Evidence-Based Policymaking: What's Absent from the Opioid Crisis

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2nd Edition *

Summary

Evidence-based policymaking requires the collection and evaluation of evidence. Failed policymaking often results when known evidence is ignored. On the subject of opioids in pain care, that ignorance begins with what the Government itself already knows about opioids and pain. Three decades of research by the National Institutes of Drug Abuse (NIDA) have conclusively demonstrated the existence of an Endogenous Opioid System that regulates oxygen metabolism, blood circulation, and sleep. Evidence that methamphetamine addiction disrupts the normal functioning of the Endogenous Opioid System causing an opioid craving, was apparent. The Centers for Disease Control systematically ignored these NIDA findings, in arriving at a set of Opioid Prescribing Guidelines, that had the perverse effect of increasing deaths by overdose among people who switched from legal opioid drugs to illegal opioid drugs, increased the suffering patients with Disabling Intractable Pain, while doing nothing to protect the stimulant-abusing population from abusing lethal mixtures of opioid and other drugs. The US did nothing about the cause of the opioid crisis, and continues to lack a workable exit strategy to end the cause of the crisis. Present tactics that focus on making opioids more-difficult to obtain legally, are not working, because they increase profits for organized criminal gangs that traffic illegally in opioids. Rather, what's needed is better medical education on how to spot patients at risk, test them for stimulant abuse, and begin detoxification from methamphetamine, cocaine and other stimulants. Also needed is better medical education on how to identify patients having a pain crisis, so that patients with disabling intractable pain can get help for pain. The lack of education generally about pain, it's causes, and treatment, has done much to make this crisis worse. Recommendations are made to change how prescription methamphetamine is labelled, so as accurately to reflect the risk of sleep disorders and of opioid dependency when the drug is given, and policy recommendations to seek alternatives to methamphetamine are also made.

1. The Law of Disability as it Affects Drug Policy.
2. What Did NIDA Know And When Did NIDA know it?
3. Politicizing the CDC: What Can Be Learned From the Failure

Part 1. The Law of Disability as it Affects Drug Policy.

The Americans With Disabilities Act of 1990, 42 USC Chapter 126 defines a disabiity as anything that substantially limits a major life activity, including major bodily functions and the performance of various activities such as walking, bending, standing and working. 42 USC §12102. Pain that substantially interferes with walking, bending, standing, and working, is thus a disability. So is pain that substantially interferes with thinking, sleeping, and brain function. 42 USC §12102(2)(B). Ameliorating a disability with medication was expressly considered by Congress to be a right of disabled people and the person is considered disabled, if the person continues to need the medication to function, but is functional while on the medication. 42 USC §12102(4)(E)(i)(I).

Significant numbers of people suffer Disabling Intractable Pain that only responds to opioid therapy. Many other people suffer nerve inflammation conditions that do not respond to opioid therapy alone. As is explained in Part 2 of this paper, everyone alive has receptors for opioids and cannabinoids, and substances that bind to these receptors are **normally present** in the human body. No one is ever absolutely free of these substances, and the mistaken belief that it is possible to live without

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endogenous substances motivated the adoption of public policies that are harmful.[Δ]

The disabled person who uses prescribed medication to ameliorate Disabling Intractable Pain, is thus exercising a protected right under 42 USC Ch 126. Public entities including states, counties, cities and their agencies may not discriminate against disabled persons in the provision of services. 42 USC Ch 126 Subchapter II Part A. (The FDA is exempt in it's rule-making functions from 42 USC Ch 126, and it's non-rulemaking functions are governed by an earlier federal law, §504 of the Rehabilitation Act. State agencies attempting to implement guidelines issued by the CDC **do not** enjoy this exemption and are at risk of being sued under ADA, for any resulting harm.)

Since patients suffering Disabling Intractable Pain clearly fall under the protection of the Act, we now examine how the Act affects persons addicted to illegal drugs such as Methamphetamine and Cocaine. That subject arises in 42 USC Ch 126 Subchapter II Part B. Discrimination in employment is allowed, when a person currently uses illegal drugs or consumes alcohol during employment. 42 USC § 12114. Such discrimination serves to protect the intoxicated worker from self-harm and from causing harm to others. Such discrimination only applies to active **current** use of illegal drugs and alcohol. No public entity may discriminate on the basis of employment, against an individual for their past use of illegal drugs or alcohol. 42 USC §12114(b). Discrimination in public services (for example, participating in a treatment program for a substance use disorder) is not allowed, on the basis of past or current drug and alcohol usage. 42 USC §12114(a). 42 USC §12132.

Applying the principles of 42 USC Ch 126 then requires that whatever policy states adopt for opioid pain drugs, must allow persons with Disabling Intractable Pain to have full use of any opioid medication that ameliorates their disabiliy. And applying the same principles of 42 USC Ch 126, whatever policy states adopt for opioid pain drugs, must not obstruct people suffering a substance use disorder from obtaining treatment for that disorder. States license physicians to practice medicine and license pharmacists to make medicines themselves or re-sell those medicines within their state. FDA's authority derives from the Commerce Clause of the US Constitution. Congress charged the FDA with the duty to regulate substances sold across state lines as medicines, requiring that any claim of safety or of therapeutic effectiveness be substantiated with proven facts, and FDA issues regulations implementing that legislation[†]. 21 USC §§301 *et seq*, implementing the Federal Food, Drug, and Cosmetic Act.

Part 2. What Did NIDA Know, and When Did NIDA Know It?

The National Institutes of Health and their drug abuse unit, the National Institute of Drug Abuse, first learned of the formation of so-called “endorphins” in a 1975 paper from the University of Aberdeen, Scotland by Hughes et al, that found a pentapeptide compound of partially-known structure that they named *enkephalin*.[1] For some years various researchers set to work clarifying what was happening inside human and animal brains. The operative questions were why we have receptors in our brains that respond to opioid and cannabinoid drugs, what function the receptors serve, and what's going wrong with people who develop addiction to opioids.

Δ The substances are not interchangeable. Just as one needs Vitamin C to treat a Vitamin C deficiency or iron to treat an iron deficiency, one cannot treat an endogenous opioid imbalance with a cannabinoid nor treat an endogenous cannabinoid imbalance with an opioid.

† In practice, most prescription medicines are manufactured centrally and sold in interstate commerce nowadays, because transportation costs have fallen since the FDA first came into existence, as a unit of the Department of Agriculture that regulated the sale of dried medicinal plants in 1906. Adulterated medicines that cost money but lacked potency were a major concern in 1906. Today, false claims of therapeutic benefit or safety have become a bigger concern.

Those questions were posed a bit earlier by Avram Goldstein, of Stanford University's Addiction Research foundation, at a drug abuse symposium held in Toronto in 1973.[2]

At first, the *enkaphalin* discoveries, which later came to be known as "endorphins", presumed there to be a profound structural difference between the endogenous "endorphins" and the exogenous drugs that were involved in drug use disorders. But by 1983 Prof. Goldstein had demonstrated that there was no such structural difference between endogenous and exogenous opioids. In what should be considered a landmark discovery, Goldstein's group found morphine being produced in the adrenal glands of cattle and proved it to be structurally identical to pharmaceutical morphine.[3] The quantities Goldstein's group found were not trivial. 33 nanogram-moles of morphine per gram of beef adrenal tissue were reported.[4] A NIDA research grant, DA-1199, funded the work[5], and at minimum, the contracting officer at NIDA knew what was discovered. Of further value to the present discussion, Goldstein's group reported high variability in morphine levels from animal to animal. Their experimental process relied on beef adrenals and brains taken randomly from a slaughterhouse. In examining the brains by radioimmunoassay,

> "analysis of coronal sections of fresh material revealed that adjacent regions of a single brain could differ by as much as a factor of 1000 in ir-morphine concentration"[6]

The radioimmunoassay was highly specific for the morphine molecule. Other molecules such as naloxone, naltrexone, codeine, and reticuline were relatively unreactive when analyzed by the method.[7]

It is useful to perform a calculation at this point, to determine how much morphine occurs in beef adrenal glands. A typical steer weighs about 1,010 lbs[8] or 458 kg. So 33 nanogram-moles per gram, multiplied by 458,000 grams of beef, give 458,000x33=15,114,000 nanogram-moles or 15.114 milligram-moles. A single milligram-mole of morphine has a mass of 285.34 milligrams. Thus

15.114 milligram-moles x 285.34 milligrams/milligram-mole = 4,312.6 mg morphine.

To cause the steer's adrenal glands to contain the levels of morphine that the Goldstein group found in them, by feeding morphine to the steer and allowing it to dilute itself inside the steer's body randomly, would require that the steer absorb four thousand three hundred milligrams of morphine. Cutting that by a factor of five, a 202-pound human would get the equivalent dose, from 862 mg of morphine (assuming all of it was absorbed). This is almost 9 times the daily level of morphine dosage that CDC recommends against taking, because of risks they claim to have found, in their Opioid Guidelines.

From these calculations it is apparent that the animal must have manufactured the morphine by some biochemical process, inside it's adrenal glands and brain, because to eat this much morphine from environmental sources would appear impossible. The steer would appear intoxicated if it consumed 4,300 mg of morphine, therefore the morphine must have gotten into it's adrenal glands and became concentrated there, by some process that's non-random. The radioimmunoassay study of the beef brain, showing a thousand-fold variation in concentration from one location to another within the brain, likewise indicates a non-random process. Last but not least, the radioimmunoassay method had ruled out substances that were not morphine. From that point on, a great deal of research effort began in various countries, seeking to determine how the drug morphine is being generated in various organisms, and what it's functions are within them. NIDA was a leading financier of this research.

Any remaining doubt about the possibility that living organisms other than opium poppies could

produce endogenous opioids was completely dispelled by the research of Christina D Smolke and colleagues, supported at Stanford University by NIH Grant AT007886, who in September 2015 reported results of a decade-long effort to construct, using recombinant DNA, a yeast strain that manufactured two opioids from ordinary sugars and nitrogen fertilizer. Smolke's group installed genes from various organisms that coded for 13 different enzymes, alongside 7 natural yeast enzymes, each of which carried out one step of the 20-step synthesis of the opioid drug hydrocodone, and yielded thebaine as a byproduct.[9] The enzyme morphine reductase, that converted thebaine into hydrocodone was taken from the genome of *Pseudomonas putida* bacteria.[10] What use a common soil bacterium would have, for an enzyme that turns thebaine into hydrocodone, would seem puzzling, unless one accepts for a fact that endogenous opioid synthesis and use, is widespread in the natural environment.

During the time period between 1985 and 2015, NIH and NIDA were far from idle in this research field. A 2005 study by Zhu et al of the Neuroscience Institute at SUNY Westbury, funded by NIDA Grant 09010, demonstrated that human white blood cells synthesize morphine using the nutrient tyrosine as a precursor, and increase their morphine yield in response to stress.[11] 164 research papers, many funded by NIH and NIDA, were reviewed in 2009 by Prof's George B Stefano and Richard Kream of the Neuroscience Institute at SUNY Westbury, in support of the contention that endogenous morphine serves as a carrier molecule for nitric oxide, acting on plant and animal mitochondria to regulate oxygen metabolism.[12] This signaling mechanism, in eukaryotes, would explain the widespread use of endogenous morphine in all plant and animal species. Two years later, Stefano and Kream, collaborating with Czech researchers, independently found a sequence of biosynthetic pathways by which 18 enzymes would convert the nutrient tyrosine into dopamine and thence into thebaine and ultimately morphine, in approximately the same order that Smolke, working independently at Stanford, found useful to bioengineer the production of thebaine and hydrocodone in genetically-engineered yeast.[13]

Research into the brain's endocannabinoid system went on in parallel. William Devane's research group at St Louis University Medical School synthesized radioactive tetrahydrocannabinol (THC) and used radiological techniques to prove that rat's brains had receptors that attached to THC in 1988.[14] Four years later, Prof Devane was part of a group, funded by NIDA Grant DA 6481, that found a substance in pig's brains they named Anandamide, that binds to the pig's THC receptors[15]. Anandamide forms in the human body from arachidonic acid[16], a fatty acid found in nuts, meats, cheese and fish[17]. An ongoing controversy over whether meats and cheeses make inflammation better or worse has divided many nutritionists, with some advocating a vegan diet to cut arachidonic acid intake to control inflammation and others favoring increased arachidonic acid intake, and what may confuse matters further, is whether individual variation in how well the person metabolizes arachidonic acid into anandamide, and individual variation in how well one's endocannabinoid receptors respond to anandamide, may cause some people to respond differently to changes in diet.[18] *

The legal implications of this scientific finding are profound.

U.S. statutes prohibiting narcotics addiction, presumed that narcotics were exogenous foreign substances brought into the United States by foreign commerce. Discovering that such eukaryotes as

* It is entirely conceivable that certain individuals react adversely to substances in the cannabis plant and dislike the plant's taste and odor because of that reaction, while others may get great benefit from it. Schizophrenia sufferers, for example, report difficulties when cannabis is taken, reports Srivastava (Reference 37 *post*). Accepting this diversity requires that people be made aware of their nutritional and therapeutic options, not that we strive for some imaginary perfect food/medicine that helps everyone equally.

common earthworms secrete endogenous morphine, would explain why common soil bacteria such as *Pseudomonas putida* developed an enzyme to exploit the substance as part of a survival strategy.

Because these endogenous substances are endogenous, mere abstinence from their intake, will not isolate one from their effects.

NIDA has clearly been aware of this fact for the past 12 years. They paid for the research that proved it. And paid for more research that continued re-demonstrating the same proof, until any effort at doubt was as futile as the Flat Earth Society's efforts, during the Apollo moon flights, to persuade television viewers that the visibly round Earth was somehow still flat.

Part 3. Politicizing the CDC: What Can be Learned From the Failure.

Local authorities in rural West Virginia were aware of a methamphetamine trafficking and addiction problem there for a number of years. A Google search using the terms "West Virginia Methamphetamine Arrest" yielded approximately 148,000 anecdotal records.[19] Among the 148,000 reports, on the first page of the search results were the criminal sentencing of a newly-elected county sheriff, who confessed to stealing methamphetamine from an evidence room to maintain his personal addiction,[20] a seizure of 75 grams of unsold methamphetamine along with money thought to be sale proceeds and "dozens of prescription pills of various types" including the tranquilizer Alprazolam,[21] and a press release by the US Department of Justice, announcing the indictment of 11 US citizens and 3 Mexican citizens, for conspiring to transport 5 pounds of 98%-pure crystal methamphetamine from Los Angeles to Charleston, West Virginia where the drug was to be sold to local distributors but was instead seized by FBI and Homeland Security personnel and the arrests made.[22]

Anyone making the slightest effort to inquire into the effects of methamphetamine addiction would discover it's actions to be similar to, but perhaps more potent than cocaine and the cocaine derivatives known as "crack" and "freebase". Among the known side effects of methamphetamine use are difficulty sleeping, muscle cramps, spasms, shakiness, uncontrolled vocal outbursts and tics, addiction, profound tiredness after long-term use, and occasional psychosis.[23] Methamphetamine remains legal in the US as a prescription drug for treatment of Attention Deficit/Hyperactivity Disorder (ADHD) that is refractory to other medications and is sold for that purpose in a time-release form.[24] Illegal traffickers who supply methamphetamine addicts, omit the safety measures of encapsulating the drug in time-release form. A NIDA public-information guide on Methamphetamine Addiction, warns that methamphetamine is more toxic than cocaine. According to the guide, cocaine blocks the re-uptake of dopamine by nerve cells, but methamphetamine both blocks the re-uptake of dopamine and causes release of dopamine, creating a toxic condition in the brain until the dopamine is flushed out.[25] What NIDA fails to mention in this 2013 report, is what it already knew from the work on Endogenous Morphine published by Zhu in 2009 that it paid for, and by Stefano in 2011: Human brains use their internal dopamine to manufacture morphine.[26] Since we humans make that morphine for some purpose, abusing methamphetamine to achieve a dopamine-induced state of altered consciousness, comes at the cost of losing dopamine from our bodies. If the methamphetamine-addicted brain flushes it's supply of dopamine away, because of a toxic condition induced by forced dopamine release and blocked dopamine re-uptake, there's a reduced supply of dopamine available to brain cells, from which to create endogenous morphine. Reasonably, anyone aware of these research results, knew or should have known that a morphine shortage would develop in the brains of people addicted to methamphetamine, which could bring about a craving for opioids, if the addict were familiar with opioids and their effects or were given the chance to use them.

Earlier in this paper it was noted in discussing Goldstein's work, *supra*, that significant variability in

morphine levels was found in different cows and in different locations within the beef brain. One possible explanation for the variability was the time of day that the animal happened to be butchered. Since dopamine promotes wakefulness and morphine promotes sleep, one may readily infer that a kind of biological clock could be at work in our brains. We create dopamine from dietary tyrosine, and a dopamine buildup awakens us from sleep. As our day wears on and we tire, morphine is made from the dopamine, accumulating until it makes us sleepy at bedtime. While asleep, morphine would eliminate from the brain as new dopamine is created, continuing the natural sleep-wake cycle. Disrupting this natural cycle with stimulants would tend to interfere with the various functions the brain and muscles must perform during sleep, which might reasonably account for the profound tiredness experienced by long-term methamphetamine users. Recent research from the Netherlands done by Meijer and de Lange indicates that rat brains follow precisely the trend required, for such a dopamine-morphine cycle to operate: Meijer and de Lange's group only examined the morphine levels in the rat brain, but found that sleeping rats eliminated morphine from their tissue 54% faster than rats which were wide awake.[27] One of the authors, Meijer, has a forthcoming article on the adverse health effects of sleep deprivation, due to be published in January 2018, which deprivation is a consequence of methamphetamine addiction, and in the published abstract, the sleep-deprivation article specifically discusses the role of dopaminergic agents in causing sleep deprivation and the related ill-effects..[28]

It is very troubling that the CDC panel which devised their Opioid Prescribing Guidelines utterly ignored the role of methamphetamine in the rising death rates, observed in rural West Virginia, among people who took mixtures of sleeping pills, alcohol, and opioids. It would be apparent, upon the slightest effort, that alcohol, opioids, and sleeping pills all tend to make a person sleepy, and that people intentionally combining all three substances were likely trying to force themselves to sleep. It should have been equally obvious, upon the slightest investigative effort, that the methamphetamine addiction problem known to have already existed in rural West Virginia, would cause people to have precisely the difficulty sleeping, that would motivate them to combine sleep-inducing drugs in an effort to get to sleep. Yet the few publications coming from the panel that created the Guidelines, refer only to a problem they characterize as “an epidemic of opioid addiction”.[29] Also troubling is the fact that contrary to law, the panel that created the Guidelines was chosen in secret, excluding people knowledgeable about the treatment of disabling intractable pain, and only including people knowledgeable about addiction. Thus, the panel sought to address the needs of people disabled by addiction but did not consider the needs of people disabled by disabling intractable pain. A FOIA action is being pursued by the Washington Legal Foundation[30], who report that the CDC has agreed to turn over all documents used by the panel[31], and that two years after so agreeing, has not actually turned over any documents at all.[32] Adding to those concerns is the fact that lead author Andrew Kolodny has a background in addiction medicine and has previously published a book on the subject of methamphetamine addiction.[33] In that book, Andrew Kolodny authored a chapter, “Psychiatric Consequences of Methamphetamine Use”[34], reiterating much of what this paper says, with the following curious quote:

> Pharmacological treatments for stimulant dependence are not yet available. Effective treatment options primarily consist of psychosocial interventions.[35]

Kolodny knew or should reasonably have known, that people addicted to methamphetamine crave any means of inducing themselves to sleep. And the fear of withdrawal symptoms, drives the methamphetamine addict to attempt self-medicating with sleep-inducing drugs, because asking a doctor for help, means being put into detoxification with no medication to reduce the

methamphetamine craving or the withdrawal symptoms. Yet this problem is completely ignored.

Equally disturbing is Andrew Kolodny's conflation of Addiction with Dependence. All humans are insulin-dependent, but some humans with diabetes are dependent on injected insulin, because they do not secrete enough endogenous insulin to meet their needs. No one would consider a diabetes patient irrational, for poking herself in the finger with a needle to measure her blood sugar level or for injecting herself with insulin before a meal. Similarly all humans are morphine-dependent, because the endogenous morphine already in our bodies performs necessary functions, and a person who has insufficient morphine may supplement that with prescribed opioids when medically necessary, e.g. for pain control or air hunger. But many people question the rationality of the methamphetamine addict, because the drug is exogenous and foreign to the body, may no longer serve any necessary purpose, and the addict is clearly suffering injury from remaining on the drug but is afraid of the harm to be suffered in quitting.

Since methamphetamine remains available as a prescription medication for treatment of ADHD, despite it's serious dangers, other therapies for ADHD merit consideration if they prove effective, particularly in treatment-resistant ADHD. A recent study done at Kings College, London, by Asherson, began from anecdotal observations that some ADHD patients self-medicated by smoking cannabis and seemed to require lower doses of stimulants to get good symptom control. Asherson's group used a drug that's legal in Britain called Sativex, which is an extract of the cannabis plant made by Bayer. Sativex is an oral spray, available in Europe by prescription for various indications. Because it is an oral spray and study participants were unfamiliar with it's taste and odor, some participants received placebo and others received Sativex, and the results of the randomized controlled trial were observed. Hyperactivity/impulsivity were reduced and attention span improved[36], without the cognitive impairment that Shrivastava reports seeing in some populations but not in other populations.[37] Asherson proposes that further study be done of the endocannabinoid system of people with ADHD to learn it's role in the disease.[38]

In short, the CDC's exclusion of everyone who might disagree with Andrew Kolodny, resulted in a set of Opioid Prescribing Guidelines that do not genuinely address the public health concern, that the Kolodny panel was impaneled to address. There was a surge in accidental overdose deaths, by mixing sleeping pills with alcohol with opioids, each of which substances independently can induce sleepiness, in a population where pre-existing addiction to methamphetamine was known to cause sleep deprivation. Moreover, the therapeutic methods Andrew Kolodny advocates for treating methamphetamine addiction, consisting solely of psychosocial intervention, were not proving sufficiently effective, because methamphetamine addicts were self-medicating with any available substances they could find, that induced sleep, and were unwilling to submit themselves to the distress of detoxification in a hospital, in order to begin the psychosocial intervention therapies that Kolodny advocates for them.

Because the CDC has failed to release the documents used by the Kolodny panel, there is no way to determine whether the needs of methamphetamine addicts were actively discussed. It is possible that the panel actively considered that it's Guidelines, by discouraging all opioid prescribing, could force methamphetamine addicts into psychosocial therapy, by making opioids too difficult to obtain. It is also possible that the panel completely ignored the role that methamphetamine addiction played in causing what Kolodny chose to call an “epidemic” of opioid-related deaths amongst the methamphetamine addict population. That cannot be established until CDC releases the documents that it promised to release. Curiously, a published paper by Chang gives insight into what the CDC panel may have been thinking: Texas in 2010 launched a crackdown on so-called “pill mills”, which were

medical practices run by a doctor who had lost his admitting privileges at a hospital, and operated by writing prescriptions that other physicians were unwilling to write themselves.[39] Chang reports up to a 24.3% decrease in opioid prescribing, "concentrated among prescribers...with the highest opioid prescribing".[40] Thus it would have appeared to CDC panel members, in view of Chang's findings, that their CDC Opioid Prescribing Guidelines would cause a shortage of diverted opioid pain medication, which might drive methamphetamine addicts into treatment, because self-medication for methamphetamine-induced sleep disorder using opioids, was no longer possible.

In response to the CDC Opioid Prescribing Guidelines, many physicians now refuse to prescribe opioids for patients whom they do not personally know. While this has been disastrous for patients with Disabling Intractable Pain and has resulted in numerous complaints to the CDC and numerous comments to the present Docket, what's been ignored is how that strategy has completely failed to deal with the underlying problem of methamphetamine addicts self-medicating for methamphetamine-induced sleep disorders with dangerous substances. The addicts are now using other dangerous substances, apparently because the psychosocial therapies advocated by members of the CDC panel are not sufficiently effective. Counterfeit pills made to look like Xanax™-brand alprazolam, that contain fentanyl mixed with alprazolam, were proven to have caused 9 deaths in one Florida county in 2016.[41] Police in Portland, Oregon reported counterfeit Xanax™ pills similar to those involved in the Florida deaths, and 8 other counterfeit pills made to appear like Xanax™ and generic oxycodone, containing various combinations of alprazolam, heroin, oxycodone, tramadol, and the synthetic opioids furanyl fentanyl, cyclopropyl fentanyl, and the investigational synthetic opioid drug U-47700.[42] The state medical examiner of Oregon is quoted as saying that synthetic opioids caused 80 deaths in Oregon since 2014, but 75 of those took place since 2016, which she considered to be an alarming rate of mortality increase.[43] A New York Times analysis of preliminary data from the CDC revealed a 22% increase in annual drug overdose deaths in 2016, led by a doubling in deaths caused by fentanyl and other synthetic opioids, and which also noted a rise in deaths from overdoses of the stimulants methamphetamine and cocaine.[44] The New York Times analysis puts the total number of deaths from synthetic opioids at 20,000 for 2016.[45]

Quite clearly, this was an unexpected consequence of the CDC Guidelines. Organized crime has proven more than capable of obtaining the machinery needed to make counterfeit pills and of obtaining raw materials from which to make dangerous synthetic opioids. Moreover, the same organized criminal gangs already manufacture illicit methamphetamine. The shift away from poppy-derived opioids to synthetic opioids, that CDC's Guidelines catalyzed, has provided gangsters with a second profit center. The gangsters make money when people first try methamphetamine and make more money when the people become addicted to it, and now make even more money selling the addicts the opioids they need to be able to sleep at night while still using the methamphetamine. There's nothing in this problem for a criminal gang not to like.

The CDC's past expertise was at statistical analysis, in support of other agencies such as FDA that make policy. Their disastrous venture into the pseudo-policy of the Opioid Prescribing Guidelines underscores the need for better adherence to their core mission and avoiding mission creep. Kolodny and others proposed a scheme of "morphine equivalence" that FDA rejected, because the scheme oversimplifies complex biochemical reaction kinetics that vary from substance to substance, with an invalid linear approximation that's equally invalid for all opioid substances, but the CDC panel decided to incorporate the invalid linear approximation into a cellphone app that CDC released.[46] Worse yet, the CDC panel departed from standard scientific practice and rejected results that did not support it's desired conclusion, say critics, for example Prof Carr at Tufts University School of Medicine.[47]

Apart from the necessity of honoring legal boundaries that define an agency's mission, what else can FDA learn from CDC's disastrous missteps?

One problem that arises in dealing with Disabling Intractable Pain, is that prescriptions say nothing about the ailment that is being treated. The patient who suffers a pain crisis and ends up in the emergency room, holding a bottle of pills that are ineffective for the pain presently felt, first must persuade the ER physician that she is not seeking drugs for diversion and is genuinely in serious pain. If one was treated for an injury at the same ER and got the prescription there, the ER can check it's own records. If one was treated elsewhere, the ER has to locate the treating doctor and confirm the patient's story. Some states have instituted prescription monitoring programs that track what prescribed drugs the patient has been given, but the programs do not provide a history of the patient's illness and injuries. This does all patients a disservice, because the drug diverter may be deterred from diverting prescribed drugs, but the patient with genuine medical needs will still face the doubts of ER personnel, as to why that patient was on a particular drug recently. Lack of patient data complicates care. A mobile population may not always have a medical emergency, convenient to the same hospital. Ambulance services generally transport patients to the nearest hospital. If their medical records don't follow them there, the patients have difficulty getting treated. Doubts about a patient's veracity can interfere with diagnosis and treatment.

The Cauda Equina Foundation have asked the Joint Commission on Accreditation of Hospitals to collect better data on emergency patients who sustain a fall or motor vehicle accident, and complain of injury and pain to the lower back, because there is a serious shortage of data on lumbar radiculopathy with which to perform evidence-based medicine studies on how best to stabilize bruised nerves and avert long-term disability from Disabling Intractable Pain.[48] This is yet another example of how lack of patient data, complicates care.

CDC could have done a much better job for all patients, had it sought better data on accidental injuries during a patient's lifetime that result in pain, rather than focusing on post-mortem data. Collection of high-quality data is essential to evidence-based medicine. Guesswork and oversimplification is not evidence-based medicine.

The lack of evidence-based psychiatric medicine is a clear problem pointed up by the rising death toll of methamphetamine addiction and self-treatment of it's side-effects with mixtures of opioids, alcohol, and other drugs. Key insights into the endocannabinoid system are missing, in the context of ADHD. Cannabinoid therapy for ADHD needs to be explored further, because long-term use of stimulants by ADHD patients, especially methamphetamine, is a known addiction risk. Various patent medicines made from cannabis and used in cannabis-legal states by nonmedical personnel, provide anecdotal guidance on the effects of the various substances in the cannabis plant. FDA needs to make it simpler for researchers to work with the plant, isolate it's constituents, and identify how each constituent behaves in ADHD and other conditions that have been treated with cannabis. The current regulatory environment makes this difficult, because state-legal cannabis medications are not uniformly recognized by federal authorities as medications. Addtionally, cannabis prohibition efforts ongoing at the DEA make it difficult for doctors to observe state-legal cannabis usage by their patients, because DEA has threatened to revoke the prescribing licenses of physicians who prescribe state-legal medical cannabis. These efforts have had the perverse effect of driving states to adopt full legalization of cannabis, so that patients may access medical cannabis without a prescription. At odds with the CDC's position on opioid prescribing, the Federation of State Medical Boards have adopted guidelines on how physicians supervise patients who require opioids for Disabling Intractable Pain,

and those guidelines, which are being adopted by various states, call for physicians to monitor closely, the use of nonprescription drugs including cannabis, by patients being treated for pain.[49] "Closely monitoring" patients is not actual prescribing of DEA-prohibited cannabis but many doctors would prefer if some safe-harbor language existed. At present, FDA has provided one such safe-harbor, in that an oral tetrahydrocannabinol spray has been allowed for indications of nausea and anorexia in AIDS patients and patients undergoing cancer chemotherapy.[50] A controversy is emerging over off-label prescribing, with DEA charging the maker of the oral spray with alleged insurance fraud, allegedly because doctors prescribed the company's products off-label to patients who did not have cancer and somehow sees bribery in that[51]. Meanwhile a patient group is suing DEA in US District Court in the Southern District of New York, alleging that DEA inaction on petitions to reschedule cannabis are part of a scheme to deny constitutional due process rights to patients.[5253] While the law courts sort all of this out, ADHD sufferers continue to be prescribed powerful and addictive stimulants including methamphetamine, and some of them, after developing a sleep disorder from the medication, are abusing opioids in an effort to get sleep, and are dying. The FDA's help in resolving this, by facilitating the process of Phase I clinical trials of cannabis constituents, would do much to alleviate this problem. Prior to 1937's Marihuana Tax Act, cannabis extracts had been commonly used in the US as prescription and nonprescription medications, and that past history should be considered in reviewing clinical trials of effectiveness and safety.

An effective exit strategy from the Opioid Crisis requires understanding of how we got in it in the first place. Ignoring the role of methamphetamine addiction in driving opioid use, obstructs us from creating better policy. Ignoring the needs of patients disabled by Disabling Intractable Pain, harms those patients while doing nothing to help the people disabled by methamphetamine addiction. CDC's approach has clearly done much harm and no measurable good. Making certain that physicians understand the dangers of untreated mental illness leading to addiction, and that mental health crisis is appropriately treated in the emergency department when patients seek treatment, is essential. Equally important is recognizing a patient having a pain crisis and providing treatment for pain. FDA's past conservatism and refusal to take the pseudo-scientific steps that came to dominate the CDC has been helpful, in that FDA first did no further harm. FDA is to be commended for that. But FDA can do better.

I recommend that FDA adopt the following policy changes:

- Methamphetamine needs to bear a black-box warning label, stating that there is a risk of addiction to methamphetamine, also a risk of sleep disorders, and that there is a further risk of opioid dependency, if methamphetamine is given concurrently with opioids.
- Long-term methamphetamine use is discouraged as it induces depletion of endogenous morphine which poses a risk of opioid dependency if opioids are given and a risk of sleep disorders if opioids are not given, because the simultaneous dopamine release and blockage of dopamine reuptake has these serious ill-effects on the patient. This should be so stated in the black-box warning label.
- Switching to any drug that does not cause dopamine release while blocking dopamine reuptake, is preferable when a patient is put on methamphetamine for short-term medical necessity, and the substitution should be made as quickly as is consistent with the medical needs of the patient. That should be stated in the black-box warning label.
- Cannabinoid phase I, II, and III clinical trials for substances that can relieve ADHD should be expedited, to provide alternatives to methamphetamine prescribing.

References

1 J Hughes, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR, "Identification of two related pentapeptides from the brain with potent opiate agonist activity", *Nature* 1975; 258: 577-579. doi:10.1038/258577a0

2 A Goldstein, in *Biological and Behavioral Approaches to Drug Dependence* eds H. Cappell and AE LeBlanc, Proceedings International Symposium on Alcohol and Drug Research, Oct 1973, Addiction Research Foundation, Toronto pp 27-41.

3 A Goldstein, Barrett RW. James IF, Lowney LI, Weitz CJ, Knifmeyer LL, and Rapoport H; "Morphine and other opiates from beef brain and adrenal"; *Proc Natl Acad Sci USA* 1983; 82(15):5203-5207 http://www.pnas.org/content/82/15/5203.full.pdf

4 Ibid. p. 5204.

5 Ibid. p. 5207.

6 Ibid. p. 5205ff.

7 Ibid. p. 5204 Table 1.

8 McMurry, Brian, "Cow Size is Growing", *Beef Magazine*, February 1, 2009. http://www.beefmagazine.com/genetics/0201-increased-beef-cows retrieived December 24, 2017.

9 Galanie S, Thodey K, Trenchard IJ, Interrante MF, and Smolke CD; "Complete biosynthesis of opioids in yeast", *Science* 2015 Sept 4; 349(6252): 1095-1199. doi:10.1126/science.aac9373.

10 Ibid Figure 1.

11 Zhu W, Cadet P, Baggerman G, Mantione KJ, Stefano GB; "Human White Blood Cells Synthesize Morphine: CYP2D6 Modulation", *J. Immunol* 2005; 175:7357-7362. doi: 10.4049/jimmunol.175.11.7357

12 Stefano GB and Kream R; "Dopamine, Morphine, and Nitric Oxide: An Evolutionary Signaling Triad", *CNS Neuroscience and Therapeutics* 2010; 16: e124-e137. doi: 10.1111/j.1755-5949.2009.00114.x

13 Stefano GB, Ptacek R, Kuzelova H, Kream RM, "Endogenous Morphine: Up-to-Date Review 2011", *Folia Biologica (Praha)* 2012; 58: 49-56. http://fb.cuni.cz/file/5635/FB2012A0008.pdf retrieved December 25, 2017.

14 Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC; "Determination and characterization of a cannabinoid receptor in rat brain", *Mol Pharmacol* 1988; 34(5): 605-13 http://molpharm.aspetjournals.org/content/34/5/605

15 Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R; "Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor", *Science* 1992, 258(5090): 1946-1949. doi: 10.1126/science.1470919

16 Devane WA and Axelrod J; "Enzymatic synthesis of anandamide, an endogenous ligand for the cannabinoid receptor, by brain membranes", *Proc Natl Acad Sci USA* 1994; 91(14): 6698-6701. http://www.pnas.org/content/91/14/6698.full.pdf

17 Pritchard, J, *Arachidonic Acid and Inflammation.* http://www.livestrong.com/article/479569-arachidonic-acid-and-inflammation/ Retrieved January14, 2018.

18 Ibid.

19 *Google* search retrieved December 25, 2017.

20 "Ex-West Virginia sheriff who took meth from police storage sentenced to home confinement", *WHSV News* March 28, 2017. http://www.whsv.com/content/news/409673195.html retrieved December 25, 2017

21 "Traffic Stop Leads to Meth 'Kingpin' Arrest", *The Weston Democrat* August 15, 2017 https://westondemocrat.com/article/traffic-stop-leads-to-meth-kingpin-arrest retrieved December 25, 2017.

22 "Another meth mule pleads guilty for role in California-to-West Virginia drug conspiracy", *US Attorney's Office for Southern District of West Virginia* September 20, 2016. https://www.justice.gov/usao-sdwv/pr/another-meth-mule-pleads-guilty-role-california-west-virginia-drug-conspiracy. Retrieved December 25, 2017.

23 https://www.drugs.com/methamphetamine.html Retrieved December 25, 2017.

24 Ibid.

25 "How is methamphetamine different from other stimulants, such as cocaine?", *NIDA Research Report Series* updated September 2013. https://www.drugabuse.gov/publications/research-reports/methamphetamine/how-methamphetamine-different-other-stimulants-such-cocaine Retrieved December 25, 2017.

26 Ref 13 *supra* p 51 Figure 1.

27 Kervezee L, Hartman R, van den Berg DJ, Meijer JH, de Lange ECM; "Diurnal variation in the pharmacokinetics and brain distribution of morphine and its major metabolite", *Eur J Pharm Sci* 2017; 109(Supplement): S123-S139.doi:10.1016/j.ejps.2017.05.048.

28 Fifel K, Meijer JH, Deboer T; "Long-term effects of sleep deprivation on neuronal activity in four hypothalamic areas", *Neurobiology of Disease* 2018; 109: 54-63. doi: 10.1016/j.nbd.2017.10.005.

29 Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, and Alexander GC; "The prescription opioid

and heroin crisis: a public health approach to an epidemic of addiction", *Annu Rev Public Health* 2015; 36: 559-574. doi: 10.1146/annurev-publhealth-031914-122957

30 http://www.wlf.org/upload/litigation/misc/CDCFOIARequest-Opioids.pdf Retrieved December 25, 2017.

31 http://www.wlf.org/upload/litigation/misc/cdc-response-to-mr-richard-a-samp-12-14-15.pdf Retrieved Dec. 25, 2017.

32 http://www.wlf.org/litigating/case_detail.asp?id=840 Retrieved December 25, 2017.

33 Wainberg ML, Kolodny A, Drescher J, *Crystal Meth and Men Who Have Sex With Men: What Mental Health Care Professionals Need to Know.*2006. The Haworth Medical Press, Binghamton, NY.

34 Ibid pp 67-72.

35 Ibid p. 70.

36 Cooper RE, Williams E, Seegobin S, Tye C, Kuntsi J, and Asherson P; "Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial", *European Neuropsychopharmacology* 2017; 27(8): 795-808. doi: 10.1016/j.euroneuro.2017.05.005

37 Shrivastava A, Johnson M, Tsuang M; "Cannabis use and cognitive dysfunction", *Indian J. Psychiatry* 2011; 53(3): 187-191. doi: 10.4103/0019-5545.86796

38 Ref 36 *supra*.

39 Lyapustina T, Rutkow L, Chang HY, Daubresse M, Ramji AF, Faul M, Stuart EA, and Alexander GC; "Effect of a 'pill mill' law on opioid prescribing and utilization: The case of Texas", *Drug Alcohol Depend* 2016: 159:190-197 Epub 2015 Dec 31 doi: 10.1016/j.drugalcdep.2015.12.025

40 Ibid at p 190.

41 Parry H; "Watch Out Spring Breakers! Fake Xanax pill which is 50 times stronger than heroin kills nine in Florida"; *The Daily Mail* March 23, 2016. http://www.dailymail.co.uk/news/article-3505025/Watch-spring-breakers-Fake-Xanax-pill-50-times-stronger-heroin-kills-9-Florida.html Retrieved December 26, 2017.

42 Bernstein M; "Fake opioid pills showing up in Portland and across Oregon", *The Oregonian* October 17, 2017. http://www.oregonlive.com/portland/index.ssf/2017/10/fake_opioid_pills_showing_up_i.html Retrieved December 26, 2017.

43 Ibid.

44 Katz J; "The First Count of Fentanyl Deaths in 2016: Up 540% in Three Years", *The New York Times* September 2, 2017. https://www.nytimes.com/interactive/2017/09/02/upshot/fentanyl-drug-overdose-deaths.html Retrieved December 26, 2017.

45 Ibid.

46 Fudin J, Raouf M, Wegrzyn EL, and Schatman ME; "Safety concerns with the Centers for Disease Control opioid calculator", *Journal of Pain Research* 2018; 11: 1-4. doi: 10.2147/JPR.S155444

47 Tayeb BO, Barreiro AE, Bradshaw YS, Chui KK, and Carr DB; "Durations of Opioid, Nonopioid Drug, and Behavioral Clinical Trials for Chronic Pain: Adequate or Inadequate?", *Pain Med* 2016; 17(11): 2036-2046. doi: 10.1093/pm/pnw245

48 Personal communication with Taylor, medical director, Cauda Equina Foundation.

49 Federation of State Medical Boards, *Guidelines for the Chronic Use of Opioid Analgesics*, April 2017, p. 9. https://www.fsmb.org/Media/Default/PDF/Advocacy/Opioid%20Guidelines%20As%20Adopted%20April%202017_FINAL.pdf Retrieved December 26, 2017.

50 https://www.syndros.com Retrieved December 28, 2017.

51 *Fortune*, November 16, 2017.http://fortune.com/2017/11/16/insys-john-kapoor-opioid-case/ Retrieved December 28, 2017.

52 *Washington v Sessions*, Case 1:17-cv-05625 Document 1 Complaint. Filed July 24, 2017. http://www.hillerpc.com/wp-content/uploads/2017/07/Filed-Complaint-with-Dkt.-No.pdf Retrieved December 28, 2017.

53 Hiller PC Attorneys at Law *Press Release,* July 24, 2017. http://www.hillerpc.com/press-release-federal-cannabis-complaint/ Retrieved December 28, 2017.