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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Marijuana

Learning objectives for this issue:
1. Detail the neurochemistry and effects of marijuana. **2.** Explain the endocannabinoid system. **3.** Summarize important points for psychiatrists to know about medicinal use of marijuana. **4.** Evaluate some of the current findings in the literature regarding psychiatric treatment.

Cannabis and the Endocannabinoid System

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Dr. Adkinson and Dr. Madan have disclosed that they have no relevant relationships or commercial interests in any companies related to this educational activity.

Cannabis, commonly known as marijuana, is the most commonly used illicit drug in the United States. In 2012, nearly 40% of American 12th graders had used it at some point, and one in four had used within the past month.

Simultaneously, as the use of marijuana has increased in recent years, the perceived risk from smoking marijuana has decreased (Johnston LD et al. *Monitoring the Future national survey results on drug use, 1975–2012: Volume I, Secondary school students.* Ann Arbor: Institute for Social Research,

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In Summary

- The *Cannabis sativa* plant contains 85 cannabinoids—compounds that act on cannabinoid receptors in the brain; the most well-known and studied of these are THC and cannabidiol.
- Clinical studies of synthetic THC have shown anti-emetic and anti-inflammatory effects, and efficacy in treating neuropathic pain, refractory cancer pain, and glaucoma.
- Negative effects of cannabis can include impairments in ability to focus, loss of coordination, poor overall mental health, and other substance use; risks are highest in females, heavy users, and those with early age of first use.

Q&A With the Expert

Marijuana in Psychiatry
Itai Danovitch, MD

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Dr. Danovitch has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: Dr. Danovitch, please tell us some of the most common medical or therapeutic uses of marijuana.

Dr. Danovitch: The answer depends whom you ask. If you ask patients who consume marijuana or individuals in the public, they cite a wide variety of different conditions for which they feel that marijuana is helpful, including chronic pain conditions, a variety of mental health disorders, sleep disorders, neurological problems, some cancers, spasticity, and the list goes on. The symptoms for which there has been the most evidence include nausea and vomiting, alterations in appetite, and muscle spasticity, and there have been some impressive reports of anticonvulsant and analgesia effects. In labs, cannabinoids have been shown to have immunomodulatory properties and impact on cancer growth (Hall WL et al, *Lancet Oncol* 2005;6(1):35–42).

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The University of Michigan;2013). Considering the increased efforts to legalize marijuana in many states, greater public awareness of marijuana and its potential medicinal uses, and new research on cannabis and its constituents, it is essential that psychiatrists understand some of its proposed benefits—and fundamental risks.

Effects of Marijuana

Marijuana is derived from the flowers and surrounding leaves of the *Cannabis sativa* plant. The psychoactive effects are experienced almost immediately after consuming it (usually by smoking or oral ingestion), peak in about 30 minutes, and diminish in about four hours.

Subjective pleasurable effects include a feeling of relaxation, euphoria, and laughter. Negative effects include dizziness, perception of slowing of time, drowsiness, paranoia, increased appetite, and short-term memory loss.

Cannabis use has also been associated with impairments in ability to focus, loss of coordination, and heightened body awareness (Campbell FA et al, *BMJ* 2001;323(7303):13–16). These effects may persist for weeks to months after discontinuing the use of cannabis, especially in heavy and frequent users (Gonzalez R, *Neuropsychol Rev* 2007;17(3):347–361).

Young brains appear to be especially sensitive to the effects of cannabis. Cannabis use increases the risk of developing poor overall mental health, depression, anxiety, attention difficulties, poor school performance, and other substance use. (Yes, there appears to be real evidence for the 'gateway drug' phenomenon [Oltheus JV et al, *Drug Alcohol Rev* 2013;32(1):67–71]).

The risk is higher in females, heavy users, and those with early age of first use (van Gastel WA et al, *Community Ment Health J* 2014;online ahead of print). A recent longitudinal study demonstrated that persistent cannabis use was associated with significant decline in IQ and global neuropsychological functioning, particularly in adolescent-onset (vs adult-onset) and chronic users, even after controlling for other substance use and years of education (Meier MH et al, *Proc Natl Acad Sci USA* 2012;109(40):E2657–E2664).

Several large-scale studies have also reported that adolescent cannabis users have an increased incidence of schizophrenia later in life, with heavier use associated with increased risk (Manrique-Garcia E, *Psychol Med* 2012;42(6):1321–1328). While the mechanism of this effect has yet to be determined, it appears that cannabis may precipitate the onset of psychosis in individuals who have a genetic or developmental vulnerability (Degenhardt L et al, *Drug Alcohol Depend* 2003;71(1):37–48).

Neurochemistry of Marijuana

The *Cannabis sativa* plant has been found to have over 500 chemical constituents, of which 85 are cannabinoids, ie, compounds that act on cannabinoid receptors.

The most psychoactive constituent of cannabis is delta-9 tetrahydrocannabinol (THC). Concentrations of THC in marijuana have been steadily rising over the years. According to the University of Mississippi's Potency Monitoring Project, THC concentrations in samples of marijuana have risen from 1%–2% in the 1960s to an average of 9% today (see for example Mehmedic Z et al, *J Forensic Sci* 2010;55(5):1209–1217). A typical marijuana cigarette ("joint") contains about 20 mg of THC derived from one gram of leaves and buds of the *C. sativa* plant.

THC may cause euphoria by inhibiting the release of neurotransmitters like GABA and glutamate. The effects may be *biphasic*, as higher doses of THC appear to increase anxiety and paranoia, presumably by increasing dopamine release (Mechoulam R & Parker LA, *Annu Rev Psychol* 2013;64:21–47). Most regular cannabis users can titrate the level of psychotropic effect to provide the outcome they desire, even though this "self-adjustment" of dose is in contrast to most of modern medicine, in which doses are determined by a prescriber.

Another cannabinoid that has received much attention in recent literature is cannabidiol (CBD), which is known to have anti-emetic, anti-inflammatory, and antipsychotic effects (Bergamaschi MM et al, *Curr Drug Saf* 2011;6(4):237–249), as well as possible neuroprotective and anxiolytic properties. It may act as a protective factor against the detrimental psychological effects of THC. Cannabis plants modified to have a high CBD:THC ratio may be useful for therapeutic purposes.

Cannabinoids bind to cannabinoid receptors in the body. First identified in 1990, two types of cannabinoid receptors (CB1 and CB2) have been characterized, both of which are G-protein coupled receptors. CB1 receptors are responsible for the psychoactive effects of THC and are widely distributed throughout the central nervous system and the gut.

Interestingly, the low concentration of CB1 receptors in the brainstem accounts for the relative safety of marijuana; a lethal overdose of marijuana in humans has never been reported (Bostwick JM, *Mayo Clin Proc* 2012;87(2):172–186). The table on page 3 shows how THC's multiple effects can be linked to its actions on various brain areas.

CB2 receptors are primarily found

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THC Effect on Brain Areas	
Location of CB1 Receptor	**Effect**
Nucleus accumbens	Rewarding effects of THC
Cerebellum	Discoordination
Basal ganglia	Reduction of spasticity, slowed reaction time
Hypothalamus	Increased appetite
Spinal cord	Decreased afferent pain perception
Prefrontal cortex	Cognitive difficulties; altered sensation
Hippocampus	Memory impairment
Brain stem	Anti-nausea effects
Amygdala	Panic, paranoia

in the immune system, where they are involved in regulating inflammation, pain perception, and host defense.

The Endocannabinoid System

In the last few decades, researchers have discovered naturally occurring substances in the body that bind to the cannabinoid receptors. The two primary "endocannabinoids" are arachidonyl ethanolamide (AEA), more commonly known as anandamide (discovered in 1992 and named after the Sanksrit word *ananda*, which means bliss or joy), and 2-arachinoyl glycerol (2-AG). The endocannabinoids, the cannabinoid receptors and the enzymes involved in their metabolism form the endocannabinoid system (ECS).

The ECS plays an important role in the process of neurogenesis. One hypothesis suggests that THC may cause overstimulation of the ECS, especially in adolescent brains, thus disrupting the process of neuronal development and causing psychiatric disturbances. The ECS also moderates the activation of hypothalamic-pituitary-adrenal axis. Chronic stress can lead to down-regulation of cannabinoid receptors, thus leading to symptoms of anxiety and depression.

Some research hints that the ECS may play an important role in the inhibition of aversively motivated learning, and could be a useful target for treatment of PTSD. Other endocannabinoids similar to anandamide have been identified, and appear to protect the brain during trauma and stroke via vasodilation, anti-inflammatory, and analgesic actions (Mechoulam R & Parker LA, *op.cit*).

Because most drugs of abuse elevate brain levels of endocannabinoids, blockade of CB1 receptors may eliminate or reduce the rewarding properties of some addictive substances. This is the rationale of rimonabant, a CB1 antagonist which showed some efficacy in treating nicotine and marijuana addiction, as well as obesity.

Rimonabant was never approved in the US; it was withdrawn from the European market in 2008 because of psychiatric side effects, including depression and anxiety. Research into CB1 neutral antagonists, which permit constitutive CB1R activity but block excess CB1 activation (like rimonabant), is ongoing.

Medical Cannabis and Pharmaceutical Cannabinoids

Cannabis has been used for medicinal purposes throughout the world for at least the past five millennia. It was used extensively in Western medicine during the late nineteenth century, but went into decline after potent synthetic medications were introduced in the early twentieth century and marijuana was vilified in the popular media, eg, in the movie *Reefer Madness*, an anti-marijuana propaganda film released in the late 1930s.

Cannabis has been studied as a potential treatment for many conditions, including chronic skin disorders, cancer-related weight loss, chronic pain, Huntington's disease, sleep disorders, glaucoma, multiple sclerosis, neuropathic pain, seizures, irritable bowel syndrome, inflammation, and hyperalgesia.

Some proponents of medical cannabis exclusively advocate the use of the plant ("botanic cannabis") and the cultivation of strains that are effective for certain ailments. Unfortunately, federal regulations, such as the classification of THC as a schedule I controlled substance, as well as the rapid and largely unscientific promulgation of medical marijuana nationwide—what some have called "medicine by popular vote" (Bostwick, *op.cit*)—have resulted in a dearth of good scientific evidence on the putative medicinal benefits of smoked marijuana.

Academic and commercial laboratories have developed a handful of pharmaceutical compounds based on THC and other components of the cannabis plant. Three cannabis-derived chemicals have been approved for human use: dronabinol (Marinol), nabilone (Cesamet), and nabiximols (Sativex).

Dronabinol (schedule III) is synthetic THC and lasts for six hours, while nabilone (schedule II) is a THC analog with a 12-hour duration of action. Both have been approved since 1985 for chemotherapy-induced nausea and vomiting and the AIDS-related anorexia/cachexia syndrome. While effective, some naïve users are susceptible to adverse effects such as euphoria, drowsiness, and cognitive clouding, due to variable absorption and first-pass kinetics. As a result, chemotherapy-related nausea and emesis are more commonly treated with serotonergic agents like ondansetron (Zofran), and THC is best reserved for resistant cases (Turcotte D et al, *Expert Opin Pharmacother* 2010;11(1):17–31).

Clinical studies have shown efficacy of synthetic THC in the treatment of neuropathic (but not nociceptive) pain, refractory cancer pain, and glaucoma, by reducing intraocular pressure. Interest has also arisen in the anti-inflammatory properties of THC, for disorders such as rheumatoid arthritis, and for epilepsy and post-stroke neuroprotection.

Nabiximols (Sativex) is a plant-derived oromucosal spray containing 2.7 mg THC and 2.5 mg CBD per dose. It has been approved in Europe since 2010 for

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Expert Interview
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TCPR: Those who use marijuana typically inhale or ingest the leaves and buds of the *Cannabis sativa* plant. Does there seem to be any difference in terms of therapeutic efficacy of the whole plant versus individual cannabinoid compounds?

Dr. Danovitch: There have been studies that have shown efficacy of the whole plant, and there is also evidence that individual constituents, like cannabidiol, have significant therapeutic potential. There are 60 cannabinoids in the whole plant and probably another 400 different hydrocarbons. In the lab, we can purify cannabinoids, or study synthetic cannabinoids or cannabinoid modulators, and try to understand what they are doing. But studying them individually doesn't replicate what they do together in the context of the whole plant. On the one hand, pharmacological purists would say we will never have standardized, consistent, high quality preparations of cannabinoids until we are able to produce them reliably, regulate them, and know exactly what their effects are. On the other hand, many advocates of "medical marijuana" say that it is exceedingly difficult to replicate whole plants, and the whole plant may have sufficient benefit that it should be studied independently from efforts to isolate therapeutic compounds. I would say that both positions and perspectives have some merit.

Ultimately there are really more questions than answers in terms of how effective marijuana is both in the short term and in the long term.

Itai Danovich, MD

TCPR: Patients often talk of the differences between the two strains of marijuana, *C. sativa* and *C. indica*. Is there any evidence showing that they differ in their therapeutic potential?

Dr. Danovitch: Well, there are almost certainly differences because patients or individuals who use them can identify clear differences in the intoxication syndrome and effects. The ratios of THC to cannabidiol and to some of the other phytocannabinoids are different; they vary across different strains and subspecies. Right now there is a lot of effort to cultivate strains that are higher in phytocannabinoids, which are thought to be more therapeutic, but we don't have any way of really knowing because these processes aren't well standardized. There is a long history of incredible ingenuity in science and agriculture of farmers trying to cultivate species of products for the tastes of the consumers. And whether it is really red, tasty tomatoes or marijuana plants that have certain effects, it's the same process. It is kind of like a guerrilla science of individuals trying to figure this stuff on their own.

TCPR: What do we have for data on long-term benefits or risks of using marijuana for certain medical conditions?

Dr. Danovitch: Ultimately there are really more questions than answers in terms of how effective marijuana is both in the short term and in the long term. Patients and individuals are much more capable in general of identifying and detecting short-term effects of an intervention than long-term effects. And so there is a disparity between the recognition of short-term alleviation of symptoms, and the question of how marijuana or its constituents impact disease progression and health outcomes in the long run.

TCPR: Why is it difficult to study marijuana? Why do so few labs use marijuana in clinical research?

Dr. Danovitch: The DEA, with input from the FDA, schedules drugs into five different categories. Schedule I means that a drug has high abuse potential, is unsafe, and has no accepted therapeutic benefit. Schedule II means that there is high abuse potential, but some therapeutic benefit. Marijuana is placed in schedule I. There have been a number of calls to have it moved into schedule II, because it is easier to study medications that are in schedule II. While it is possible to study agents that are in schedule I, there is a pretty rigorous federal regulatory process to navigate. Critics, including several major professional associations, have pointed out that the current scheduling designation has made it difficult to conduct research because only a handful of labs with the right infrastructure can be successful in getting approval to study marijuana.

TCPR: Is it clear how addictive marijuana is?

Dr. Danovitch: About nine percent of marijuana users go on to develop a marijuana use disorder; which means that about 91 percent don't develop any problems related to marijuana addiction. This illustrates the point that it is not just a property of the substance that determines who develops a substance use disorder on cannabis or anything else. It is properties of the individual, of their biology, of their genetics, and also multiple psychosocial factors, such as their development, their psychology, and their environment.

TCPR: How about the risk of psychosis?

Dr. Danovitch: The majority of people are not at heightened risk for developing a psychotic disorder with the use of marijuana. However, for the one or two percent of the population that may have a vulnerability to develop a psychotic disorder, marijuana may double the risk that they actually will (Moore THM, *Lancet* 2007;370(9584):319–328). While two percent may sound like a small number, given the prevalence of marijuana use, the number of people potentially impacted is significant.

TCPR: Are there any screening tools or genetic profiling that could be done to sort out those who are more susceptible to the longer-term consequences of marijuana use?

Dr. Danovitch: Well, there are some specific genes like the COMT [catechol-O-methyltransferase] gene that has been associated with psychosis. But practically speaking, anybody who has a family history of schizophrenia or a psychotic disorder is somebody whom I really carefully educate about the risks of marijuana in creating and contributing to psychoses. Certainly anybody who has a family history of a substance use disorder is at risk of developing a substance use disorder, and anybody who is young and whose brain hasn't finished developing is at higher risk of the cognitive problems associated with using marijuana, especially if they smoke heavily. I really try to take time to educate marijuana users about the profile of the substance so that they can make an educated decision about it, and also try to understand what it is doing for them, because everybody uses for a reason, and without understanding what that reason is it is really hard to actually help them with it.

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Expert Interview
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TCPR: Are there distinct risks related to the age at which someone starts smoking marijuana?

Dr. Danovitch: Yes. The risk of harm associated with marijuana is highest among children and adolescents. Marijuana appears to have subtle but distinctive effects on brain development. We know that the brain finishes developing in the mid-20s. Studies that have looked prospectively at marijuana's effect on cognitive function have found that their findings hinged on marijuana being used prior to the age of 18. So, for instance, the Dunedin study found that the adverse effects of marijuana on IQ only happened among people who started smoking marijuana prior to the age of 18, and were not found in those that started smoking marijuana after the age of 18, irrespective of whether they met criteria for marijuana use disorder (Meier MH et al, *Proc Natl Acad Sci USA* 2012;109(40):E2657–E2664). At the same time, researchers have characterized wide-ranging trajectories of marijuana use. Some people start smoking really early on and progressively increase over the course of their lives. Other people start smoking and use heavily during their college years, but then stop after college. Some people smoke small amounts throughout their lives. And so, not surprisingly, there are differences in outcomes as a function of how heavily people use, how early they use, and other contributing factors. So earliness of use matters, quantity of use matters, and then existing vulnerabilities, both physiological and environmental, matter as well.

TCPR: As marijuana becomes more accepted and more legalized, how can we preserve the well-being of people who may suffer from the negative consequences of marijuana?

Dr. Danovitch: First, treatment works, but it can only work if it is accessible. We have to ensure that individuals who develop marijuana use disorders, particularly adolescents, have access to quality treatment. Second, we need appropriate safeguards. There have to be effective restrictions minimizing access for underage individuals. And, there needs to be a regulatory system to protect users by implementing quality controls, using warning labels, and preventing inappropriate marketing. Third, if there's going to be a major policy change, there needs to be a mechanism to study its effects. Across the country there are many different initiatives that have increased availability of marijuana, and this has happened faster than our ability to systematically analyze the public health impacts of these changes. This deserves further study. And then, there are a number of technical challenges like documenting driving under the influence that have yet to be sorted out.

TCPR: And there's an idea that funding for these programs could come from earmarking revenue, from taxing marijuana for example.

Dr. Danovitch: Yes, there is a notion that any revenues that might be generated from taxation should first be designated to address public health problems associated with marijuana. However, there is also concern about the feasibility of appropriating funds for that purpose—if you look at alcohol or tobacco, big business has tended to be far more successful than public health advocates in controlling taxation and appropriation. Several medical societies are concerned about the public health effects and are trying to educate the public about it. The question is, how can we inform our legislators so they can appropriately govern and protect the public health with respect to this issue? And the wariness is that no matter how much we beat the drums on the risks, that the influence of big business interests on government will be greater than the impact of public health and medical interests on government.

TCPR: Let's say that you are a psychiatrist somewhere in a state that permits the medical use of marijuana. If a patient

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the treatment of moderate to severe spasticity associated with multiple sclerosis. As with THC, trials have shown efficacy of nabiximols for the management of pain, nausea, and AIDS-related anorexia, but not without frequent side effects like dizziness, sedation, and "thinking abnormalities" (Robson PJ, *Drug Test Analysis* 2014;6(1-2):24–30).

No cannabinoid drug has been approved for any psychiatric indication, and the effects of THC seem too unpredictable to assure any consistent therapeutic response. However, as mentioned earlier, the antipsychotic effects of CBD have been demonstrated in animals and in humans, and supported by functional MRI studies.

In a double-blind trial of 42 patients with schizophrenia, CBD showed comparable results to the antipsychotic amisulpride (Leweke FM et al, *Transl Psychiatry* 2012;2:e94). It is plausible that CBD-containing agents (which do not act on the dopamine system) may emerge as adjunctive medications to existing antipsychotics.

CBD may also block a process called "reconsolidation," in which memories of stressful life events are strengthened by brief exposure to conditioned stimuli, suggesting a potential use in PTSD (Stern CAJ et al, *Neuropsychopharmacol* 2012;37:2132–2142). There are several case reports and small trials of CBD improving seizures in patients with treatment refractory epilepsy, although the mechanism is unknown (Robson, *op.cit*). CBD has also shown to improve memory loss in animal studies and is being explored as a potential treatment for Alzheimer's disease, alcohol-induced neurotoxicity, and migraines (Russo E & Guy GW, *Medical Hypotheses* 2006;66:234–246).

TCPR'S VERDICT: Claims for the therapeutic use of marijuana are numerous, but the adverse effects of marijuana consumption—especially in young adults—are many, and the evidence base is, at present, relatively weak. That said, the human endocannabinoid system is widespread and involved in the regulation of several physiological mechanisms. Targeted pharmacotherapies based on specific compounds found in cannabis may usher in a new paradigm in the treatment of psychiatric and other illnesses.

Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

BIPOLAR DISORDER

Maternal Flu and Risk of Bipolar Disorder

Several past studies have investigated a possible link between infections during pregnancy and psychiatric illness in the offspring. These studies may be biased, however, by poor recall or by a clinical, as opposed to serological, diagnosis of infection in the mother. A recent study attempted to overcome this bias by measuring influenza antibodies—a more precise manner of identifying influenza exposure—drawn from the mothers of bipolar offspring.

Researchers used data from the Child Health and Development Study birth cohort, a representative sample of all people born to women who received obstetric care in a Northern California HMO between 1959 and 1966. They obtained frozen serum samples from the mothers of 85 individuals with bipolar disorder and measured influenza antibodies, comparing them to matched samples from 170 control peers. The bipolar individuals included 36 with psychotic features and 49 without.

The mothers of 23 of the bipolar subjects had influenza antibodies in their blood (27%). Overall, no increased risk of bipolar disorder was found among the offspring of women exposed to the flu during pregnancy (odds ratio 1.26, 95% CI=0.625-2.44, p=0.49) when compared to matched peers.

However, when the bipolar individuals were separated into those with psychotic features and those without, the picture changed. Maternal influenza exposure was related to a five-fold greater risk of bipolar disorder with psychotic features (odds ratio 4.87, 95% CI=1.18-20.06, p=0.028). Thirty-nine percent of the mothers of adults with bipolar disorder with psychotic features had influenza antibodies in their blood, versus only 18.4% of the moms of the bipolar individuals without psychotic features (Canetta SE et al, *Am J Psychiatry* 2014;171(5):557—563).

TCPR's Take: This study lends additional support to the idea that maternal infection increases the risk for psychiatric illness in the offspring. While the current study found no increased risk of bipolar disorder, it did identify a greater risk of bipolar disorder with psychotic features, supporting earlier observations that maternal influenza may contribute to the development of schizophrenia. The authors argue that maternal influenza may affect brain development to increase the risk of psychosis, suggesting novel neurobiological approaches for research into the diagnosis and treatment of psychotic disorders.

SUICIDE

The Media's Role in Suicide Clusters

Does newspaper coverage of suicide promote copycat suicides? A recent retrospective study examined this question by comparing suicide clusters among teens to isolated suicides, and how local newspapers covered these events.

Researchers looked at 48 suicide clusters (three or more suicides occurring in the same community within a span of 23 weeks) among teens ages 13 to 20, all of which occurred in the US between 1988 and 1996. They collected newspaper reports published between the first and the second suicide of the cluster, to determine whether any aspects of the newspaper report (headline, front-page placement, graphic descriptions, etc) were more highly associated with the onset of a "cluster" than others.

For each cluster, researchers identified two control suicides, in other communities in the same state, which were *not* part of a suicide cluster. They evaluated newspaper reports of these suicides as well.

Researchers found that significantly more newspaper articles were published between the first and second suicides in suicide clusters than during the same period of time after an isolated suicide (7.42 vs 5.14, p<0.0001).

Using a statistical process assessing both the number of articles and specific features of those accounts, researchers found that the articles published in communities where clusters developed were significantly more likely to feature the name of the victim and the method used, and to feature the word "suicide" in the headline. They were also more likely to mention the name of the victim's school and to be accompanied by a "sad" photograph (Gould M et al, *Lancet Psychiatry* 2014;online ahead of print).

TCPR's Take: Knowledge about a suicide—particularly when detailed and explicit—may increase the risk of subsequent suicides in teenagers. The authors of this study hypothesize that newspaper reports might "normalize" suicide or may "prime" other individuals to consider suicide.

However, because the data were collected before the age of social media, conclusions cannot be drawn about online accounts of suicide. The ubiquity of social media may enable the rapid dissemination of suicide stories and increase the risk of subsequent suicides, but it may also facilitate productive dialogue about the unfortunate nature of such events and provide a measure of safety.

CME Post-Test

This CME post-test is intended for participants only seeking AMA PRA Category 1 Credit™. For those seeking ABPN self-assessment (MOC) credit, a 13 question pre- and post-test must be taken online. For all others, to earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by June 30, 2015. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. Which of the following is a cannabinoid that has received much recent attention for having anti-emetic, anti-inflammatory, and antipsychotic effects, as well as possible neuroprotective and anxiolytic properties (Learning Objective #1)?
   [ ] a) Tetrahydrocannabinol (THC) [ ] b) Cannabigerol (CBG)
   [ ] c) Cannabidiol (CBD) [ ] d) Cannabichromene (CBC)

2. One hypothesis about the endocannabinoid system (ECS) suggests that THC may cause overstimulation of the ECS, especially in adolescent brains, thus disrupting the process of neuronal development and causing psychiatric disturbances (LO #2).
   [ ] a) True [ ] b) False

3. According to Dr. Itai Danovitch, about how many marijuana users develop marijuana use disorders (LO #3)?
   [ ] a) 2% [ ] b) 9% [ ] c) 17% [ ] d) 25%

4. In the Gould et al study of newspaper accounts of suicide, which feature of newspaper articles was found to be more frequent after the index suicide in a suicide cluster than after an isolated suicide (LO #4)?
   [ ] a) A favorable depiction of the victim [ ] b) Glorification of the suicide
   [ ] c) The name of victim and method used [ ] d) A list of community resources for suicide prevention

5. Which of the following was found to be true in the Canneta et al study of flu and bipolar (LO #4)?
   [ ] a) Maternal influenza exposure was related to a five-fold greater risk of bipolar disorder overall
   [ ] b) Maternal influenza exposure was related to a five-fold greater risk of bipolar disorder with psychotic features
   [ ] c) Maternal influenza exposure was related to a five-fold greater risk of bipolar disorder without psychotic features
   [ ] d) There was no association between maternal influenza exposure and risk of bipolar disorder

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News of Note

FDA Issues Safety Warning on Lunesta

In mid-May, the FDA released a warning that eszopiclone (Lunesta) can cause next-day impairment when taken at the recommended target dose of 3 mg/day. As a result, the FDA has lowered the recommended starting dose to 1 mg/day.

The FDA cites a double blind, placebo controlled study of 91 adults that found working memory and the psychomotor coordination required to drive a car were impaired for up to 11.5 hours after a 3 mg bedtime dose of Lunesta. They also determined that subjective perception of sedation and coordination—in other words, patients' abilities to realize they were sleepy or impaired—were no different than placebo, although these patients were actually quite impaired. Women and men were equally affected.

In fact, according to the data summary from the FDA, a 3-mg dose of Lunesta was almost as impairing as 7.5 mg zopiclone, a medication often used as a positive control in studies of driving impairment (and, interestingly, the parent compound of Lunesta).

Doses can be titrated up to 3 mg from the new starting dose of 1 mg, says the FDA, but patients taking the 3 mg dose are cautioned against driving and related activities the next day. Read the warning at http://1.usa.gov/1l6FCs0.

Move Over Ketamine? New Fast-Acting Antidepressant Shows Promise

A new drug is showing rapid, long-lasting results in early rodent studies, according to a paper presented by Jeffrey Talbot of Roseman University of Health Sciences at the annual meeting of the Federation of American Societies of Experimental Biology (FASEB) in April.

The drug, Ro-25-6981 (nicknamed "MI-4") has been shown to reduce depressive symptoms almost immediately, similar to ketamine. However, unlike the ketamine data thus far, this new study shows that those effects can be maintained for about three weeks, says Dr. Roseman.

The medication has a unique mechanism of action according to an April article on the website *Science Daily* (http://bit.ly/1rIvkOL). While working as an NMDA antagonist and stimulator of neurogenesis (at least in vitro), MI-4 also works through triple reuptake inhibition to increase levels of dopamine, norepinephrine, and serotonin.

Triple reuptake inhibitors are also known as serotonin–norepinephrine–dopamine reuptake inhibitors (SNDRIs). Amitifadine, a SNDRI developed by Euthymics Bioscience has shown posi-

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This Month's Focus:
Marijuana

Next month in *The Carlat Psychiatry Report:* Special Summer Double Issue—Research in Psychiatry

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comes to you with a psychiatric complaint and inquires about medical marijuana, what kind of approach do you take?

Dr. Danovitch: I would start by assessing the complaint itself, making a diagnosis, and recommending treatments based on existing evidence. At this point in time I have not seen any high-quality studies demonstrating that marijuana is effective for any psychiatric diagnoses. And a lot of the symptoms that patients report marijuana is helpful for—like reduction in anxiety, improvement with sleep, reduction in irritability or quickness to anger, and enhancement of appetite—these are all things that are associated with marijuana withdrawal, too. As a result, it is often difficult to disentangle the patient's perception of marijuana benefits from the possibility that they may just be treating their own withdrawal symptoms and experiencing alleviation of symptoms on account of that. Ultimately as a psychiatrist, I really can't think of any psychiatric condition for which I would recommend marijuana.

TCPR: Thank you, Dr. Danovitch.

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tive results in clinical trials. The SNDRI liafensine was dropped by Bristol-Myers Squibb in phase IIb trials when it failed to perform better than Cymbalta. Dr. Roseman's research will be published later in 2014.