Drug trial of cannabinoid painkiller in France results in brain damage, death

The search for nonopioid pain relievers has created a great deal of interest in endogenous cannabinoids — chemicals that occur naturally in the brain that are similar to marijuana. But the cannabinoid research community was shaken by a recent tragedy that occurred during a clinical trial of such a drug in Rennes, France.

On January 15, the French government announced that a “serious accident” had occurred as part of a Phase 1 clinical trial conducted in Rennes, where the minister of health, Marisol Touraine, met with families of victims. The accident entailed brain damage in several of the previously healthy volunteers that had been discovered six days earlier. “This accident resulted in the hospitalization of six of the volunteers at the University Hospital of Rennes,” according to a press release from the Ministry of Health. “One of them, in intensive care, is brain dead.” That person has since died.

The next day, more details emerged, according to a report by Martin Enserink in Science, published See Drug Trial page 2

Bottom Line...
A recent drug trial of an endocannabinoid FAAH blocker has resulted in brain damage and death in healthy volunteers.

Fast-track bills on opioid crisis in N.H. would ease insurance limits

A series of bills addressing everything from insurance protections to upgrades to the prescription drug monitoring program (PDMP) as part of a multipronged strategy to combat New Hampshire’s opioid crisis is making significant inroads with state legislators. As ADAW was going to press, House action appeared imminent on three bills that cleared the state Senate on the week of January 11. While these bills are being fast-tracked, it will take longer into the year to determine what state lawmakers do with requests for additional funding to fight opioid addiction and overdose, as well as a possible call for even stronger insurance regulation.

Two insurance-related components of Senate Bill 576 are receiving a great deal of attention in the treatment and advocacy communities. One provision would eliminate prior-authorization requirements for initial outpatient services and would align insurance review to American Society of Addiction Medicine criteria.
Drug Trial from page 1

by the American Association for the Advancement of Science. Enserink, who reports from Amsterdam, wrote that volunteers in the study conducted by the private research firm in Rennes, Biotrial, had been paid to stay at the facility for two weeks, take a drug for 10 days and provide at least 40 blood samples. The Portuguese pharmaceutical company that sponsored the trial, Bial, confirmed that the drug tested was a fatty acid amid hydrolase (FAAH) inhibitor, which was being tested for the treatment of chronic pain.

Of the six patients who had taken the drug, one has died and four others had brain damage. Magnetic resonance imaging showed “deep, necrotic, and hemorrhagic lesions in the brain(s)” of the patients.

According to Enserink’s report, the trial enrolled healthy nonsmoking men and women aged between 18 and 55. The Science report also said that according to Bial, the new drug had already been given to 108 patients without any adverse reactions.

FAAH inhibitors and endocannabinoids

Endogenous cannabinoids exist in the body and are broken down by FAAH. By inhibiting FAAH, this breakdown could be slowed, leaving the body’s endogenous cannabinoids to help fight pain. Other possible indications for the Bial drug, called BIA 10-2474, were anxiety, Parkinson’s disease, multiple sclerosis, cancer, hypertension and obesity.

Meanwhile, drug researchers urge caution in determining that FAAH inhibitors are the cause of the tragedy, ADAW has learned. “In the absence of more information about the toxicity, I would ask the scientific community to withhold judgment on FAAH inhibitors being the cause of this,” Margaret Haney, M.D., professor of neurobiology and psychiatry at Columbia University Medical Center, told ADAW.

Haney, an endocannabinoid researcher, said she was surprised by the news that FAAH inhibitors were being blamed for the tragedy. “I was stunned, as most cannabinoid researchers were, when I heard about this, given the safety of cannabinoids in general and these FAAH inhibitors in particular,” she told ADAW. “My working hypothesis in the absence of any other evidence is that it was some protein interaction,” she said. “There’s no evidence that FAAH inhibition could cause brain damage.

There could be many explanations for the problems with the Bial compound, even though these were not foreseen by animal tests, said Haney. “It could be something unique about the humanized versions of the compound,” she said.

Not cannabis

Cannabis — the plant — works by a very different mechanism than FAAH inhibitors, said Haney. The brain has endogenous cannabinoids that in some ways mimic tetrahydrocannabinol, the active ingredient of marijuana, said Haney. “The scientific community is still sorting out what role these endocannabinoids have, but they are ubiquitous in the brain,” she said. “We think that they can affect anxiety and, potentially, pain.” FAAH is not a cannabis-based drug.

NIH funding

Meanwhile, the National Institute on Drug Abuse, along with other institutes at the National Institutes of Health (NIH), is encouraging research targeting the endocannabinoid system. In one funding opportunity, “Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment” (http://grants.nih.gov/grants/guide/pa-files/PA-15-188.html), the NIH is seeking to find alternatives to opioids for pain, due to the increase in opioid abuse and overdoses. “Pain is a substantial public health issue, where it is estimated that about 100 million

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‘In the absence of more information about the toxicity, I would ask the scientific community to withhold judgment on FAAH inhibitors being the cause of this.’

Margaret Haney, M.D.

Americans suffer from chronic pain,” according to the funding announcement. Instead of using cannabis, NIH wants to look at alternatives such as the endocannabinoid system in the treatment of pain.

More transparency needed

Phase 1 studies are for safety and tolerability, not for effectiveness. Typically, they are done with healthy volunteers, and serious incidents rarely occur, partly because they are preceded by basic research with animals and partly because the doses are so low.

Researchers and experts quoted in pharmaceutical journalist Ed Silverman’s January 19 article (www.statnews.com/pharmalot/2016/01/19/clinical-trial-bial-deaths) were critical of Bial for not disclosing more about the drug involved. “It is not unusual for drug makers to closely guard details of their medicines, notably the structure of a compound, for competitive reasons,” wrote Silverman in his Pharmalot blog for STAT. “But in this instance, the lack of information may be an impediment to understanding how similar molecules can function and prevent further harm.”

Industry expert Sean Ekins told Silverman that more transparency is needed. “We would not have this problem if people were transparent about molecule structures,” he said. And medical ethicist Arthur Caplan told Silverman: “There is a duty to release some information so that anyone else using even an analogous agent can be alerted to an issue. That’s where the obligation lies. Protecting human subjects has to come ahead of defending proprietary concerns.”

Ultimately, though, researchers like Haney are left guessing about what went wrong in Rennes. Haney said that other pharmaceutical companies have made it through Phase 1 trials of FAAH inhibitors “without incident.” But the fact is that nobody really knows what’s in Phase 1 compounds, as Silverman’s report showed.

“The big problem is there is no requirement for reporting those Phase 1 trials anywhere,” Silverman told ADAW. So how do we know if there were adverse effects of FAAH inhibitors in Phase 1 trials? “We don’t,” he said.

District attorney weighs in on Good Samaritan laws

In last week’s issue, we wrote about how Good Samaritan laws are being undercut by prosecutors charging suppliers of the drugs that led to overdoses with “drug-induced homicide,” even if those suppliers were loved ones of the user. The result in many jurisdictions is that people are afraid to call 911 in the event of a suspected overdose (see ADAW, January 18).

We asked the National District Attorneys Association (NDAA) to comment for the story, but they were not able to by press time. So we sent them last week’s article, which featured comments from Kathie Kane Willis, Ph.D., and Daniel Raymond taking the treatment and harm-reduction side of the argument. For this week’s article, we interviewed Joseph D. Coronato, district attorney for Ocean County in New Jersey, who was speaking on behalf of the NDAA in discussing his view of Good Samaritan laws.

Essentially, he would not arrest anybody for calling 911, unless there were an outstanding warrant for an arrest.

Coronato was appointed and confirmed as district attorney two years ago, and within a relatively short time there were eight overdose deaths within a week in his county. “They were all under the age of 28,” Coronato recalled. “So as a result, we started drilling down on the overdose deaths, and also became very interested in getting these numbers down” by distributing naloxone.

Ocean County was the first county in the state to give naloxone nasal spray kits to all of the police chiefs in the county’s 33 towns, said Coronato. Forfeiture money was used to buy the naloxone. The first rescue by police in the county was in April of 2013; there were more than 100 rescues in 2014, and 272 in 2015. Overdose deaths went down, from 112 in 2013 to 101 in 2014 to 95 in 2015.

The naloxone rescues are closely connected to Coronato’s reading of Good Samaritan laws — people are never charged for calling in the overdose. “Nobody who gets sprayed gets charged with anything, and nobody who makes a call gets charged,” he told ADAW. “I am the chief law enforcement officer for this county, and this is my discretion — not to charge,” he said, adding that he doesn’t know of any other prosecutors.

Continues on next page
Coronato said he goes after dealers well outside his jurisdiction — in the Bronx in New York City, in Philadelphia, in northern New Jersey and in Trenton.

“Drug-induced homicide is declared by the medical examiner,” said Coronato. In some cases, people who overdose also have alcohol in their systems, and in those cases, the medical examiner can’t be sure that it was the drug that caused the overdose, said Coronato.

**Linking with treatment**

The prosecutor said he has a “partnership” with treatment programs.

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**‘When somebody overdoses and dies, I treat it as a murder case.’**

*Joseph D. Coronato*

The link is the naloxone rescue, or “spray,” as Coronato refers to it. “My orders are that anybody who is sprayed has to go to the emergency room,” he said. “We have recovery people who go to the ER when somebody’s been sprayed and will confront that person and make them agree to go to detox.” He acknowledged that the overdose victim must consent first. “Then they are brought to a detox facility and held there from 24 to 48 hours — with their consent,” he said. If they don’t consent, “the recovery person still contacts them” after discharge from the emergency room, he said. “If they do consent, the detox facility drills down and then we’ll decide with them what treatment program will be good for them — in some instances methadone, in some Suboxone, and in some Vivitrol,” he said.

Coronato was originally in favor of drug-free treatment only, but “the problem is so widespread that we’ll never have enough beds.” So he has come around to supporting medicated treatment, but he prefers Vivitrol to methadone or buprenorphine. “If you really look into it, Vivitrol has the most hope because it’s a total block,” he said. He also said that mental illness needs to be handled. “Which came first, mental health [problems] causing substance abuse or substance abuse causing mental health [problems]?” he asked.

Treatment providers are happy to work with the district attorney, according to Coronato. “They embrace us,” he said. “They understand that we’re not looking to lock up addicts; what we want to do is break the cycle of addiction.”

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Readers are encouraged to write *ADAW* with comments. Send them to adawnewsletter@gmail.com.

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**Oops from journal: Marijuana use is linked to later psychosis**

Last summer, *Psychology of Addictive Behaviors* published a study purporting to show that teen marijuana use is not linked to later problems, including psychotic disorders. Last week, the American Psychological Association (APA), which publishes the journal, ran a correction. In fact, teen marijuana use is associated with later psychosis, according to a correction, which stated that “a re-analysis of the raw data found that teen marijuana users did have an increased risk for psychotic disorders compared to non-users.” The other findings — no increased risk for depression or other physical diseases — remain the same.

The correction was prompted by Smart Approaches to Marijuana (SAM), which reanalyzed the data and urged reporters to correct their stories. *The Washington Post* was the first to do so. On January 19, SAM issued a press release about the correction, including a reference to the APA’s correction. After that, the associate executive director of the APA, Geoff Mumford, Ph.D., alerted Kim I. Mills, deputy executive director of the APA for communications, of the correction “since he oversees our work regarding addictions,” Mills told *ADAW*. “He had received a release from the *Washington Post* before we even had the opportunity to issue a press release.”

*Continued on page 6*
Protect your center and provider network from insurance fraud

By David Lisonbee

Ten years ago, managed care organizations were first and foremost referral agents for those seeking addiction treatment. This was a time when case management and referrals were managed by real people in real time. Since that time, insured members have found substance use disorder (SUD) treatment providers independently and often through misleading call centers/patient brokers on the Internet. Headhunters get paid top dollar by out-of-network providers for preferred provider organization (PPO)–insured or well-funded candidates.

As some unscrupulous entrepreneurs have built profitable businesses through unethical practices, their abundant marketing budgets have overtaken the market. Ethical, in-network, insurance-contracted providers do not have comparable marketing capital to compete. They operate off of a highly discounted rate of reimbursement that results in meager marketing/promotion budgets.

SUD treatment providers are incentivized to drop or avoid insurance contracts. Reimbursement is too low and contractual restrictions are too high.

The entrepreneurs are being rewarded by the same PPO plans they abuse, by being paid a percentage of their indiscriminately escalated “usual and customary” rates. Rather than managing American Society of Addiction Medicine (ASAM) continuing care where the patient resides, the PPO carrier enables the continuation of long residential stays away from home. Insurance carriers willingly pay out-of-area residential programs to extend residential stays by using the day treatment and intensive outpatient (IOP) treatment benefit while the patient continues to reside in residential, away-from-home care. No benefits are left to help the patient integrate recovery back where the wreckage, triggers and real-life problems reside. “Institutionalization” is reinforced by today’s commercial health care market.

Following are increasingly common breaches in lawful or ethical practice allowed by an absence of regulation and oversight and willing reinforcement by third-party payers:

- Out-of-network providers pay for prospective patient premiums (new PPO policies and COBRA) for the duration of treatment and then allow the policies to lapse.
- Patients are induced to admit by out-of-network providers waiving co-pays and providing sober living to IOP patients.
- “Usual and customary” services rates are overstated (by ten times) by out-of-network providers to enhance revenues.
- Out-of-network providers escalate their retail “usual and customary rate” for PPOs, which differs from that offered to their self-pay clientele. Out-of-network PPO reimbursement is maximized.
- Payment for referrals is exchanged between out-of-network providers and to “call centers posed as treatment programs” on the Internet.
- Patients are brokered to out-of-network providers from Internet call centers, which gauge the rate of kickback based upon the quality and quantity of the caller’s insurance coverage or capacity to pay top dollar out of pocket.
- Revenues are enhanced by unnecessarily elaborate, costly and frequent urinalysis testing by out-of-network providers and laboratories.
- Intensive outpatient program providers provide “sober living” residence to clientele through the combination of overstated “reasonable and customary” service rates and urinalysis overutilization.
- UR and billing is contracted out by providers to specialty companies that overstate/falsify acuity levels and “lethality” to heighten the level-of-care need and length of stay.
- Internet call centers and corporate providers mislead viewers and callers about the level of care, type and location of services needed for their condition.
- Patients are flown from state to state and across the country to engage in out-of-network residential treatment. Once the patients arrive, their choices for level of care and between service providers end.
- Patients are misled about the amount that the insurance will pay and what will be their likely self-pay amount: “We take your insurance, and whatever they don’t cover, we’ll put on a reasonable payment plan.” Residential treatment lengths of stay of 30 to 90 days are rarely medically necessary or covered by insurance.

Following are some tips:

- Require that day treatment and intensive treatment benefits are paid when the patient returns to their residence to enable recovery to be integrated in real time to their real-life circumstances.

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Continued from page 4

organization Smart Approaches to Marijuana urging reporters to correct their stories, which Ariana Cha at The Washington Post has already done. Since this reanalysis changed a fundamental finding of the study, APA believed it was important to correct the record.”

We emailed the corresponding author of the original study, Jordan Bechtold, Ph.D., for a comment on the correction but did not hear back by press time.

“T’m happy that the truth about the data came out,” Kevin A. Sabet, Ph.D., told ADAW. Sabet is director of the Drug Policy Institute and assistant professor at the University of Florida, and president and CEO of SAM. “Our Maryland coordinator, Dr. Christine Miller, first pointed this out to the journal, since the findings completely contradicted decades of research,” he said. “Of course, the legalizers took it [the original story] and ran with it to the media, and hence misinformation spread. But we’re now grateful the record has been corrected.”

ADAW never publicized the original journal article.

Correction

Last week’s top lead, “Behavioral pharmacologist with addiction history now helps MAT patients,” had an editing error in one sentence in the first column on page 2. The corrected sentence follows:

Snodgrass has a lot of credibility: he was trained as a behavioral pharmacologist with one of the best researchers in the country, but he was addicted to opioids himself.

Alcoholism & Drug Abuse Weekly regrets the error.

New Hampshire

Sessions and one subsequent outpatient visit. The other provision would require New Hampshire insurers to base their medical necessity standards for substance use treatment on American Society of Addiction Medicine (ASAM) criteria, which advocates say would eliminate the morass of standards that apply in the state’s insurance market today.

“To align the criteria would reduce the burden on providers who are already overburdened by the volume of people now seeking treatment,” Michele Merritt, policy director for New Futures, a New Hampshire nonprofit advocacy organization with a mission of reducing drug-related problems in the state, told ADAW. The three bills are made up of components that were crafted in discussions of a legislative task force empowered last year by Gov. Maggie Hassan to address issues such as facilitating access to treatment (see ADAW, Dec. 7, 2015).

Erasing disparities

Merritt explained that passage of the ASAM-related provision also would eliminate an inconsistency that exists for the state’s provider community. Providers are required to use the ASAM criteria as a condition of state certification, but then must learn in the insurance world to...
work with other placement criteria that may or may not resemble ASAM language, she said.

Referring to this provision and the potential elimination of prior authorization for initial outpatient services, state Bureau of Drug and Alcohol Services Director Joe Harding told AD AW, “Both of these provisions are critically important. People need to be able to access these services as quickly as possible.”

Merritt said that an earlier version of SB 576 had also included a removal of prior-authorization requirements for certain services of higher intensity, such as medical detox and some residential treatment, but that language did not survive pushback from the insurance industry. She believes this discussion could resume later in this year’s legislative session, however.

But Harding warns that the state should not repeat past patterns where a shortage of residential services was exacerbated by the notion that anyone in need of substance use treatment services required a residential level of care. “There is not a basis in fact for that,” he said.

Not on the fast track for approval, but on the horizon this year, will be a possible addition of around $5 million in funding over the next biennium for prevention and treatment services, Harding indicated. Hassan also has asked legislators to act on extending the state’s Medicaid expansion (the New Hampshire Health Protection Program), the covered population under expansion has access to an array of substance abuse benefits that Harding says will be extended across the Medicaid program as of July 1.

Other items that are part of the three bills that could reach the governor’s desk within days include a tightening of the penalties for fentanyl possession and distribution to mirror those for heroin; a requirement for more detailed utilization of the state’s PDMP by prescribers of opioids; a requirement that public schools offer age-appropriate drug and alcohol prevention education from kindergarten through high school; and the establishment of a commission to study ways to expand use of the opioid overdose reversal medication naloxone.

Sins of the past

The provider community in New Hampshire broadly agrees that historic underfunding of the service system in the state has played a major role in the crisis scenario being experienced today, says Stephanie Savard, chief operating officer of the multilocation Families in Transition and chair of a longstanding treatment task force that is part of the Governor’s Commission on Alcohol and Drug Prevention, Treatment and Recovery. She told AD AW that she sees Medicaid expansion as the first sign that the tide may be turning on a policy level toward greater funding support.

New Futures’ Merritt believes that more investment in outpatient services with coordinated sober housing over time would have made a significant difference. “Had the state made lower levels of care available, many wouldn’t have reached a higher level of acuity,” she said.

Today, however, residential capacity for the most seriously ill patients appears to be the area where the New Hampshire system is struggling most. “It has been so difficult to get people in, and there wasn’t a good payment mechanism until recently,” with Medicaid expansion, Merritt said.

Savard added that identifying in—

Continues on next page

Letter to the Editor

Don’t confuse cannabis with molecular entities

It is critical that we not confuse the plant, cannabis, with the hundreds of individual molecules incorporated into the plant. The article, “Cannabis for psychotic disorders or PTSD: Does it help?” (AD AW, Dec. 21, 2015), appears to compare use of the plant with use of specific molecular entities within. While there are no medical indications for use of the plant, there are in fact medical indications for use of at least one component of the plant. This is similar, of course, to other plants. If we look at willow bark, we know it contains a salicylate similar to aspirin. There are medical indications for aspirin, but there are no such indications for willow bark, which contains hundreds of other compounds, some of which may be hazardous. This hasn’t stopped people from promoting the use of willow bark; in fact, one can even order it in capsule form from the usual online sources. Yet there have been no studies comparing and contrasting aspirin to willow bark capsules.

Use of the plant cannabis is not the same as medical use of components of cannabis demonstrated to have specific risks and benefits with applicability for medical purposes. Similarly, use of willow bark capsules is not the same as medical use of aspirin.

Stuart Gitlow, M.D.
Immediate past president, American Society of Addiction Medicine
Continued from previous page
dividual providers to fill staff slots also is proving challenging. In her organization, which provides housing and intensive outpatient services for homeless families in the state, two clinical positions are open and applications are only trickling in, with many candidates lacking the necessary credentials for practice in the state. “Every provider has positions posted right now,” Savard said.

Amid the flurry of legislative activity this month came news of the resignation of Jack Wozmak as the state’s drug czar, as of Feb. 1. Wozmak had a controversial tenure marked by criticism of a lack of outreach to certain stakeholders, and some providers have said he never fulfilled a promise to establish a database of available treatment and recovery services in the state.

The sources interviewed by ADAW for this article generally steered clear of commenting about the resignation, with some suggesting it was more a matter of politics than a development directly relevant to the policy items now on the table.

The Massachusetts opioid bill proceeds without 3-day hold

The Massachusetts House has passed an opioid bill without a controversial measure that would have allowed health care providers to detain people with opioid use disorders for three days. Gov. Charlie Baker proposed the provision as part of his opioid package presented to the legislature last fall (see ADAW, Nov. 16, 2015). Instead, the bill requires that anyone who goes to the emergency room with an opioid overdose must be evaluated by a mental health professional within 24 hours, but that the patient would have to consent to any treatment. Some legislators said that voluntary treatment would be more effective than coerced treatment, and were also concerned about lack of space for the 72-hour holds. There is a lack of beds, according to treatment providers and some legislators. The bill, H.3944, now goes to a House-Senate negotiating team.

In case you haven’t heard...

Last week, The Washington Post reported that President Obama would appoint Agriculture Secretary Tom Vilsack to lead a new interagency initiative at The Rural Council to address rural America’s opioid abuse problem, as well as physical and mental health programs and financial problems. Naloxone appears to be the centerpiece of the opioid initiative. Vilsack said his adoptive mother had addictions to alcohol and prescription medicine. Matt Chase, executive director of the National Association of Counties, told The Washington Post that the increase in drug and alcohol abuse in rural areas indicates problems with the economy, which is shedding workers in favor of automation. “To me, it really boils down to the lack of economic opportunity in so many of these areas,” he said. The National Association of Counties and several other state and local government groups also banded together to buy naloxone. Mark Publicker, past president of the Northern New England Society of Addiction Medicine, told The Washington Post that he was “utterly pessimistic” that a government task force would help. “There’s value in identifying the fact that we’re dealing with a multidimensional, complex problem that deserves more than the simple answers that are being floated,” said Publicker, who treats patients with opioid use disorders in Maine. Last fall, the Health Resources and Services Administration announced a $1.5 million grant program to fund naloxone in rural areas.

Coming up...

The Addiction eXecutives Industry Summit will be held January 31–February 3 in Naples, Florida. For more information, go to www.axissummit.com.

The Community Anti-Drug Coalitions of America will hold its leadership forum February 1–4 in National Harbor, Maryland. Go to www.cadca.org for more information.

The annual meeting of the American Academy of Pain Medicine will be held February 18–21 in Palm Springs, California. For more information, go to www.painmed.org/annualmeeting/main.aspx.

The National Council for Behavioral Health will hold its annual meeting March 7–9 in Las Vegas, Nevada. For more information, go to www.thenationalcouncil.org/events-and-training/conference.

The 2016 National Rx Drug Abuse & Heroin Summit will be held March 28–31 in Atlanta, Georgia. Go to http://nationalrxdrugabusesummit.org for more information.

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