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In This Issue

This issue of the *Residents' Journal* focuses on the topic of addiction psychiatry. Adriane M. dela Cruz, M.D., Ph.D., provides informative data on the diagnosis and treatment of prescription opioid abuse in patients with chronic noncancer pain. The rise in opioid overdoses is discussed in an article by Matt Goldenberg, D.O. Rachel Katz, M.D., outlines evolving approaches to the pharmacologic treatment of alcohol withdrawal. In a case report, Adriana de Julio, M.D., M.S.P.H., Jude Registre, B.S., M.S., and Merlyn Abraham, B.S., discuss complicated intoxication and withdrawal in a patient using synthetic cannabis, emphasizing the psychiatrist's role in integrative medical teams. Juliet Muzere, D.O., presents a comprehensive review on the use of an illicit street drug called "krokodil," including data on epidemiology, pharmacology, diagnosis, and treatment. Lastly, Lynn Yen, M.D., offers a commentary on a model for the use of tele-mental health services in addiction psychiatry.

Diagnosis and Treatment of Prescription Opioid Use Disorder in Patients With Chronic Noncancer Pain

Adriane M. dela Cruz, M.D., Ph.D.

The number of cases of prescription opioid abuse and addiction continue to rise. In 2012, 4.9 million Americans ages 12 and older used these drugs illicitly, making them the second most commonly used illicit drugs (1). This increase has been attributed to increases in the use of opioids for chronic noncancer pain. The majority of misused opioids are obtained (directly or indirectly) through legal prescriptions (1). The number of patients seeking treatment for prescription opioid addiction nearly tripled from 360,000 in 2002 to 973,00 in 2012 (1). The rate of opioid-attributable deaths has increased in parallel with increases in prescription opioid misuse and addiction. More Americans die from prescription opioid overdoses than from heroin and cocaine combined (2). The present review aims to provide psychiatrists with an overview of the diagnosis and treatment of prescription opioid addiction.

Diagnosis of Prescription Opioid Addiction

"Opioid use disorder" and "opioid addiction" are interchangeable and define the clinical syndrome of impaired function related to opioid use (Table 1). Opioid use disorder replaces the DSM-IV diagnoses of "opioid abuse" and "opioid dependence." "Physical dependence" describes physical adaptations in response to repeated opioid exposure that are expected in all patients, whether or not an addiction develops (3); thus, physical dependence is not a sign of prescription opioid addiction. Consistent with this idea, DSM-5 notes that the criteria for withdrawal and tolerance, which indicate physical dependence, are not used when making a diagnosis of opioid use disorder for patients taking opioids under medical supervision (4). Concern by the opioid-prescribing physician for

the development of prescription opioid addiction as evidenced by aberrant drug-related behavior is likely to prompt referral for psychiatric evaluation. Formal diagnosis of opioid use disorder is made using DSM-5 criteria.

Assessment for the risk of prescription opioid addiction begins even before the opioid pain medication is first prescribed and can involve a multidisciplinary team, including a primary care provider, pain management physician, psychiatrist, psychologist, and physical therapist, particularly for patients at high risk for prescription opioid addiction (5). Expert consensus guidelines recommend a thorough pain history and physical examination (with appropriate laboratory tests and imaging) and detailed psychiatric history, including any personal or family history of drug or alcohol use disorders (5), prior to prescription of opioids for chronic noncancer pain as a means to decrease inappropriate prescriptions for patients with conditions that are not likely to improve with opioid therapy. Screening tools can aid in risk stratification, and although no single assessment can be considered a gold-standard at this time, use of at least one instrument is recommended for all patients (5). Risk stratification should be used to guide prescription practices and ongoing monitoring for aberrant drug-related behavior as a means to identify those with problem opioid use as soon as possible. Guidelines recommend presenting opioid therapy to patients as a medication trial after the patient and provider have worked together to establish clear treatment goals (5), which can limit ongoing exposure to opioids and thus decrease the risk of prescription opioid addiction. Treatment goals are best when focused on functional outcomes, with the patient and provider aware that complete resolution of pain is unlikely (5). Nonopioid treatments

for pain, including adjunct medications (e.g., nonsteroidal anti-inflammatory medications and antiepileptic drugs), physical and occupational therapy, and cognitive-behavioral therapy, are important components of pain management for all patients with chronic noncancer pain (5), which further limits opioid exposure. Ongoing monitoring may include urine drug tests and measures of pain and aberrant drug-related behavior (5). Monitoring of state-based prescription databases throughout opioid therapy can help ensure that patients are not receiving controlled medications from multiple providers, although use of these databases is somewhat limited by the lack of a national database that includes medications prescribed in the VA system (6). Thus, the assessment and diagnosis of prescription opioid addiction involve several steps: careful pain assessment prior to opioid prescription, monitoring the risk-benefit ratio of ongoing opioid therapy and aberrant drug-related behavior, and use of DSM-5 criteria for formal diagnosis of prescription opioid addiction when necessary.

Treatment of Prescription Opioid Addiction

Pharmacotherapy for prescription opioid addiction is an emerging field, with knowledge gained from the treatment of heroin addiction. In the United States, the two mainstays of pharmacotherapy for heroin addiction are methadone, administered through a federally licensed methadone maintenance program, and office-based treatment with buprenorphine-naloxone. The depot preparation of naltrexone is approved by the Food and Drug Administration for maintenance therapy of opioid addiction, and oral naltrexone tablets are available. Use of naltrexone for heroin addiction is limited by

TABLE 1. Definition of Diagnostic Terms

Term	Definition
Opioid addiction	"A primary, chronic, neurobiological disease … characterized by … one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving" (see reference [3]).
Physical dependence	"A state of adaptation that is manifested by a drug class specific withdrawal syndrome" (see reference [3]).
Opioid use disorder	"A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two [criteria], occurring within a 12-month period" (see reference [4]).
Pseudoaddiction	Behaviors that appear consistent with addiction that are secondary to undertreatment of pain (see reference [3]).
Aberrant drug-related behavior	Any inappropriate medication-related behavior (e.g., doctor shopping, tampering with prescriptions, loss of prescriptions, urine negative for prescribed opioid/positive for illicit substance) (see reference [6]).

concerns regarding efficacy (similar abstinence outcomes when compared with placebo (see reference [7]) and difficulties with patient adherence (6). Methadone maintenance decreases heroin use by 66%, even 5 years after initial treatment, with concomitant decreases in cocaine and alcohol use and crime participation (8). Treatment with buprenorphine-naloxone is likely equally efficacious as methadone treatment for heroin addiction (9).

Initial knowledge regarding the treatment of prescription opioid addiction was derived from secondary analyses of treatment trials with heroin-addicted and prescription opioid-addicted participants. These analyses demonstrated improved treatment outcomes among those with prescription opioid addiction compared with heroin addiction: 10% higher treatment retention in methadone treatment (10) and 20% higher rate of opioid-free urine screen results with buprenorphine-naloxone treatment (11). No differences in abstinence outcomes for buprenorphine-naloxone compared with methadone treatment were observed in the Starting Treatment with Agonist Replacement Therapies study (12). These trials supported the idea that patients with prescription opioid addiction were higher functioning and less ill (younger age, higher income, fewer years of drug use, less drug experience, and less injection drug use) than those with heroin addiction (10–12), suggesting that those with prescription opioid addiction were presenting for treatment earlier. Thus, it was thought that short-term treatment would be efficacious for prescription opioid addiction.

Two randomized controlled trials tested the efficacy of short-term pharmacotherapy in patients with prescription opioid addiction, including the very large Prescription Opioid Addiction Treatment Study. Opioid abstinence rates as high as 50%–60% during acute (6–12 weeks) buprenorphine-naloxone treatment at doses of 2 mg–32 mg of buprenorphine were observed (13, 14). Following buprenorphine-naloxone cessation, the continued abstinence rate dropped to <10% without adjunctive medication in the Prescription Opioid Addiction Treatment Study (13) and to 17%–50% among patients maintained on thrice-weekly oral naltrexone (14). Higher abstinence rates were observed among patients who received longer buprenorphine-naloxone treatment (14). Thus, while short-term buprenorphine-naloxone treatment is effective during treatment, the benefits of treatment are not sustained when the medication is discontinued.

Evidence for long-term treatment comes primarily from case reports that describe effective long-term (>1 year) office-based treatment with buprenorphine-naloxone (buprenorphine 16 mg/day–40 mg/day) for patients with prescription opioid addiction (15, 16). One clinical trial directly compared 6 months of buprenorphine-naloxone with methadone for patients with chronic pain and prescription opioid addiction (17), although serious methodological flaws (e.g., participants could change groups during the trial) limit interpretation. Similar outcomes for pain control with less illicit opioid use with methadone compared with buprenorphine-naloxone were observed, with each medicine titrated for pain control (17). An additional limitation to applying the study results to psychiatric practice is that methadone was dosed as a pain medication (oral tablets, twice daily) and not under the auspices of a methadone maintenance treatment. The study does, however, provide evidence that the medications used in the management of prescription opioid addiction may also provide pain management and thus be of dual benefit to patients.

The roles of psychotherapy and addiction counseling remain unclear. The Prescription Opioid Addiction Treatment Study trial did not demonstrate any additional benefit from counseling when used with buprenorphine-naloxone (13), although a secondary analysis demonstrated double the rate of abstinence in the subpopulation of prescription opioid users with any heroin experience who attended ≥60% of addiction counseling sessions compared with those with heroin experience who did not receive counseling (18). A small (N=20/group) trial demonstrated efficacy for decreasing aberrant drug-related behavior with combined individual and group therapy focused on medication misuse in patients currently receiving opioid therapy for chronic noncancer pain at high risk for aberrant drug-related behavior (19). Patients with co-occurring mood, anxiety, and personality disorders might receive additional benefit from long-term psychotherapy that targets these symptoms (16).

Additionally, there is hope that the use of newly developed abuse-deterrent formulations will decrease diversion and prescription opioid addiction, thus decreasing the demand for treatment directed at this form of addiction. Decreased diversion has been observed with a reformulation of oxycodone that contains physical barriers to breaking, crushing, and injection (20); an additional reformulation of oxycodone is under development (20). A combination of extended-release morphine and na-

ltrexone is expected to be re-released in 2015, following a 2011 recall (20). Other abuse-deterrent formulations include a reformulation of extended-release tapentadol and combination extended-release oxycodone and naloxone (20).

Summary and Recommendations

The initial psychiatric evaluation of a patient presenting with or referred for prescription opioid addiction focuses on determining whether the patient's symptoms fulfill DSM-5 criteria for opioid use disorder, remembering that withdrawal and tolerance are not counted as symptoms toward the diagnosis for patients taking a prescribed opioid. The patient's level of functioning can be maximized when the psychiatrist treating the addiction works closely with the patient's other treatment providers to help the patient achieve appropriate pain control while addressing addiction. Current evidence supports beginning treatment for prescription opioid addiction with at least 3 months of either office-based buprenorphine-naloxone or methadone in a methadone maintenance program. While there is no direct evidence to indicate the ideal length of time for medication treatment, it is evident from the current literature that short-term (≤3 months) treatment leads to high rates of relapse when treatment is discontinued. Determining whether methadone or buprenorphine-naloxone is most appropriate for the patient is left to the clinical judgment of the psychiatrist, with patient adherence to treatment likely to be the most important factor. Drug counseling to enhance motivation for treatment and support relapse prevention is generally included in treatment, although evidence gathered in patients with prescription opioid addiction has yet to demonstrate clear benefits of counseling. Future areas for research include prospective studies comparing buprenorphine-naloxone with methadone, further exploration of the role of counseling, and examination of treatment length beyond 3 months.

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Opioid Overdoses:
A Guide to Stem the Tide

Matt Goldenberg, D.O.

There is an epidemic of drug overdose facing our country. According to the Office of National Drug Control Policy, 100 Americans die from drug overdose every day (1). The Centers for Disease Control and Prevention has reported that about 50% of overdoses are due to prescription pain medication (2). This problem is nationwide and affects all types of Americans, regardless of age, race, or environment. The five states with the highest rates of overdose deaths in 2010 were West Virginia, New Mexico, Kentucky, Nevada, and Oklahoma (3).

One explanation is that opioid medications have been increasingly prescribed for the treatment of nonmalignant pain. According to the Centers for Disease Control and Prevention, health care providers wrote 259 million prescriptions for painkillers in 2012. An unforeseen consequence is that many users of narcotic pain medication transition to heroin use. Users of pain medications can develop tolerance and subsequently require more medication than what is prescribed. Heroin is lower in cost than prescription pain medication and easy to access on the black market. In several recent nationwide studies, nearly one-half of young people who used heroin intravenously reported abusing prescription opioids prior to initiating heroin (4). This information could help to explain why heroin overdoses increased 45% from 2006 to 2010 (5).

Another reason for the rise in heroin overdoses is that it is now often cut with fentanyl, an opiate that is 30 to 50 times more potent than heroin. Users are often unaware that their supply is stronger than usual, creating an extremely dangerous situation (6). When a user takes a higher dose than intended, a potential consequence is cessation of breathing. Nearly one-quarter of users suffer a near miss (an overdose from which a person nearly dies but is able to recover). Nationwide, there are an estimated 2,500 to 5,000 near misses daily (5).

The Office of the National Drug Control Policy has developed several recommendations to prevent opioid deaths, including providing addicted individuals with an accessible referral line, learning the symptoms of overdose, calling 911, and administering naloxone (an opioid receptor antagonist to reverse intoxication and overdose) (1). In April 2014, the Food and Drug Administration approved the first naloxone auto-injector (naloxone hydrochloride injection), which acts similar to an automated defibrillator, with verbal instructions provided.

An effective treatment plan, however, not only addresses the symptoms of opioid intoxication and withdrawal but focuses on the disease of addiction itself. There are behavioral and pharmacological treatments for opioid use disorder (now a DSM-5 diagnosis), and utilization of both approaches is usually most effective. Medications include opioid receptor agonists (i.e., methadone), partial agonists (i.e., buprenorphine), and antagonists (i.e., naltrexone). Behavioral therapies include contingency management, cognitive-behavioral therapy, and motivational interviewing (4).

The more we as a society are educated about substance use disorders, the more they become destigmatized and viewed as chronic medical conditions like other medical illnesses. Overdose is often a complication of the disease of addiction. Furthermore, reporting of research findings and treatment options helps to raise public awareness and may potentially decrease the number of overdoses. The epidemic should grab our attention; however, it is the disease of addiction that requires the best of our energies and skills.

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For further information on the topic of mental health and addiction, visit Dr. Goldenberg's blog Mind Matters.

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Evolving Approaches to the Pharmacologic Treatment of Alcohol Withdrawal

Rachel Katz, M.D.

Alcohol withdrawal is a frequently encountered and variably treated clinical syndrome that can result in significant morbidity and cost. Management of alcohol withdrawal targets the underlying pathophysiologic changes that occur with chronic alcohol exposure and acute withdrawal. Acute intoxication causes transient changes in the brain, and chronic exposure can fundamentally alter receptor activity and neurotransmitter concentration in multiple pathways.

Alcohol directly stimulates the GABA-A receptor complex by binding to the gamma subunit, which opens voltage-gated chloride channels leading to decreased neuronal excitability, and also increases GABA-mediated dopamine release in the nucleus accumbens (1–3). Inhibition of N-methyl-D-aspartic acid (NMDA) receptor activity leads to decreased glutamate and increased serotonin release, resulting in sedation and euphoria (1). Mu and delta opioid receptors are also activated, which leads to endogenous opioid and dopamine release, also contributing to alcohol's acute euphoric effect.

Chronic alcohol exposure causes downregulation of GABA-A and upregulation of NMDA receptors. These changes lead to tolerance, reduced gabaminergic function, and increased glutamate levels, which all contribute to neuronal hyperexcitability (2). Alterations in opioid and 5-HT$_3$ receptor activity result in withdrawal dysphoria and urges for "relief drinking" without euphoric effect (4). Alpha-2 receptors become desensitized, increasing extracellular dopamine and norepinephrine (a dopamine metabolite), which eventually causes increases in receptor concentration and hypersensitivity of the autonomic adrenergic system (2). While the exact mechanisms are not fully understood, hyperexcitability due to dysregulation of the balance of GABA and glutamate activity, and hypersensitivity of the noradrenergic system, are thought to contribute to the symptoms of alcohol withdrawal, including anxiety, tremors, delirium, and seizures (5). Benzodiazepines are commonly used to treat severe withdrawal, but a standard regimen is debated, and a growing body of evidence for mild-to-moderate withdrawal exists for alternative agents.

Medication selection depends upon estimated risk of withdrawal severity, including evaluation for alcoholic hallucinosis or delirium tremens. Risk factors include a history of previous delirium tremens, withdrawal seizures, multiple previous detoxifications, and high amounts of daily alcohol consumption (6). A basic metabolic panel, complete blood count, liver function tests, thyroid-stimulating hormone measurement, and urine toxicology screen can help rule out alternative causes of delirium and common metabolic abnormalities in alcoholism, such as hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, ketoacidosis, and lactic acidosis.

Alcoholic hallucinosis, or persistent hallucinations with clear sensorium, begins 7–48 hours after the last drink and can be treated with antipsychotics. Withdrawal seizures, which also typically occur 7–48 hours after the last drink, warrant intensive care unit admission and can be treated with benzodiazepines and valproic acid (2). Delirium tremens, a syndrome of autonomic hyperactivity, delirium, psychosis, hallucinations, seizures, and coma, can occur 48 hours to 10 days after the last drink. Delirium tremens requires intensive care unit admission due to high morbidity and is treated with intravenous benzodiazepines and sedating agents that target the underlying pathophysiologic mechanisms of withdrawal. Thiamine is provided to prevent Wernicke-Korsakoff syndrome. Magnesium repletion is also important; as an NMDA antagonist, symptomatic magnesium deficiency can mimic alcohol withdrawal and may be correlated with delirium tremens severity (3).

Benzodiazepines

Alcohol withdrawal is commonly treated with shorter-acting agents, such as lorazepam or oxazepam, or longer-acting agents, such as diazepam or chlordiazepoxide. Lorazepam and oxazepam are typically administered with standing or symptom-triggered approaches according to Clinical Institute Withdrawal Assessment for Alcohol–Revised scores. Longer-acting agents can also be used for loading, standing, or symptom-triggered regimens due to active metabolites present for 50–100 hours with marked accumulation. Lorazepam and diazepam come in parenteral form to treat severe alcohol withdrawal, including withdrawal seizures and delirium tremens.

Many studies compare symptom-triggered and loading approaches with conflicting results. A Cochrane review found no statistically significant advantage of any approach, corroborated by a 2012 randomized controlled trial by Maldonado et al. (7, 8). Although chlordiazepoxide showed slight advantage for seizure prophylaxis, conclusions were limited by sample sizes and varied regimens, and there was no clear benefit of any regimen. However, there are merits to both symptom-triggered and loading approaches. Some studies suggest that short-acting agents minimize overmedication, decrease length of stay, and are safer for patients with underlying liver or respiratory disease (9, 10). Long-acting medications can yield "smoother" detoxifications due to fewer breakthrough symptoms, faster subjective symptom resolution, decreased seizure risk, decreased monitoring requirements, and lower medication cost. Loading or parenteral regimens are recommended for severe alcohol withdrawal, reflected by scores >15 on the Clinical Institute Withdrawal Assessment for Alcohol–Revised (2).

However, long-acting agents may result in unpredictable accumulation of active metabolites in geriatric patients and in those with liver or respiratory disease (8, 11, 12).

Anticonvulsants and Gabaminergic Agents

Historically, anticonvulsants and sedatives, such as valproic acid, phenobarbital, and clomethiazole, have been used as independent or adjunct treatments for alcohol withdrawal with varying safety and efficacy. Direct GABA-modulating agents (gabaminergics), such as gabapentin, pregabalin, and baclofen, are increasingly studied as alternative treatments for mild-to-moderate withdrawal symptoms. Anticonvulsants and gabaminergics may offer benefit because of their decreased abuse potential, decreased risk of oversedation, and less cognitive blunting. Gabaminergics are also advantageous in patients with liver disease because of their predominantly renal excretion. If continued after withdrawal, gabaminergics may also provide superior prophylaxis from early relapse (13).

A second Cochrane review found no statistically significant evidence for anticonvulsants when compared with benzodiazepines, although their side effect profiles were at times advantageous (14). Carbamazepine demonstrated superiority to short-acting benzodiazepines based on Clinical Institute Withdrawal Assessment for Alcohol–Revised scores and seizure frequency (14). No other anticonvulsants demonstrated compelling benefit over benzodiazepines, including valproic acid and levetiracetam. While this review did not compare anticonvulsants with individual benzodiazepines, there was not sufficient evidence to favor anticonvulsants. A review of carbamazepine and oxcarbazepine, conducted by Barrons et al. (15), demonstrated efficacy for symptom relief, but these agents were not reliably protective for withdrawal seizures and delirium tremens (15).

Gabaminergics have shown promising evidence in early trials as independent agents for mild-to-moderate withdrawal. Gabapentin, a GABA-mimetic, offers advantages in patients with liver disease and has fewer adverse effects than benzodiazepines or anticonvulsants. In a randomized controlled trial of 100 patients, high-dose gabapentin (800 mg q.d.–1,200 mg q.d.) was clinically similar to lorazepam in the reduction of scores on the Clinical Institute Withdrawal Assessment for Alcohol–Revised, with less sedation, less subjective anxiety, and decreased likelihood for early relapse (13). However, gabapentin is often insufficient for severe alcohol withdrawal, necessitating additional treatment with benzodiazepines (13, 16). In a 2013 Cochrane review, baclofen, a GABA-B receptor agonist, showed comparable efficacy to both lorazepam and diazepam (17). Baclofen rapidly reduced withdrawal symptoms and decreased the need for benzodiazepines, although evidence was insufficient for recommendation as an independent agent (14, 17). Pregabalin, a GABA analog similar to gabapentin, has not demonstrated efficacy for alcohol withdrawal, although it may decrease cravings when administered chronically (18).

Propofol

Propofol activates GABA-A receptors, inhibits glutamate and NMDA receptors, and decreases extracellular glutamate by inhibiting sodium channel-dependent release. Unlike benzodiazepines, propofol does not require the presence of endogenous GABA for efficacy and actually promotes improved benzodiazepine binding to the GABA-A receptor (3). It is a helpful agent in treatment-refractory cases of withdrawal, is easily titratable, and rapidly cleared. However, propofol can cause hypotension, as well as respiratory and cardiac depression, therefore necessitating intensive care unit admission, intubation, and close monitoring.

Alpha-2 Agonists

Alpha-2 receptor activation causes inhibition of catecholamine release in the CNS. Receptor desensitization in chronic alcohol abuse leads to autonomic hyperactivity in withdrawal. Alpha-2 agonists such as dexmedetomidine and clonidine are becoming more commonly used as adjunct agents but do not have anticonvulsant properties. Dexmedetomidine provides sedation without causing respiratory depression and has a low propensity for delirium. Clonidine may also be helpful for symptomatic relief of mild-to-moderate withdrawal symptoms (2).

Antipsychotics

Historically, antipsychotics such as chlorpromazine, promazine, and triflupromazine were used with some efficacy for mild-to-moderate withdrawal symptoms (2). Haloperidol is still used in combination with benzodiazepines for some cases of benzodiazepine-resistant agitation, alcoholic hallucinosis, or delirium tremens. Risk of respiratory depression is low, but these agents do not provide protection from withdrawal seizures and therefore should not be used independently (2).

Beta Blockers

Propranolol has been used to treat the autonomic symptoms of alcohol withdrawal, such as tachycardia and hypertension. Beta blockers may mask worsening withdrawal symptoms, and in one study were suggested to increase the risk of developing alcoholic hallucinosis (2, 6).

Summary

There is a growing body of evidence that anticonvulsants and gabaminergics are effective for the treatment of mild-to-moderate alcohol withdrawal symptoms. These medications may offer fewer side effects and decreased addictive potential compared with benzodiazepines. Further research is needed to evaluate the safety of anticonvulsants and gabaminergics as both independent and adjunctive agents. Gababinergics and alpha-2 agonists may be helpful as adjunct agents to treat symptoms and to decrease total benzodiazepine requirements. There is no convincing evidence that anticonvulsants and gabaminergics are superior to benzodiazepines for most cases of alcohol withdrawal. Benzodiazepine regimens vary, with choice influenced by patient age and medical comorbidities. Long-acting benzodiazepines show benefit for subjective symptom relief and seizure prophylaxis. Short-acting benzo-

diazepines minimize overmedication and length of stay and are preferred in geriatric patients and in those with liver and respiratory disease.

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Synthetic Cannabis: A Case of Complicated Intoxication and Withdrawal

Adriana de Julio, M.D., M.S.P.H.
Jude Registre, B.S., M.S.
Merlyn Abraham, B.S.

Synthetic cannabis has become well-known as a drug of abuse. It is reported that approximately 12% of U.S. high school students have used synthetic cannabis in the past year (1). Although the use of synthetic cannabis is growing, treating synthetic cannabis intoxication and withdrawal continues to be difficult. A recent survey of emergency department physicians practicing in urban areas revealed that only 20% of the physicians surveyed felt prepared to take care of a patient with acute synthetic cannabis intoxication (2).

We present a case that highlights the medical, neurological, and psychiatric sequelae from acute synthetic cannabis intoxication, as well as the psychiatrist's role in integrative medical teams treating synthetic cannabis withdrawal.

Case

"Mr. S" is a healthy 28-year-old single, Middle Eastern man, who works as a sales manager. He has a history of alcohol, tobacco, and cannabis use but no prior neurologic or psychiatric disorders. Paramedics found him unresponsive and unconscious at a train station. Upon arrival, the paramedics noted the patient's Glasgow Coma Scale score as 9, that blood was on his mouth and lips, and that he had abrasions along his right side. Soon after initial assessment, the patient had a tonic-clonic seizure for approximately 1 minute. Midazolam was administered, and the patient was intubated and transported to an emergency department. In the emergency department, he was confused and combative. Telemetry readings revealed sinus tachycardia. The patient subsequently experienced two more tonic-clonic seizures, and midazolam, succinylcholine, propofol, and lorazepam were administered. Laboratory results revealed a white blood cell count of 33,000, elevated creatinine levels, and negative standard urine drug screen. His blood alcohol content was undetectable, and toxicology for acetaminophen and salicylate was unremarkable. CT of the head showed no acute injury. In the emergency department, the patient's family reported that he was using "K2," a type of synthetic cannabis. However, little attention was given to this vital piece of information, and consequently the differential diagnosis did not include synthetic cannabis intoxication. Neurology performed a lumbar puncture and ordered levetiracetam. Infectious disease ordered vancomycin, ceftriaxone, and acyclovir. The patient was stabilized and admitted to the intensive care unit.

On day 1, he was extubated, placed on oxygen, and was able to participate in an interview. He stated that he had noticed blood in his urine for the past 34 weeks, but he had not sought medical attention. He also admitted using synthetic cannabis sporadically. On day 2, CSF analysis was reported as normal. However, his renal function continued to decline, his creatinine levels increased from 1.47 mg/dL to 3.98 mg/dL overnight, and he became anuric. Nephrology was consulted and decided to dialyze the patient, start piperacillin/tazobactam, and start a course of steroids. By day 4, there was great improvement in the patient's respiratory function, and he required no further supplemental oxygen. He underwent dialysis and a kidney biopsy that revealed acute tubular necrosis. On day 5, he began reporting increasing anxiety, chest pain, palpitations, fear of dying, and uncontrollable crying that was accompanied by tachycardia and sweating. These symptoms were treated with lorazepam.

Psychiatry was consulted on day 7 because he continued to experience frequent panic attacks. A complete psychiatric history was obtained, which revealed that the patient had suffered from social anxiety. His social anxiety caused him to sweat, and 5 years prior, he sought a medical consult from a plastic surgeon for hyperhidrosis of the axilla. He underwent botulinum toxin injections that improved the hyperhidrosis but admitted that he was also using cannabis to feel comfortable in social situations. He began a job 4 years prior with an employer who administered regular urine drug screens, and he then decided to use synthetic cannabis to avoid detection. Initially, he was using 1 gram/day but reported that over the past 2 months, he had been using up to 3 grams/day. He endorsed a history of panic attacks associated with withdrawal from synthetic cannabis. Since being admitted, he had complaints of severe anxiety, restlessness, nightmares, chest pain, headache, and nausea. He had profuse diaphoresis, hypertension, and tachycardia. Psychiatry diagnosed him with synthetic cannabis withdrawal syndrome. Working with the nephrology and internal medicine teams, the psychiatry team started the patient on low-dose clonazepam and clonidine. As the patient's renal function improved, clonazepam and clonidine were discontinued, and he was prescribed gabapentin for anxiety. His somatic symptoms subsided by day 9. His anxiety improved but was still present at discharge on day 11. At discharge, he was prescribed gabapentin for 30 days, and neurology prescribed levetiracetam with recommendations to continue for 2 years. The patient enrolled in an intensive substance abuse day program. He has been an active participant in the program, and all drug screens, ordered to include synthetic cannabis, have been negative.

Discussion

This case illustrates the perils of synthetic cannabis intoxication and withdrawal, as well as the need for an integrative team approach to successfully treat patients

experiencing short- and long-term adverse effects of synthetic cannabis use. To our knowledge, the present report is one of three reports in the literature (patients, N=22) linking synthetic cannabis intoxication to acute kidney injury (3). In our patient, initial laboratory results showed elevated creatinine levels in a healthy young man, but owing in part to the physicians' overall unfamiliarity with treating synthetic cannabis intoxication, it was not initially identified as the cause of the seizure or acute kidney injury. The patient's initial creatinine level was 1.47 mg/dL and peaked at 8.29 mg/dL. Dialysis was started on day 2 of hospitalization. Biopsy revealed acute tubular necrosis. The pathogenic mechanism in acute tubular necrosis in patients with synthetic cannabis intoxication remains unknown, but it might be that synthetic cannabis substrate metabolism may be nephrotoxic (4). Ultimately, the patient's renal function improved, and at discharge his creatinine level was 4.67 mg/dL.

The present case is one of three case reports of prolonged withdrawal syndrome from synthetic cannabis use (5, 6). During the patient's withdrawal from synthetic cannabis use, he became acutely anxious, with panic attacks occurring up to 10 times per day. Unlike marijuana (9THC), which is a partial agonist at cannabinoidal receptors, synthetic cannabis is a full agonist as demonstrated in both cellular assays and animal studies (7). Additionally, synthetic cannabis binds with higher affinity than 9THC.

This distinct pharmacology of synthetic cannabis compared with 9THC makes it much more toxic and may be part of the explanation for its seizure potential and prolonged anxiogenic effects during withdrawal (6). The chemical mechanisms that increase levels of anxiety have been studied in the rodent model. There is a body of evidence demonstrating that synthetic cannabis increases the noradrenergic activity by increasing the firing

rate of locus coeruleus neurons (7–9), causing anxiogenic-like responses that last up to 8 days. Our patient was initially given lorazepam for anxiety, which was modified to longer-lasting clonazepam and clonidine and ultimately gabapentin alone. Additionally, psychiatry utilized relaxation and meditation techniques to improve his anxiety.

Conclusions

While alcohol, tobacco, and cannabis have higher rates of use among youths and young adults, synthetic cannabis is a large public health concern (10). Identifying patients with synthetic cannabis use is a challenge because standard urine drug screens do not detect it. Physicians should be aware that a negative drug screen may not guarantee that a patient is substance free. Integrative teams must carefully monitor patient's neurological, psychiatric, and renal status if synthetic cannabis is suspected. The serious neurological and psychiatric sequelae of synthetic cannabis use are often the reason psychiatrists will be consulted to assist in treatment. Psychiatrists should remain mindful about synthetic cannabis so as not to misdiagnose symptoms as psychiatric rather than substance related. Additionally, they must consider the serious medical sequelae before prescribing medications to assist with intoxication and withdrawal symptoms.

Dr. de Julio is a third-year psychiatry resident in the Department of Psychiatry, Advocate Lutheran General Hospital, Chicago. Mr. Registre is a fourth-year medical student at the University of Illinois at Chicago. Ms. Abraham is a second-year medical student at Chicago Medical School, Rosalind Franklin University of Medicine and Science.

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Krokodil

Juliet Muzere, D.O.

Krokodil is the Russian word for "crocodile." It is also the designated street name for an illicit drug used primarily in Russia and Ukraine and consists of desomorphine, a synthetic opioid analogue. Krokodil consists of impurities such as gasoline, paint thinner, iodine, hydrochloric acid, lighter fluid, and red phosphorous (1). The clandestine manufacturing process resembles that of methamphetamine. The suspension is then injected intravenously or intramuscularly into the tissue. Repeated use of this drug creates a coarse, scaly, green rash that resembles crocodile skin, hence the origin of the reptilian name. The tissue may further decompose, exposing bones and tendons through the flesh. Abusers of this "flesh-eating" drug have an average life expectancy of 2 years (2). This is a dangerous drug with deleterious effects.

History

Russia, Ukraine, and the former Soviet countries share a history of homemade production of opioid drugs, primarily heroin, which predate before the fall of the Soviet Union. Heroin use was also rampant due to its proximity to Afghanistan, a major importer of heroin (3). Desomorphine abuse first appeared in Russia around 2003 (4). Its production occurred at a time of restriction of heroin trafficking in Afghanistan. Over the last 3–5 years, there has been a dramatic increase in the use of krokodil. Possible explanations for this rise include the difficulty in obtaining heroin compared with the relative ease in acquiring krokodil. Additionally, if one were to produce krokodil, the process requires limited laboratory equipment and inexpensive and accessible chemicals and solvents. For poor individuals with opiate addiction, desomorphine could serve as a cost-effective alternative to heroin (5, 6).

Epidemiology

It has been estimated that about 100,000 people use krokodil in Russia and approximately 200,000 in Ukraine (3). Use of this drug has largely been confined to these areas. There have been several suspected cases of krokodil use in several regions in the United States; however, according to the Drug Enforcement Administration, there is no confirmation that desomorphine has been found in any clinical specimen or drug sample (7). The majority of the individuals who are consuming krokodil are young people between the ages of 18 and 25, with no differences in gender (1, 8). It is estimated that about 30,000 people die each year from using this dangerous drug (9)

Pharmacology

Desomorphine was first synthesized in the 1930s, with the goal of providing an alternative to morphine regarding tolerance, addiction properties, and improved side-effect profile (10). The medication was marketed in Switzerland as a postoperative analgesic (7).

Desomorphine is a potent μ-opioid agonist and similar in chemical structure to morphine, although it has a faster onset of action and a shorter elimination half-life (11). Additionally, it has 10 times the analgesic power, 15 times the depression effect, and three times the toxicity of morphine. This makes the substance more lipophilic, with greater ability to penetrate the brain, thus contributing to higher and faster pain-relieving effect and increased addictive potential (10, 11).

Production/Effects

The production of Krokodil is a two-step process that involves the extraction of codeine from pharmaceutical products and the synthesis of desomorphine from codeine (6). This is mixed with paint thinner, gasoline, and a strong base-potassium or sodium hydroxide (4). Hydrochloric acid is then added to acidify the mixture. The final product is a caramel-colored, foul-smelling concoction of desomorphine, as well as the agents involved in production (1, 2). The desomorphine content of krokodil can vary from trace amounts to 75%. The elapsed time is about 45 minutes (12). The effects of desomorphine are compatible with that of other opiates/opioids. The euphoric effects from krokodil can be experienced within seconds to minutes, and the high can last an hour and a half, while the effects of heroin can last from 4 to 8 hours (1).

Health Problems

Complications include open sores, abscesses, thrombophlebitis, and gangrene. The skin will often slough off as a result of the damaged blood vessels, exposing the underlying bone. Krokodil causes peripheral limb ischemia with subsequent necrosis. Surgical intervention and amputations are frequently indicated (5, 13). Krokodil can also cause infections in the blood stream, coronary artery burst, septicemia, and other systemic damage due to pneumonia and meningitis (3, 7) Users are also prone to contracting HIV, hepatitis C, and other blood-borne illness (3). Neurological, endocrine, and organ damage are results of the chemicals and heavy metals associated with the krokodil production. These consist of motor and speech impairments, memory and personality changes, thyroid abnormalities, and liver and kidney damage (3, 5).

Diagnosis

Desomorphine may be detectable in blood samples within a few hours and in urine samples within a couple of hours to 2–3 days after Krokodil use (14). Although a routine urine drug screen can detect opiates, it cannot distinguish desomorphine from its counterparts. Recent developments propose that novel sol-gel titania film-coated needles for solid-phase dynamic extraction gas chromatography/mass spectrometry analysis will be a favorable technique in the future to detect the presence of desomorphine and desocodeine in urine (15).

Treatment

Krokodil users often present to the emergency department with serious conditions, such as soft tissue infections and gangrene. The initial treatment involves synchronization between the surgical and intensive care team. The treatment involves radical debridement, broad-spectrum antimicrobial therapy (penicillin G, clindamycin, vacomycin, and gentamicin), and hemodynamic support. In severe cases, surgical amputation may be necessary (16). Wound management commences during the surgical debridement, and a negative pressure device can augment revascularization and decrease the need for daily wound dressing changes, which can be painful. Collaborating with the pain management team is beneficial in managing pain. Pharmacologic recommendations often include use of a long-acting narcotic, such as methadone, to alleviate the discomfort. Nonpharmacologic approaches consist of virtual reality, relaxation techniques, distraction interventions, music, massage, and hypnosis (16). The Integrated Soft Tissue Infection Services Clinic, based in San Francisco, provides coordinated surgical intervention for individuals with soft tissue infections, as well as substance abuse counseling and social services. This clinic could serve as an example of multidisciplinary care for hospitals across the country (17).

In addition to soft tissue infections, krokodil users are prone to contracting HIV, hepatitis C, and other blood-borne illness. Reasons for the increased risk include sharing of needles, potential contamination of drug mixtures, and promiscuous sexual behavior leading to the transmission of hepatitis B (18). Screening and vaccination services are recommended for this population. These interventions could occur at methadone maintenance clinics, as well as other drug treatment programs (18). Needle and syringe exchange programs can also help to reduce the contraction of hepatitis and HIV.

In an acute setting, when an individual is undergoing detoxification, buprenorphine/naloxone is administered. Buprenorphine acts as a partial agonist at the μ-receptor and an antagonist at the κ-receptor (19). Naloxone is an opioid antagonist. This medication can be initiated 6–24 hours after the last opiate dose or when signs of mild-to-moderate withdrawal are present. If the patient is not experiencing adequate withdrawal symptoms and the first dose of buprenorphine/naloxone is provided, buprenorphine will displace the full opioid agonist (desomorphine) and intensify rather than relieve withdrawal symptoms, and the patient will experience enhanced withdrawal symptoms after the first dose (19). The Clinical Opioid Withdrawal Scale can be used to monitor withdrawal symptoms, which include nausea, diarrhea, and muscle cramping (6).

Maintenance treatment involves buprenorphine, as well as methadone. Buprenorphine is more widespread and can be prescribed in office settings, whereas methadone is confined to pain clinics and treatment centers. Home treatment can be initiated sooner with buprenorphine compared with methadone due to regulation and oversight requirements (20).

The side effects of buprenorphine tend to be more tolerable than those of methadone. This full agonist can cause chronic sweats, gastrointestinal discomfort, and sexual dysfunction. Methadone can be provided to individuals with chronic liver issues, such as Hepatitis C. Buprenorphine can cause an increase in liver enzymes. Both medications can be used during pregnancy; however, for women who use buprenorphine instead of methadone, there is decreased risk of delivering a baby with neonatal abstinence syndrome. Maintenance treatment is optimal when combined with psychosocial counseling, prevention education, and recovery support services in the community, such as faith-based organizations and support groups, including peer support groups (20).

Conclusions

Krokodil is a dangerous drug with catastrophic consequences that include disfigurement, systemic medical problems, and ultimately death. Although there have been no confirmed cases in the United States, it is imperative that providers in the health field become cognizant of this illicit substance. It is cheap and relatively easy to produce, which may appeal to opioid users in the United States. Although a routine urine drug screen can detect opiates, it cannot distinguish desomorphine. Recent developments propose that novel sol-gel titania film-coated needles for solid-phase dynamic extraction gas chromatography/mass spectrometry analysis might be a favorable technique for detection in the future. Recommendations for treatment involve multidisciplinary approaches to tend to both medical and psychiatric problems and long-term opioid maintenance therapy consisting of psychosocial education, counseling, and support groups.

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Please direct all inquiries to Rajiv Radhakrishnan, M.B.B.S., M.D., Senior Deputy Editor (rajiv.radhakrishnan@yale.edu).

Integrating Addiction Psychiatry and SBIRT Using Tele-Mental Health

Lynn Yen, M.D.

The SBIRT (Screening, Brief Intervention and Referral to Treatment) model is presently recommended by the Substance Abuse and Mental Health Services Administration as a screening and referral process but is unfortunately not presently routinely used in primary care settings. Since early-career psychiatrists are likely to encounter primary care settings or emergency departments without present screening modalities, psychiatry could take the lead in developing screening and referral processes within resource-limited areas.

SBIRT consists of 1) screening using tools such as the Alcohol Use Disorders Identification Test and the Alcohol, Smoking and Substance Involvement Screening Test; 2) brief intervention usually involving 1–5 sessions lasting about 5 minutes to 1 hour, with emphasis on psychoeducation and brief motivational interviewing; 3) brief treatment usually involving 5–12 sessions, with the provider using motivational interviewing to address the immediate behavior, as well as long-standing problems, with harmful drinking and drug misuse; and 4) referral to treatment that is recommended when patients meet the diagnostic criteria for substance dependence or other mental illnesses (1).

Various states are analyzing the cost savings of SBIRT implementation in their patient populations. The cost savings for Wisconsin's SBIRT program (named the Trial for Early Alcohol Treatment) was estimated at approximately $7,000 per patient due to differences in motor vehicle accidents (2). The Washington SBIRT study found that Medicaid cost savings per member per month to be $542 for patients receiving behavioral intervention alone. The study also found a reduction in hospital days of 0.12 per member per month (3).

Unfortunately, rural settings may face difficulties acquiring sufficient counselors

Tele-mental health offers promise in overcoming … barriers.

available for screening and treatment, as demonstrated previously in New Mexico SBIRT sites located in federally qualified health centers, public health offices, and Indian health service clinics (4). This barrier can be particularly problematic in screening patients with co-occurring mental health conditions, potentially resulting in selective rather than universal screening of individuals, which has occurred in California prenatal and jail setting sites.

Tele-mental health offers promise in overcoming these barriers. The Counseling and Psychological Services Center at the University of California, Los Angeles, developed a self-administered computer version of screening tools, such as the Alcohol Use Disorders Identification Test-C Plus and the Alcohol, Smoking and Substance Involvement Screening Test, for their student populations (5). A smart-phone application called A-CHESS (Addiction–Comprehensive Health Enhancement Support System) was developed and studied in populations of patients recovering from alcohol dependence. The program offered several features unique to the smartphone: 1) monthly alcohol use screening though BAM (Brief Addiction Monitor); 2) GPS tracking tools to help contact patients when they approached locations of prior alcohol use; 3) social networking tools for patients to post bulletins regarding their recovery and to identify nearby meetings; and 4) assistance in contacting support when in crisis (panic button). When utilized, patients reported higher

rates of abstinence for up to 12 months after graduation from residential programs compared with treatment as usual groups (6).

As patients gain access to treatment for substance use disorders under the Affordable Care Act, and with the growth of tele-mental health, psychiatrists may become leaders in facilitating implementation of SBIRT within resource-poor areas.

Dr. Yen is a sixth-year Addiction Psychiatry Fellow in the Department of Psychiatry, University of California, Los Angeles.

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Residents' Resources

We would like to welcome all our readers to this new feature of the Journal! Here we hope to highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

To contribute to the Residents' Resources feature, contact Tobias Wasser, M.D., Deputy Editor (tobias.wasser@yale.edu).

October Deadlines

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
American Psychiatric Foundation (APF) Schizophrenia Research Fellowship **Deadline: October 15, 2014**	APF	A 1-year psychiatric research fellowship for three postgraduate psychiatry trainees specifically to focus on research and personal scholarship. Minimal time (less than 15%) will be devoted to teaching, patient care, consultation, or other duties. The protection of time for research should be assured by the department chairperson.	APA Resident-Fellow Member (RFM); Not already an established investigator	Marilyn King schizophrenia@psych.org 703-907-8653	http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/schizophrenia-research-fellowship
APA/Lilly Psychiatric Research Fellowship **Deadline: October 15, 2014**	APA	This fellowship provides funding for a postgraduate psychiatry trainee, under the supervision and guidance of his/her mentor, to design and conduct a research study on a major research topic.	APA RFM; Not already an established investigator	psychresearch@psych.org	http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/psychiatric-research-fellowship
Kempf Fund Award for Research Development in Psychobiological Psychiatry **Deadline: October 15, 2014**	APA	This award recognizes a senior researcher who has made a significant contribution to research on the causes and treatment of schizophrenia as both a researcher and a mentor. A $1,500 award will be made to the senior researcher, and $20,000 will support the research career development of a young research psychiatrist working in a mentor-trainee relationship with the award winner on further research in this field.	Completed training in the United States or Canada (senior researcher)	Marilyn King kempf@psych.org	http://www.psychiatry.org/researchers/research-training-and-career-distinction-awards/kempf-fund-award-for-research-development-in-psychobiological-psychiatry

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1. **Commentary:** Generally includes descriptions of recent events, opinion pieces, or narratives. Limited to 500 words and five references.

2. **Treatment in Psychiatry:** This article type begins with a brief, common clinical vignette and involves a description of the evaluation and management of a clinical scenario that house officers frequently encounter. This article type should also include 2-4 multiple choice questions based on the article's content. Limited to 1,500 words, 15 references, and one figure.

3. **Clinical Case Conference:** A presentation and discussion of an unusual clinical event. Limited to 1,250 words, 10 references, and one figure.

4. **Original Research:** Reports of novel observations and research. Limited to 1,250 words, 10 references, and two figures.

5. **Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure.

6. **Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in *The Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.

7. **Book Review:** Limited to 500 words and 3 references.

Abstracts: Articles should not include an abstract.

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Please note that we will consider articles outside of the theme.

Women's Health

If you have a submission related to this theme, contact the Section Editor, Kathleen Mary Patchan, M.D. (kpatchan@psych.umaryland.edu).

Violence and Mental Health

If you have a submission related to this theme, contact the Section Editor, Ijeoma Chukwu, M.D., M.P.H. (ichukwu@uci.edu).

*If you are interested in serving as a **Guest Section Editor** for the *Residents' Journal*, please send your CV, and include your ideas for topics, to Misty Richards, M.D., M.S., Editor-in-Chief (mcrichards@mednet.ucla.edu).