'Cannabis and the Opioid Epidemic'

Researchers Share Lofty Perspective at UCI Forum

By Dale Gieringer

NAS Beckman Center, Irvine CA, Feb 9 2018.

The UC Irvine forum, "Cannabis and the Opioid Crisis: A Multidisciplinary Review" featured a dozen academic experts trying to figure out whether cannabis can be shown to have a favorable effect on the opioid crisis. The event was hosted by UCI's Cannabis Research Center and moderated by Prof. Joe Dunn and Robert Solomon of the Law School. Notably absent was any physician or patient with practical experience in treating pain with medical cannabis (except for Donald Abrams, MD, who has conducted clinical trials, but not issued recommendations).

I brought along a couple of handouts which I managed to distribute to a few attendees —one listing published studies on cannabis and opioids, the other documenting complaints California NORML has received from pain patients denied treatment or prescriptions for controlled substances on account of using medical marijuana.

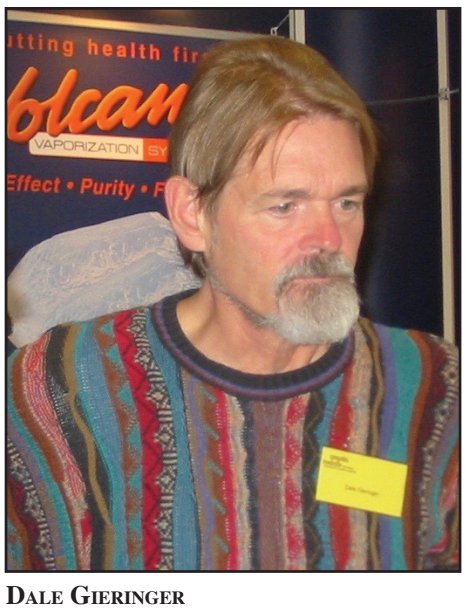
Most of the experts agreed that cannabis probably does help reduce opiate use, but that "more research is needed" to figure out whether this is truly the case.

Dr. Daniele Piomelli of UCI led off with an artfully presented overview of opiates and cannabinoids from ancient Greece and China to the present day. Searching PubMed, he found a total of 2,555 papers on cannabis and pain going back to 1972. A meta-analysis of animal data showed the effective dose of morphine is 3.6x lower when combined with cannabis and 9.5x lower for codeine!

Piomelli went on to declare that there were "no human studies." His concerns: How does cannabis affect opioid dependence? Cannabis withdrawal (a defining feature of Cannabis Use Disorder) "is no laughing matter," he said. Also, "Cannabis can cause toxicity, but we have little or no evidence of fatalities."

Dr. Susan Weiss from the National Institutes of Health spoke on the "Evolving Opioid Crisis." She explained how it began with Rx opioid users, based on favorable reports in the 1980s of extremely low addiction rates among patients treated in hospitals. More recently, there has been a trend to greater use of illegal fentanyl and heroin. Seventy percent of addicts start on Rx opioids, 30% on heroin.

Weiss lamented the lack of research funding for NIDA to develop new therapies, including new, targeted, safer opioids; new non-opioid pharmaceuticals; and non-drug therapies like meditation. She acknowledged that cannabis could be beneficial, but noted the counter-argument: cannabis use increases the risk of opioid misuse. She said that current evidence was from the "30,000 foot level" (ignoring from her ivory tower the many patient and doctor surveys documented in our handout).



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Weiss also lamented the many research barriers caused by the Schedule I status of cannabis.

UCSF's Dr. Donald Abrams summarized his studies on cannabis and pain conducted with funding from the Center for Medical Cannabis Research (CMCR). One of them incidentally showed a 10% reduction in pain when cannabis was added to opioids. A meta-analysis showed more efficacy with smoked cannabis than those with nabiximols (Sativex). Abrams also mentioned the HelloMD study showing 97% of patients agreeing cannabis could reduce opioid use. This was the *only* patient survey mentioned by any participants in the forum throughout the day.

Dr. Ziva Cooper from Columbia University warned about Cannabis Use Disorder, asserting that 19.5% of all cannabis users become dependent at some point, and 25% of them show severe symptoms. Potency has risen, which could have some harm reduction benefits to the lungs, but dab extracts have now reached the extreme high of 93% THC.

UCSD Professor Igor Grant (the founding director of CMCR) spoke briefly, saying that we have a legalization "experiment" underway, patients are using cannabis, and we need to know more. He said use in pregnancy was a significant concern. Piomelli and Weiss strongly agreed. Abrams noted that the only adverse effect seems to be somewhat lower birthweight.

The floor was opened to questions, giving me the chance to discuss the handouts I'd brought along:

"Let me put in a word for the patients. California NORML has heard from countless users who say they've been able to reduce or eliminate their opiate use by medical cannabis. Here is this list of scientific studies we've compiled, with numerous patient and doctor surveys involving thousands of patients who confirm this. Sure, we could use research on which patients are helped most, how big the effect is, etc., but it's a scientific fact that many patients find cannabis helpful in reducing opiate use. Can we agree?"

The panelists demurred. "We'll be discussing that more this afternoon," the moderator promised. I hoped that discussion would give me the opportunity to bring up my second handout (about pain clinics discriminating against MMJ patients) but as it turned out the proceedings veered in a different direction, and I never had the opportunity to publicly explain the problem to the academics 30,000 feet on high. Later I did have a private discussion about it with Rosalie Pacula of the RAND Corporation and she was shocked to learn it was happening.

The afternoon opened with a presentation by UCSF Prof. Stanton Glantz, "Avoiding a new tobacco crisis." His theme was that "Tobacco, marijuana and e-cigs are tied up with each other," posing an "upcoming disaster of marijuana legalization" from commercial exploitation.

Glantz hastened to add that he had no use for the war on drugs, and didn't think marijuana should be illegal, but rather regulated along strict public health lines like tobacco, so as to be legal but socially unacceptable. He warned of the lobbying influence of Marijuana, Inc. and was outraged that the industry had representatives on the state's Board of Cannabis Control advisory board.

Glantz said the carcinogenicity of marijuana smoke is clear from the fact that it's on California's Prop 65 list. He took credit for putting it there himself. "It's hard to get on the list" he claimed with a straight face. He's especially concerned about cardiac effects of cannabis, which he thinks are due to the smoke, not cannabinoids.

Glantz predicted that legalization will bring an upsurge in cancer, heart and lung disease.

He criticized California for poor label warnings, inadequate potency limits, the too-generous eight-ounce allotment for medical sales, and especially for allowing licensed indoor use and special events, in defiance of all of California's rules against tobacco. Cannabis packages should have gruesome pictures like Australia's packaging for cigarettes. He predicted that legalization will bring an upsurge in cancer, heart and lung disease.

Graham Boyd of New Approaches, a pro-cannabis Political Action Committee, spoke about his legalization work. He played a major role in crafting Prop 64. New Approaches is supported by 15 major funders, none of whom have any stake in the cannabis industry. Boyd took credit for writing research funding into Prop 64 —in particular $10 million for implementation studies, some of which seems destined to go to UCI, UC San Diego, and the new UCLA center.

Glantz groused that $10 million wasn't nearly enough for the large-scale epidemiological studies he'd like to see.

Polling data from the legalization campaigns found that the cannabis-opioid issue didn't have much appeal to voters in California, but did poll well in Maine and Massachusetts.

Glantz showed a powerful TV campaign ad for the Maine initiative in which a worker thanked MJ for ridding himself of opiate addiction. He worried about the current direction of federal policy, warning that California could be in the crosshairs of AG Sessions.

Dr. Marcus Bachhuber of the Albert Einstein College of Medicine discussed data showing that states with medical marijuana laws have fewer opioid deaths. He emphasized that states with medical marijuana laws had a higher than average rate of opiate use to begin with, but experienced a decline in deaths relative to what might otherwise be expected.

Likewise, studies show lower Medicare and Medicaid expenditures for MMJ states. Apparent paradox: cannabis use is associated with higher risk of opioid use but *medical* cannabis is associated with lower opioid use. Possible explanation: people with the worst disease are the heaviest users.

Rosalie Pacula of RAND discussed her latest research on opioid deaths and access to cannabis. Her analysis shows that access to dispensaries is the significant factor in reducing opiate abuse, not whether a law protecting patients is on the books.

Data pre-2013 showed significant reductions in opioid use in states with dispensaries. However subsequent analysis showed a weaker effect post-2013. One possible factor: earlier, the opioid epidemic was driven by Rx opioids, but more recently by illicit heroin and fentanyl.

It's too early to judge long-term effects of legalization, Pacula said. Driving studies are inconsistent. An article in the American Journal of Public Health showed no increase in traffic fatalities in Colorado and Washington State, but an insurance industry study showed a 2.7% increase in collision claims. Overall message: be cautious about evaluating policy, both sides abuse data to support claims still unproven.

Dr. Keith Humphreys of Stanford said he'd like to think that cannabis can alleviate the opiate crisis, but is skeptical of the data. There is evidence of a "modest" benefit of cannabis in treating chronic pain, he acknowledged, but massive use would be needed to significantly affect the statistics. Local trends don't necessarily affect the overall average, due to what's called the statistical aggregation fallacy. Bottom line: "We just don't know if cannabis will cure the opiate epidemic." Randomized prospective trials are needed.

(By the time such trials are completed the epidemic may have run its course. While panelists repeatedly stressed that more research was needed to inform policy decisions, they failed to cite an instance in which policy had ever been determined by research. It isn't science, but politics that saddled us with the Marihuana Tax Act and Controlled Substances Act for most of the past century.)

Prof. Mireille Jacobsen, a former DPA staffer turned business economist at UCI, led the question session. I used the opportunity to take on Stan Glantz, whom I'd not met before, in a good humored manner, disputing his parallel between MJ and tobacco. I said cannabis has a long history of advocacy by consumers like us, who value its use for various purposes and consider it a matter of personal freedom. In contrast, tobacco consumers are mostly sorry they use it in the first place and leave advocacy to the industry.

We are more like social use devotees of alcoholic beverages like beer and wine. Cal NORML has actively supported measures to prevent monopolization by large-scale corporate interests. Show us the evidence that marijuana causes lung cancer in humans —the best studies from Dr. Tashkin and others have found none. Furthermore, our vaporizer research shows that whatever toxins may still be present in MJ smoke can be 97-100% eliminated by vaporization.

"Marijuana smoke is on the Prop 65 list," answered Glantz, as if that settled the matter.

Humphreys observed that people smoke far lower quantities of MJ than tobacco. Piomelli agreed with me on pharmacological grounds about not lumping cannabis with nicotine, noting how much more difficult it is to get animals to self-administer cannabis.

"We shouldn't expect things to go wrong with marijuana," he said, "They can go right this time."

Glantz concluded by saying there was "a very good case" that marijuana could be mitigating the opium epidemic. He also mentioned that he'd been dis-invited from a CADCA (Community Anti-Drug Coalitions of America) conference after informing them he supported legalization.

About 60 people attended the forum, less than half the capacity of the room, although event registrations had been advertised as full up.

Other attendees included field staffers from Sen. Harris and Feinstein's offices, a Green State reporter, Nick Morrow of LEAP, Bill Britt and Kandace Hawes of OC NORML. A couple of LAPD narcotics officers audited from the back of the hall.

Dale Gieringer is the director of California NORML.

CMCR hosts meeting on the future of MCR (Medical Cannabis Research)

By Dale Gieringer

"Cannabis and Health" was the stated theme of a conference held June 8 at the Center for Medicinal Cannabis Research on the UC San Diego campus. Benefit, not harm, is the new focus. $10 million in tax revenue collected from cannabis consumers and providers will be allocated to researchers by the Bureau of Cannabis Control. The looming questions are: what research to fund, and which researchers.

The conference drew about a hundred attendees from every facet of the field.

Sherry Yafai, MD, represented the Society of Cannabis Clinicians. She was articulate, organized, on-target and passionate in defense of her practice. She only began practicing after Prop 64 on January 1, 2018, and only takes physician referrals. "I'm not a pot doc," she said.

Yafai described her patient population, which ranges from age 2 to 100 (!), and their various indications —mainly pain, cancer, and narcotics reduction. Most had tried marijuana in their youth and most don't want inhaled medicine.

Yafai emphasized how patients decrease use of other medications, including opiates, other controlled substances, and blood pressure drugs. She works with a "High Sobriety" group that uses non-smokable cannabis to treat drug addiction. Her patients —longterm addicts— are given maintenance doses of CBD-rich oils to get off drugs. She said she had successfully treated four long-term opiate addicts, helping them get entirely "clean" in 10 days using nothing more than cannabis oil.

Yafai noted that high-potency products are used in cancer treatment and formulations for epilepsy and drug abuse.

A French addiction specialist in the audience questioned her claim. Yafai said she would soon have data to present. (Earlier in the session she had taken the microphone to respond to a presenter who questioned the medical need for high-potency products. Yafai explained that high doses were used in cancer treatment and formulations for epilepsy and drug abuse.

The conference began with a lucid presentation by Dr. Piomelli about the history of medical cannabis, the cannabinoid receptor system, endocnnabinoids, and the National Academy of Sciences, Engineering & Medicine (NAS) report.

Piomelli said he wanted to work on specific chemical agonists, antagonists, and FAAH inhibitors. "I don't think cannabis is really a good drug," he said. "I think we can have better drugs." He remains concerned about prenatal exposure to cannabis, not because of the lower birth weight, which can be explained by smoking, but by possible effects on fetal stem cells, which haven't been investigated. (Overall though he is pro-cannabis and anti-prohibition).

Ziva Cooper from Columbia University presented her research on pain treatment with cannabis and opioids. Subjects given sub-clinical doses of oxycodone and cannabis to treat cold-pressor-induced pain showed no response; but when the two drugs were combined, they were effective. Conclusion: cannabis increases analgesic but not intoxicating effects of opioids.

Marcel Bonn-Miller of University of Pennsylvania and Tilray discussed the lack of studies regarding cannabis and PTSD. Surveys of patients at SPARC et al show widespread use of cannabis amongst PTSD patients. They prefer high THC to CBD. Early results of an ongoing study of cannabis use by Bonn-Miller: only minor reductions in PTSD symptoms, but a high association with problematic use.

Doris Trauner of UCSD has received a grant from Insys and the Noorda Foundation to study cannabis in autism. She cited an Israeli study finding that 61% of parents reported behavioral improvements in autistic kids using CBD-rich cannabis.

Iain McGregor of University of Sydney, GW and Tilray, has received $33 million from the Lambert family to study cannabis in Gervais syndorme. Australian GPs are more accepting of cannabis than specialists, he said. Quality control of CBD products is a big problem. The placebo effect is strong. In a survey of epileptic children treated with cannabis, many samples deemed "effective" turned out to contain no CBD or CBDA. Surprisingly, driving performance tests found that patients given a mixture of 50-50 CBD/THC were no less impaired than those given pure THC.

Staci Gruber of McLean Hospital noted that studies on cannabis and cognition have focused mainly on young recreational users, not the older medical population. Those exposed to cannabis before age 16 tend to score significantly poorer on cognitive tests, but not those exposed later.

Rodent studies suggest that cannabis can help reverse age-related cognitive decline. Her studies of older medical users found reductions in opioid and drug use, reduction in depression, improvements in sleep, improvement in executive function, but the usual memory impairment.

Tom Marcotte of UCSD gave a good presentation on cannabis and driving ability. Some signs of impairment observed in driving studies may be offset by subjects' awareness of their condition. No apparent increase in accidents in Colorado post-legalization; more drivers are being screened for drugs than before. THC less impairing than anti-depressants, hypnotics, alcohol. Need to look at effects of oral dosing.

Alan Budney of Dartmouth apologized for being the one addiction specialist at the forum. His presentation was disorganized, informal and lacking in data. His bogeyman: the "'popular myth that cannabis is good for everything."

Yafai was part of the "Real World Cannabis Use" panel. Ryan Vandrey of John Hopkins and Insys spoke on "What's in real-world cannabis?" He was the first speaker to bring up terpenes and flavonoids, which remain totally unstudied. He complained about the general lack of standardization in current products, poor testing quality control, inadquate labeling, questionable contaminants, etc.

Mahmoud ElSohly spoke about his drug development at the University of Mississippi. He showed pictures of the Ol' Miss farm, which features both indoor and outdoor gardens. El Sohly's surveys show a substantial increase over the last 10 years in THC/CBD ratio of cannabis grown in the US —despite the popularization of CBD. This could be because El Sohly tests samples confiscated by law enforcement, not legal products from medical states.

He is working on suppositories. He said that THC by itself is useless in suppositories and tampons, it needs to be in modified form of THC-hemisuccinate in order to penetrate. He is also working on glaucoma formulations with longer activity than inhaled/ingested THC, which wear off too quickly. He has a promising formulation that is active for four hours and is seeking to extend it to eight hours.

El Sohly is also doing research on CBD and opioids. He has found that CBD combined with a sub-active dose of oxycodone produces analgesic effects. I asked him about the many cannabis topicals, creams, lotions, etc., on the market. He wasn't sure about CBD, but THC can't penetrate the skin, he said. Topicals and suppositories claiming to provide THC are "fakes."

(A representative from Mary's Medicinals told me they sell epidermal patches that use a patented carrier to help THC penetrate the skin).

Three manufacturing companies were invited to discuss their activities. Tiffany Devitt of Cannacraft, Lynn Honderd of Mary's Medicinals, which specializes in transdermal patches, and Catherine Jacobson of Tilray, which is working on childhood epilepsy and has applied to FDA to do clinical trials. Jacobson previously worked with GW on Epidiolex, which should be approved by FDA in the next month or so. After that the DEA must still grant it a special schedule.

The last session featured government officials speaking on regulations and barriers to research. Dominic Chiapperino of the FDA Controlled Substances Office described the agency's role in cannabis regulation. The FDA oversees the "8-factor analysis" that is required for rescheduling. Chiapperino pointed to the need for larger clinical trails, alternatives to smoked marijuana (e.g., vaporizing), and evaluation of longer-term chronic use. He mentioned that his agency sent 20 warning letters to CBD manufacturers who had nationally marketed products and were making egrergious health claims.

Lori Ajax of California's Bureau of Cannabis Control outlined her agency's ongoing efforts to implement state regulations. The emergency regulations have beeen extended to Dec 31, but can't be extended again; they will shortly be issuing their permanent regulations for comment. Addressing the many concerns expressed at the forum about the quality of existing products, Ajax said that state-regulated products are thoroughly tested and labeled so as to meet requisite standards for product control. There is still a shortage of licensed labs: just 31 out of a statewide goal of 100.

Steve Gust from NIDA spoke about the agency's cannabinoid research program. Most of the projects are non-marijuana: $15 million for CBD research; another $139 million for cannabinoid research, $62 million for endocannabinoids, and $36 million for therapeutic research. Altogether, some 70 projects.

Ellen Auriti, an attorney from the University of California's Office of the President, gave an overview of the many legal challenges to conducting research. Schedule 1 licenses must be had from DEA; state approval by the Reseach Advisory Panel of California (conveniently re-named RAPC from CRAP) is still needed. Indsutrial hemp can only be researched under an agricultural pilot program that hasn't yet been developed in CA. CBD from hemp is illegal under DEA's latest rules, upheld by the 9th Circuit Court of Appeal. A Schedule 1 license is needed to work with CBD. UC must comply with the Drug Free Schools and Communities Act, which requires standards of conduct that clearly prohibit illicit drugs (including CBD). Also. the Drug Free Workplace Act.

Everyone at the forum —including Gust of NIDA— agreed that there was a need for additional sources of cannabis for research. Igor Grant wondered aloud what CMCR could do. Apply for a DEA license? Expensive and uncertain (a bill to authorize CMCR to apply for a DEA license was killed by the Assembly Appropriations Committee this year).

Work with a private company? But what private company would be willing to invest in FDA drug development, given that so many companies were already able to market their products legally in CA and other states. Given all of the difficulties, Grant ventured that CMCR's best alternative might be to import products from other countries.

"We'd love to work with you," Devitt said. Cannacraft sold two million units in 2017, and would gladly provide products to researchers conducting clinical trials. She also offered to share the information that the company has collected via surveys —for example, people using cannabis to treat Aspberger's Syndrome showed a preference for a 4-to-1 CBD-to-THC ratio.

PS as we got to press: The CMCR has received federal permission to import a high-CBD/low-THC product produced by Tilray in Canada for a study of essential tremor.

Despite promise to add sources:

Ol' Miss still lone supplier of cannabis for research

In August 2016 —towards the end of the Obama era— the Drug Enforcement Administration said it would license more cultivators of cannabis for research purposes. Two years later, after accepting 26 applications from would-be suppliers, DEA has licensed none and has stopped taking applications. Mahmoud Elsohly, PhD, at the University of Mississippi, retains his monopoly status.

Supervising the stall is US Attorney General Jeff Sessions. "It'd be healthy to have some more competition in the supply, but I'm sure we don't need 26 new suppliers," he twinkled in an October 2017 press conference.

Lyle Craker, a professor at the University of Massachusetts at Amherst, has been applying for a DEA license to cultivate cannabis for research since 1999! Craker is among the 26 who haven't heard back as we go to press in November 2018.

Mahmoud Elsohly (right) shows Sanjay Gupta the walk-in safe where cannabis grown on the Ol' Miss campus under contract with NIDA is stored. Graphic from CNN.