescription drug take-back drop off locations. Individuals who have accumulated unwanted, unused prescription drugs now have options to safely dispose of those medications.

Addressing the addiction and putting an end to the cycle of criminal behavior is crucial in the successful recovery of any drug addict, including prescription drug abusers. Drug courts and alternative sentencing are innovative options that have developed as a result of nonviolent offenders populating prisons and jails. The first drug court in South Dakota was established in 2007 and has grown to seven covering different jurisdictions statewide. South Dakota drug courts are all post-plea and designed to help those battling underlying addiction issues. Keeping the offenders out of jail, addressing the addiction and getting them back into society can have a long term positive impact on the user's lives, their families and their employers.

Law enforcement will continue diversion efforts and focus on finding ways to help those afflicted with addiction. Assisting the abusers to find lifestyles free from drug abuse, addiction and crime is the ultimate goal for all those affected.

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No Pain, No Thebaine: Opioids in the Emergency Department

By Benjamin C. Aaker, MD, FACEP; Collin Michels, MS III; and
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Abstract

Background: Opioid misuse has reached epidemic levels. Forty-six people die every day in the U.S. from prescription opioids. Opioid-taking patients cost emergency departments (EDs) and society more than non-opioid-taking patients. Many patients prescribed opioids will go on to become addicted, yet we find it much easier to prescribe these medications than explain to the patient why they are not indicated. The ED takes care of many of these people, whether by prescribing opioids, or treating opioid misuse. We examine the ED's role in this epidemic.

Methods: Data were obtained through literature search and the authors' personal experiences treating patients in the ED. The search was limited to specific harm to patients, hospitals, and society caused by opioid misuse, physiology of pain, and possible methods to manage the problem.

Conclusions: The ED clearly deserves some of the blame for the opioid epidemic. A consistent reinforcement of appropriate expectations for management of chronic pain across the medical spectrum will do much to manage the problem. We offer some ways to improve the problem, including pain contracts, pain guidelines, alternative therapies, pain management referrals, high-risk patient profiles, legislation, and drug take-back programs.

Introduction

A young man walked into the local emergency department (ED) on a Friday afternoon complaining of wrist pain. The pain started three years ago when he was drilling a well. He was struck by a wrench attached to a drill. The ED radiographs were negative. He was splinted and given a 30-day course of hydrocodone/acetaminophen tablets. He continued to have pain and was diagnosed with reflex sympathetic dystrophy. The doctor prescribed long-term oxycodone/acetaminophen.

Two days ago he ran out of his pain pills and his pain specialist was unreachable. The ED physician was courteous but firm. He refused to refill the oxycodone/acetaminophen, instead recommending an intramuscular dose of ketorolac and a short oral course of the same.

Later that evening, the patient drove to the next closest ED. He complained that he had fallen that night and struck his wrist on the ground. Radiographs were performed and were negative. He complained of an allergy to ketorolac and hydrocodone, but oxycodone worked for him in the past. The patient was prescribed a two-week supply of oxycodone/acetaminophen and left the ED happy.

The Problem

Every day in the U.S., 46 people die from an overdose of prescription opioids.¹ South Dakota fares better, with one death per week.² Despite these deaths, almost 2 million people over age 12 in the U.S. use prescription opioids non-medically.³

Of patients prescribed chronic opioid therapy (COT), 11.5 percent develop aberrant drug-related behaviors, which include: demand for a specific opioid, acquisition of opioids from someone other than a physician, and repeated visits to the ED. Three percent of patients taking COT will become addicted to opioids.⁴ COT patients can suffer from constipation, nausea, bladder retention, sedation, and opioid-induced hyperalgesia (a condition characterized by pain to stimuli that would not normally be considered painful). Opioids are well known to have adverse interactions with many other drugs.

Opioid prescriptions have an impact on the ED. Patients who take opioid medications for over 90 days are more likely to have a visit to the ED.⁵ Visits for opioid-related complications amount to over 500,000 visits to U.S. EDs annually. In the ED, opioid abusers cost on average \$14,054 more per year than non-abusers,⁶ and almost one-quarter of them have no form of insurance.⁷

The prescription of opioids may also expose the provider to civil liability. Increased liability may drive physicians to order more testing in order to protect themselves from a lawsuit. These tests translate into increased health care expenses. In May 2015, the West Virginia Supreme Court ruled a physician can have liability for patient addiction and the subsequent addiction-related damages.⁸ The cost of opioid misuse to society in 2007 was almost \$56 billion. This included \$25 billion in health care costs.⁷

Dollars aside, it is unlikely that our society will be able to manage the problem of opioid misuse without managing our expectations: the patient afflicted with chronic pain should not seek to eliminate pain but rather seek to manage pain. The society afflicted with opioid misuse should not seek to eliminate opioid misuse but rather seek to manage misuse.

The Cause of the Problem

It is easy for us to blame the patient for aberrant drug behaviors. The public may perceive that using prescription opioids non-medically is safer than using illicit drugs. Blaming the patient results in laws which punish aberrant behavior rather than laws that encourage treatment.

Society as a whole bears some of the blame. We have the expectation that we can be made to be pain-free. This expectation may cause patients to demand a particular treatment, even if it is unsuited to their particular situation. In order to produce a satisfied patient, providers may acquiesce to these demands.

Many health care providers drive the expectation to live pain-free. The opioid is the quick and easy relief. The patient leaves the department happy and gets a quick fix. In 10 minutes, the provider can feel like a hero and be relieved that a 30 minute argument about the proper treatment strategy was avoided. We give patients the expectation that we will be able to take their pain away. The reality is that with a high enough dose of opioids, we can make any patient ignore the pain for a while. The patient then believes that this medication was beneficial for them and seeks more of the same drug. George R. Hansen, MD, in his article, "The Drug-Seeking Patient in the Emergency Room," states: "When used for chronic pain, opioids can reinforce behavior that leads to their administration... when opioid use is made contingent on the experience of pain, opioids may reinforce the perception of pain... Rapid-onset opioids, paired with the experience of pain, are greater reinforcers for pain and medication-taking than are slow-onset medications, and are more likely to increase the patient's perception of pain."⁹

Opioids create a euphoric effect, leading some patients to take them for non-pain reasons. Opioids interact with the mu receptor our bodies use for pain control leading to down regulation of these mu receptors. This in turn leads to less effective pain control resulting in need for increased doses to obtain similar pain relief. Thus, we reward the patient's perception of pain with the administration of an opioid. If we could educate ourselves on the physiology of our patients' pain, we may be able to tailor our treatment to better manage it.

The Physiology of Pain

Clinicians routinely divide pain into acute and chronic pain and have attempted to classify different types of pain. Unfortunately, agreement has not been reached. Acute pain is caused by a specific offending agent¹⁰ that we should be able to discover. The pain resolves when the agent is removed, such as a fracture healing. Chronic pain, on the other hand, has no specific nociceptive stimulus. Persistent pain syndromes are thought to result from changes to the nervous system and are termed neuropathic pain.

Neuropathic pain is typically difficult to control and patients have often failed multiple therapies. Compounding this issue, randomized controlled trials have shown that patients with neuropathic pain continue to have moderate to severe pain on average despite taking prescribed medications for their pain.¹¹ Types of neuropathic pain that may be encountered in the ED include but are not limited to the following: complex regional pain syndrome, severe diabetic peripheral neuropathy, and post-herpetic neuralgia. Recommendations for rescue treatment of breakthrough chronic pain are multimodal and dependent on patient presentation.¹² It is easy to state that management of chronic pain is not the role of the ED but rather best done by pain management experts who have guidelines that utilize cognitive and behavioral interventions along with drug therapy. It is more difficult to implement these interventions in practice.

The Barriers to Change

Opioids work very well for acute somatic pain. It seems reasonable that opioids would also help with chronic pain. Clinicians know that pain is often under-treated. Pain as the "5th vital sign" originated in the Veterans Health Administration hospital system in the 1990s and later became a Joint Commission standard. It requires that pain be assessed on each patient, by each provider, during each shift. The Pain as the 5th Vital Sign Toolkit¹³ states that a 0 to 10 scale should be documented along with a

comprehensive pain assessment. While the goal of improved treatment to pain is laudable, Pain as the 5th Vital Sign was found to yield no improvement in pain management or quality of care.¹⁴

As providers, we feel we have the training and experience to detect which patients are "drug-seekers" without using any outside help. Unfortunately, classically drug-seeking behaviors, such as a request for a specific medication by name, reporting 10 or greater out of 10 pain, and reporting a chief complaint of back pain, headache, or dental pain, are only exhibited 30 percent of the time.¹⁵ It is unlikely providers can detect the majority of people abusing prescription opioids by historical methods alone.

It is not just provider beliefs that cause the problem. Laws such as the Emergency Medical Treatment and Labor Act (EMTALA) are misinterpreted and have a large influence on the ED. Some interpret EMTALA such that the provider has a legal obligation to relieve pain. In reality, EMTALA requires that patients with an emergent condition be given a medical screening examination regardless of ability to pay. Once the provider is satisfied that an emergency medical condition does not exist, the provider's responsibility under EMTALA (with regards to pain) is ended.

Lack of finances drives patients to the ED. Patients without health insurance can find it more difficult to obtain an appointment with their primary physician or pain specialist. Many of these patients will find themselves with nowhere to turn but to the ED. ED providers are forced to make a decision regarding care with little data, or turn to expensive testing.

Inconsistency in treatment can lead to inappropriate expectations. Physicians do not seem to agree on which patients require opioid therapy.¹⁶ The patient with chronic pain can simply return to the ED or clinic at a different time to find a favorable provider. Privacy rules make identification of abusers more difficult.

Suggestions for Change

The following is a short list of possible changes that may have an impact. Practically speaking, not all changes will work for every state or provider. All offer some benefit, but some have an impact on the doctor-patient relationship or patient privacy that may not be acceptable.

Pain Contracts

A pain contract is a document signed by both patient and provider stating each person's rights and responsibilities regarding pain control. Common points include:

- I will only obtain pain medication from a single provider;
- I will fill my pain medication from a single pharmacy only;
- I will tell all other providers I have a pain medication agreement; and
- I will submit to drug testing when asked to do so.

The South Dakota State Medical Association (SDSMA) provides a sample pain contract with its white paper *Opiate Analgesics for Chronic Non-Cancer Pain*.¹⁷

About 60 percent of patients adhere to pain contracts.¹⁸ These contracts are helpful for patients invested in using opioids properly; they do not limit misuse of opioids in those who don't have a contract or those who intentionally choose to misuse opioids.

Pain Guidelines

Medical associations, hospitals/health systems and state medical boards might all publish guidelines. The SDSMA recently published a white paper that gives evidence-based guidance for providers.¹⁷

The authors have found the American Academy of Emergency Medicine's *Guidelines for the Treatment of Non-Cancer Related Pain* to be beneficial in the ED setting.¹⁹ Some highlights of these guidelines are:

- Provide a three-day course or less of opioids for acute pain;
- Address exacerbations of chronic pain with non-opioid analgesics or other non-pharmacological therapies;
- Refrain from initiating treatment with long-acting opioid formulations;

- Refrain from replacing lost, stolen, or destroyed opioid prescriptions; and
- Refrain from refilling chronic opioid prescriptions.

Pain treatment guidelines have no effect on ED patient volume but are associated with an increase in both patient and provider satisfaction.²⁰

Alternative Treatments to Opioids

Non-chemical alternative treatments are gaining in popularity. These treatments are thought to lack many of the side effects seen in opioids. Rather than seeking to mask our bodies' pain control mechanism, these methods seek to work in synergy with it. Some possible strategies include acupuncture, exercise, biofeedback, massage, transcutaneous electrical nerve stimulation, and psychological interventions. Scientific and efficacy data are lacking on many of these treatments.

The specific treatment strategies for each non-opioid drug are outside the scope of this article; however, we list some possible treatments for each condition (Table). The table is not meant to be exhaustive and some drugs could be listed in more than one class. Each treatment should be tailored to the individual patient's medical history.

A meta-analysis of 41 randomized trials concluded that while strong opioids such as oxycodone and morphine were significantly better in patients' reported pain-relief, nonsteroidal anti-inflammatory drugs such as diclofenac were either no different or significantly *more effective* in functional outcomes than opioids.²¹

Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMPs) allow access to prescription or pharmacy records. PDMP access does have an effect on prescribing patterns 41 percent of the time. PDMPs are associated with decreased drug diversion and doctor shopping²² but they don't seem to have an effect on opioid overdose rates.²³

Pain Management Specialist Referrals

Diagnosing and treating a patient with chronic pain is time-consuming and difficult. Comprehensive pain programs can be more efficacious and cost-effective than traditional

Table

Class	Drug
Non-Steroidal Anti-inflammatory Drugs	ibuprofen, naproxen, ketorolac, etodolac, diclofenac
Anticonvulsants	gabapentin, carbamazepine, pregabalin
Tricyclic Antidepressants	nortriptyline, amitriptyline
Anticholinergics	prochlorperazine, metoclopramide, diphenhydramine
Neuroleptics	droperidol, haloperidol, quetiapine
Topical Anesthetics	lidocaine (intra dermal or patch), bupivacaine
Ergotamines	dihydroergotamine (DHE), Cafergot (ergotamine/caffeine)
Triptans	sumatriptan, zolmitriptan
Anesthetics	nitrous oxide
Muscle Relaxants	diazepam, methocarbamol
Analgesic	acetaminophen

medical treatment.²⁴ These programs utilize a multidisciplinary approach to pain management rather than solo drug therapy.

High-Risk Patient Profiles

Medical providers have searched for a tool to help them identify those at highest risk for opioid misuse. We offer two of the many tools:

- Opioid Risk Tool (ORT) has 11 questions and can be administered and scored in less than one minute. Researchers used the C-statistic (probability that predicting the outcome is better than chance) to validate the tool and found $c = 0.82$ to 0.85 .²⁵
- Screener and Opioid Assessment for Patients with Pain – Revised (SOAP-R) was found to have sensitivity 91 percent and specificity 67 percent.²⁶ While it may perform slightly better than the ORT, the 24 questions required takes about five minutes to administer and may prove difficult to do so in a busy clinic or ED environment.

When used by an experienced provider prior to beginning a course of opioid medication, these tools may limit misuse.

Laws

Mandatory Identification Laws require or give discretion for a pharmacist to check identification before dispensing opioid prescriptions. Currently South Dakota does not have such a law.

Doctor Shopping Laws target patients who obtain multiple prescriptions from different providers without the providers' knowledge of the other prescriptions. South Dakota has enacted such a law (SDCL 22-42-17).

Some states have allowed opioid antagonists such as naloxone to be administered by personnel other than a physician. These laws are designed to increase availability and speed of administration of opioid antagonists in an opioid overdose. With the urging of the SDSMA, South Dakota passed a law in 2015 which allows trained first responders to administer naloxone under a standing physician order and provides immunity from civil liability to prescribers, providers and employers.

Some states have attempted to provide a legal shield to those who help assist in an emergency. Also known as Good Samaritan Laws, these laws provide decreased penalties or immunity from prosecution to those who are illegally under the influence of a controlled substance but render assistance in an emergency. One such law was enacted in Washington state in 2010. This state saw a 38

percent increase in persons willing to call 911 during an overdose.²⁷ While legal protections for Good Samaritans currently do not exist in our state, in 2016 the South Dakota legislature passed legislation to allow physicians the ability to prescribe naloxone to individuals and/or family members and friends of individuals at risk of a drug overdose. The SDSMA played a key role in the introduction of that legislation.

Other laws include tamper-resistant prescription forms (South Dakota has such a law), physical examination requirements (South Dakota has no law), and dosage and time limitation for controlled substances (South Dakota regulates refills only).

Drug Take-Back Programs

These programs properly dispose of unused prescription drugs. Many law enforcement agencies accept prescription drugs for disposal. Each year the U.S. Drug Enforcement Administration hosts the National Prescription Drug Take-Back Day.

Conclusion

A young man walked into the ED on a Monday afternoon. He had been diagnosed with chronic pain from a prior injury. He was currently under treatment by a local pain specialist. The patient had been given physical therapy and clear instructions on the use of his pain medication but on Monday, the pain flared. He had signed a pain contract and it was available on the ED's computer system. The ED provider accessed this along with the state's PDMP website. The ED physician performed a thorough examination, avoided expensive testing, and diagnosed the patient with an acute exacerbation of chronic pain. He kindly informed the patient of the ED policy for opioid administration in the ED and treated the patient with an NSAID and a local injection of an anesthetic medication. He explained to the patient the expectation that these medications would help but not eradicate the pain. The ED physician advised the patient to call the specialist in the morning to arrange for follow-up. The patient left the ED satisfied with his treatment and able to drive home.

Opioid medications have a real benefit to patients. They provide relief of acute somatic pain. Many of the problems of opioids arise when acute treatment becomes chronic; the longer a patient takes opioids and the higher the dose, the more risk of ill effects. While opioids are good for helping patients ignore pain centrally, they do little to improve the patient's ability to function in society. Opioids may be beneficial for acute pain, but their use in

treating chronic pain leads to extensive side effects, tipping the scales against their favor. We surmise that a person with pain who can function would be preferable to a patient with no pain but cannot function.

The ED is certainly a place where opioids can be misused. It is easy to reach for the prescription pad and prescribe opioids. This would seem to make for a satisfied patient, happy government regulators, and a quick encounter. But this activity causes more side effects, more unscheduled visits, greater misuse, and higher mortality.

Truly, a multidisciplinary approach is necessary. The ED ideally only sees a patient once but must have adequate follow-up in its community. Patients who are not

adequately treated in the outpatient setting will likely find themselves in the ED. As providers, we need to be consistent in our application of science. Once we agree on this, we can give our patients reasonable expectations regarding prognosis and treatment. We should promote the expectation that the treatment for non-cancer-related chronic pain will be the same whether in the primary care clinic, specialty clinic, or in the ED. State regulators can also help by passing sensible laws to prevent prescription drug misuse but not impact the patient-doctor relationship. Any regulation should focus on treatment rather than punishment. After diagnosis, any encounter in the clinic or ED should focus on management of pain rather than its elimination.

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Cannabis and Medicinal Properties

By Bertha K. Madras, PhD

Terminology

Marijuana. The term marijuana is used instead of cannabis. Its use for medicinal, ritual or recreational purposes results from the actions primarily of cannabinoids in the cannabis plant.

Cannabinoids. Cannabinoids are basically derived from three sources: (a) *Phytocannabinoids* are cannabinoid compounds produced by plants *Cannabis sativa* or *Cannabis indica* or *Cannabis ruderalis*;¹ (b) *Endocannabinoids* are neurotransmitters produced in the brain or in peripheral tissues, and act on cannabinoid receptors (CB); altering metabolism or CB function can affect cannabinoid function. (c) *Synthetic cannabinoids*, synthesized in the laboratory, are structurally analogous to phytocannabinoids or endocannabinoids and act by the same biological mechanisms.

A Focus on Marijuana and Not Isolated Cannabinoids

The evidence presented on potential medical uses and risks of marijuana in humans focuses on unprocessed, botanical or dispensary marijuana and not isolated cannabinoids, some of which are medically approved following quality clinical trials. The restricted review is based on the use of whole plant or concentrated marijuana dispensed in various preparations, for treating illnesses or symptoms. The plant contains at least 750 chemicals, among which are some 104 different cannabinoids.^{2,3} Boundaries between marijuana and isolated cannabinoids are based on the following considerations: (a) to avoid confusing whole plant with approved, isolated cannabinoid terminology; (b) the composition, purity, bioavailability, pharmacokinetics and pharmacodynamics of botanical marijuana (delivered via smoke inhalation, vaporization, liquids, foods, creams) differs from extracts or purified individual cannabinoids delivered orally; (c) the bioavailability of active cannabinoids in marijuana, e.g. delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are unpredictable because of their various concentrations in dispensary marijuana, differences in smoking, vapor inhalation or ingestion between users, form of product, and types of delivery systems. In contrast, a fixed, known

oral dose of a cannabinoid can yield relatively predictable levels in plasma or whole blood samples; (d) to avoid extrapolating conclusions drawn from meta-analyses and primary sources reporting efficacy from randomized controlled trials (RCT) of purified and medically approved cannabinoid formulations at known, fixed doses. Approved cannabinoids are oral or sublingual spray preparations, whereas marijuana is used predominantly by smoking or vaporizing, a rapid form of brain delivery acknowledged to be a route of administration with higher addiction potential (see Pharmacokinetics, below); (e) to avoid extrapolation and appropriation of safety data generated from isolated and medically approved cannabinoids (with known, relatively low doses) to whole plant marijuana, for which there are no guidelines for doses and no packet insets providing adverse effects, precautions, or warnings.

As the concentration of THC or CBD in marijuana is not fixed, with THC levels rising and CBD levels declining, increasing, adverse events such as psychosis, anxiety, hallucinations are problematic. A description of cannabinoids that have undergone rigorous approval processes as legitimate medications (with reproducible composition of matter, purity and stability, fixed doses and known pharmacokinetic properties, dose-response efficacy, safety testing, documented side effects, other criteria), is beyond the scope of this summary. At times, information on specific cannabinoids may be included, if comparisons with botanical marijuana are instructive. Approval of marijuana to treat qualifying conditions is driven essentially by small RCT, surveys of low or moderate quality, self-reports, preclinical studies in vitro or in animals, testimonials, anecdotes delivered in state houses or court rooms, ballot or legislative initiatives, and by advocacy groups. This approach has circumvented the rigorous Food and Drug Administration (FDA) drug approval process and is akin to a mostly unregulated alternative treatment/herbal remedy market.

THC and CBD are instructive. The isolation and purification of THC and CBD from the marijuana plant have revealed distinctions in the mechanisms of action of

THC, its psychoactive, intoxicating, and addictive properties and the non-psychoactive CBD; CBD can oppose some of the memory and behavioral impairment of THC, CBD does not impair memory as does THC, THC can promote psychotic symptoms, whereas CBD may suppress them; CBD and other cannabinoids also contain potential therapeutic benefits, not as clearly shown with THC, the main psychoactive constituent of marijuana.^{4,5,6,7,8,9} Accordingly, their targets, therapeutic indications and benefits are likely to be very different.¹⁰ This compelling evidence supports the need to continue the process and methodologies of modern medicine for the marijuana plant. Since the discovery of its most active chemicals from the 1940's to 1960's, the evolution of marijuana research is following the same principles as those used for nearly 200 years in developing drug therapies based on botanicals^{11,12} to isolate pure cannabinoids from marijuana and evaluate them individually, to determine whether they have medicinal value, synergistic or opposing effects, at safe and effective doses, through an evidence-based process designed to protect patients and the general public.

The Marijuana Plant and History of Medical Use (Abbreviated)

Marijuana extracts were listed in the British, and later in the U.S. Pharmacopeia (1850), for sedative and anticonvulsant effects. However, within a century, the British initially, and then the U.S. Pharmacopeia removed marijuana listings (1932, 1941, respectively), as a result of the variable composition of plant preparations, short shelf-life, unpredictable doses, and overshadowing by newer, more targeted, effective pure drugs prescribed at known and reliable doses, with doses that did not elicit overlapping psychoactive and therapeutic responses.⁴ Subsequently, the risks of abuse, intoxication, and other negative consequences of marijuana consumption led to restrictive laws prohibiting the growth, possession and consumption of marijuana. The movement to revive marijuana as a medicine is driven by multiple factors, many beyond the domain of science.¹³ One propellant of the movement is the inadequate relief of current approaches to address a number of debilitating chronic diseases or symptoms, including multiple sclerosis, Crohn's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, cancer, seizure disorders, arthritis, spasticity, chronic pain, inflammation, cachexia. These and other medical conditions are frequently cited by proponents of medicinal marijuana.

Troublesome and critical questions persist: is marijuana a

safe and effective medicine for one or all of these conditions? For all people of all ages? Before addressing this central question, it is essential to survey endocannabinoid biology and function, as it is the foundation of the ever-expanding claims for marijuana use in numerous medical conditions.

Marijuana Chemistry, Preparations

Known chemistry of *Marijuana sativa*. The principal cannabinoids in the marijuana plant include THC, CBD, and cannabiol (CBN). THC is the primary psychoactive compound, with CBD, a minimally psychoactive compound, ranking second. THC is found at higher concentrations than CBD, unless the ratio is deliberately altered by genetic selection. The known chemical composition of *Marijuana sativa* is constantly changing. New non-cannabinoid and cannabinoid constituents in the plant are discovered frequently. From 2005 to present, the number of cannabinoids identified in the whole plant increased from 70 to 104, and other known compounds in the plant increased from approximately 400 to approximately 650.^{2,14,15} THC levels are also shifting, as breeding of different strains are yielding plants and resins with dramatic increases in THC content over the past decade, from approximately 3 percent to 12-16 percent or higher.^{16,17,18,19} In some marijuana preparations, THC levels have risen to radically higher levels, by concentrating processes that yield levels approaching 80 percent THC.^{20,21} Special strains have also been developed to raise the ratio of THC to CBD, so as to minimize putative THC antagonism by CBD.²² In an unregulated environment, other factors such as soil quality, bacterial and fungal contamination, the use of herbicides, pesticides, insecticides, water, light, soil availability or quality, temperature, bacterial or viral contamination, animal waste, insects, toxic chemicals, active compounds, heavy metals, bear on marijuana quality.²³ Preclinical research has shown that a number of non-psychoactive phytocannabinoids elicit pharmacological responses of therapeutic interest. For example, CBD has putative therapeutic applications for treating psychosis, affective and seizure disorders, inflammation, and neurodegenerative diseases. CBD has a good safety profile in humans. Other plant cannabinoids, such as delta-9-tetrahydrocannabivarin, may also be prove therapeutic for epilepsy or obesity. Other plant cannabinoids, such as delta-9-tetrahydrocannabivarin, may also be prove therapeutic for epilepsy or obesity.^{24,25,26}

Dose and dose delivery via different routes (smoking, vaporizers, edibles). Marijuana is consumed by various

routes, with the most common route smoking,²⁷ followed by vaporization, and then by the oral route. Marijuana products may be taken by ingesting edibles, liquids, via sublingual or rectal administration, via transdermal delivery, eye drops, creams and aerosols. Inhalation by smoking or vaporization releases maximal levels of THC into blood within minutes, peaking at 15 to 30 minutes, and decreasing within two to three hours. Even with a fixed dose of THC in a marijuana cigarette, THC pharmacokinetics and effects vary as a function of the weight of a marijuana cigarette, THC potency in the cigarette, its preparation, the concentration of other cannabinoids, the rate of inhalation, depth and duration of puffs, volume inhaled, extent of breath-holding, and dose titration.^{27,28} An extensive comparison of smoke (mainstream and sidestream) generated by igniting marijuana and tobacco cigarettes, showed markedly qualitative similarities in specific compounds (e.g., ammonia, carbon monoxide, among others), and also significant quantitative differences.²⁹ The presence of known carcinogens and other chemicals in mainstream smoke of marijuana cigarettes and implicated in respiratory diseases, is an important consideration when evaluating the safety and risks associated with marijuana smoking.³⁰ Lower temperature vaporization of marijuana has been postulated as safer than smoking, as it may deliver fewer high molecular weight components than smoked marijuana.³¹ Vaporization reduces the characteristic odor of marijuana smoke, enabling diminished awareness by others. Combined with alcohol, vaporized marijuana yields higher maximum concentrations of blood THC (than without alcohol) possibly explaining why performance is more impaired if marijuana is combined with alcohol.^{32,33} Hashish oil, a solvent-extracted liquid is consumed by smoking or inhalation, vaporization or as a food additive.³⁴ Users report more addictive behaviors and withdrawal symptoms with the high THC levels in this preparation.

Oral ingestion from edibles is a slow, absorption process and varies with the ingested matrix, as bioavailability is low (10 to 20 percent). Nevertheless, this route does not result in a loss of pharmacological activity, because the major first-pass metabolite, 11-OH-THC, is also psychoactive. Oral ingestion delays the psychoactive effects to 30 to 90 minutes, with peaks at two to three hours and effects lasting for longer periods of time (four to 12 hours), depending on THC levels. Smoking multiple marijuana cigarettes or chronic long term use leads to higher maximal concentrations, longer duration in blood, and longer biological half-life, compared with smoking a

single cigarette or infrequent smoking. Chronic frequent marijuana smokers exhibit extended detection windows for plasma cannabinoids, reflecting a large cannabinoid body burden. Lipophilicity of THC accounts for its accumulation after chronic repeated use.^{35,36,37,38,39} Metabolic elimination of THC is much slower after years of heavy marijuana use and is detectable in blood for 30 days or longer.^{40,46,47}

Cannabinoid Biology, Signaling in Brain and Body

From an evolutionary perspective the cannabinoid signaling system is ancient, and found in invertebrates and advanced vertebrate organisms.^{41,42} The endocannabinoid system has four main components: (1) G protein-coupled cannabinoid CB1 and CB2 receptors, (2) endogenous endocannabinoids that target these receptors, and possibly other receptors, (3) enzymes that catalyze endocannabinoid biosynthesis and metabolism, and (4) mechanisms involved in cell accumulation of specific endocannabinoids.

Cannabinoid receptors: distribution, regulation, function.

The CB1 receptor is expressed in the brain and peripheral tissues. In both locales, it has multiple functions.⁴³ In brain, it is the most abundant of the G-protein coupled receptors, and mediates most, if not all the psychoactive effects of THC in marijuana. Its brain distribution is strikingly consistent with the pharmacology of marijuana: CB1 receptors are enriched in the cerebellum (cognition, coordination), hippocampus (learning and memory), cortex (cognitive function, executive function and control, integration of sensory input), basal ganglia (motor control, planning) ventral striatum (prediction and feeling of reward), amygdala (anxiety, emotion, fear), hypothalamus (appetite, hormone levels, sexual behavior), brain stem and spinal cord (vomiting, pain).^{44,45,46,47,48} CB2 receptors are predominant in the periphery, on immune cells, hematopoietic systems and other locales. There is evidence of CB2 receptor expression in brain.^{49, 50,51} In the brain, CB2 receptors also modulate the release of chemical signals primarily engaged in immune system functions (cytokines, immune cell migration). CB2 receptors are of considerable interest because THC activation of CB2 does not produce psychoactive effects, as does THC on the CB1 receptor. Accordingly, it is a promising target for therapeutics that may circumvent the adverse effects promulgated by drugs (marijuana or THC) that engender psychoactive effects via CB1 receptors.

Endocannabinoids and signaling. Endocannabinoids play a fundamental role in regulating pleasure, memory, thinking, concentration, body movement, awareness of time,

appetite, pain, and sensory processing (taste, touch, smell, hearing, and sight). Endocannabinoids acting at CB1 receptors (and possibly CB2 receptors) modulate and “fine-tune” signaling in most brain regions, to enable the brain to adapt to signals generated by multiple sources.

Function of the endocannabinoid system in the brain.

Understanding the multiple functions of endocannabinoid signaling in the brain offers insight into the pharmacological effects of marijuana and other exogenous cannabinoids, their therapeutic potential and undesirable adverse effects. Brain development, neurogenesis, psychiatric disorders: endocannabinoid signaling is crucial for brain development, and guides neural stem cell survival and proliferation, cell fate decisions and the motility and differentiation of ensuing neuronal and glial cells.⁵² Developmental endocannabinoid signaling, from fetus to young adult, may be susceptible to marijuana use during pregnancy and adolescence, possibly affecting brain structure and function. Endocannabinoids and marijuana-altered endocannabinoid signaling may contribute to neuropsychiatric diseases of developmental origins and in which modifications to signaling have been observed: autism, schizophrenia, bipolar disorder and depression. The central role of the cannabinoid system in promoting adult neurogenesis in the hippocampus and the lateral ventricles provides insight into the processes underlying post-developmental neurogenesis in the mammalian brain. Both THC⁵³ and CBD⁵⁴ inhibit neurogenesis in adolescent or adult rodent brain, a process of potential relevance to a wide range of marijuana-induced adverse events. Cannabinoids and CB1, CB2 receptors display neuroprotective effects in the brain by preventing or decreasing the severity of damage resulting from mechanical, blood flow, or other forms of injury. Genetic ablation of the CB1 receptor exacerbates ischemic stroke,⁵⁵ with CB2 agonists providing anti-inflammatory protection and CB1 activation promoting hypothermia. The use of marijuana for this purpose is compromised by psychoactive effects and the development of tolerance to its neuroprotective effects. The endocannabinoid system contributes to olfactory, auditory and pain sensations. A review of these other functions is beyond the scope of this summary but readers are referred to an excellent overview.⁵⁶ There is extensive anatomical overlap of the opioid and cannabinoid receptor systems, and it appears probable that functional interactions between them occur in the production of analgesia. A number of nuclei in the medulla are involved in the regulation of appetite and nausea. These nuclei coordinate sensory input from the

brainstem, vagal complex, vestibular organs, and peripheral organs. Endocannabinoids and CB1 agonists inhibit vagal fibers to promote eating and CB1 antagonists to decrease or inhibit food intake.⁵⁷ Endogenous and exogenous cannabinoids, including marijuana and THC affect sleep patterns and promote sleep. The endocannabinoid system has mood elevating, anti-depressant and anxiolytic effects. The anxiolytic response to marijuana is biphasic, implying that marijuana dosing is a critical factor in minimizing risk of anxiety, depression and maximizing benefit.^{58,59,60} Yet, marijuana at high doses, possibly by down-regulating CB1 receptors, increases the risk for depression or anxiety. The endogenous cannabinoid system inhibits seizure susceptibility. Marijuana has antiseizure activity. However, if the dose of THC is high or marijuana is consumed by susceptible individuals, THC may promote seizures. CBD has therapeutic potential as antiepileptic drug without the psychoactive effects, or potential for pro-seizure activity of whole plant marijuana.^{61,62} The endocannabinoid system plays a complex role in regulating motor pathways, which conceivably are relevant to symptomatic relief, or to addressing the underlying pathology in a wide range of neurological diseases characterized by motor impairment.⁶³ CB1 receptors are abundant in brain regions that regulate motor function and coordination, including the basal ganglia, cerebellum. CB1 receptors are down-regulated in several neurological conditions.⁶⁴ Endocannabinoids apparently facilitate various forms of learning and memory processes in a number of brain regions. The endogenous cannabinoid system is also implicated in extinguishing learning of aversive situations.^{65,66,67} THC and marijuana decrease working memory, apparently by actions in the hippocampus, a brain region critical for learning and memory. The memory decrements induced by THC or marijuana resemble hippocampal lesions. These impairments may result from suppression of glutamate release in the hippocampus, which is responsible for the establishment of synaptic plasticity.

Function of the endocannabinoid system in peripheral tissues. Endocannabinoid signaling systems are found nearly ubiquitously in the peripheral tissues, with their distribution possibly accounting for the myriad of effects and potential medical applications of cannabinoids. This summary is based on a recent review.⁶⁸ Differences in CB1 and CB2 receptor function in the body is a focus of this segment, because THC in the marijuana plant activates both CB1 and CB2 receptors and could have detrimental effects in tissues in which CB1 receptor activity may contribute to pathophysiological states. CB1 and CB2

receptors are highly expressed on enteric nerves and on enteroendocrine cells (CB2) throughout the intestinal mucosa, on immune cells (CB1 and CB2), and enterocytes (CB1 and CB2). Virtually all gut functions are regulated by endocannabinoids, critical for CNS control of its metabolic and homeostatic functions. CB1, CB2, endocannabinoids and their enzymes are present in cardiovascular tissues and may contribute to the development of common cardiovascular disorders. An acute action of marijuana is mild tachycardia, with increases in cardiac output and increased myocardial oxygen requirement. Case reports of cardiovascular side effects of THC/marijuana have been reported and it is essential to proceed cautiously with marijuana and other cannabinoids in susceptible individuals. Cannabinoid receptor expression is normally low in liver, with CB1 and CB2 receptors acting in opposite directions: CB2 receptors mediate several biological functions in various types of liver cells, and CB1 blockade contributes to beneficial metabolic effects. CB1 expression increases in pathological states, promoting fibrogenesis, steatosis, and the cardiovascular complications of liver disease. In contrast, CB2 is protective, reducing these indices of liver dysfunction. Endocannabinoids modulate the functional activities of immune cells, largely through CB2 receptors, providing novel targets for therapeutic manipulation. Endocannabinoid signaling (largely through CB2 receptors) contributes to regulating energy metabolism in muscle and the formation of new muscle fibers. Endocannabinoid signaling, primarily mediated by the CB2 receptor regulates all critical stages of pregnancy and affects pregnancy events. Signaling is also involved in the preservation of normal sperm function, and thus male fertility.

Marijuana Toxicity in Humans

The primary risks of using marijuana have been discovered by investigating users of marijuana for recreational purposes. Few studies have reported on long term consequences of marijuana if used for medical purposes, although there may be few differences in response in the two cohorts as the therapeutic and psychoactive doses overlap extensively. Marijuana engenders acute pharmacological effects, longer term health risks for the brain, body and behavior, and public safety concerns. These effects are summarized in a recent report by the World Health Organization.⁶⁹ Topics include acute and persistent effects of marijuana on cognitive function, on recently abstinent marijuana users, on persistent effects one month after last use.^{70,71,72,73,74,75} Other effects, especially relevant to adolescents, include

the association of marijuana with psychosis and schizophrenia, and effects during development,^{76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,}

^{113,114} risks for using other drugs.^{115,116,117,118,119} Marijuana impairs driving ability and confers a higher risk for motor vehicle accidents, and workplace disruptions.^{120,121,122,123} Marijuana use is associated with an increased risk for cognitive decline, psychosocial impairment, vehicle crashes, emergency department visits, psychiatric symptoms, poor quality of life, educational and employment achievement, use of other drugs, adverse health effects, and fetal development.^{124,125,126}

Marijuana Use Disorder

Marijuana is the most widely used illicit substance in the world.¹²⁷ There is strong scientific support for concluding that marijuana has high potential for abuse, is actually abused and is addictive, particularly in youth with other consequences (e.g. psychosis) related to age on onset, marijuana potency and frequency of use.^{128,129,130,131,132,133,134,135}

Marijuana as a Medicine for Symptom Relief, for Treatment of Disorders/Diseases

Overview of safety, efficacy standards. Several countries (Canada, Netherlands, Israel) and 24 of 50 states in the U.S. have approved the use of marijuana for medicinal purposes, with or without undergoing a systematic medicines approval process. In this review of the current status of marijuana as a medicine, a simple question is addressed: are clinical trials that report marijuana-induced therapeutic benefit sufficient to establish “currently accepted medical use?” Globally, the efficacy, safety and quality of the medical products on the market in countries has benefited enormously from a robust scientific and evidence based process. This should continue to be the central organizing principle in evaluating and approving substances for use as medicine. If effective and safe medical applications emerge for phytocannabinoids, synthetic cannabinoids or metabolic modulators, the scientific process is not a barrier to their approval.

Marijuana chemistry and route of administration. The two main cannabinoids in marijuana, THC and CBD are instructive. A safe therapeutic window for marijuana has not been established, and clinical trials have used THC from 1 to 23 percent (a 23-fold dose range). If it is ineffective at low doses, how high can THC levels be driven before susceptible users experience intense and severe psychological or neurological symptoms such as anxiety, psychosis and seizures?^{136,137} The same marijuana plant contains another cannabinoid that can oppose the

adverse effects of THC.¹³⁸ Even though CBD levels are declining, CBD reduces anxiety, may function as an anti-psychotic and anti-convulsant.^{139,140} Yet, the ratio of THC to CBD has been rising in the marijuana plant, even though this shift may result in more adverse mental health consequences among users. The therapeutic potential of CBD, the non-psychoactive constituent of the marijuana plant, is currently under investigation in 20 ongoing or planned clinical trials. These include treatment of psychosis, inflammatory bowel disease, seizure disorders, addiction, and as an immunosuppressant.¹⁴¹

Entourage effect.¹⁴² A widely held and user-reported belief is that the benefit of whole plant marijuana provides more relief than isolated cannabinoids, the “entourage effect.” This is not a trivial issue, as it is a motivating force for whole plant medicinal marijuana in lieu of isolated compounds. Conceivably, at least four explanations may contribute to these self-reports: (1) as noted above, CBD may ease THC-induced anxiety or psychosis; (2) pharmacokinetics may account for these perceived differences. Side-by-side comparisons with the two preparations can clarify this claim. Yet, a clinical trial comparing the effects of smoked marijuana with dronabinol (THC alone) suggested that, under controlled conditions, marijuana and dronabinol decreased pain, but dronabinol produced longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana.¹⁴³ In another pilot study, caloric intake and body weight were measured in HIV-positive marijuana smokers, and compared with placebo or dronabinol. Marijuana and dronabinol effects were comparable, with both dronabinol and marijuana well-tolerated and producing substantial and comparable increases in food intake.¹⁴⁴ All cannabinoid conditions produced significant intoxication, except for low-dose dronabinol. No other clinical trials have compared smoked marijuana to oral/spray THC or THC/CBD for other medical conditions, leaving the issue of whether smoked marijuana confers an advantage in efficacy and safety unresolved. Randomized Clinical trials comparing smoked marijuana with alternative medications are scant. (3) Marijuana users prefer inhalation because swift brain entry conceivably produces rapid euphoria. Yet most medications that provide symptom relief are delivered orally. (4) Cannabinoids are not the only products of the marijuana plant with putative medicinal properties. Marijuana terpenoids share a precursor to cannabinoids, e.g. limonene, myrcene, -pinene, linalool, and some are under investigation as candidate therapies or as facilitators of cannabinoid efficacy. Evidence is needed

to prove the validity of the widely held belief and self-reporting, that whole plant marijuana is superior to isolated compounds because of synergism between various components.

It is generally recognized that smoking can be harmful to health.¹⁴⁵ Standard medicines are not smoked, but enter the body by other routes (pill, injection, topical creams, patches, inhalants, eye drops, liquid drinks, suppositories). Clinical trials measure pharmacokinetic, pharmacodynamic properties of each drug, along with metabolic rates and metabolites. To confound clinical results with marijuana, the percent of THC that enters the body is variable depending on the type of smoking ritual or route of administration.^{146,147,148} Smoking remains a controversial route of delivery, even with a recent report that found no major changes in spirometric measures of lung health of light, but not heavy, recreational marijuana smokers.¹⁴⁹ Nearly all cross-sectional and longitudinal studies evaluating marijuana use association with chronic respiratory symptoms (cough, phlegm, wheezing and breathlessness) have found a positive relationship of active smoking with symptoms of chronic bronchitis (mainly cough and phlegm), but not with shortness of breath or lung cancer, but possible cancer risks remaining for heavy smokers.^{150,151} Whether vaping is a safer alternative to smoking marijuana remains uncertain, as health benefits derived from reducing toxic smoke components, (except in persons with chronic lung disease), need to be weighed against hazards of acute intoxication and long term consequences to the brain. Two studies with vaporized marijuana showed modest relief of neuropathic pain in 39 and 8 patients,^{152,153} with one at a very low dose of THC (1.29 percent). In support of this method of delivery, vaporized or smoked marijuana yielded similar maximal, but a *wide range of inter-subject blood levels* of THC. Given similar blood levels from both routes of administration, is it not surprising that CB1 receptor activation was comparable with smoked or vaporized sources of THC.¹⁵⁴

Missing safety data. Isolated cannabinoids have undergone a number of randomized, controlled clinical trials documenting safety, efficacy and side effect profiles, as required in a formalized drug approval process, whereas few RCT are reported for whole plant marijuana. In the absence of long term clinical trials, most data by necessity is extrapolated from recreational users. We failed to identify clinical trials of long duration that investigate outcomes in people using marijuana long-term for chronic medical conditions, even though marijuana is

used primarily by people with chronic medical conditions (e.g., AIDS neuropathy, AIDS wasting, multiple sclerosis, chronic pain, seizures, others). Current estimates are that 25 to 50 percent of daily marijuana users develop an addiction to marijuana. On the basis of current information and especially in view of negative side effects of chronic use (addiction, compromised cognition and executive control), one cannot be assured that marijuana can be safely used under medical supervision, for long term open-ended use. This segment provides guidance on the quality of existing clinical trials and a roadmap for future research. Key information about side-effects and safety would be collected if marijuana went through the normal evaluation process for approval as a medicine. Of randomized controlled trials, the majority of trials do not report a full dose-response evaluation, inclusion criteria generally require subjects to be experienced marijuana users, trials are of short duration (days to weeks, not six to 12 months), the sample populations are low, they do not assess quality of daily life or function when using a psychoactive substance (e.g., driving, work quality, school attentiveness, cognitive impairment) or effects after prolonged use (e.g., addiction, cognition, executive function, motivation, psychosis).

Missing safety data. Cognitive impairment in medical conditions with cognitive decline. Side effects of marijuana have to be viewed in the context of immediate effects and after repeated long term use. In research of subjects under the influence of marijuana, dose-related impairments of immediate and delayed recall of information can be quantified. Various phases of learning and memory can be affected, as well as signs of depersonalization, distorted sensory perception, and altered time perception. Executive function in marijuana users (attention, concentration, decision-making, impulsivity, self-control, reaction time, risk taking, verbal fluency and working memory) is impaired acutely in a dose-dependent manner.¹⁵⁵ Regular marijuana use for medicinal purposes is so recent that its long-term effects on seriously ill people is comparatively unknown, especially among those harboring disease-related cognitive decline (e.g., cancer, HIV-AIDS, multiple sclerosis, Alzheimer's, Parkinson's disease, certain seizure disorders). For example, cancer or chemotherapy promote cognitive decline before, during or after chemotherapy, with memory loss, loss of concentration and attention the most frequent symptoms.^{156,157} Conceivably, the combination of chemotherapy and marijuana reduces cognitive functions in additive or synergistic ways. Yet the impact of marijuana on parameters

of cognition has not been tested, although the number of patients using marijuana during chemotherapy is growing. For multiple sclerosis, another disease beleaguered by cognitive impairment, it is now recognized that marijuana worsens cognitive deficits.¹⁵⁸ Reports on marijuana-induced relief of physical symptoms in other neurodegenerative disorders with cognitive impairment (Parkinson's disease, Alzheimer's disease), do not judiciously measure cognition. Marijuana may compromise quality of life for these populations but this parameter remains inadequately explored.

Long-term effects. A significant number of individuals report paranoia, persecutory ideas, or hallucinations while under the influence of marijuana¹⁵⁹ and with drug-naïve study subjects, high drop-out rates would compromise the integrity of the clinical trial. Considering the concerted effort during the 20th century to minimize or eliminate psychoactive effects of any medication, clinical trials should include side-by-side comparisons of marijuana with isolated cannabinoids or alternative drugs (e.g., for chemotherapy-induced nausea, pain, or glaucoma). For chronic users, other side effects can include altered brain structure and brain circuits impaired short-term memory, compromised judgment and decision-making, and mood effects that can range from severe anxiety manifest as paranoia or even psychosis, especially after high doses, as reviewed earlier. Marijuana can reduce motor coordination alone, or combined with alcohol, slow the reaction time of drivers.¹⁶⁰ Marijuana smoking can cause or worsen breathing problems such as bronchitis or chronic cough and evidence is increasing that it may cause serious cardiovascular problems in some users.¹⁶¹ The impact of long-term use on young people, whose frequent use for asserted medical reasons is increasing rapidly, cannot be adequately predicted at this time either.

Evidence of marijuana for medicinal use: Use of marijuana by individuals, internationally. A recent international survey of 31 countries investigated self-reported medicinal use of marijuana (and cannabinoids). Respondents (953) from the U.S., Germany, Canada, France, the Netherlands, and Spain were generally male (64 percent), relatively young (mean age 40.7 years) with a smaller cohort using over the age of 51 (24 percent), and far fewer past the age of 60 or 70 (6 percent, 1 percent). Marijuana was used primarily for back pain (11.9 percent), sleeping disorders (6.9 percent), depression (6.7 percent), injury or accident-generated pain (6.2 percent), and multiple sclerosis (4.1 percent).¹⁶² With the exception of multiple sclerosis, and neuropathic pain, randomized

controlled trials (RCT) with marijuana use for these symptoms are scant.

It is within reason to acknowledge that certain people report relief and symptom improvement while under the influence of marijuana, as corroborated by surveys, case-based studies, anecdotal self-reports, laboratory-based short-term trials. Nonetheless, rigorous criteria need to be applied as would be required by the FDA, EMA or WHO, using the gold standard of RCTs for the drug approval process. Evidence from RCTs is presented, with sources from primary manuscripts and 10 meta-analyses.^{163,164} The psychoactive responses engendered by marijuana confound clinical research, as it is a significant obstacle to designing randomized, double-blinded clinical trials. Nor are there adequate, well-controlled double-blinded long-term RCTs demonstrating efficacy in drug-naïve populations compared with marijuana-using populations.¹⁶⁵ The majority of RCT trials recruit experienced marijuana using subjects for a number of reasons, including concerns of unacceptably high drop-out rates among marijuana-naïve subjects.¹⁶⁶

Neuropathic pain. Pain can be classified as acute or chronic, or by site of origin, (nociceptive) or nerves (neuropathic). Neuropathic pain occurs in various disease states (e.g., diabetes, HIV-AIDS, post-traumatic pain, cancer, excess alcohol use, rheumatoid arthritis) and can be a persistent, debilitating condition. HIV neuropathic pain affects 30 percent or more of HIV-infected individuals and some antiretroviral therapies can worsen the condition. HIV-infected individuals report improvements in health from smoking marijuana. Of over 200 people with HIV-AIDS, 23 percent used marijuana in the previous month.^{167,168} The association between marijuana use for psychoactive purposes and marijuana used medically for HIV-AIDS is relevant,¹⁶⁹ with considerations including both marijuana use and duration of HIV infection may affect cognitive functioning that may impair their ability to follow important treatment guidance.^{170,171} While evidence for an effect of inhaled marijuana on chronic neuropathic pain is promising, trials followed their patients for a maximum of two weeks. Long-term trials, which also examine pragmatic outcomes, are needed to increase confidence that short term trials, conducted largely in experienced marijuana users are relevant to an overall cost-benefit analysis of long term marijuana use to treat chronic neuropathic pain.

Six recent manuscripts reporting randomized controlled clinical trials with marijuana smoked or vaporized marijuana. Five were recently summarized positively in a

review co-authored by investigators of the primary studies.¹⁷² The pilot studies showed beneficial effects on alleviating pain, and by inhalation, enabled patients to titrate the effects. Yet these six reports did not establish a conclusive dose effect versus adverse events therapeutic window, as doses used varied. Acceptable limits of cognitive impairment were not described and no report addressed cognitive impairment outside a clinical research setting. Others have reviewed the overall evidence for marijuana and cannabinoids for pain.^{173,174} These RCT are currently insufficient and inadequate to recommend use of marijuana (smoked or vaporized) for the treatment of neuropathic pain. No RCT are reported for ingested marijuana, which displays variable onset times, inability to titrate doses, and more side effects.

Cancer, symptom management (nausea, vomiting, appetite, pain). Marijuana has been proposed to alleviate symptoms of cancer, including reduced appetite, chemotherapy-induced nausea and vomiting, cancer pain and even to attenuate the disease process. **Cancer, chemotherapy and anti-emesis.** Chemotherapy-induced nausea and vomiting were inadequately controlled in the 1960's and 1970's, motivating investigation of the anti-emetic properties of cannabinoids and leading to FDA approval of nabilone and THC (dronabinol or Marinol). There have been only three small clinical trials on the use of marijuana in cancer patients.¹⁷⁵ All three studies assessed antiemetic activity, with different patient populations and chemotherapy regimens. One study demonstrated no effect, the second study showed a positive effect versus placebo. The report of the third study did not provide enough information to characterize the overall outcome as positive or neutral. Consequently, there are insufficient data to provide an overall level of evidence for the use of marijuana for chemotherapy-induced nausea and vomiting. There are no published data on the use of marijuana for other cancer-related or cancer treatment-related symptoms.¹⁷⁶

Yet some patients prefer smoked marijuana over oral cannabinoids, with rationales that include ability to self-titrate smoked marijuana, the swallowing of pills is difficult while experiencing emesis, onset of relief is faster with smoking, and the whole plant ("entourage") is more effective.¹⁷⁷ Side-by-side clinical trials with oral cannabinoid compared with smoked marijuana in HIV-AIDS (see above) show scant evidence for therapeutic advantage of smoked marijuana. Furthermore, if the goal is to prevent nausea, factors such as speed of brain entry, challenges of swallowing pills while vomiting, dose titration, are not

important factors; an oral cannabinoid can be administered long before chemotherapy to avoid its unpleasant side effects. Inhaled marijuana engenders a higher rate of brain entry and associated undesirable side effects, which can include intoxication, anxiety, acute psychotic reactions, and orthostatic hypotension.¹⁷⁸ It is questionable whether the beneficial effects of inhaled marijuana outweigh the risks. Recent drug discovery programs have introduced newer anti-nausea drugs that are superior to cannabinoids in clinical trials. It is also possible that non-psychoactive isolated cannabinoids may prove to be effective for nausea and vomiting.¹⁷⁹ A significant proportion of older cancer patients with no previous marijuana experience refused to continue its use because they found the psychoactive effects too unpleasant. For such reasons, there is doubt whether smoked marijuana will find widespread clinical application, except among those who have previously used it for nonmedical purposes.¹⁸⁰ Paradoxically cannabinoids can be both anti-emetic and pro-emetic. A cannabinoid hyperemesis syndrome has recently been described, in which persistent and regular marijuana use (i.e., daily or weekly use for more than one year) is associated with episodic nausea and vomiting¹⁸¹ and nonresponse to treatment for cyclic vomiting other than hot showers.¹⁸²

Marijuana, symptoms and anti-tumor activity. At present, there is insufficient evidence to recommend inhaling marijuana as a treatment for cancer-related symptoms or cancer treatment-related side effects.¹⁸³ There is no credible evidence that smoked marijuana is an anti-tumor agent.¹⁸⁴ In fact data show contradictory results. The promise of cannabinoids as anti-tumor agent stems from preclinical research, using either cultured cells derived from human or rodent tumors, or mouse tumor models. These initial steps are insufficient to satisfy stringent criteria for recommending marijuana to treat human cancers. Cell cultures have yielded contradictory results, with THC potentiating or inhibiting tumor proliferation, as a function of tumor type and its pathology. In one small Phase I trial of nine patients with aggressive glioblastoma multiforme treated with direct infusions of THC,¹⁸⁵ THC did not extend the life span of these patients.

Post-traumatic stress disorder (PTSD) or sleep disorders. There are no large scale randomized controlled trials with marijuana to alleviate PTSD symptoms. On the contrary, marijuana use may impede the effectiveness of treatment for PTSD, and is associated with poorer clinical outcomes with PTSD.^{186,187}

Summary

1. The chemical composition of marijuana and its various preparations (smoke, vapor, edibles, beverages, creams, suppositories, etc.) is variable; safe and effective dose ranges (and plant strain) for each medical condition remain uncertain, unresolved.
2. Efficacy criteria have not been fulfilled by rigorous research.
3. Side-by-side studies comparing currently approved, and possibly safer medications are rare. Similar unknowns exist for opioids.
4. Safety studies are inadequate and of short duration; a growing body of scientific evidence shows that marijuana use for psychoactive purposes is unsafe and associated with unhealthy outcomes. Long term studies on use of various forms of dispensary marijuana for medicinal purposes are not widely available. Similar unknowns exist for opioids.
5. There is no consensus by qualified experts that marijuana is a medicine.
6. Raw data are not available for a number of clinical reports.

The 1999 Institute of Medicine report summarized the status of marijuana plant by concluding that, "if there is any future in marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives."

Editor's note: In addition to those listed in this article, the author has conducted research on numerous other disease states. This article was limited to neuropathic pain, cancer symptom management and PTSD for the purposes of this special issue of South Dakota Medicine.

This is an abbreviated version of a report written by the author and commissioned by the World Health Organization: Update of Cannabis and its Medical Use December 2015. www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf.

Components of this article were incorporated into a WHO report: The Health and Social Effects of nonmedical cannabis use, April 2016. www.who.int/substance_abuse/publications/cannabis/en/.

A link to the WHO report is available on the SDSMA website, www.sdsma.org, under the South Dakota Medicine tab.

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Psychotropic Medication Prescription Trends in South Dakota Youth

By Sarah Flynn, MD

Abstract

Following the 1999 U.S. Surgeon General's Report on Mental Health, support for the collection of national statistics on mental health disorders and treatment in children was indicated.¹ The National Institute of Mental Health followed by funding research to conduct national surveys.² The National Health and Nutrition Examination Survey, National Comorbidity Survey Adolescent Supplement, and National Ambulatory Medical Care surveys were reviewed and compared to trends in children and adolescents enrolled in South Dakota Medicaid. The South Dakota Medicaid data was consistent with the national trend of increased psychotropic medication prescriptions in youth.

Over the past decade, there has been a striking increase in prescriptions nationally for psychotropic medications in youth.³ It has been hypothesized that changes to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and drug marketing has led to the increase in youth seeking mental health care.⁴ Yet multiple national epidemiological community surveys have found that only one-quarter to one-half of youth with mental illness receive mental health services.^{3,5}

Several large national surveys were reviewed for information about psychotropic prescribing practices in youth. The National Health and Nutrition Examination Survey (NHANES) is a continuous, multipurpose cross-sectional study of the outpatient population. The NHANES survey collects data by in-home interview and physical examination at examination centers. Data from the NHANES survey of 3,024 children of a national representative probability cluster were reviewed from 2005 to 2010. The survey found 6.3 percent of adolescents aged 12 to 19 years reported psychotropic use within the past month. Of the psychotropic prescriptions 3.2 percent were for ADHD medications, 1 percent were for antipsychotic medications, 0.5 percent were for anxiolytic medications, and 0.2 percent were prescribed for mood stabilization.⁶ The survey also found antidepressant medications were more commonly prescribed to females and ADHD medication more often prescribed to males. The survey reported that poor children had increased diagnoses of

mental health disorders including ADHD and fewer diagnoses of anxiety than children from wealthier socioeconomic backgrounds.²

The National Comorbidity Survey Adolescent Supplement surveyed 10,148 adolescents aged 13 to 18 years conducted from 2002 to 2004. The survey included a representative national sample of households based on the U.S. census. Of the total surveyed a subset of 6,483 that included a parent response were considered. The subgroup was administered a modified version of the World Health Organization Composite International Diagnostic Interview, and if indicated given DSM-IV diagnoses. The survey found one-third of adolescents with mental disorders received treatment for the identified disorder according to parent response. The disruptive behavior disorders had the highest treatment rates with 59.8 percent of adolescents with ADHD and 45.4 percent with ODD or CD prescribed treatment. The survey found 37.7 percent of adolescents with mood disorder diagnosis received treatment. Only 17.8 percent of adolescents with anxiety disorders, 15.4 percent with substance use, and 12.8 percent with eating disorders received treatment.⁵ The survey also found the treatment of depression was associated with severity level and suicidal ideation and more often treated with medication in rural areas. The survey noted antipsychotic use was uncommon and most often prescribed to youth with bipolar disorder or developmental disorders.³ A concern about metabolic

adverse effects of antipsychotic medications and other side effects may have limited an increase in prescriptions to children.^{7,8}

Another large epidemiological survey, the National Ambulatory Medical Care Surveys (NAMCS) were conducted from 1995 to 2010. The survey conducted annually by the National Center for Health Statistics samples national groups of 446,542 outpatient visits to physicians' ambulatory offices.⁹ The survey noted a trend in increased office visits in youth for disruptive behavior, anxiety, and psychosis and development diagnoses. The survey also found a corresponding trend of increased prescriptions for ADHD medication and lesser increases for anxiolytics and antipsychotic medication to adolescents. The survey found a significant expansion of mental health visits to non-psychiatrist physicians.¹⁰ The increase may reflect reduced availability of child and adolescent psychiatrists,¹¹ a change in reimbursement, or evolving practice.¹⁰ The NAMCS study also found an increase in outpatient mental health visits in children where two or more psychotropic classes of medication were prescribed. Although prescriptions were indicated for the disorders treated in the survey, little is currently known about the safety of the use of two or more psychotropic medications in children.⁶

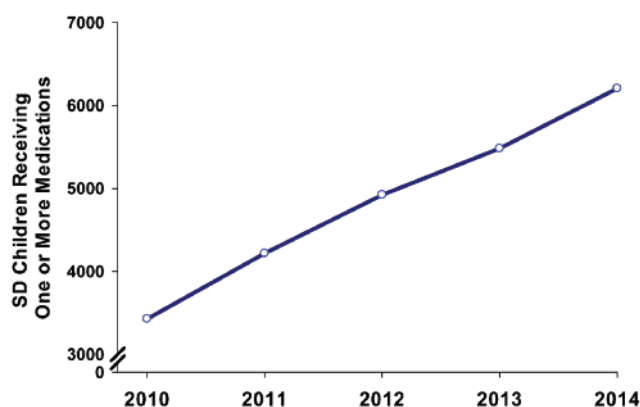
Psychotropic medication prescriptions for South Dakota youth were compared to national trends with data from the national surveys. South Dakota Medicaid claims data from the Medicaid Management Information System for children aged 3 to 17 years were obtained from 2010 to 2014. The data was reviewed for prescribing trends of mood stabilizers, antipsychotics, antidepressants, and ADHD classes of psychotropic medications. Of the roughly 79,000 children receiving medical coverage through SD Medicaid per year, an average of 4,852 children or 6.1 percent received one or more psychotropic medications. From 2010 to 2014, the number of children receiving psychotropic medication increased by over 80 percent (3,427 to 6,207). This represents a 3.4 percent increase in the number of South Dakota Medicaid-eligible children receiving psychotropic medication prescriptions for the years 2010 to 2014.

Consistent with the national epidemiological surveys of psychotropic medication use, the South Dakota Medicaid data show trends of increased ADHD and mood disorder prescriptions. The increase in mental health treatment may reflect increased public acceptance of psychotropic medication.¹² The increase in the South Dakota

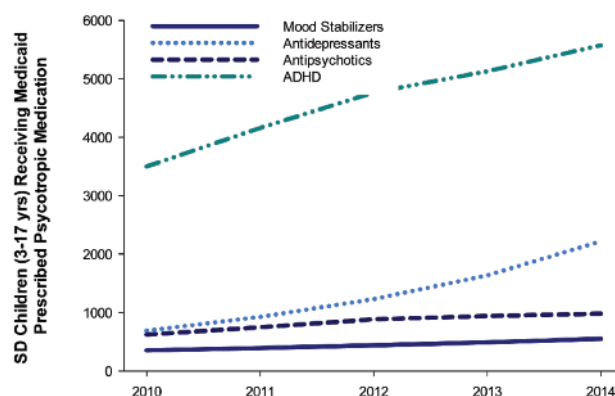
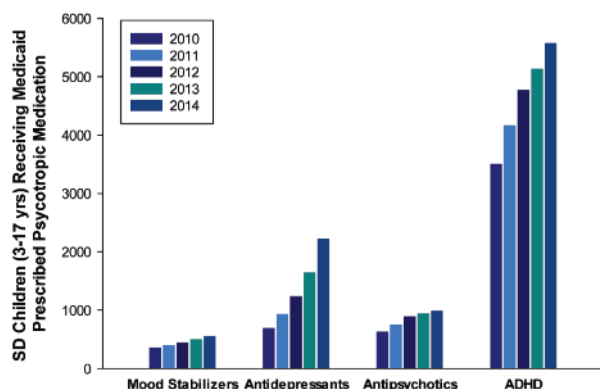
psychotropic medication prescriptions may also reflect the sample data reviewed. The other national surveys included data from non-Medicaid enrolled children in addition to Medicaid enrolled children. The number of children enrolled in Medicaid nationally approaches 50 percent in some areas. Enrollees in the Medicaid program have high rates of access of care, particularly children in foster care who have increased need.¹³⁻¹⁶ Therefore, psychotropic medication use trends in the Medicaid enrolled youth are likely higher estimates than for all children receiving mental health treatment in South Dakota (figures 1, 2 and 3).

Despite the increase in ADHD medication prescriptions for youth, a study reviewing the National Comorbidity Survey Adolescent Supplement found no evidence for overmedication or misuse of psychotropic medication and supported the need for increased identification and treatment of youth with mental illness.³ However, prescription drug misuse, including Schedule 2 ADHD medication, is considered an epidemic in the U.S.¹⁷ The Prescription Drug Monitoring Program (PDMP) is available to all prescribers in the state and can produce a controlled substance prescription history. According to South Dakota law, unless a lack of good faith is shown, a prescriber may not be held liable for damages to any person in any civil action if the provider did or did not seek to obtain information from the central repository (South Dakota Codified Law 34-20E-11). The law does not necessarily excuse all responsibility for what a physician should or should not do in a given situation. Inquiring into a patient's prescription history may reduce the diversion and misuse of controlled substances meant to treat ADHD.

Figure 1. The number of Medicaid enrolled children aged 3 to 17 in South Dakota receiving one or more psychotropic medications from years 2010 through 2014.



Figures 2 and 3. The classes of medications prescribed to Medicaid enrolled children aged 3 to 17 in South Dakota receiving one or more psychotropic medications from years 2010 through 2014.



Clearly, the number of children prescribed psychotropic medication in South Dakota is increasing. This trend is likely to continue given increased access to care through Medicaid expansion programs. Nationally, non-psychiatrist providers are increasingly prescribing psychotropic medications to meet the increased need for psychiatric services in children. Some states have responded with a specialist consultation available by phone or providing increased mental health training to non-psychiatrists.^{10,18,19}

While severity of illness appears to increase youth access to mental health treatment, up to half of adolescents

identified in national surveys as having a diagnosis of a severe mental illness have never received mental health treatment.^{2,5,20,22} The disruptive behavior disorder ADHD most often receives mental health intervention. The number of comorbid conditions also increases the likelihood of access to psychiatric service and psychotropic medications.⁵ With the expansion of Medicaid for children, access to mental health treatment and psychotropic medication, prescriptions are expected to continue to rise.

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Child and Adolescent Drug Abuse Prevention: A Rural Community-Based Approach

By Wallace Jackmon, PhD, LCSW-PIP; Brooke Balaalid, MSW; and Heather Chester-Adam, MD

Abstract

Substance abuse is a significant problem among South Dakota youth. Other than marijuana, prescription drugs and over the counter medications account for the most commonly abused drugs by high school seniors. Physicians play a significant role in future substance prevention efforts. Adolescents and research related to rural communities are areas of discussion. Community prevention coalitions are a commonly utilized mechanism for supporting community-based substance prevention efforts. Access to community coalitions, relevant student data, evidence-based practices, school based interventions and the use of technology are essential areas of prevention efforts in South Dakota and other rural communities in the U.S.

The authors discuss child and adolescent substance abuse prevention, especially as it relates to physicians and families in rural populations. Effective prevention efforts in rural communities must integrate alliances with physicians, community coalitions and evidence-based school prevention programs with existing social media. It is crucial to have culturally specific programming within the context of prevention, especially for the Native American youth in South Dakota. This paper recommends the use of community coalitions and computer technologies to reduce the costs associated with other outpatient and inpatient substance abuse programs.

Introduction

Last year, roughly 22.5 million Americans 12 years and older reported the need for treatment for alcohol and/or illicit drug use, according to the Substance Abuse and Mental Health Services Administration (SAMHSA).¹ SAMHSA predicts that by 2020, mental and substance abuse disorders will exceed all physical diseases “as a major cause of disability worldwide.”¹ For the past 40 years, public and private agencies have focused their attention on collecting data on the initiation and widespread use of substances among youth and the behavioral, social, educational, and economic outcomes associated with this use. Practitioners and scholars have investigated strategies and programs that prevent the use of substances and encourage positive youth development. Attention has now turned to how to make prevention efforts as effective and efficient as possible. This article will present the most recent data on substance use in the U.S. and South Dakota, prevention in South Dakota, how this affects physicians, and how we can work together to decrease youth substance abuse in rural areas of South Dakota.

Literature Review

Early users of alcohol, tobacco, or other drugs are significantly more likely than nonusers to intensify their drug use, do poorly in school, and engage in multiple behavior problems as they mature.² Individuals who consume alcohol before the age of 15 are also five times more likely to develop an alcohol addiction later in life compared to those who start drinking at or after age of 21.³ Native American youth begin using substances at an earlier age, with a higher degree of frequency and amount, and they experience more consequences that are negative. By 12th grade, 80 percent of Native American youth are active drinkers.⁴ An increase in use is associated with early users of substances, which often result in poor school performance and disruptive behavioral problems as the youth mature.²

In the U.S., 13.2 percent of adults who first used marijuana at the age of 14 or younger developed drug dependence or abuse, which is six times higher than that of adults who first used marijuana after age 18.⁵ While overall illicit drug use for youth (12 to 17 years old) has decreased by 13

percent since 2009, use of marijuana by youth has increased and over a majority of youth do not perceive weekly or monthly use of marijuana to be harmful.⁶ Cannabis smokers have a five time increased risk of myocardial infarction in the hour after (just) one use, and are exposed to many of the same chemicals associated with cigarette smokers. This places them at greater risk for developing lung cancer, bronchitis and recurrent lung infections. Marijuana users also have an increased risk of depression, anxiety, psychosis and schizophrenia.⁵ Additional problems associated with substance use by youth include but are not limited to public health consequences, school failure, violence, motor vehicle accidents, and adverse physical and other psychological problems.^{5,7} Many of these issues are of concern to physicians, as physicians confront these problems daily, whether it be in the emergency room or in a family practice setting.

In 2010, SAMHSA found that, other than marijuana, prescription and over the counter medications account for the most commonly abused drugs by high school seniors.⁸ Additionally, 2.7 percent of eighth graders, 7.7 percent of 10th graders, and 8 percent of 12th graders had abused Vicodin during the previous year. National data indicates the highest rate of prescription drug abuse is in persons under age 25 years.⁸ Prescription drugs have replaced heroin and cocaine as the leading drugs involved in fatal drug overdose in all urban-rural categories.⁸ In particular, narcotic painkiller abuse in rural America has reached epidemic proportions.^{9,10} Over 1.1 million adolescents (4.7 percent of youth aged 12 to 17) abused prescription painkillers in 2014. Only marijuana and alcohol are abused more frequently among teens. Adolescents abuse painkillers more than crack/cocaine, ecstasy, heroin, hallucinogens, inhalants and methamphetamine combined.^{9,10}

There is a tremendous economic cost associated with substance use, as states spend over \$16 million per day to incarcerate over 250,000 drug offenders. Incarceration of one drug abuser costs \$30,000 annually.¹¹ Programs aimed toward prevention of substance abuse are likely to be much more cost effective, as research indicates such programs have success in decreasing substance abuse rates. Miller and Hendrie estimate that school-based programs cost roughly \$220 per student.¹² School-based drug prevention curricula, many of which focus on countering social influences to use drugs, have succeeded in delaying initial use of tobacco, alcohol, and other drugs in the general population of middle school adolescents.² Most prevention programs for substance use and abuse take place within the school setting due in part to access to a

large number of children at one time. School-based prevention programs are likely to be accepted by the community, as schools are viewed as an entity to build competencies and prevent development of unhealthy behaviors.^{2,13} Low levels of parental knowledge about youths' activities and whereabouts are associated with higher levels of a host of adolescent substance use.¹⁴ Furthermore, evidence from social-influence-based evaluations indicate perceived peer norms and attitudes shape adolescents' drug-use behavior.¹⁵ Not only are school-based programs seeing success in regards to reducing substance abuse statistics, they are also cost effective with a return investment of 18:1. For every \$1 a community invests in prevention, there is a potential savings of \$18 due to the alarming costs associated with substance use.¹² Ideally, the community would reallocate funding from the justice and treatment systems to front-load prevention resources to improve their community and youth.

Substance Use in South Dakota

Adolescent substance abuse in South Dakota is a major economic, social, family and legal problem, especially concerning the South Dakota rural populations. In 2012, the rate of alcohol dependence for individuals 12 and older in South Dakota was higher (8 percent) than the National average (6.7 percent).¹⁶ In the years from 2009 to 2013, about 5,000 South Dakota adolescents (8.1 percent of all adolescents, ages 12 to 18) reported using illicit drugs, about 6,000 (9.3 percent of all adolescents) reported using cigarettes, and about 18,000 people aged 12 to 20 (18.3 percent of all people in this age group) reported binge alcohol use.^{11,16} Over 29 percent of South Dakota students (ninth through 12th grade) reported having used cannabis one or more times in their lifetime, with 7.2 percent indicating first use prior to age 13.⁵

Prevention in South Dakota

In 1975, the South Dakota Department of Health hired its first prevention coordinator (see Chart 1 for detailed history). The trends during the 1970s to 2000 for substance misuse approaches in the U.S. and South Dakota had been focused on telling individuals to "just say no." However, evidence now suggests that in order to maintain the decreasing trend in substance use, there needs to be a "greater emphasis on: 1) preventing use in the first place; 2) intervening and providing support earlier after use has started; and 3) viewing treatment and recovery as a sustained and long-term commitment."⁶

In 2009, the South Dakota Prevention Program was

awarded the Strategic Prevention Framework State Incentive Grant (SPF SIG). The sole focus of the SPF SIG was to help states and tribal entities establish a solid base for delivering and sustaining effective prevention programming. A major emphasis was on reducing instances of underage drinking, reducing substance misuse-related problems within the communities, and building a prevention capacity and infrastructure at the state and local level, according to the Substance Abuse and Mental Health Services Administration.¹ Twenty-six community coalitions in South Dakota applied for SPF SIG funding through the Prevention Program; however, only 15 coalitions were fully-funded to implement prevention strategies due to financial cap of the award.¹⁷ The coalitions used community data to tailor their prevention efforts and used a mixture of individual-level and environmental evidence-based practices.¹⁷ Individual-level evidence-based practices use approaches that focus on changing the individual's behavior by increasing their knowledge, skills, and attitudes. Environmental strategies approach prevention on a broader level by changing conditions within a community by addressing physical, social, and/or cultural factors that lead to substance use.

The Strategic Prevention Framework State Initiative Grant was a complex effort to change the substance abuse system at the state and local levels. One of the most significant changes was the increase in workforce development of prevention providers due to numerous trainings and technical assistance.¹⁷ South Dakota's prevention system also increased its knowledge on cultural competency, started collecting data on demographics and cultural categories, and funded two coalitions whose primary focus was providing culturally relevant prevention programming to Native American youth.¹⁷

Analysis of alcohol-related arrests found there was a significant decrease in alcohol-related arrests in the 15 SPF SIG communities among young adult's ages 20 to 24 years of age. However, there was no statistically significant difference in alcohol-related arrests of youth 19 years and younger between the two groups. Piper and Blaaid contribute this result to the "maturation effect" as youth gets older there tends to be a "normal" pattern of increase in use; however, the goal for an outcome evaluation of substance abuse programs for adolescents is to slow the increase in use.¹⁷

With the successful completion of SPF SIG in 2014, South Dakota Prevention Program submitted an RFP for SAMHSA's next round of prevention funding,

Partnership for Success (PFS). South Dakota was awarded the PFS grant in the fall of 2014 and 15 community coalitions were selected to receive funding. Unfortunately, the Prevention Program does not have enough funding through grants to fully-fund all of the prevention efforts of the community coalitions across the state.

South Dakota Physicians

South Dakota is unique concerning its population and geography, as close to 50 percent of the population resides in rural areas.¹⁸ The definition of rural is a nonmetropolitan county with an urban population of less than 20,000 residents.¹⁹ Practitioners and physicians located in South Dakota's rural areas are often at a distinct disadvantage due to the wide service area, lack of resources and other problems associated with such settings. Additionally, use of tobacco products and alcohol tended to be highest among youth in rural counties.¹⁹ Socioeconomic factors of rural youth are a risk factor, as rural youth are more likely to be poor, to have younger and less educated parents, and to have repeated a grade in school.¹¹ Lack of economic, educational, and social opportunities may create feelings of despondency among rural youth, making earlier and increased substance use appear to be an attractive means of escape from their problems.¹⁸

Rural physicians are often overwhelmed with many responsibilities, and often have limited community resources. Evidence suggests that substance use among rural adolescents is definitely a matter of pressing concern for rural physicians. Substance use disorders pose a particular challenge for the rural primary care physician, even though such disorders are common in the primary care setting. Many physicians lack confidence in the assessment and treatment of substance use issues,²⁰ and their training is often inconsistent or inadequate.^{21,22} As members of the community, rural physicians have a stake in the global social, legal and community issues that are associated with adolescent substance use. What may be even more important for physicians, however, is that one of the prominent features of rural adolescent substance use is the problem of prescription medication abuse.

For example, youth stimulant and methamphetamine use is higher in rural counties than metropolitan counties.¹⁹ Recent data suggested rates for other substances such as inhalants and prescription drugs (Adderall, Vicodin, OxyContin), are higher among rural youth than among urban youth.^{9,18} With specific regard to the rural teen population, rural teens abuse prescription painkillers more commonly than urban teens.⁹ Of specific importance to

rural physicians, rural teens are more likely to get the pills they abuse directly from the physician.¹⁰

It is a national and state public health priority to prevent adolescent substance use and misuse. The American Medical Association and the American Academy of Pediatrics (AAP) issued guidelines and policy statements urging physicians to actively support and participate in substance abuse prevention efforts.¹³ Researchers found that health professionals often have negative attitudes toward patients who have substance use issues, which impacts health care delivery for these patients.²³ Additionally, physicians may feel that substance use issues are not part of mainstream medical care.

Rural teenagers and their families have limited access to specialized treatment and mental health services, often having to travel long distances to access the programs or care they need to remedy their substance use problems.¹⁸ Physicians may be the only resources available to the rural youth and their families. This is even more alarming concerning the South Dakota Native American population, as health care resources are extremely sparse. Many major causes of Native American deaths and an array of physical conditions such as diabetes and HIV-AIDS correlate to problematic youth substance use.⁴

Physicians can play an important role in prevention and identification efforts with regard to substance use disorders. Contrary to the notion of substance issues being outside the scope of primary care, the preventive medicine focus of primary care applies equally well to the construct of prevention and early identification of substance issues in adolescents, before the issues have had a long time to become entrenched. Rural practitioners may feel that lack of resources creates an impediment to adequate care for substance related issues. One of the most valuable resources to rural and urban physicians is their local community coalition. Physicians can support their local community coalition and/or school prevention programs by connecting to and referring to their local coalitions. Physicians can also review over 390 EBPs through SAMHSA's National Registry of Evidence-based Programs and Practices (NREPP), which is an evidence-based resource system, developed to provide the public with accurate and research-based information on mental health and substance abuse interventions.¹

A recent international study showed promising results for a computer-facilitated screening instrument and provider brief advice system for substance use in teens in the primary care setting.²⁴ The Communities That Care

(CTC) prevention system has shown reductions in risk levels and problematic teen behaviors in small towns in the U.S.²⁵ Additionally, the growth of telemedicine and electronic behavioral health services in recent years will allow for easier specialty consultations and referral access in rural areas. There is a growing body of online resources, screening tools, community based treatment approaches and telemedicine offerings that will hopefully help to alleviate these access barriers. The AAP recommends child and adolescent alcohol screening.²⁶ The AAP and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) published *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* in 2011.²⁷ This resource includes a pocket reference, a brief screening tool, and includes CME if practitioners choose to complete online training.

Conclusion

There is a need for additional study and data on the long-term effects and outcome of prevention efforts, especially EBPs that address "rural life" and the Native American culture. Native American youth in South Dakota face vastly different obstacles compared to the majority of Caucasian youth within the state. Prevention programming must center around learning about their cultural traditions and increasing their knowledge on the devastating effects of substance use. As noted previously, there are many contributing factors to substance use that youth face in rural areas compared to youth in urban areas and vice versa. It is imperative that community coalitions provide prevention education that is specific to the population they are working with and incorporates cultural, community, and contextual variables.²⁸

Evidence suggests that computer and web-based interventions have been successful in promoting positive behavior changes among youth in such areas as underage drinking, drug use, depression, violence, and sexually transmitted diseases.^{13,28} There is a need to further explore prevention services that utilize computer and web-based interventions especially for communities in rural South Dakota. Schools in rural South Dakota are increasingly using the internet and computer technology in the classroom, and this would greatly benefit the youth who are also actively engaged in the world of technology. It is also essential to integrate available social media such as Twitter, Facebook and instant messaging as a means to maintain connection and "stream" information and programming content to youth within future proposed prevention programs. Considering a majority of youth 13 to 18 have either a computer, tablet and/or a phone, such

devices provide an immediate forum from which to disseminate materials without placing additional burden onto physicians and other providers.

For example, one aspect of such a delivery model might include a forum from which peers might support efforts of other peers attempting to resist using substances. In addition, it may provide positive reinforcement and incentive for maintaining sobriety and/or connections

with risky, substance abusing peers. Partnerships with others schools of practice and learning, such as technological, web-based professionals may offer an opportunity to develop new and innovative applications and programs with a more interactive and inclusive format. Imagine an “app” which includes youth, their parents, their peers, physician, social worker and mental health substance abuse prevention staff all working together to prevent

Chart 1: History of South Dakota Prevention Services

Date	Prevention Events
1975	First prevention coordinator is hired under the South Dakota Department of Health (SDDOH).
1980's	Establishment of new liquor law tax; monies are allocated to prevention to provide for resources and mini-grants.
1980's	Prevention resource centers (PRCs) are established due to allocation.
1989	Department of Human Services is formed (DHS).
1989	Alcohol and drug services housed under SDDOH are transitioned to DHS and Division of Alcohol and Drug Abuse (DADA) is formed.
1991	DADA received federal monies from Center of Substance Abuse Prevention (CSAP) in the form of treatment and prevention block grant. Twenty percent is allocated to prevention.
1996	DADA creates a statewide prevention plan with goals.
1996	Tobacco prevention coordinator position is created.
1996	Mini-grants end.
1997	DADA puts an RFP process together for agencies and organizations to obtain prevention monies. Thirteen community mobilization projects were funded.
1997	Diversion is seen as a priority area and Prime for Life curriculum is selected for statewide diversion program.
2000	Tobacco prevention coordinator is moved to SDDOH.
2000s	Strategic Prevention Enhancement (SPE) Grant (Award \$600,000): develop a comprehensive strategic prevention plan to expand and enhance the state and communities' ability to incorporate evidence-based prevention strategies across South Dakota.
2009-2014	Strategic Prevention Framework State Incentive Grants (SPF SIG): grant award of roughly \$10.7 million. South Dakota focused on utilizing data-driven approaches to identify high-risk substance abuse areas and communities and build the infrastructure of the communities and the state to respond with evidence-based prevention programming. Thirteen communities conducted the SPF process and implemented EBP's focused on the prevention of underage drinking or binge drinking.
2011	Gov. Dennis Daugaard reorganizes departments and agencies. Prevention program is established under the Department of Social Services: Division of Behavioral Health.
2014-2019	Partnership for Success Grant (PFS): grant award total for five years is roughly \$6.8 million. PFS project will seek to reduce underage alcohol use by persons aged 12 to 20. The project will fund community coalitions in 12 counties to implement a range of evidence-based programs using both individual and environmental evidence-based approaches.
2014-2019	Suicide Prevention Grant: grant award total for five years is approximately \$3.68 million. Primary focus is on youth who have made a suicide attempt or expressed suicidal ideation at an emergency department or inpatient psychiatric unit along with improving the continuity of care and follow-up with youth identified at risk for suicide, and ensuring there are clinically trained professionals for youth to access.

(Rechtenbaugh, 2012) (Substance Abuse and Mental Health Services Administration (SAMHSA), 2015)

future substance abuse. With the advances in technology, such innovations are a genuine possibility.

While these two areas are long-term goals for prevention services in the state, there are several short-term goals that can be accomplished relatively quickly to improve the prevention system in South Dakota. As a physician, you have many assets and resources to offer your local community coalition, especially your ability to analyze research and draw conclusions from said research. Community coalitions often lack the medical perspective due to a

disconnect in how the two systems can work together and physicians being pulled in multiple directions. Physicians could also play a role in helping local coalitions obtain greatly needed ER data in relation to prescription drug use and re-enforce to the community the need to collect data from our youth through reliable survey methods. Substance abuse is like any other medical disease, there is usually more success for the patient if prevention methods are taken to preempt the problem.

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Substance Abuse Treatment for Adolescents in South Dakota

By Shawn Van Gerpen, MD; and Tamara Vik, MD

Abstract

In the state of South Dakota, there are 39 accredited substance abuse providers who service over 11,000 individuals each year. Knowledge of which substance abuse providers are accredited is important for families looking to find financially affordable substance abuse treatment/care for their loved ones. In order to begin the process of entry into a substance abuse treatment program, an adolescent must first complete a needs assessment with one of the accredited providers. The needs assessment will help to identify the severity of the substance use disorder as well as identify the appropriate level of treatment/care for the individual.

Introduction

A South Dakota Department of Social Services report on community behavioral health attributes 39 accredited substance abuse providers in South Dakota with servicing over 11,000 individuals annually.¹ Services provided range from assessments and crisis intervention, to individual and group counseling, all the way to residential and inpatient treatment.

Accreditation is important when considering payment for substance abuse treatment, as well as giving reassurance to adolescents and their families about a provider's commitment to quality care. South Dakota Medicaid covers substance abuse services for adolescents and pregnant women if the provider is accredited by the South Dakota Division of Behavioral Health. The Division may also provide funding for other individuals who have no insurance or other medical coverage.¹

Community mental health centers and substance abuse providers can be accredited by the South Dakota Division of Behavioral Health, or through deemed status by one of the following: The Joint Commission, an Indian Health Service's quality assurance review under the Indian Health Service Manual, Professional Standards – Alcohol/Substance Abuse, The Commission on Accreditation of Rehabilitation Facilities (CARF), or The Council on Accreditation (COA).¹ A complete list of

the accredited substance abuse providers in South Dakota is located in Table 1. This list, along with contact information and levels of care provided, is available through the State of South Dakota website.

The first step toward receiving substance abuse treatment in South Dakota is a needs assessment. A needs assessment can be completed by one of the numerous accredited providers listed in Table 1. A needs assessment will provide a diagnosis, and a recommendation for an appropriate level of care.

The diagnoses for substance abuse have changed recently, due to the introduction of the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM 5)* and ICD-10. Unlike in *DSM IV*, the diagnoses of substance “abuse” and “dependence” no longer exist. *DSM 5* differentiates the levels of substance use based on severity: substance use disorder, mild; substance use disorder, moderate; and substance use disorder, severe.² The appropriate level of care is based on a combination of factors including severity based on diagnosis, previous treatment, and other risk factors.

Adolescents, by their nature of being minors and dependent on others to care for them, have a long list of potential risk factors which can influence the level of care recommendation. Adolescents with high risk or life threatening behaviors will receive a recommendation for a higher

Table 1. South Dakota Accredited Substance Abuse Providers¹

Location	Agency Name	Phone Number
Aberdeen	Avera St. Luke's Worthmore Addiction Services	800-952-2250
Belle Fourche	Addiction Family Resources	605-892-3039
Brookings	East Central Behavioral Health First Step Counseling Services	605-697-2850 605-693-3629
Canton	Keystone Treatment Center	800-922-1921
Chamberlain	Dakota Counseling Institute-Stepping Stones	605-734-6535
Custer	Addiction Recovery Center	605-673-2844
Eagle Butte	Three Rivers Mental Health and Chemical Dependency Center	605-964-4210
Faith	Three Rivers Mental Health and Chemical Dependency Center	605-964-4210
Flandreau	Community Counseling Services	605-997-3771
Hot Springs	Addiction Recovery Centers of the Black Hills	605-745-6300
Howard	Community Counseling Services	605-772-4574
Huron	Community Counseling Services Our Home, Inc. Rediscovery	605-352-8596 605-353-1025
Kyle	Ogalala Sioux Tribe – Anpetu Luta Otipi	605-455-2331
Lake Andes	Lewis and Clark Behavioral Health Services	605-487-6143
Lake Preston	Community Counseling Services	605-847-4484
Lemmon	Three Rivers Mental Health and Chemical Dependency Center	605-374-3862
Madison	Community Counseling Services	605-256-9656
Martin	Martin Addiction Recovery Center	605-685-6710
McLaughlin	Three Rivers Mental Health and Chemical Dependency Center	605-823-4212
Milbank	Human Service Agency	605-886-0123
Mitchell	Dakota Counseling Institute – Stepping Stones	605-995-8180
Mobridge	Three Rivers Mental Health and Chemical Dependency Center	605-845-5176
Pierre	Capital Area Counseling Services South Dakota Urban Indian Health	605-224-5811 605-224-8841
Rapid City	Addiction Recovery Center of the Black Hills Behavior Management Systems HorsePlay Productions Healing Center Lifeways Pennington County dba City/County Alcohol and Drug Programs (Satellite Office) Pennington County dba City/County Alcohol and Drug Programs ROADS Outpatient Treatment Program, Inc. Wellspring, Inc. Youth and Family Services	605-716-7841 800-299-6023 877-343-1620 605-716-6555 605-716-2865 605-394-6128 605-348-8026 605-718-4870 605-342-4789

Table 1. South Dakota Accredited Substance Abuse Providers' (cont.)

Location	Agency Name	Phone Number
Sioux Falls	Avera Behavioral Health Outpatient Clinic	605-322-4079
	Bartels Counseling Services	605-310-0032
	Carroll Institute	888-254-4543
	Choices Recovery Services	605-334-1822
	Counseling Resources	605-331-2419
	Dakota Drug and Alcohol dba PrairieView Prevention	605-331-5724
	First Step Counseling Services	605-361-1505
	Glory House	605-988-9100
	Keystone Treatment Center – Outreach	800-992-1921
	Minnehaha County Detox	605-367-5297
	Sioux Falls Treatment Center	605-332-3236
	South Dakota Urban Indian Health	605-339-0420
	Southeastern Behavioral HealthCare	605-336-0510
	Volunteers Of America – Dakotas	800-365-8336
Sisseton	Dakotah Pride Treatment Center	605-698-3917
	Human Service Agency	605-698-7688
Spearfish	Northern Hills Alcohol and Drug Services, Inc. dba Compass Point	605-642-7093
Sturgis	Northern Hills Alcohol and Drug Services, Inc. dba Compass Point	605-347-3003
Vale	New Dawn Center	605-456-2968
Vermillion	Lewis and Clark Behavioral Health Services	605-624-9148
	USD - Student Counseling Center	605-677-5777
Watertown	Human Service Agency	605-886-0123
	Human Service Agency (Satellite Office)	605-884-0650
	Dr. Mark Bontreger	605-882-0800
Winner	Main Gate Counseling Services	605-842-0312
Yankton	Human Services Center	605-668-3316
	Lewis and Clark Behavioral Health Services	800-765-3382

level of care. Some of these high risk factors include substance use by caregivers, poor supervision at home, and abusive caregivers. Adolescents who use IV drugs, have sexual relationships with adults, or are doing illegal things to obtain drugs are also at a higher risk. Other important factors in determining the level of care recommendation include previous treatment, whether the adolescent failed treatment, and the adolescent's length of sobriety following treatment. All of these potential factors put the safety of the adolescent at risk, and can push the level of care recommendation from a low level of outpatient care to a

more restrictive level of inpatient care.

Levels of Care

The American Society of Addiction Medicine (ASAM) defines the levels of care for substance use disorders. For a complete list of the ASAM levels of care, see Table 2. Common levels of care recommended for adolescents in South Dakota include early intervention, outpatient services, intensive outpatient services, and inpatient services.

Level 0.5, called Early Intervention, is a level of care for adolescents at risk for developing substance use disorders,

Table 2. American Society of Addiction Medicine Levels of Care³

0.5	Early Intervention
1	Outpatient Services
2.1	Intensive Outpatient Services
2.5	Partial Hospitalization Services
3.1	Clinically Managed Low-Intensity Residential Services
3.3	Clinically Managed Population-Specific High-Intensity Residential Services
3.5	Clinically Managed High-Intensity Residential Services - for adults Clinically Managed Medium-Intensity Residential Services - for adolescents
3.7	Medically Monitored Intensive Inpatient Services
4	Medically Managed Intensive Inpatient Services

or for those who have not yet received a diagnosis of a substance use disorder due to insufficient information.³

Outpatient Services, or Level 1, can be delivered by a variety of different substance abuse providers. This level of care often involves individual counseling, and consists of less than six hours of treatment per week for adolescents.³

Level 2.1, or Intensive Outpatient Services, consists of six or more hours of treatment weekly for adolescents. This level of care can address the needs of adolescents with both substance use disorders and other co-occurring diagnoses. Intensive Outpatient Services often include group therapy, typically three nights a week after school.³

Levels 3 and 4 include a variety of inpatient and residential services. In South Dakota, adolescents are typically referred for inpatient substance abuse treatment if they have tried and failed outpatient services, have a higher level substance abuse diagnosis, or have a higher level of life threatening risk factors.³ There are five substance abuse providers in South Dakota that offer inpatient treatment for adolescents: Human Services Center, Keystone, Volunteers of America, Our Home Rediscovery, and Wellfully, formerly Wellspring, Inc.

Inpatient Substance Use Providers

South Dakota Human Services Center (HSC) is the state hospital located in Yankton and has a unit dedicated to the treatment of adolescents with substance use disorders. Admission to this facility requires the approval of the South Dakota Division of Behavioral Health. A variety of payment methods are accepted, including self-pay, Medicaid, state insurance (other than Medicaid), and

private health insurance. Financial assistance is available in the form of sliding fee scales. HSC is accredited by the South Dakota Division of Behavioral Health and CARE. Adolescents on the 20-bed inpatient substance abuse unit participate in the Steps Beyond Adolescent Chemical Dependency program. Treatment is based on the 12-step program of Alcoholics/Narcotics Anonymous, which is evidence-based, and the length of stay is typically 90 days. The treatment team includes a child and adolescent psychiatrist, psychologist, nurses, social worker, and licensed/certified chemical dependency counselors. Adolescents must be between the ages of 13 and 17 years, and have a substance use disorder diagnosis.⁴

Keystone Treatment Center is located in Canton. The adolescent residential program is modeled on the 12-step philosophy and offers both a specialized Christian and a specialized Native American track. Therapies include individual, group, and family. The treatment team includes a psychiatrist, psychologists, a primary care physician, an addictionologist, a licensed chemical dependency counselor, and nursing staff. Additional support comes from dietitians, social workers, medical and rehab technicians, recreational therapists, pastors, and Native American cultural advisors. Keystone accepts adolescents between the ages of 13 and 18 years. The average length of stay is 30 to 60 days. Payment is accepted in the form of a large variety of private insurance companies.⁵

Our Home, Inc. Rediscovery is located in Huron and accepts adolescents with a substance use diagnosis. Length of stay is typically 45 days, but can go to 60 days, and treatment includes 12-step groups, Alcoholics Anonymous, and Narcotics Anonymous. Our Home, Inc. is accredited by the South Dakota Division of Community Behavioral Health and CARE. It serves adolescents between the ages of 12 and 18 years.⁶

Volunteers of America – Dakotas, Heisler Substance Abuse Program (VOA) is located in Sioux Falls and serves adolescents from ages 12 to 18 years for up to 60 days. Each adolescent is provided a chemical dependency counselor who develops an individualized treatment plan to address both substance abuse issues as well as other co-occurring mental health issues. VOA accepts Medicaid and most insurance plans.⁷

Wellfully is located in Rapid City and accepts self-payment, Medicaid, and private health insurance. It serves adolescents ages 12 to 17 years. The Wellfully residential

addiction recovery program is a 45 to 60 day program, and is accredited by the South Dakota Division of Community Behavioral Health. Programming consists of individual, group, and family therapy. An adolescent in treatment will also receive a mental health evaluation, emotional support, and a clinical treatment plan.⁸

Summary

In conclusion, South Dakota adolescents have access to substance abuse treatment through a large variety of accredited substance abuse treatment centers. There are additional providers across the state who are not accredited, both inpatient and outpatient providers. The first step toward receiving treatment is a needs assessment, which can be completed by almost any of the outpatient substance abuse providers listed in Table 1. Importantly, a needs assessment can be initiated by any concerned individual in the adolescent's life, it does not require a special referral. Payment options include self-payment, Medicaid, and private insurance. Some adolescents who are not covered by Medicaid or private insurance may be

granted coverage by the Division of Behavioral Health. Another route toward treatment for some adolescents is through a court order or tribal court order.

ADDENDUM: The South Dakota Division of Behavioral Health gradually quit admitting patients to the adolescent substance abuse unit at HSC and eventually closed it in April of 2016.

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Case Report of Intractable Vomiting and Abdominal Pain Related to Heavy Daily Cannabis Use

By W. Bryce Gammeter, MD; Kyle A. Duke, MPAS; and
Timothy J. Soundy, MD

Abstract

Case: A highly anxious and dehydrated adolescent came to a local emergency department with complaints of intractable emesis, weight loss, and abdominal pain. He stated that bathing and “guzzling water” ameliorated symptoms. He admitted to using marijuana socially. Efforts at palliation with benzodiazepines, atypical antipsychotics, and antiemetic medications were unable to soothe the patient. After thorough initial diagnostics and physical exam failed to elucidate etiology, the patient was referred to an inpatient psychiatric facility for further evaluation of potential psychosomatic or affective causes.

During psychiatric evaluation and upon obtaining additional information from family and reviewing the work done by primary care providers, the patient was questioned stringently about his marijuana use patterns. Questioning revealed that the patient had previous chemical dependency treatment, legal charges related to drug use, and heavy daily marijuana use including “dabbing,” ingestion of THC candy, and smoking up to several grams a day.

Discussion: Cannabinoid hyperemesis syndrome (CHS) consists of intractable emesis, abdominal pain, and weight loss. There is often a history of symptom amelioration with bathing and showering. These patients may or may not admit to heavy marijuana use. Cannabis effects vary and are dose dependent. Historically, CHS would require over a year of heavy daily use. In this day and age of higher THC potency marijuana and even higher THC potency “dabs,” it is anticipated that more cases of cannabis related syndromes in general, and CHS in particular will be presenting more frequently to ambulatory and emergency room settings. The patients will potentially be younger and have a shorter duration of heavy cannabis use before symptoms start. A high index of suspicion will be required to prevent expensive and potentially invasive workups and thus delaying diagnosis and treatment.

Introduction

Cannabinoid hyperemesis syndrome is characterized by intractable vomiting, abdominal pain, weight loss. A unique feature is a history of compulsive bathing, oftentimes with multiple hot showers which provides temporary symptom relief. This condition was first reported in the medical literature in 2004. The typical patient has a several year history of heavy marijuana use. Patients presenting to an acute care provider with the above symptomatology should be questioned about marijuana use and undergo a urine drug abuse survey for detection of THC.

Case

A dehydrated and anxious 15-year-old male presented to

the local emergency department

(ED) with intractable vomiting and sharp right upper quadrant (RUQ) pain for the last four days. The abdominal pain was occasionally made worse after eating greasy and fatty meals. He had lost 30 pounds in the last six months. The patient stated that taking showers relieved his severe anxiety, pain and vomiting. Ancillary information from family members indicates that the patient has been “guzzling” water and would then throw up. They reported he had been drinking heavily and smoking marijuana the night before. The patient states that he rarely drinks, though he will drink heavily when he does. He admits to smoking marijuana “socially.”

Vitals signs were stable. On physical exam he is anxious, dehydrated, with a tender RUQ to palpation. The remainder of the physical exam was unremarkable though he continued vomiting clear fluids while in the ED. An EKG showed tachycardia at 121 bpm and a QTc of 498 msec. Comprehensive metabolic panel (CMP) showed Na 133 mmol/L, K 3.2 mmol/L, Cl 94 mmol/L, BUN 29 mg/dl, creatinine 1.9 mg/dl, total bilirubin 1.8 mg/dl, glucose 177 mg/dl, AST 44 U/L, ALT 17 U/L, and complete blood count (CBC) with differential showed white blood cell count (WBC) of 14.1 K/uL otherwise unremarkable. IV started with normal saline for fluid replacement. He was given lorazepam for anxiety and ondansetron for vomiting without relief. He was then tried on promethazine. An ultrasound of the gallbladder was completed and showed biliary sludge with no stones present. The patient was aggravated with staff due to his NPO status and constantly asked for water. The patient discharged to follow up with his primary care provider (PCP) the following day on oral potassium chloride and ondansetron.

He presented the next day to his PCP with continued symptoms of vomiting and pain. He was admitted to the hospital for rehydration and further evaluation. A more thorough history revealed multiple psychiatric medication failures as well chemical dependency failure for moderate to heavy marijuana use. He had a series of marijuana ingestion and possession charges. The patient was on olanzapine/fluoxetine 6/50 mg daily. He had tried alprazolam 0.25 mg for anxiety in the past. His PCP started him on ziprasidone 10 mg q six hours in the hospital for the possibility of a manic episode as the patient had not slept for four nights and in light of his past psychiatric history.

The patient displayed bizarre behaviors of compulsively wanting to shower up to 20 times per day and became severely agitated when not able to do so. He threatened, on multiple occasions, to remove his IV so he would be able to shower. While on ziprasidone, the patient became less agitated. A CT of the head was obtained due to patient claiming to have hit his head two weeks earlier and was unremarkable for any abnormality. Repeat labs showed a potassium level of 3.0 mmol/L and all other labs were normal. The hospitalist determined that the patient was experiencing an acute manic episode and sought transfer to a psychiatric facility.

Upon arrival at the psychiatric facility, he was eager to please and in no distress. He claimed that he was “all better” and was not experiencing any pain or vomiting

since transferring from his local hospital. Psychiatric evaluation of the patient revealed significant history of substance abuse, with previous inpatient chemical dependency treatment, relapse, and legal charges related to ingestion and possession. He was an unreliable historian regarding his substance use, so additional information from his family was obtained. The information provided by the patient's guardian revealed that the patient had been “dabbing” and orally ingesting marijuana as a container of dabs and a dabbing pipe was found in his possession along with an empty bag of marijuana gummies. The container stated the dabs contained 81 percent THC. When questioned regarding the family report, the patient admitted to dabbing several times a day for over a month, and heavy daily use with up to several grams of cannabis smoked per day.

After an unremarkable intake physical examination that morning, the patient became panicky and agitated in the afternoon. The patient began reporting severe RUQ pain, and self-induced vomiting episodes. The patient was adamant that he needed surgery to help his pain. An emergency consult was obtained which recommended no further imaging at this time unless labs and physical warranted further evaluation. CBC, CMP, thyroid stimulating hormone (TSH), lipase, gamma glutamyl transpeptidase (GGTP), lactic acid and urinalysis were all normal. Urine drug screen was positive for cannabis and benzodiazepines. The patient insisted that he needed to take a shower to help with his anxiety, pain and vomiting. With showering, his symptoms resolved. Inpatient staff noted that patient was showering up to 10 times per day. His ziprasidone was discontinued and fluoxetine was decreased and eventually discontinued. He was started on clonidine 0.1 mg HS with 0.05 mg daily PRN for agitation/withdrawal. Clonazepam 0.25 mg scheduled HS and eventually increased to 0.5 mg HS which helped with anxiety and sleep. The patient reported numerous psychopharmacological intervention failures previously. Pharmacogenomic testing was completed and he was found to be a poor metabolizer of clonidine. The clonidine was discontinued and he was started on guanfacine 1 mg daily and lamotrigine 25 mg daily. His mood stabilized with significant improvement in agitation and lability. The RUQ pain and vomiting dissipated the longer he remained as an inpatient and abstinent from cannabis.

Discussion

RUQ pain with vomiting carries a lengthy differential diagnosis. The elevated labs in the CMP led to an ultra-

sound of the gallbladder which ruled out a biliary cause. The possibility of biliary dysfunction could not be totally eliminated without a HIDA scan or endoscopic retrograde cholangiopancreatography (ERCP); but because of the patient's age, history of marijuana use, and symptom presentation, no further studies were done.

Historically, marijuana has been the most frequently abused illegal drug in the U.S.¹ The reported medical benefits of marijuana include increasing appetite in AIDS patients, antiemetic effects in chemotherapy recipients, decreasing intraocular eye pressure in glaucoma patients, and relieving spasticity in multiple sclerosis and other neurologic disorders. The literature suggests that most of these medical marijuana benefits are not clearly superior to the already available treatments.²

Marijuana's adverse effects vary depending on dose, frequency and duration of use. Both animal and human studies demonstrate a process of "neuroadaptation" with use. The neuroadaptation has mostly been seen with chronic heavy use with activation of CB1 and CB2 cannabis receptors.

These receptors are involved in metabolism, thermoregulation, pain, osteogenesis, mood, and immune function.^{3,4} The cannabinoid receptors are highly concentrated in brain regions implicated in memory, coordination, appetite, and reward pathways.⁵ Withdrawal can occur within 10 hours of marijuana cessation and may consist of typical withdrawal symptoms such as adverse mood changes, sleep difficulty, gastrointestinal symptoms, anorexia and tremor.⁵ Symptoms can peak in 48 hours and last up to five to seven days.¹ Despite the assertions of this patient experiencing withdrawal, the withdrawal has not been known to be lethal.¹

Cannabinoid hyperemesis syndrome (CHS) was first described in 2004 by Allen and colleagues. CHS is often misdiagnosed as cyclic vomiting syndrome (CVS). CHS is hallmarked by intractable vomiting, abdominal discomfort, daily marijuana use and increased tendency of bathing for palliation of symptoms. CVS differs diagnostically from CHS in that patients need to have periods of "normal health" between vomiting episodes. The literature suggests three phases of CHS; prodromal, hyperemetic and recovery phase.⁶ Patients tend to self-medicate in the prodromal phase for symptom relief of early morning nausea, fear of future vomiting and abdominal discomfort. The prodromal phase may last months. The hyperemetic phase is characterized by nausea, intractable vomiting,

and possible weight loss. In one study, 70 percent of patients had a loss of at least 5 kg in the preceding months. In addition, bathing multiple times per day is noted in the hyperemetic phase. Per reports, this is a learned behavior that becomes compulsory to relieve symptoms. In the recovery phase, patient's nausea, vomiting, and abdominal pain dissipate, appetite improves and weight loss is regained.⁶

Nicolson and colleagues in a case series review reported the average age of onset of nausea and vomiting was 25.6 years (range 16-51) with subjects having used cannabis for an average of 9.8 years.⁷ The patient in the above case study began using cannabis just months before the onset of symptoms. However, he was using highly concentrated THC called "dabbing," multiple times a day. A dab refers to a highly concentrated dose of THC and other cannabinoids that are extracted out of the bud of the marijuana plant using a solvent like butane. The dabs appear as a small yellow waxy translucent resin often on wax sheets. The dabs are heated on a hot surface (usually a nail) and inhaled thru a dab rig. Some dabs had THC concentrations as high as 90 percent.⁸

The most likely reason for CHS being a relative new phenomenon is, as stated by Van Gerpen in 2015, "One of the greatest misconceptions surrounding marijuana safety is a false belief that the marijuana of the boomer generation is the same marijuana that is being used by our youth today."⁸ The National Institute on Drug Abuse reports, "the amount of tetrahydrocannabinol (THC) has been increasing. In 2012 the THC concentration in marijuana averaged close to 15 percent, compared to around 4 percent in the 1980s."⁹

Wallace et al. in 2011 proposed an algorithm with a series of questions that would imply it may be cannabinoid hyperemesis syndrome:

Do the symptoms improve while taking a hot shower or bath?

Is the bathing compulsive?

Does the patient use cannabis daily or almost daily, and the patient done so for at least the past year?¹⁰

Although with the high THC potency of dabs; we would encourage the physician to ask specifically if the patient has been dabbing since it may not require use for more than a year.

Treatment of CHS mainly consists of continued abstinence

of cannabinoid use. Little to no evidence exists that supports the use of synthetic marijuana to help with cessation. It is more important to initiate palliative treatment of the coexisting symptoms such as anxiety, agitation, pain and/or vomiting. Interestingly, literature does not support the use of antiemetic medications as they have shown little to no benefit in reducing nausea/vomiting. The use of proton pump inhibitors is supported by the possibility of concurrent inflammation of the upper GI tract. Continued bathing should be allowed as it seems to be the only treatment that relieves symptoms besides marijuana use, which would continue the condition. In addition, any sequelae should be treated such as metabolic derangement secondary to fluid loss.⁶

Summary

Cannabinoid hyperemesis syndrome consists of intractable emesis, abdominal pain, weight loss in a person who has a history of heavy cannabis use. Individuals report symptom amelioration with bathing. Cannabis effects vary and are dose dependent. Historically, CHS would require over a year of heavy daily use. In this day and age of higher THC potency marijuana and even higher THC potency “dabs,” it is anticipated that more cases of cannabis related syndromes in general, and CHS in particular, will present more frequently to ambulatory and emergency room settings. The patient will potentially be younger and have a shorter duration of heavy cannabis use before symptoms start. A high index of suspicion will be required to prevent expensive and potentially invasive workups and a delay in diagnosis and treatment.

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Treating Addiction to Prescription Opioids

By Xiaofan Li, MD, PhD; and Thomas Kosten, MD

Abstract

For over 30 years, medication-assisted treatment for preventing relapse in opiate use disorder has been limited to methadone maintenance and withdrawal treatments followed by naltrexone; however, buprenorphine has emerged as an exciting and successful pharmacotherapy alternative. Buprenorphine is a partial μ -opioid receptor agonist with less abuse potential and a favorable safety profile compared to methadone and offers a great opportunity of office-based opioid addiction treatment (OBOT) to improve patient access. However, we have limited number of providers certified to prescribe buprenorphine in South Dakota. We need to address potential barriers for its expansion, including concerns of diversion and abuse, insufficient knowledge on buprenorphine and addiction treatment, and lack of access to addiction specialists and treatment resources. Since buprenorphine does retain some abuse potential, good office practice needs to be implemented as we expand its access. We need to choose appropriate candidates for OBOT with clear expectations at the intake. We need to enforce urine drug screens, pill counts, and use of prescription monitoring programs. It is also important to provide or refer patients to addiction counseling services and more intensive levels of care including methadone maintenance and residential care when needed.

Overview of Prescription Opioid Abuse Epidemic

The use, misuse and dependence on prescription opioid medications have significantly increased in the past decades. For example, sales of prescription opioids

increased four times from 1999 to 2010, equivalent to 710 mg per person per year in the U.S., according to the Centers for Disease Control and Prevention (CDC).¹ The admission rate into substance abuse treatment for opioid

use disorders in 2009 was almost six times the rate in 1999.¹ Finally, opioids have the second highest rate of illicit use, exceeded only by cannabis, and the rate is far above the prevalence of other illicit substances (www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/DetTabs/NSDUH-DetTabsTOC2012.htm). Consequently, the associated medical and societal ramifications have increased as well. Opioid overdose mortality in 2008 almost quadrupled the rate observed in 1999;¹ estimated emergency department visits from non-medical use of opioid analgesics increased 111 percent, from 143,500 visits in 2004 to 271,700 visits in 2008.²

In response to the epidemic of opioid misuse and abuse, a variety of approaches have been employed to address different aspects of the problem, including development of various abuse-deterrent formulations of opioid pain medications, development and dissemination of prescription monitoring programs, promotion of safe and responsible practice in pain management, and increasing the access to treatment for prescription opioid addiction.

Overview of Strategies to Treat Addiction to Prescription Opioids

Despite the prescription opioid abuse epidemic, services for opioid-dependent individuals are limited. Only one-sixth of people with opioid addiction have received treatment, according to a recent report in the *Journal of the American Medical Association*.³ It calls attention to the need for expanded access to effective treatments.

Traditionally, psychosocial intervention is the primary approach in addiction treatment, for example, the 12-step model and cognitive behavioral therapy-relapse prevention. It is still the main modality of treatment for many addictive disorders. However, medication-assisted treatment has a long tradition for opioid use disorder, including the agonist methadone and the antagonist naltrexone. Using naltrexone requires initially managing opioid withdrawal, and several different categories of medications are used, including α -adrenergic agonists, i.e., clonidine and lofexidine, and agonists like methadone. Full μ -receptor agonists, levo- α -acetylmethadol (LAAM), sustained-release oral morphine, and methadone, have all been used for maintenance therapy. Buprenorphine is a partial agonist with less abuse potential and better safety profile than full agonists. Methadone and buprenorphine are probably the two most commonly used agonists to treat opioid dependence currently. Agonist therapy has stronger evidence than antagonist therapy in terms of efficacy in treating opioid addiction,⁴ although some data show more positive outcomes with extended-release intramuscular naltrexone than oral naltrexone.^{5,6}

From the 1970s until early 2000, methadone remained the primary pharmacological intervention for opioid addiction. Although initially started as a harm reduction measure, it has also demonstrated reduced crime rates and spread of infectious diseases among IV drug users, as well as reduced illicit opioid use.⁷ However, methadone is also extremely limited in terms of its access, being available only through federally regulated facilities and to patients with documented chronic addiction. With continued escalation in opioid addiction and the shift to prescription opioid use, buprenorphine emerged as an essential treatment strategy.

Buprenorphine

In 2000, Congress passed the Drug Abuse Treatment Act of 2000 (DATA 2000), which allowed qualified physicians to obtain a waiver to treat opioid addiction with Schedule 3 to 5 narcotic medications in an office setting. Soon, the Food and Drug Administration (FDA) approved buprenorphine for treatment of opioid dependence in October 2002 as a Schedule 3 narcotic medication. It is the first and only pharmacologic agent so far meeting DATA 2000 requirements, allowing medication-assisted treatment for opioid addiction outside the realm of more traditional settings of addiction treatment. Buprenorphine allows the access to medication-assisted treatment to patients who either do not have access to a methadone program or do not meet criteria for methadone treatment, such as people with duration of addiction less than one year.

Pharmacology of Buprenorphine

Buprenorphine has been studied for detoxification (i.e., medically assisted withdrawal) and to transition from detoxification to antagonist therapy. In this review, we will focus mainly on buprenorphine as maintenance therapy.

Buprenorphine is administered sublingually due to poor bioavailability from extensive first pass metabolism by the liver. Currently, the most commonly prescribed buprenorphine formulation for opioid dependence treatment is the combined formulation of buprenorphine:naloxone at a ratio of 4:1 in order to decrease its IV abuse potential.

Buprenorphine can produce withdrawal discomfort among opioid-dependent individuals, either due to insufficient substitution for the full agonist, or displacement of the abused opioid(s) due to buprenorphine's higher affinity. TIP 40 (for buprenorphine) from the Center for Substance Abuse Treatment (CSAT) provides useful general guidelines for beginning buprenorphine therapy at <http://store.samhsa.gov/product/TIP-40-Clinical-Guidelines-for-the-Use-of-Buprenorphine-in-the>

Treatment-of-Opioid-Addiction/SMA07-3939.

In general, patients need to have a diagnosis of opioid addiction based on history, exam and laboratory tests. They need to be in mild withdrawal before the induction of buprenorphine. The typical first dose of buprenorphine is 4 mg, and patients should be assessed for acute adverse effects 30 to 60 minutes after receiving the medication. A repeat 4 mg dose, for a maximum first day dose of 8 mg of buprenorphine, can be given if withdrawal symptoms persist two to four hours after the first dosing. The first day's dose should be followed by dosage increases over subsequent days until withdrawal symptoms are suppressed within about two hours after taking the medication and last until the next day's dosing.

The recommended therapeutic maintenance dose of sublingual buprenorphine/naloxone is 8 mg/2 mg to 24 mg/6 mg per day. Currently, there are no guidelines on the optimal duration of buprenorphine maintenance. General consensus suggests treatment continue for greater than six months, or as long as needed, so that patients may establish psychosocial stability. The overall length of treatment, a decision best made by both the patient and clinician, is likely correlated with the severity of opioid addiction, the quality of psychosocial support and the recovery environment.

Buprenorphine's usual adverse effects are typical of μ -opioid agonists and may include sedation, nausea and/or vomiting, dizziness, lowered libido, headache, constipation and respiratory depression.

The Efficacy of Buprenorphine

Buprenorphine has been demonstrated to be an effective medication for maintenance treatment in heroin dependence in a meta-analysis study done by Cochrane collaborations, which summarized the data of 31 randomized control trials with good quality.¹⁰ Real world studies have demonstrated similar effectiveness compared to the results of clinical trials. Haddad et al. showed buprenorphine in a population with comorbid cocaine use disorder and mood disorder has retention rates and rates for opioid-free urine tests similar to rates in clinical trials in primary opiate dependent subjects.¹¹ A German non-interventional, post-marketing surveillance study also demonstrated high effectiveness and safety in office-based routine care with buprenorphine.¹² Access to buprenorphine therapy has been associated with declines in heroin mortality of more than 50 percent in France and 37 percent in Baltimore, Maryland.^{13,14} More importantly, buprenorphine therapy may improve overall quality of life and psychosocial functioning.¹⁵

Concerns of Buprenorphine in OBOT

Legitimate concerns about buprenorphine abuse make physicians hesitant to prescribe buprenorphine, especially in OBOT. As a partial opioid agonist, buprenorphine does retain addictive potential, albeit reduced. In Finland, buprenorphine was the most frequently used IV drug, reported by 73 percent of community survey respondents in 2007.¹⁶ In the U.S., a recent national survey combined with qualitative interviews found misuse of buprenorphine has increased substantially in the past five years, especially among past month heroin users. It serves as a substitute for other drugs, for example, heroin, when heroin is not available. Alarming, this study also found over one-third of buprenorphine misusers had injected it in the month before the treatment. Participants reported a number of simple and easy methods, which they believed separated buprenorphine from naloxone.¹⁷

Current Status on Buprenorphine Prescribing

Since its approval in 2002, the utilization of buprenorphine therapy has gradually, but significantly, increased. The number of buprenorphine/naloxone tablets sold increased from 8 million tablets in 2005 to over 145 million in 2009.¹⁸ Medical use of buprenorphine increased from 70,332 grams per 100,000 population in 2004 to 1,700,414 grams per 100,000 population in 2011, an increase of 2,318 percent.¹⁹ As of October 2015, over 30,670 physicians are qualified to prescribe buprenorphine for addiction treatment with the number doubled over a 17-month period (compared to the number accessed in May 2014), according to the Service Administration for Mental Health and Substance Abuse (SAMHSA). However, South Dakota has currently only 14 providers certified to prescribe buprenorphine for addiction (www.samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator?field_bup_physician_us_state_value=SD), which is the lowest number of prescribers among all states. Patients on buprenorphine have a difficult time with continuing the medication after relocation from other states.

The logistic issues of buprenorphine induction and routine monitoring in an office setting, the stigma of seeing addictive patients in a primary care office setting, limited access to addiction specialists, and the misconception of agonist therapy being "replacing one addictive substance using another" probably all contribute to the slow growth of buprenorphine prescribing in South Dakota.

Discussion and Conclusions

Methadone has been utilized to treat opioid dependence since the 1970s. Buprenorphine has been used to treat opioid dependence in Europe since 1996 and in the U.S.

since 2003. The National Institutes of Health Consensus statement in 1997 concluded, "All persons dependent on opiates should have access to opiate agonist treatment." Buprenorphine has become the first line medication over methadone to treat opioid addiction due to its favorable side-effect profile, less abuse potential and availability in an office-based setting. OBOT offers several advantages, including an opportunity to match services to individual patient needs, minimization of the stigma associated with opioid dependence and its treatment, limiting patient contact with other substance-abusing individuals, and integrating treatment of substance abuse with other medical disorders in primary care clinical settings. Since 2002, the utilization of buprenorphine therapy has increased significantly; however, we also see a jump in misuse and diversion rates. The recent emerging IV abuse of buprenorphine in the U.S. is especially concerning. Thus, it creates conflicting attitudes about buprenorphine. There are reports on limited access for buprenorphine therapy (www.huffingtonpost.com/2015/05/27/heroin-addiction-senate_n_7456492.html), and its possible contribution to diversion and misuse,¹⁸ which has led to proposals for liberating the prescribing of buprenorphine. One proposal asks DATA 2000 to be amended to allow qualified advanced nurse practitioners and physician assistants to prescribe buprenorphine.²⁰ In the bill "the Recovery Enhancement for Addiction Treatment Act," or TREAT Act, it also requests lifting the cap of patient numbers from 100 to unlimited after one year of prescribing experience by a waived physician (www.congress.gov/bill/113th-congress/senate-bill/2645).

Buprenorphine is clearly an effective treatment for opioid addiction with strong biological and clinical evidence to support its utilization in daily clinical practice, although its abuse and diversion is inevitable with increased

availability. Once a medication with abuse potential has gained popularity and has good availability, its abuse potential will inevitably be explored by drug abusers. Thus the question is not how to limit the use of buprenorphine, but how to ensure safe expansion of buprenorphine therapy. We need to choose appropriate patients for OBOT. The ideal OBOT patients are exclusively dependent on prescription opioids, have a shorter dependence duration, have not had prior opioid dependence treatment, use opioids primarily orally, and have greater social stability.²¹ We also need to implement good office practice. It should include clear expectations at the intake, enforcing urine drug screens, pill counts, and use of prescription monitoring programs. Connection with addiction counseling services and availability of more intensive levels of care are other components of good patient care to allow patients easy transfer to a higher level of care than office-based treatment, when needed. Ongoing education on buprenorphine therapy through graduate medical education and continuing medical education is also important in the course of expansion of buprenorphine prescribing.

In summary, as with other addictive disorders, opioid addiction is a chronic and complex disorder with high relapse rates, high comorbidity of psychiatric diseases, and a need for psychosocial support. The effective medications to treat opioid dependence also carry significant addictive potential, i.e., buprenorphine and methadone. Thus, any single approach will only have transient benefits. The efforts to expand buprenorphine therapy deserve support; however, simultaneously, we will need to ensure safe practice and to develop other measures, including enforcement of urine monitoring and counseling compliance, especially in high risk populations.

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Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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DAKOTACARE Update:

South Dakota Prescription Drug Monitoring Program – More Than Just a Database

By Craig Beers, PharmD; and E. Paul Amundson, MD

First of all, we applaud our partners at the South Dakota State Medical Association (SDSMA) for bringing the important public health issue of prescription drug abuse to physicians by producing this special issue. As a commercial payer with a large and broad presence in this state, DAKOTACARE shares concerns about this growing phenomenon, and we have been working with many entities around the state to find ways to battle (ideally, eliminate) this problem in our region. We work diligently with South Dakota physicians to assist them in their care of our members; by utilizing medication therapy management tools through our pharmacy department which identify members at high risk and inform providers when abuse of a prescribed product(s) is likely.

According to the National Institutes of Health, 52 million people (20 percent of those aged 12 and older) in the U.S. have used prescription medications for non-medical purpose, and it is estimated that 44 people *each day* will die in this country from prescription pain killers. This is an epidemic on the forefront of our medical community (see Dr. Bob Van Demark's excellent related article in the January 2016 issue of *South Dakota Medicine*) and many state and federal government agencies, but thus far our efforts have failed to come up with the "magical" solution to help curb the issue. Although there hasn't been, and probably never will be, one single solution to eradicate this epidemic, there have been important steps taken to attempt to mitigate this issue: PhRMA companies are increasing the development of abuse deterrent/resistant medications; DAKOTACARE and other payers oversee utilization and have implemented formulary restrictions and quantity level limits on products considered to have a high abuse potential; and payer organizations that have access to prescribing information (certain payers and pharmacy benefit management companies) review claims to identify potential abusers and notify prescribers if they identify those "outside the norm," a somewhat controversial process historically as this has the potential to focus on

providers (i.e., oncology, pain specialists) with higher average opioid prescribing based solely on their practice focus. While the above efforts have helped, abusers are still finding ways to circumvent our oversight processes. We need to find a way to limit these medications from getting in the hands of abusers, and we feel that the Prescription Drug Monitoring Program (PDMP) in place in South Dakota is a highly effective tool that, if utilized correctly, could help immensely.

The first PDMPs were developed in the 1930s and were therefore all paper-based. In 1990, Oklahoma launched the first electronic database which helped to increase accuracy and timeliness of the submission data. In 2003, the Harold Rogers Prescription Monitoring grant was established to support states' efforts to collect and analyze data around the dispensing of controlled substances. Currently there are 49 states which have an electronic PDMP in place. The wide spread of this type of program belies the effectiveness. PDMPs are run by a variety of state agencies but they all share the common goal of reducing drug abuse and diversion. These databases are used to collect, monitor and analyze electronically transmitted prescribing and dispensing data submitted by pharmacies and dispensing practitioners. This data can be accessed by entities authorized by state law and used for research, educational, enforcement and abuse prevention.

The PDMP originated when a bill was passed by the South Dakota Legislature and signed by the governor during the 2010 session (South Dakota Codified Law 34-20E). It became operational in 2011 and is overseen by the South Dakota Board of Pharmacy. The original purpose was to improve patient care by providing prescribers and pharmacists with a controlled substance dispensing history for their patients, with an additional goal to reduce drug diversion and inappropriate use of controlled substances by assisting in the investigation of specific cases. We encourage you to visit <https://doh.sd.gov/boards/pharmacy/PDMP-FAQ> to learn more.

When to Use the South Dakota PDMP

New patients – confirming a prescription history or lack thereof.

Chronic pain patients – verify compliance and/or potential diverting medications to unlawful channels.

Acute pain patients – ensure continuity of care.

Patient on pain agreements – ensure medications are being filled and used per agreement.

In the ER – suspect a “doctor shopper” or “pharmacy shopper.”

Chronic early filling patient – potentially on the path to abuse/addiction – early intervention – treatment.

Unimaginative patient – “the dog ate my prescription... it fell down the toilet, again.”

Treatment plan patient – what has been effective drug therapy.

Every six months – check prescribing history to monitor for misuse of your DEA number. Information provided by the South Dakota Board of Pharmacy.

With this legislation, dispensing pharmacies and prescribers are required to report all Schedule 2 through 4 prescriptions filled on a weekly basis. The information provided is saved in the database for three years and patient profiles can be retrieved by any covered entity that has a current patient relationship or a new appointment scheduled. Certainly a point of concern by physicians via SDSMA, when this legislation was being formulated in Pierre, was that law enforcement officers may request information from the database to assist them when conducting an investigation related to illegally obtaining or the illegal use of controlled drugs. To date, we are not aware of any problems which have arisen from this allowance.

Pharmacies and dispensing prescribers are required to report when a controlled substance is *dispensed*; however, the law states that “nothing in this chapter *requires* a prescriber or dispenser to obtain information about a patient from the central repository prior to prescribing or dispensing a controlled substance.” DAKOTACARE and the South Dakota Board of Pharmacy strongly encourage all eligible pharmacists and health care providers to

register for access and implement internal clinic policies to check this readily accessible database before writing/dispensing a controlled prescription.

To get the most out of the PDMP, providers need to obtain access and should check it prior to prescribing or dispensing these controlled substances. Using the PDMP as a resource and not just a database can help providers to make informed decisions before prescribing. It might be a few extra key strokes, but it can save a life. According to the South Dakota PDMP program, only 22 percent of the prescribers and 34 percent of the pharmacists approved for access are using the PDMP to query patients. We can do better.

Health Care Providers Approved for South Dakota PDMP Access

Provider	Number Approved	Percent Approved
Pharmacist	948	85%
Physicians	697	25%
Physician Assistants	247	53%
Nurse Practitioners	208	45%
Dentists	87	20%

Even though drug abuse and diversion will probably never be *completely* eradicated, we as health care providers need to utilize *all* resources available, including the South Dakota PDMP to help mitigate this growing public health problem as much as possible. Please take the time to do your part and not only register for the South Dakota PDMP, but use it regularly.

For more information on how to register for the South Dakota PDMP please visit <http://doh.sd.gov/boards/pharmacy/pdmp> or contact Melissa DeNoon at 605.362.2737.

Quality Focus:

Appropriate Prescription Drug Pain Management

By Stephan D. Schroeder, MD

Medical Director, South Dakota Foundation for Medical Care

Prescription opioid medication plays an important role in controlling pain in elderly patients. It is well accepted that these medications can be involved in adverse drug events and preventable patient harm. Medication safety depends on coordinated care as multiple providers, pharmacies and care settings complicate safe prescribing and appropriate use. Data concerning adverse drug events, (ADEs) such as what occurs with these opioids, can sometimes be surprising and concerning, yet it allows prescribers and pharmacists as well as facilities to vision and target areas for improvement to prevent such events. Patients and their families play a crucial role in preventing these adverse events as well.

To develop and promote evidence-based ADE prevention, South Dakota Foundation for Medical Care (SDFMC) will offer toolkits for overall medication safety as an objective. SDFMC is part of the Great Plains Quality Innovation Network (QIN). This organization serves the needs of health care providers and Medicare consumers across Kansas, Nebraska, North Dakota and South Dakota.

Prescription drug monitoring programs (PDMPs) are statewide electronic databases that collect information regarding patient prescriptions for controlled substances. These programs can be a repository of prescription data that can be utilized to improve patient care and protect prescribers as well. PDMP offers a source of information to help identify potential high use or abuse of narcotic medication.

The Office of the National Coordinator for Health Information Technology, in a presentation on Feb. 17, 2016, to the Centers for Medicare and Medicaid Services (CMS) Quality Innovation Networks, described areas of priority including prescribing practices to reduce opioid use disorders. The objectives and standards included: 1) improving clinical decision making to reduce inappropriate opioid prescribing; 2) furthering the PDMP and health IT interoperability; and 3) expanding efforts to harmonize

technical standards to support PDMP and health IT work in this area. The key is improved communication among all providers and all patients and pharmacies to improve quality measurement and ultimately health outcomes of individuals.

Opioids in the elderly are an ever present challenge complicated by the need to balance pain control versus fall risk assessment. Integrated evaluation of opioid use should be constantly undertaken and reductions or changes made whenever possible. The potential problems of nonsteroidal anti-inflammatory drugs can limit choices in this vulnerable elderly population. It would seem desirable that all elderly patients on opioids, whether in long-term care, assisted living or living at home, receive constant attention to pain medication use.

Perhaps the most challenging aspect of ADEs lies in its accepted definition. A recent survey by the Great Plains QIN among several different categories of providers and facilities showed a fair amount of variation within the groups as to their distinct definition of such an event. Among the respondents, skilled nursing facilities and home health agencies had the highest proportion using the same definition. Hospitals and pharmacies were the most likely to track ADEs over time. The definitions ranged from not receiving the medication as ordered or scheduled all the way to unexpected, undesirable, and unintended effect at usual dose for appropriate diagnosis and therapy. This represents a challenge on how to compare data from facilities and whether barriers may include voluntary/under reporting.

While a majority track ADEs through electronic health records, it is likely that manual review of the activity is needed to create accurate incident reports; again a need for educated staff and time. Clearly, a future challenge remains on how to define and measure a safe, effective use of narcotic medication as well as many other pharmaceutical categories. Medication safety among opioids remains a daunting task.

"Quality Focus" is a paid feature presented by the SDFMC, South Dakota's Quality Improvement Organization.
For more information about the SDFMC, visit their website at www.sdfmc.org.

Patient Education:

The Power of the Flower

By Richard P. Holm, MD

Thousands of years ago our ancestors discovered that the extract of the poppy flower helped relieve pain. Through the ages, narcotics were developed by refining and reforming the chemicals from that poppy in order to provide for merciful relief for countless people in times of great suffering. In the same way we have discovered many medicines from the natural world. Tea made from the coca plant also has been used medicinally through the ages, like many other natural plant-based medicines.

Many of these medicines can alter the way people feel and perceive reality, all to help people through illnesses of various types, and even during the dying process. The paradox is that sometimes lives are destroyed with an inappropriate use of these medicines.

For example, when a 35 year-old woman, struggling with a painful and eroding cancer, receives a narcotic to ease her suffering and agony, this is good. But when another 35 year-old woman, facing a disinterest in any and everything, takes multiple daily doses of narcotic pain pills to numb the boredom and the discomfort of withdrawal, this is bad.

When a 15 year-old boy with attention deficit disorder, struggling as a frenetic, disruptive, and failing student, receives a slow release low dose amphetamine such as Ritalin to allow him to concentrate and become a productive classmate, this is good. But when a 15 year-old boy, no longer able to find any sense of fun or contentment when sober or straight, snorts a fresh batch of Methamphetamine to find an artificial thrill and sense of value, this is bad.



Thank you Mother Nature for the poppy, the coca plant, and other medicines from the natural world. And thank you science for discovering how to use those plants to rescue a dying woman from excruciating pain or a struggling boy from an inability to concentrate. But may we have the wisdom to use the power of the flower for the good of human kind, and may we have the strength and insight to save our loved ones and ourselves from the danger of abuse.

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