SUPREME COURT OF ARIZONA

STATE OF ARIZONA,

Appellee,

v.

RODNEY CHRISTOPHER JONES,

Appellant.

Arizona Supreme Court No.
No. CR-18-0370-PR

Court of Appeals
No. 1 CA-CR 16-0703

Yavapai County
Superior Court
No. P1300CR201400328

BRIEF OF *AMICI CURIAE* PHYSICIANS

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INTRODUCTION

The Court of Appeals majority decision in *Jones* denies the benefits of medical marijuana to a large proportion of the patients most needing it. It is undisputed that the resin in the marijuana plant's trichomes contains the cannabinoids that are the medicine. Yet the *Jones* majority holds that only the "green leafy substance" of the plant is medical marijuana and nothing else extracted from the plant is protected for medical use. From the doctors' perspective, it is inconceivable that the drafters and voters would have intended medical marijuana not to include the resin and resin-infused products. Under the lower Court's interpretation of the Arizona Medical Marijuana Act ("AMMA"), many patients will be unable to use forms of marijuana products that work best for them, and others will be unable (without violating the law) to benefit from medical marijuana at all.

Appellant's Briefs and the other Amicus Briefs outline interpretive, historical and practical arguments why the "green leafy substance" restriction makes no sense. This Brief, on behalf of physicians, establishes why the *Jones* majority position also makes no sense medically. The Arizona voters, the scientific and medical literature, and the Federal Government, recognize that the medicines that benefit patients are in

extracts of the marijuana plant.[1]

The products and methods of administering medical marijuana must be individualized for patients because each patient has different needs, and each product and route has unique advantages and disadvantages. The extracted resin is prepared to offer patients different strengths and ratios, and the medicine enters the body in different ways for different medical conditions. If patients are only allowed to smoke or eat the plant without extracting the resin, a large percentage of patients — many children and the most ill and disabled — will be denied the medical benefits of the plant.

INTEREST OF AMICI CURIAE

The *Amici*, Gina Mecagni Berman, M.D. and Jeffrey A. Singer, M.D., are doctors concerned for the welfare of their own and other patients and for Arizona physicians' ability to appropriately treat their patients without facing criminal and/or practice repercussions. They seek to ensure that the AMMA's purpose is not dismantled: "to protect patients with debilitating medical conditions, as well as their physicians and providers, from arrest

[1] https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine. All hyperlinks to internet sources were valid as of February 14, 2019, the last date they were checked.

and prosecution, criminal and other penalties . . . if such patients engage in the medical use of marijuana." *State v. Maestas*, 244 Ariz. 9, 14, ¶ 20 (2018); A.R.S. § 36-2811. They also seek to have all forms of medical marijuana available to help wean patients off opioids.

In addition, declarations from other physicians and a research scientist support the need for treating patients with marijuana extracts and extract-infused products such as pills, oils, tinctures, edibles, lotions, etc. These physicians have a strong interest in ensuring that marijuana extracts continue to be legally available to patients who need them.

ARGUMENT

A. The voters, scientific and medical studies, and the U.S. Government have already established that cannabis and cannabinoids benefit patients dealing with a variety of illnesses and symptoms.

1. Background

The human body naturally produces cannabinoids, which play a role in regulating pleasure, memory, thinking, concentration, body movement, appetite, pain, and the senses.[2] *See also* Society of Cannabis Clinicians ("Society") Declaration ¶ 3, APP036. The parties and amici agree, and it is beyond dispute, that cannabis plant resin contains more than 100

[2] https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine

cannabinoids.[3] The two cannabinoids most commonly used for medical reasons, at least currently, are tetrahydrocannabinol (THC) and cannabidiol (CBD).[4] Gina Mecagni Berman, M.D. Declaration ¶ 8, APP-002.

While the U.S. Drug Enforcement Administration (DEA) for many decades has refused to acknowledge marijuana's medical benefits, other Federal agencies have taken a different view and are building upon existing research and evidence of marijuana's medical efficacy. In fiscal year 2017, the National Institute of Health (NIH) spent $140 million on 330 projects researching cannabinoids, with 70 of those projects examining therapeutic properties of cannabinoids and 26 projects focused on CBD.[5]

The National Institute on Drug Abuse (NIDA), a NIH institute, discusses on its website many benefits of cannabinoids, and reports that researchers are exploring possible uses of THC, CBD, and other cannabinoids for medical treatment.[6] According to the NIH:

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[3] *Id.*

[4] *Id.*

[5] https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids

[6] https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine

> NIDA has provided and continues to provide funding for research related to therapeutic uses of cannabinoids as it pertains to its mission, including studies on the use of THC and cannabidiol (CBD), another chemical constituent of marijuana, for the treatment of pain (as an alternative to opioid pain relievers), addiction, and other disorders.[7]

NIDA also reports that preclinical and clinical trials of marijuana and its extracts are being performed for numerous medical conditions, including diseases that affect the immune system (AIDS, MS), inflammation, pain, seizures, substance use disorders and mental disorders.[8]

2. Arizona's voters incorporated scientific studies and findings on marijuana's medical benefits into the AMMA.

This Court is not being called on to conduct an independent scientific review of the medical benefits of marijuana. Arizona voters in 2010, almost a decade ago, approved the scientific findings and studies cited in the text of Proposition 203. These "Findings" cited a 1999 study by the National Academy of Sciences' Institute of Medicine and noted that a wide range of medical and public health organizations have confirmed beneficial medical uses for marijuana in treating pain, nausea and other symptoms associated with a variety of debilitating medical conditions, including cancer, multiple

[7] https://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-marijuana-cannabinoids

[8] https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine

sclerosis, HIV/AIDS, hepatitis C, etc. Jones Petition for Review APPX030.

Since AMMA's 2010 approval, thousands of additional studies have occurred. In January 2017, The National Academies of Sciences, Engineering, and Medicine published an updated study after considering another 10,700 medical abstracts.[9] The 2017 study reported that substantial evidence exists that cannabis or cannabinoids are effective:

- To treat chronic pain in adults (cannabis);
- To treat chemotherapy-induced nausea and vomiting (oral cannabinoids);
- To treat multiple sclerosis spasticity symptoms (oral cannabinoids).

The report also found moderate evidence that cannabis or cannabinoids are effective for improving short-term sleep in people with chronic pain, fibromyalgia, sleep apnea and multiple sclerosis.[10]

3. The FDA has approved several cannabis-based medicines for specific conditions, and others are being studied.

The State implies that medical marijuana has no medical value because if it did, the Food and Drug Administration (FDA) would have

[9] http://www.nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx

[10] *Id.*

approved it since the FDA has already approved several cannabis-based medicines. State's Supp. Brief at 15. This statement is circular and ignores the historical difficulty of studying marijuana given its status as a Schedule I controlled substance.[11]

As noted in the State's supplemental brief, the FDA in the 1980s approved two medicines that contain cannabinoids (primarily THC) in capsules: Dronabinol and Nabilone.[12] These medicines treat nausea and vomiting in cancer patients, and anorexia.[13] Berman Dec. ¶ 9, APP003.

In June 2018, the FDA approved a CBD-based liquid medicine called Epidiolex that helps to prevent seizures in two rare forms of severe childhood epilepsy.[14] In addition, the United Kingdom, Canada and several other countries have approved a mouth spray containing a 1:1 ratio of THC to CBD (nabiximols, brand name Sativex®), to treat muscle control and

[11] https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq#section/_3

[12] https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine

[13] https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq#section/_9

[14] https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-safe-effective-medicine

pain in MS patients.[15] NIDA Director Nora D. Volkow, M.D. reports that more medicines based on cannabinoid chemicals are being developed.[16] In other words, the FDA has approved several cannabis-based medicines, and more are undergoing clinical trials.

4. Mainstream healthcare entities recognize medical marijuana's benefits

As outlined, cannabinoids in various mixtures and concentrations clearly work for some patients and some symptoms. Given that a majority of states have legalized medical marijuana, more doctors and mainstream healthcare providers are educating people about it:

- **WebMD** provides background, lists medical conditions for which cannabis is being used, how to get it and how to take it (by smoking, inhaling, eating, applying to skin, or placing liquid under the tongue).[17]

- **Mayo Clinic** states medical cannabis appears to be most effective for treating muscle spasms, chronic pain and nausea. Mayo notes that cannabis may also benefit patients with anxiety and depression, amyotrophic lateral sclerosis (ALS), inflammatory bowel disease, Tourette

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[15] *Id.*

[16] https://www.drugabuse.gov/publications/research-reports/marijuana/letter-director

[17] https://www.webmd.com/a-to-z-guides/medical-marijuana-faq

syndrome, PTSD, and autism.[18] According to Mayo, medical marijuana may be smoked, inhaled, ingested, or taken as a pill, an oil, or nasal spray.[19]

- Dr. Peter Grinspoon, M.D. a contributing editor to the **Harvard Health Blog**, lists the types of conditions for which medical marijuana can provide relief and advises doctors to learn about it, and be open-minded.[20]

- **Dr. Sanjay Gupta**, the chief medical correspondent for **Cable News Network**, is calling for medical marijuana to be made available nationally, both for medical reasons and to help decrease the nation's opioid epidemic.[21]

- An **American Society of Clinical Oncology** 2018 survey found that 80 percent of oncologists have discussed medical marijuana use with their patients.[22]

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[18] https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-q-and-a-treatment-with-medical-cannabis/

[19] https://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/medical-marijuana/art-20137855

[20] https://www.health.harvard.edu/blog/medical-marijuana-20180115130855

[21] https://www.cnn.com/2018/04/24/health/medical-marijuana-opioid-epidemic-sanjay-gupta/index.html

[22] https://www.asco.org/about-asco/press-center/news-releases/most-oncologists-have-discussed-medical-marijuana-patients/feed

B. The medicine is in the cannabinoids, which must be extracted from the plant.

The lower Court's belief that the AMMA only protects possession of the dried whole flowers of the cannabis plant fundamentally misunderstands the plant. The medicine in the cannabis plant come from its *resin*, a distinct part of the plant's flowers, and not from the "green leafy substance" identified by the majority opinion. Berman Dec. ¶ 7, APP002. The "green leafy substance" of the plant is worthless without extracting the resin in some form because the resin contains the cannabinoids. *Id.*

Creating marijuana medicine that meets individual patient needs necessarily requires extraction. Berman Dec. ¶¶ 8-13, APP002-006. The lower Court did not seem to recognize that the ingestion of all marijuana — whether by eating, smoking, vaping, oils or tincture — requires an extraction process. *Id*. A person smoking the marijuana dried flowers in a cigarette or pipe is using fire to extract the cannabinoids. *Id*. ¶ 11. A person using the dried flowers in a brownie or other food items also must first extract the resin into butter or oil, and then use the now extract-infused butter or oil in the recipe. *Id.* ¶ 13. Otherwise, as explained in other Briefs, the dried flowers will not get hot enough to release their cannabinoids.

All other medical cannabis products similarly require extracting the resin, as explained in the Amicus briefs of the Arizona Dispensaries Association and MPX Bioceutical Corporation. Once the resin has been extracted, what remains of the flowers and its parts has no value and are discarded. Berman Dec. ¶ 12, APP004. After the resin has been extracted from the plant in some manner, many products then require that the cannabinoids be separated from the resin. Only then can these extracts be dosed and mixed for different medical treatments, and be inserted into capsules, oils, tinctures, lotions, suppositories and edibles. *Id*. ¶¶ 8, 16, APP002, -005. Likewise, the FDA-approved cannabis medicine are pills, capsules and liquids, which are extracts. For this reason, most NIH studies focus on individual cannabinoid compounds which have been isolated and purified from the plant.[23]

C. The medical benefits of extracts and extract-infused products.

The many extract products that are being made and used nationwide, including in Arizona, have different uses and work differently for different patients. Patients require different doses of cannabis "depending on many

[23] https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids

variables, such as age, metabolism, genetics and severity of illness." Society Dec. ¶ 4, APP037. "Patient dosing should be 'patient-determined' and 'self-titrating," meaning there is no standardized dosing for cannabis medicine, because each person has different ECS function." *Id.* "Clinicians must work with patients to determine what cannabis dosing, delivery method, and form of cannabis works best for each patient's specific ailments." *Id.*; *accord* Berman Dec. ¶¶ 14-16, 21, APP005, -007; David J. Casarett, M.D. Declaration ¶ 8, APP046 (the route of administration needs to be individualized, because each route has unique advantages and disadvantages).

Extracts and concentrates have at least four significant benefits for medical use over smoking marijuana: (1) concentration level; (2) dosing, combinations and ratios; (3) greater choice of products and delivery methods for different ailments; and (4) cleaner than smoking.

1. Concentration levels

The marijuana extracts in their various forms can be more concentrated for ease of administration and to meet individual patients' specific needs. Society Dec. ¶¶ 5-7, APP037; Berman Dec. ¶¶ 14-21, APP005-008. Many healthcare providers advise their patients to use more

concentrated cannabis, including hashish, to treat serious illnesses, because patients are able to take higher doses without requiring large volumes of less-concentrated forms of the plant medicine. Society Dec. ¶¶ 5-7, APP037. Extracted or concentrate products are more effective and palatable for many patients. Berman Dec. ¶ 14, APP005.

2. Dosing, combinations and ratios

Moreover, marijuana in extracted forms allows patients and providers to better determine proper dosing and combinations of medicine considerably more accurately than does smoking. Berman Dec. ¶ 16, APP 005. NIDA reports standardizing doses of a smoked plant is difficult because of highly variable cannabinoid concentrations.[24] By using extracts, the manufacturers can isolate particular compounds and test for proper and precise dosing.[25]

In addition, many of the extract products — like the FDA-approved medications — are specifically designed and dosed for specific medical conditions. For example, epileptic patients are treated with oils and

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[24] https://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-marijuana-cannabinoids

[25] William Troutt Dec. ¶ 11, Brief of Qualifying Patients and Caregivers APP-40.

tinctures with CBD-THC ratios of 20 to 1.[26] Extracts are also sought after because many patients want the benefits provided by the non-psychoactive component CBD for pain relief, inflammation reduction, etc., without the psychoactive properties in the THC. Berman Dec. ¶ 15, APP005. Extracts allow the THC ratio to be lowered or the THC to be removed entirely.

3. Greater choices in products and delivery methods

As discussed above, cannabis extracts are used in many types of products, each with different delivery methods and benefits. Many patients either cannot smoke or would not want to smoke marijuana, including non-smokers, elderly patients, pediatric patients and those with pulmonary issues. Berman Dec. ¶ 14, APP005. In fact, a recent Canada National Cannabis Survey reported that higher numbers of medical users consume cannabis through methods other than smoking.[27]

Extract products have different benefits for different patients:

a. **Concentrated oil** (also called Rick Simpson Oil): Useful for pediatric or cancer patients, or others with high pain levels. Small amounts of concentrated oil contain high doses, making it economical and

[26] Troutt Dec. ¶ 15, APP-041.

[27] https://www150.statcan.gc.ca/n1/daily-quotidien/190207/dq190207b-eng.htm?HPA=1

easier to administer to children and patients with feeding tubes.

b. **Tinctures:** Preferred by novice and elderly patients. Tinctures allow fairly quick (1 hour) onset of effects through submucosal absorption, as well as allowing for more customized CBD/THC ratios.

c. **Creams/lotions:** Typically useful for patients with painful arthritic conditions, who can use these without experiencing side effects because they generally are not absorbed systemically.

d. **Suppositories:** Can be administered rectally or vaginally and are effective for abdominopelvic pain with few side effects.

e. **Edibles:** Because edibles are processed by the liver, the peak effect takes up to two hours, but the effects last for up to six hours. In addition, the parent compound delta 9 THC is metabolized by the cytochrome p450 system in the liver to a more potent metabolite, 11-OH THC, making edibles, milligram for milligram, more potent and longer lasting than other routes of administration. Used by patients with painful conditions (including opioid withdrawal).

Berman ¶ 21, APP007.

James B. Adams, Ph.D., the Director of the Autism/Asperger's Research Program at Arizona State University, has been studying medical

marijuana's affects on conditions frequently present in autistic patients. Adams Declaration ¶¶ 1-7, APP057. After an initial study ranked marijuana as providing greater benefit than traditional psychiatric and seizure medicines, Dr. Adams started a second study comparing the effectiveness of marijuana alone versus a THC/CBD combination and CBD alone. *Id*. ¶¶ 7-9, APP058. To date, the study is showing higher benefit for all three cannabis products than for 26 commonly used psychiatric and seizure medications, with lower adverse effect scores. The lowest adverse effect score was for the CBD alone, ordinarily administered as an oil or tincture. Adams Dec. ¶¶ 12-18, APP059. A recent Israeli study reached similar results, with most of the patients receiving cannabis oil under the tongue at a 30% CBD and 1.5% THC ratio. *Id*. ¶ 19 and study, APP062, -066.

4. Cleaner than smoking

The 1999 National Academy report expressly referenced in Proposition 203 stated that smoked marijuana is a "crude delivery system" that also delivers harmful substances. The January 2017 updated report pointed out that cannabis smoking was statistically associated with decreased respiratory health and more frequent bronchitis. NIDA also states that marijuana smoke irritates the throat and lungs and contains

levels of volatile chemicals and tar similar to tobacco smoke, raising concerns about risks for cancer and lung disease.[28]

Most NIH studies on the therapeutic benefits of cannabis examine individual cannabinoid chemicals and not the dried flowers. According to NIDA, smoked marijuana is less therapeutically promising than cannabis medications delivered through other routes, partially because the flowers contain numerous poorly understood chemicals in addition to THC and CBD.[29] Moreover, as discussed in other Amicus briefs, a number of other states that have legalized medical marijuana allow only extracts and extract products and do not even allow smoking the dried flowers.

5. Marijuana has the added benefit of decreasing opioid use

On June 5, 2017, Arizona Governor Douglas A. Ducey declared a state of emergency arising out of opioid overdoses and deaths.[30] In May 2018, Gov. Ducey called the "opioid epidemic" "one of the most significant public health and safety emergencies our nation and the state of Arizona

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[28] https://www.drugabuse.gov/publications/research-reports/marijuana/what-are-marijuanas-effects-lung-health

[29] https://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-marijuana-cannabinoids

[30] https://www.azdhs.gov/documents/prevention/womens-childrens-health/injury-prevention/opioid-prevention/2017-opioid-emergency-response-report.pdf

has faced in a generation — and we continue to lose too many Arizonans to it."[31] Data collected by the Arizona Department of Health Services (ADHS) since June 15, 2017 in real time shows 2,384 suspect opioid deaths in Arizona from June 15, 2017 to February 7, 2019, and another 17,492 overdoses during that same period.[32]

Many of Dr. Singer's surgery patients have told him that using medical marijuana in various forms, including tinctures, oils and lotions, works better for them than prescription pain medicine, including opioids, with fewer side effects. Jeffrey A. Singer, M.D. Declaration ¶ 6, APP017. States in which medical marijuana is available to patients have significantly lower opioid overdose deaths. *Id*. ¶ 12, APP018. Based on these and other studies and patient reports to Dr. Singer of their own experiences with medical marijuana, he believes that medical marijuana is a viable alternative to opioids that may result in fewer deaths and overdoses. *Id*., ¶ 15, APP021.

Dr. Berman in 2016 co-founded a clinic in Arizona called Blue Door Therapeutics, in which a multi-discriplinary team used both traditional and

[31] https://azgovernor.gov/print/3595

[32] https://www.azdhs.gov/prevention/womens-childrens-health/injury-prevention/opioid-prevention/index.php

complementary therapies to wean patients off opioids, including recommending medical cannabis to treat painful acute opioid withdrawal and to stem cravings during the withdrawal period. Berman Dec. ¶ 25, APP009. The team submitted a case series paper for publication detailing Blue Door's success in weaning seven patients ages 20 to 76 off opioids by using dosed forms of medical cannabis, mainly in capsules. At the one year review, none of these patients had returned to using opioids. *Id*. ¶ 26. Blue Door could not have treated these patients as effectively without using concentrates. *Id*.

CONCLUSION

Instead of facilitating treatment of debilitated patients in accordance with the AMMA, the *Jones* majority opinion criminalizes possession and distribution of the part of the cannabis plant that offers the most medical benefits. Eliminating a health care professional's ability to recommend cannabis extracts to their patients is akin to requiring a physician to recommend that a patient eat moldy bread until they feel better rather than prescribing penicillin for an infection. Berman Dec. ¶¶ 17-18, 27, APP006.

Patient care is better and more precise because effective medicinal components today have been extracted from naturally occurring plants:

moldy bread (penicillin), willow bark (aspirin), foxglove (digoxin), jimsonweed (scopolamine), etc. Berman Dec. ¶ 18, APP006. Because treating patients with cannabis should be no different, the drafters of the Arizona Medical Marijuana Act made sure to define marijuana broadly enough to encompass the plant's extracted resins. *Id.*

Restricting patients to specific forms and delivery methods of cannabis—or restricting the treating physician's choices—when addressing diseases and conditions that are known to benefit from the use of medical cannabis would be antithetical to the AMMA's purpose of treating patients with debilitating conditions and would punish the patients most in need of the medical benefits. Society Dec. ¶ 8, APP039; Berman Dec. ¶ 27, APP010. This Court should reverse the majority *Jones* opinion.

DATED this 15th day of February, 2019.

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DECLARATION OF GINA MECAGNI BERMAN, M.D.

I, Gina Mecagni Berman, M.D., declare pursuant to Rule 80(c), Ariz. R. Civ. P., under penalty of perjury that this Declaration is true and correct, as follows:

1. I submit this Declaration in support of the *Amicus Curiae* Brief filed on my behalf with the Arizona Supreme Court in support of reversing the Court of Appeals decision in *State v. Jones*, 245 Ariz. 46 (App. 2018).

2. I am a Medical Doctor and am Board Certified in both Addiction Medicine and Emergency Medicine.

3. I graduated from the University of California, Santa Barbara in December 1995 with a B.S. in Biopsychology. I graduated from medical school at Georgetown University School of Medicine in May 2001. I graduated from the Emergency Medicine residency program at Maricopa Medical Center as Chief Resident in 2004.

4. After working as an Emergency Physician in Phoenix for more than a decade (until 2015), I became frustrated at the pressure to administer and prescribe opioids and the lack of alternatives for patients with episodic or chronic pain.

5. In 2012, I became the Medical Director of two medical cannabis dispensaries in Phoenix and Mesa, The Giving Tree Wellness Centers. I am now the Medical Director for the three Arizona Natural Selections dispensaries in

Scottsdale, Mesa and Peoria. As Medical Director, I develop educational materials, research medical conditions for patients, train dispensary agents on guidelines for informing qualifying patients on the risks, benefits, and side effects associated with medical marijuana and the different methods, forms and routes of medical marijuana administration, perform other tasks as outlined in A.A.C. R9-17-313, and advocate for additional research on the medicinal qualities of cannabis.

6. I believe that the Court of Appeals majority opinion in the *Jones* case misunderstands the medicinal components of the cannabis plant and is blind to the extract-permissive regulations and guidance under which dispensaries have faithfully operated for nearly eight years.

7. The medicines in the cannabis plant come from its *resin*. The resin is stored in the plant's trichomes. Together with the leaves, stems and other parts, the trichomes and resin are distinct components of what historically has been called the flowers or buds of the cannabis plant. The "green leafy substance" of the cannabis plant is worthless without the resin because the resin contains the medicine.

8. The resin contains the cannabinoids, two of which are cannabidiol (CBD) and tetrahydrocannabinol (THC), commonly used medically. To be useful for medical treatments, the resin must first be separated (or *extracted*) from the

plant and then the cannabinoids must be separated from the resin. The cannabinoids can then be dosed and mixed for different medical treatments by health care professionals.

9. Cannabis has been used medicinally for centuries. It was part of the physician's pharmacopoeia until the Marihuana Tax Act of 1937, which the American Medical Association opposed because it was a tax on physicians prescribing cannabis. More recently, in the 1980s, the United States Food and Drug Administration (FDA) approved Dronabinol (Marinol) capsules which is a preparation of synthetic THC in an oil base. Dronabinol is FDA approved to treat nausea and vomiting caused by chemotherapy and anorexia in patients with HIV/AIDS. As an FDA-approved medication, Dronabinol necessarily went through the rigorous FDA testing required of all drugs available by prescription, which means that THC has been rigorously tested and prescribed for almost thirty years without deleterious effects. In the 1990s, after about 10 years of use as a prescription mediation, Dronabinol was downgraded by the DEA from a Schedule II to Schedule III substance because the drug showed low potential for abuse.

10. More recently, the FDA approved a formulation of CBD called Epidiolex to treat two rare types of childhood epilepsy: Dravet and Lennox-Gastaut syndromes. Epidiolex is an extract product; it does not contain THC.

11. Even smoking the whole dried flower clusters of the cannabis plant requires a method of extraction. The heat of the flame burning the cannabis plant material results in the decarboxylation and release of cannabinoids from the resin for inhalation.

12. Likewise, all other medical cannabis products require extracting the resin containing the cannabinoids from the plant. This can be done in many ways, as explained in some of the other Amicus briefs. Once the resin has been extracted, the dried flowers remaining have no value and are discarded.

13. The majority Court of Appeals opinion suggests that patients do not need to use extracts because they can combine marijuana with non-marijuana elements to make "brownies and the like." Again, this comment shows a fundamental misunderstanding of how cannabis is processed and used to treat patients. Even with brownies and cookies, the plant's whole dried flowers are not simply combined with flour and other food items. Instead, the dried flowers must be heated in butter or oil to extract the resin from the plant. The butter or oil, now infused with the medicinal resin, is then used in the recipe to make the brownies. Simply adding cannabis flower to a brownie mix and baking it without extracting the resin first in butter or oil will not extract the resin, resulting in a near inedible brownie with no appreciable medical benefit. Further, patients extracting the cannabis resin at home in this manner are still considered to be breaking the law, if

the *Jones* decision stands.

14. In my medical opinion, extracted or concentrated marijuana products are effective and palatable for many patients. There is a large group of patients who either cannot or would not want to smoke marijuana, such as: non-smoking patients, elderly patients, patients with pulmonary issues, and pediatric patients. As a physician, I do not advocate smoking of anything. For those who decide not to smoke, I believe there should be options available to them. In my medical training, I am not aware of an instance in which a patient was required to engage in what is commonly accepted in medical practice as unhealthy (smoking) in order to obtain treatment.

15. Further, a considerable number of patients only want the benefits provided by the non-psychoactive component CBD, for chronic pain relief, inflammation reduction, etc., without the psychoactive properties in the THC. Extracts allow the possibility of fractioning the various cannabinoids in the final product. Likewise, extracts allow for other beneficial cannabinoids (such as THCV, CBN, CBG, etc.) to be added to preparations to enhance medicinal benefit.

16. Moreover, marijuana in extracted forms allows patients and providers to better determine proper dosing and combinations of medicine considerably more accurately than smoking. Concentrated products (extracts) are tested for potency, which allows patients to dose as they would with any other medication. My

recommendations for patients are almost always in the form of a traditional prescription (e.g., take x number of milligrams QHS, QAM, QAC, Q4-6 hours, PRN, etc.). This allows me to have a starting point by which I can tailor each patient's regimen, as you would with any other medication.

17. Eliminating a health care professional's ability to recommend extracts and resin from the cannabis plant to their patients is akin to requiring a physician to recommend that a patient eat moldy bread until they feel better rather than prescribing penicillin for an infection. As an example, we do not ask our patients to eat moldy bread (which contains penicillin) to treat Strep throat. Rather, we prepare penicillin so that we know how many milligrams is in a preparation, and patients take a certain amount in milligrams to treat their infection.

18. Patient care is better and more precise because the effective medicinal components today were originally found in naturally occurring plants: moldy bread (penicillin), willow bark (aspirin), foxglove (digoxin), jimsonweed (scopolamine), etc. Treating patients with extracted cannabis should be no different. Fortunately, the drafters of the Arizona Medical Marijuana Act made sure to define marijuana broadly enough to encompass the plant's extracted resins.

19. Ultimately, health care professionals would not be able to treat their patients as effectively if their patients are limited solely to smoking or ingesting the "green leafy substance" of the cannabis plant rather than using resin extracted from

the plant.

20. Arizona medical marijuana dispensaries and those around the country sell many extract or concentrate products. Analysis of sales data from Arizona, Colorado and Washington shows that products sold by dispensaries in those states are about 40 percent extracts.

21. Likewise, Arizona Natural Selections sells many extract products, including tinctures, oils, creams and lotions, suppositories, and edibles. These extract products have different benefits for different patients:

a. **Concentrated oil** (sometimes referred to as Rick Simpson Oil or RSO): Is used by pediatric patients and those with cancer and/or high levels of pain. Small amounts of concentrated oil contain high doses, so it is more economic for patients and easier, because of the small quantity needed, to administer to children (after dilution in a lipophilic base such as oil or butter) and to patients with feeding tubes.

b. **Tinctures:** Preferred by novice and elderly patients. Tinctures allow fairly quick (1 hour) onset of effects through submucosal absorption as well as allowing for more customized cannabinoid ratios.

c. **Creams/lotions:** Typically useful for patients with painful arthritic conditions, who can use these without experiencing side effects because they generally are not absorbed systemically.

d. **Suppositories:** Can be administered rectally or vaginally and are effective for abdominopelvic pain with few side effects.

e. **Edibles:** Because edibles are processed by the liver, the peak effect takes up to two hours, but the effects last for up to six hours. In addition, the parent compound delta 9 THC is metabolized by the cytochrome p450 system in the liver to a more potent metabolite, 11-OH THC. This means edibles are, milligram for milligram, more potent and longer lasting than other routes of administration, making them a good choice for patients with painful conditions, including opioid withdrawal.

22. Recently, the U.S. Government changed the definition of THC so that CBD oil with a THC concentration of less than 0.3 percent is not Federally prohibited. While industrial hemp can provide CBD, it excludes the other cannabinoids and terpenes found in the cannabis resin, which are also therapeutic, as I have already discussed.

23. The story of Dronabinol highlights the shortsightedness of extracting one compound (THC) from the cannabis resin and trying to utilize it as a treatment. Dronabinol is an expensive and uncommonly used medication because it is not very effective, despite being pure THC in oil. Likewise with "pure" CBD because it is much more effective medically when the other therapeutic compounds are included in the preparation.

24. The recently FDA-approved medication Epidiolex is a preparation of the cannabis resin. Sativex is another resin product that is approved in 25 countries and is in Phase III FDA trials here in the United States. This inclusion of both major and minor cannabinoids as well as terpenes in the cannabis resin is known as the "entourage effect" and is why single-cannabinoid preparations are found generally to be less medicinally beneficial than those preparations that contain a more well-rounded cannabinoid/terpene profile.

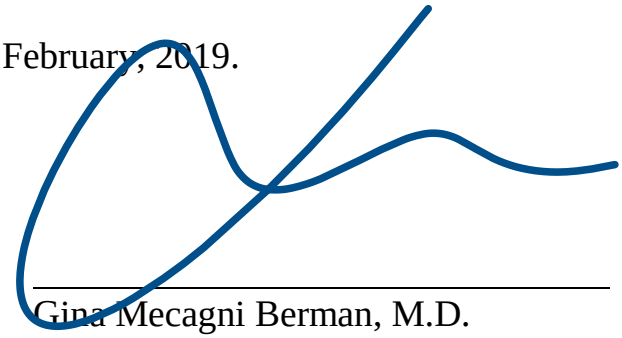
25. In 2016, I co-founded a clinic in Arizona called Blue Door Therapeutics, in which a multi-disciplinary team used both traditional and complementary therapies to wean patients dependent on prescripion opioids. Our program included recommending medical cannabis to treat painful acute opioid withdrawal as well as help to stem cravings during the protracted Post-Acute Withdrawal Symptons (PAWS) period.

26. We have submitted a case-series paper for publication detailing Blue Door's findings after treating patients during a four-month opioid weaning program. The nine patients, (ages 20-76) described in the case series used dosed forms of medical cannabis, mainly capsules. All but two patients were completely weaned from opioids after four months and had minimal cannabis use after that time. At a one-year review, no patients who were weaned from opioids after the program had returned to using opioids, as verified by third-party databases

(CSPMP and AZDHS MMJ verification systems). The two patients still using opioids after four months of treatment had cut their opioid dose significantly and had not increased that dose at the one-year follow-up. We could not have treated these patients as effectively without using dosed forms of cannabis because accurate dosing is impossible without concentrates.

27. In my medical opinion, the *Jones* opinion criminalizes commonly accepted methods of treatment with cannabis extracts, and would punish the patients most in need of the medical benefits.

EXECUTED this 14th day of February, 2019.



Gina Mecagni Berman, M.D.

Gina Mecagni Berman, MD

(602) 380-5757 cell
ginamecagni@gmail.com

Employment:

July 1, 2018 – Present
Medical Director: Arizona Natural Selections of Scottsdale
7320 E Butherus Drive #100, Scottsdale, Arizona 85260
(480) 575-1245

July 1, 2018 – Present
Medical Director: Arizona Natural Selections of Peoria
9275 W Peoria Avenue #3, Peoria, Arizona 85345
(623) 878-5954

August 7, 2012 – Present
Medical Director: The Giving Tree Wellness Center of Mesa DBA Arizona Natural Selections of Mesa
938 East Juanita Avenue Mesa, Arizona 85204
(480) 272-9888

August 7, 2012 – March 19, 2018
Medical Director: The Giving Tree Wellness Center of North Phoenix
21617 N. 9th Avenue Phoenix, Arizona 85027
(623) 242-9080

July 2004- July 2015
Emergency Department Physician: Empower Emergency Physicians
St Joseph's Hospital and Medical Center/Barrows Neurological Institute
Director of Human Relations, 2006-2012
Phoenix, Arizona

2013 – 2015
Clinical Professor, Creighton School of Medicine
via St. Joseph's Hospital and Medical Center Emergency Department
Phoenix, Arizona

2003-2005
Emergency Department Physician: Arizona Heart Hospital
Phoenix, Arizona

Certifications:

American Board of Addiction Medicine (ABMS subspecialty)
Diplomate
Original Certification: 2005

Current Certificate Expires: Dec 31, 2025

American Board of Emergency Medicine (ABMS main specialty)
Diplomate
Original certification: 2005
Current Certificate expires: 2025

Arizona Board of Medical Licensure
Expires 8/17/2019
License Number 31260

Drug Enforcement Agency (DEA)
Expires 1/31/2021

Provider:
Advanced Cardiac Life Support (ATLS)
Basic Life Support (BLS)
Pediatric Advanced Life Support (PALS)
Advanced Trauma Life Support (ATLS)

Education:

University of California, Santa Barbara
September 1993 - December 1995
Bachelor of Science, Biopsychology
Graduated with Honors
Santa Barbara, California

Georgetown University School of Medicine
September 1997 - May 2001
Doctor of Medicine
Washington, District of Columbia

Maricopa Medical Center
Chief Resident June 2003 – June 2004
Emergency Medicine
June 2001-June 2004

Recent engagements:

September 6, 2017: Speaker: Managing medical marijuana patients in the hospital. 6th Annual Dignity Health Pain Management Symposium.

September 6, 2017: Speaker: Addiction and opioids: what's a patient to do? 6th Annual Dignity Health Pain Management Symposium.

February 16, 2016: Job Corps: The business of medical marijuana

January 13, 2016: Ironwood Cancer Center Grand Rounds

Ironwood Cancer Center: Head and Neck Support Group

September 10, 2015: Speaker: Medical Marijuana: The use of a controversial plant in the chronic pain patient. Dignity Health (previously St. Joseph's Hospital) annual pain symposium

April 2015: Glendale Community College Sociology class lecture: The road to medical Cannabis in Arizona: How did we get here and where are we going?

March, 2015: Gemini Hospice guest lecturer at Grand Rounds: Brief overview of medical Cannabis in Arizona and Q&A with care providers (MDs and RNs)

August 30, 2014: Seizures and the Pediatric Patient: The Role for Cannabis
Attendees: T-Gen, Phoenix Children's Hospital Pediatric Neurologists, St. Joseph's Hospital Neurologists, Parents of children with seizures.

September 10, 2014: Medical Marijuana: The use of a controversial plant in the chronic pain patient. St Joseph's Hospital and Medical Center annual pain symposium.

October 3, 2014: Arizona Bar Association:
Lecture: The Arizona Medical Marijuana Act: Addressing criticisms.
Panel Discussion: Gina Berman, MD; Will Humble, Director, Arizona Department of health; Andrew Myers, Executive Director of the Arizona Dispensaries Association; Dr. Sue Sisley clinical professor, University of Arizona.

October 27: Arizona Medical Marijuana Program Speaker's Bureau
Physician outreach, funded by a grant from the Department of Health to the University of Arizona: **www.azmmjnow.com**

Affiliations:

Arizona Dispensaries Association
Board Member, Treasurer, August 2013- June 2014
Board Member, Secretary, June 2014-present

Arizona Department of Health Dispensary Liaison, 2014

Medical Marijuana Patient Advocate:

1. Arizona Republic Op. Ed. November 22nd, 2013
"Arizona's Medical-pot Program Actually Works Like This"
http://www.azcentral.com/opinions/articles/20131123medical-pot-arizona-mecagni.html

2. Legal testimony (Administrative Court) and research updates with the Director of the Department of Health directly contributed to the addition of PTSD as a Qualifying Condition in Arizona. Estimated PTSD patients in Arizona: 500,000

Hosted Marla Williams, Nevada Department of Public Health: Informational for NV rules package (Giving Tree Wellness Center of North Phoenix)

Member, Maricopa Medical Society

Member, American College of Emergency Physicians

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SUPREME COURT OF ARIZONA

STATE OF ARIZONA, Appellee, v. RODNEY CHRISTOPHER JONES, Appellant.	Arizona Supreme Court No. No. CR-18-0267-PR Court of Appeals No. 1 CA-CR 16-0703 Yavapai County Superior Court No. P1300CR201400328 **DECLARATION OF JEFFREY A. SINGER, M.D.**

I, Jeffrey A. Singer, M.D., declare pursuant to Rule 80(c), Ariz. R. Civ. P., under penalty of perjury that this Declaration is true and correct, as follows:

1. I am a Medical Doctor who has been licensed by the State of Arizona and practiced medicine in Arizona since 1976, after graduating from New York

Medical College. A portion of my c.v. is attached. I submit this Declaration in support of the Amicus Curiae Brief filed on my behalf with the Arizona Supreme Court in support of reversing the Court of Appeals decision in *State v. Jones*, 245 Ariz. 46 (App. 2018).

2. I am a general surgeon and Fellow of the American College of Surgeons. In 1987, I co-founded Valley Surgical Clinics, Ltd., to my knowledge the largest and oldest group private general surgical practice in Arizona.

3. I have been interested in and involved in public health policy for many years, and write and speak extensively on regional and national health care policy.

4. My patients often visit me because of pain in various forms. Both before and after surgery, many patients need pain management. Some of my patients have nausea and/or trouble eating because of terminal cancer.

5. Doctors in Arizona and around the country do not 'prescribe' medical marijuana because marijuana is classified as a Schedule I controlled substance under Federal law. Instead, under Arizona laws and regulations, doctors may certify that a patient has a debilitating medical condition as defined in the Arizona Medical Marijuana Act (A.R.S. § 36-2801) and that, in the doctor's professional opinion, the qualifying patient is likely to receive therapeutic or palliative benefits from the medical use of marijuana. See Arizona Health Department of Health Services Medical Marijuana Physician Certification form, attached. A number of Arizona

doctors, myself included, are not comfortable providing patients with this medical marijuana certification because of the Federal law.

6. As a general surgeon, an increasing number of my patients have reported to me that they are using or have used medical marijuana to treat, eliminate or control their pain, neuropathies, seizures and for other medical reasons. Many patients have told me that medical marijuana in various forms – including tinctures, oils and lotions -- works better for them than prescription pain medicine, including opioids, with fewer side effects.

7. As a physician, I can readily understand why such extracted forms of marijuana are welcome alternatives for patients who either cannot or should not smoke marijuana flowers. A recent Canada National Cannabis Survey found that higher proportions of medical cannabis users reported consuming cannabis through methods other than smoking. https://www150.statcan.gc.ca/n1/daily-quotidien/190207/dq190207b-eng.htm?HPA=1.

8. I have at times suggested to other patients that they may want to try medical marijuana in its various forms to ease their pain and other symptoms, and I have referred them to doctors who will certify their medical condition in accordance with the Act.

9. A survey performed by the American Society of Clinical Oncology last year and published online in the Journal of Clinical Oncology found that as many as

80 percent of oncologists have discussed medical marijuana use with their patients. https://www.asco.org/about-asco/press-center/news-releases/most-oncologists-have-discussed-medical-marijuana-patients/feed

10. Opioid deaths and overdoses have become epidemic in both Arizona and the United States. Real-time data from the Arizona Department of Health Services (ADHS) shows 2,384 suspected opioid deaths in Arizona from June 15, 2017 to February 7, 2019, and another 17,492 overdoses during that period. https://www.azdhs.gov/prevention/womens-childrens-health/injury-prevention/opioid-prevention/index.php (last visited February 8, 2019).

11. As a public policy researcher and physician, I keep up to date on available scientific data and research on medical marijuana and opioids.

12. The research, outlined below, shows that states in which medical marijuana is available to patients have significantly lower rates of opioid overdose deaths:

a. A 2014 study from the Johns Hopkins School of Public Health examined medical cannabis laws and death certificates from all 50 states from 1999 to 2010 and found that the yearly rate of opioid painkiller overdose deaths in states with medical marijuana laws was about 25 percent lower, on average, than the rate in states without these laws. https://www.jhsph.edu/news/news-releases/2014/state-medical-marijuana-laws-linked-to-lower-prescription-

overdose-deaths.html.

b. Likewise, a 2018 study by the RAND Corporation determined that permitting access to medical marijuana reduced use of opioids and opioid deaths. https://doi.org/10.1016/j.jhealeco.2017.12.007

c. A University of Michigan School of Public Health study found that patients using medical marijuana to control chronic pain reduced their use of opioids by 64 percent. https://www.sciencedirect.com/science/article/pii/S1526590016005678

d. A June 2017 University of California, Berkeley study reported that medical cannabis enabled 97 percent of chronic pain patients to decrease the amount of opioids they were taking, and that 81 percent found cannabis alone more effective than cannabis and opioids in combination. https://doi.org/10.1089/can.2017.0012

e. A 2018 study of Medicare Part D patients by researchers at the University of Georgia found a decreased rate of opioid use for the control of pain in states where medical cannabis was legally available. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2676999.

f. A 2018 report from the University of Kentucky on a study of all Medicaid fee-for-service and managed care patients across the United States from 2011 to 2016 found a decrease in opioid prescribing in states where medical

marijuana was legally available, with an even greater reduction in states where both medical and recreational marijuana were available. https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2677000?redirect=true

13. This evidence suggests that, among other medical benefits, a bonus effect of legalizing medical marijuana may be a decrease in opioid use, dependence, and overdose deaths.

14. The National Institute of Drug Abuse (NIDA) cites these and other studies for the conclusion that "medical marijuana products may play a role in reducing the use of opioids needed to control pain," although acknowledging that the products come with some risks. https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-safe-effective-medicine. NIDA continues, "More research is needed to investigate the potential therapeutic role of marijuana including its role as a treatment opion for opioid use disorder and its ability to reduce specific types of pain."

15. Based on these and other studies and my patients' reports of their own experiences with medical marijuana treatments for pain and other symptoms, I have concluded that medical marijuana in any form is a viable alternative to opioids that may result in fewer deaths and overdoses.

EXECUTED this 8th day of February, 2019.

Jeffrey A. Singer, M.D., FACS

CURRICULUM VITAE
JEFFREY A. SINGER, MD, FACS

BORN: Brooklyn, New York
February 2, 1952

PERSONAL: Married wife--Margaret Gordon Singer
children: Deborah (b. 12/29/79)
Pamela (b. 5/30/83)

EDUCATION:

Bachelor of Arts (BA), Cum Laude, Biology 1973, Brooklyn College, City University of New York

Doctor of Medicine (MD), 1976 New York Medical College
Valhalla, New York

Internship 1976-77	Maricopa County General Hospital Categorical Surgical Internship Phoenix, Arizona
Surgical Residency 1977-81	Maricopa County General Hospital General Surgical Residency Phoenix, Arizona
Specialty Board Certification:	American Board of Surgery- General Surgery February 1982, No. 27546 Recertified October, 1991; October 2001
Arizona State Medical License:	1977, No. 10089

Honors:

Alpha Omega Alpha, Honor Medical Society
Elected into Iona Chapter, 1976

Upjohn Achievement Award for Outstanding Clinical Skills--1976

American Medical Association Physicians' Recognition Award

“Who’s Who in America”

"Who's Who in the West"

"Who's Who in Science and Engineering"

"Who's Who in the World"

"Who's Who in Medicine and Healthcare"

“Top Doc,” Phoenix Magazine Award, 1999

“Arizona Medical Association `Walk the Talk’ Award,” June 2001

“Doctor of the Quarter,” Paradise Valley Hospital, Phoenix, AZ., March 2002

PROFESSIONAL SOCIETIES:

Fellow, American College of Surgeons

Fellow, International College of Surgeons (Past Vice Regent)

Fellow, Southwestern Surgical Congress

Fellow, American Society of Abdominal Surgeons

Past Member, Society of Laparoendoscopic Surgeons

Member, Phoenix Gastroenterological Society

Member, Phoenix Surgical Society

Member, Arizona Chapter, American College of Surgeons

Past Member, New York Academy of Sciences

OTHER PROFESSIONAL ORGANIZATIONS (PAST AND PRESENT):

American Medical Association

Association of American Physicians and Surgeons (AAPS)

Arizona Medical Association

Arizona Chapter, AAPS

Maricopa County Medical Society

Associate, American College of Legal Medicine

POSITIONS HELD:

Private Solo Practice, General Surgery,
Jeffrey A. Singer, MD, PC----1981-87

Private Group Surgical Practice, Principal and Co-Founder,
Valley Surgical Clinics, Ltd., 1987-present

Private Group Surgical Practice, Principal and Co-Founder,
Southwest Surgical Clinics, P.C., 1996-99

Partner, Tom Paine Products, Direct Mail Marketing
Company, 1995-96

Voluntary Teaching Faculty, Maricopa County Medical
Center Surgical Residency Program, Phoenix, AZ.,
1981-85

Traumatologist, John C. Lincoln Hospital Trauma Center,
Phoenix, AZ., 1981-83

Arizona State University/Scottsdale Memorial Hospital
Pre-medical Student Preceptor, 1990-98

Chief of Surgery, Humana Hospital Desert Valley, Phoenix,
AZ., 1985-87

Executive Committee, Humana Hospital Desert Valley, Phoenix,
AZ, 1985-91

Chief of Surgery, Paradise Valley Hospital, Phoenix, AZ., 1991-93

Executive Committee, Paradise Valley Hospital, Phoenix, AZ., 1991-95

Member, Credentials Committee, Paradise Valley Hospital, Phoenix, AZ., 1993-97

Arizona Medical Association, Committee on Legislative Affairs, 1985-2016

Member, Board of Directors, Arizona Medical Association Political Action Committee, 1985-2016

Chairman, Arizona Medical Association Political Action Committee, 1991-93

Member, Arizona Medical Association Task Force on Health System Reform, 1993-94

Vice-President, Arizona Chapter, Association of American Physicians and Surgeons, 1993-94

Associate Editor, *ARIZONA MEDICINE,* the Journal of the Arizona Medical Association, 1994-99; Contributing Writer, 1999-2016 (journal called *AZMED* since 2000)

Member, House of Delegates, Arizona Medical Association, 1995, 2000

Member, Maricopa County Medical Society Managed Care Task Force, 1995-96

President, Arizona Chapter, New York Medical College Alumni Association, 1990-2002

Arizona Republican Party, Precinct Committeeman, District 24,1986-2000

Arizona Republican Party Finance Committee, 1994-97

Arizona Republican Party State Committeeman, 1995-99

Policy Advisor for Health Affairs, JD Hayworth Congressional Campaign, 1993-94

Finance Chairman, "JD Hayworth for Congress," 1993-94, 1995-96

Member, Medicare Reform Task Force, Congressman JD Hayworth, 1995-96

Member, Health Care Advisory Council, Congressman Matt Salmon, 1995-2000

Member, Maricopa County Fiscal Committee, Citizens Advisory Panel, 8/17/94-4/17/95

Vice-Chairman, Arizona Republican Liberty

Caucus, 1994-95

Chairman, Arizona Republican Liberty Caucus, 1995

National Committee Alternate, Republican Liberty Caucus, 1994-95

Member of Steering Committee, and Medical Spokesperson, Arizonans for Drug Policy Reform (Sponsors of "Drug Medicalization, Prevention and Control Act of 1996" [Prop. 200]), 1995-2006

Chairman, Republican Alliance for Liberty, 1996

Director of Communications, Arizona Republican Roundtable, 1996-98

Member, Staff Selection Board, Maricopa County Charter Committee, January 1996

Member, Medical Advisory Group, US Senator Jon Kyl, 1996-2003

Member, Board of Directors, Arizona School Choice Trust, 1996-2004; Member of Advisory Board, 2004-2008

Member, Board of Directors, Citizens for an Alternative Tax System, Arizona Chapter, 1996-2002

Member, Board of Directors (Trustee), Healthcare Providers, Inc., (Maricopa County General Hospital Proposed Privatization Entity), October-December 1996

Surrogate Speaker, Arizona "Dole-Kemp '96" Campaign, September-October 1996

Member, Board of Directors, Goldwater Institute, Phoenix, Arizona, December 1996-December 2012

Founding Member, Republican Business Council, 1997

Co-Chairman, Doctors for Medical Rights, 1997-2002

Co-Chairman, "The People Have Spoken," Arizona Referendum and Initiative Committee (Sponsors of The Drug Medicalization, Prevention, and Control Act of 2002," Proposition 203), 1997-2002

Member, Steering Committee, Voter Protection Alliance, Sponsor of "Voter Protection Act of 1998(Proposition 105)," April 1997-98

Vice-President, Maricopa County Medical Society, 1998

Member, Steering Committee, and Finance Chairman, Arizonans for Fair Tax Reform, Sponsor of "The IRS Elimination Pledge Act of 1998 (Proposition 202)," 1998-2000

Member, Board of Directors, Maricopa County Medical Society, 1999 through 2001

Clinical Assistant Professor, Division of Clinical Education, Arizona College of Osteopathic Medicine, Midwestern University, Glendale, Arizona1998-present

Preceptor, Kirksville College of Osteopathic Medicine, Arizona School of Health Sciences, Adjunct Clinical Faculty, Phoenix, Arizona, 1999-2006

Member, Board of Directors, Americans for Limited Terms, 1999-2002

Member, Board of Directors, Americans for Limited Government, 2002-2005

Member, Board of Directors, Americans for Limited Government Foundation, 2002-2005

Treasurer, Taxpayer Protection Alliance, Sponsors of the "Taxpayer Protection Act of 2000" Ballot Initiative, 1999-2000

Treasurer, "It's Time Again," Campaign Committee for Ballot Initiative Limiting State Government Spending, 2003-2004

"Freedom and Liberty Correspondent" for Phxnews.com, 2003-2005

Treasurer, AAPS—PAC (Arizona), 2004-2006

Adjunct Scholar, Reason Foundation, 2004-2005

Member, Board of Directors, North Mountain Ambulatory Surgery Center, Phoenix, AZ—2006-2009

Member, Board of Directors, Arizona Federation of Taxpayers, 2006-2008

Treasurer, US Health Care Freedom Coalition (Formerly, Benjamin Rush League), 2007-present

Treasurer, “Medical Choice for Arizona,” Ballot Initiative Committee, June 2007-January 2009

Treasurer, “Arizonans for Health Care Freedom,” Ballot Initiative Committee, January 2009-December 31, 2010

Co-Chair, Peri-operative Services Committee, Paradise Valley Hospital, Phoenix, AZ, January 2010-December 2013

Adjunct Scholar, Cato Institute, Washington, DC, March 2012-July 31, 2017

Member, Board of Advisors, Freedom and Entrepreneurship Foundation, Krakow, Poland, April 2013-present

Treasurer, Citizens for Phoenix Pension Reform, December 2013-December 2014

Chief of Surgery, Paradise Valley Hospital, 2014-2016

Member, Health Care Freedom Advisory Council, Our America Initiative, February 2014-present

Member, Advisory Board Council, Arizona State University Center for Political Thought and Leadership, May 2014-June 2018

Ambassador, Program in Political Thought and Leadership at Arizona State University, July 2018-present

Member, Advisory Board, Our Patients First Political Action Committee, Sacramento, CA, September 2014-December 2016

Instructor, Arizona State University Center for Political Thought and Leadership, Continuing Education Program, January-February, 2015

Visiting Fellow, Goldwater Institute for Public Policy Research, Phoenix, AZ, January 2017-present

Senior Fellow, Cato Institute, August 1, 2017-present

OTHER ORGANIZATIONS:

Physicians for the Phoenix Symphony, 1989-93, 1999-2002

Arizona Humanities Council, 1990-93

Greater Phoenix Chamber of Commerce, 1992-2000

National Federation of Independent Business/Arizona
1994-present

Arizona Republican Caucus, 1987-1997

Arizona Republican Roundtable, 1995-97

Republican Liberty Caucus, 1993-95

Benefactor, Cato Institute, Washington, DC, 1993-present

"Torchbearer Society" Member, Reason Foundation, Los Angeles, California, 1998-present

Sponsor, Simon Weisenthal Center, Los Angeles, Ca., 1986-present

Sponsor, Future of Freedom Foundation, 1993-present

Sponsor, Foundation for Economic Education, 1992-present

Sponsor, National Center for Policy Analysis, Dallas, TX, 1997-2006

HOSPITAL STAFF AFFILIATIONS:

Phoenix Baptist Hospital 1981-2002
John C. Lincoln Hospital and Medical Center
John C. Lincoln Hospital Deer Valley
St. Joseph's Hospital and Medical Center, 1981-99
Paradise Valley Hospital
Thunderbird Samaritan Hospital 1982-2001
Good Samaritan Medical Center, 1981-99
Scottsdale Memorial Hospital-Osborn 1981-2002
Scottsdale Healthcare—Shea
Scottsdale Healthcare—Thompson Peak

PUBLICATIONS:

"Frosty Mornings No Longer," a poem, RIVERRUN, Brooklyn College Literary Review, June 1973

ARIZONA DEPARTMENT OF HEALTH SERVICES

LICENSING

MEDICAL MARIJUANA PHYSICIAN CERTIFICATION
PHYSICIAN INFORMATION
FOR ALL QUALIFYING PATIENTS

Physician's Name:	Type: MD ☐ DO ☐ NMD/ND ☐ MD(H) DO(H) ☐
Arizona Issued License Number:	
Physician Office Address:	
Physician Telephone Number:	Physician Email Address:
Qualifying Patient Name:	Qualifying Patient Date of Birth (mm/dd/yyyy):

☐ Acquired immune deficiency syndrome (AIDS) ☐ Amyotrophic lateral sclerosis (ALS) ☐ Crohn's disease
☐ Human immunodeficiency virus (HIV) ☐ Agitation of Alzheimer's disease ☐ Cancer ☐ Glaucoma ☐ Hepatitis C
☐ Post-Traumatic Stress Disorder (PTSD) ***(If checked, please review and attest item 6)***

IF A CHRONIC OR DEBILITATING DISEASE OR MEDICAL CONDITION OR THE TREATMENT FOR A CHRONIC OR DEBILITATING DISEASE OR MEDICAL CONDITION CAUSES:

☐ Cachexia or wasting syndrome ☐ Severe and chronic pain ☐ Severe nausea ☐ Seizures, including epilepsy characteristic
☐ Severe or persistent muscle spasms, including those characteristic of multiple sclerosis

IF ANY CONDITION ABOVE IS CHECKED, INDICATE THE UNDERLYING CHRONIC OR DEBILITATING DISEASE OR MEDICAL CONDITION:

I,_____, THE PHYSICIAN:
(PRINT NAME)

1. Have made or confirmed diagnosis of a debilitating medical condition as defined in A.R.S. § 36-2801 for the qualifying patient.
   Initial: _____
2. Have established a medical record for the qualifying patient and am maintaining the qualifying patient's medical record as required in A.R.S. § 12-2297.
   Initial: _____
3. Have conducted an in-person physical examination of the qualifying patient within the last 90 calendar days appropriate to the qualifying patient's presenting symptoms and the debilitating medical condition I diagnosed or confirmed.
   Date of Examination:_____Initial: _____
4. Have reviewed the qualifying patient's medical records, including medical records from other treating physicians from the previous 12 months; the qualifying patient's responses to conventional medications and medical therapies; and the qualifying patient's profile on the Arizona Board of Pharmacy Controlled Substances Prescription Monitoring Program database.
   Initial: _____
5. Have explained the potential risks and benefits of the medical use of marijuana to the qualifying patient, or if applicable, the qualifying patient's custodial parent or legal guardian.
   Initial: _____
6. Have reviewed evidence documenting that the patient is currently undergoing conventional treatment for PTSD *(PTSD patients only)*.
   Initial: _____
7. If the qualifying patient has been referred to a dispensary, I have disclosed to the qualifying patient, or if applicable, the qualifying patient's custodial parent or legal guardian, any personal or professional relationship I have with the dispensary.
   Initial: _____
8. I have addressed the potential dangers to fetuses caused by smoking or ingesting marijuana while pregnant or to infants while breastfeeding. I have also informed the patient that the use of marijuana during pregnancy may result in a risk of being reported to the Department of Child Safety during pregnancy or at the birth of the child by persons who are required to report.
   Initial: _____

PHYSICIAN'S ATTESTATION

I,_____, in my professional opinion believe that the qualifying patient is likely to receive therapeutic or palliative benefit from the qualifying patient's medical use of marijuana to treat or alleviate the qualifying patient's debilitating medical condition. I attest that the information provided in this written certification is true and correct.

_____ _____
Physician's Signature Date Signed

SOCIETY of CANNABIS CLINICIANS

Declaration from The Society of Cannabis Clinicians

1. The Society of Cannabis Clinicians (SCC)

The Society of Cannabis Clinicians is a nonprofit educational and scientific society of qualified physicians dedicated to the promotion, protection and support of cannabis for medical use. The group was formed as a project of the California Cannabis Research Medical Group, a 501(c)(3) corporation founded in 1999, whose mission includes the promulgation of voluntary standards for healthcare providers engaged in the recommendation and approval of cannabis under various state laws. Our outreach has expanded worldwide, with a membership of 350 collaborating to help meet the needs of physicians and other healthcare providers seeking clinically relevant cannabis education and research.

2. SCC Mission and Activities

Our goals include expanding knowledge on the medical use of cannabis, recommending research and policy directions related to the use of medical cannabis and facilitating best practice standards of care for clinicians who are recommending

cannabis to ill patients. We offer formal evidence-based continuing medical education (CME) resources to physicians and other healthcare professionals and host quarterly educational seminars featuring expert scientists and physicians. Additionally, our members collect and evaluate research data in connection with clinical research programs around the globe in order to advance the knowledge of cannabis for medical use.

3. The Endocannabinoid System (ECS)

Research on the effects of cannabis in the late 1980s led to the discovery of a previously unknown biochemical communication system in the human body called the endocannabinoid system (ECS), which plays a critical role in regulating our physiology. This system modulates our stress, pain response, sleep, appetite, behavior, energy metabolism, immunity and many other important bodily functions. A major part of this system uses a “lock-and-key” mechanism, with natural endocannabinoid compounds as the keys and the cannabinoid receptors as the locks.

4. ECS Dysfunction

Recent scientific investigations prove that dysfunction of the ECS (specifically a deficiency of the endocannabinoid locks and keys) can result in illnesses such as anxiety, depression, autism, seizures, migraines and dozens of other serious medical conditions. This mechanism is the basis of the use of cannabis as medicine:

augmenting the naturally occurring ECS by using the phytocannabinoid “keys” from the cannabis plant to boost the deficient endocannabinoid system (ECS). This assist serves to restore physiologic function in the body to homeostasis (a stable, balanced state).

Patients suffering from ECS-related conditions may require different doses of cannabis depending on many variables such as age, metabolism, genetics and severity of illness. Patient dosing should be “patient-determined and self-titrating,” meaning there is no standardized dosing for cannabis medicine, because each person has different ECS function. Clinicians must work with patients to determine what cannabis dosing, delivery method, and form of cannabis works best for each patient’s specific ailments.

5. Concentrated Cannabis Products, Including Hashish

High-quality cannabis flowers — exclusive of such parts of the plant as stems and leaves — can contain up to about 25% active cannabinoid constituents. As new strains and growing techniques are developed, the percentage of active cannabinoid constituents has increased. Accordingly, the difference in content between hashish (with a higher concentration of cannabinoids) and flowers has narrowed.

The medicinal phytocannabinoids and other therapeutic compounds in cannabis preparations containing higher concentrations of cannabinoids (including hashish and

concentrated oils) are a cleaner form as explained in ¶ 6. Many healthcare providers advise their patients to use more concentrated cannabis in the treatment of serious illnesses, as it has been shown that patients are able to take higher doses without requiring large volumes of other, less-concentrated forms of the plant medicine.

6. Advantages of Concentrated Cannabis Products

There are multiple beneficial effects of concentrated preparations such as hashish:

1) They are more stable, with less odor than dried flowers.

2) An inhaled dose is achieved with fewer pyrolitic compounds (meaning the decompositions of materials at high heat), affording a safer product compared with smoked flowers.

3) Hashish doesn't require the use of solvents in the production of the concentrate from female dried flowers.

4) Duration of action is frequently longer, providing patients with the ability to medicate less often. This longer duration of effect is important for those with chronic pain or other debilitating conditions, as these patients experience a poor quality of life if they are able to achieve pain relief for only brief periods. For some patients, hashish can be quite sedating, a desired effect for patients who struggle with sleep disturbances due to serious illness.

Unlike other concentrated forms of cannabis, hashish traditionally has been produced by simply sifting the cannabis dried flowers to obtain the crystals (called trichomes),

pressing the resulting powder into a solid cake. It is a clean and useful concentrate that is valued by clinicians and patients for its use in inhaled, ingested and topical products.

7. As physicians who have worked with many thousands of patients, all of the doctors signing below can categorically state that the form of cannabis called "hashish" has medical uses and value similar to other forms of cannabis.

Our collective clinical experience supports the use of concentrated cannabis medicines, including hashish, for a wide variety of medical conditions. Vape oils, RSO or FECO oils, hashish, kief, shatter, resin, rosin, infused oils and tinctures are all slightly different extracts of the cannabis female flower. All are cannabis-based medicines. All have similar risks and benefits that are indistinguishable among the family of cannabis products. All chemovars (also known as strains) of the cannabis plant and the many varied forms of cannabis are valued medicines by the physicians and their patients who are dealing with serious medical conditions for which cannabis provides relief. Different preparations and ways of ingesting help different patients in different ways.

8. The Arizona Medical Marijuana Act

Restricting patients to specific forms of cannabis — or restricting the treating physician's choices — when addressing diseases and conditions that are known to

benefit from the use of medical cannabis would be inconsistent with the Arizona Medical Marijuana Act's purpose of treating patients with debilitating conditions. When the AMMA was written, the drafters could not have been expected to enumerate the many forms of marijuana/cannabis that would enter the marketplace as marijuana medicines so they defined marijuana inclusively to include all of the parts of the plant, including its resin. Again, all of the concentrated products are valuable for medical purposes.

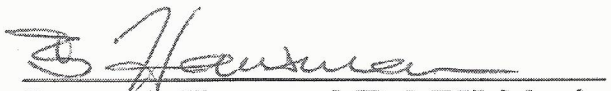
We the undersigned declare, under penalty of perjury and pursuant to Rule 80(c), Arizona Rules of Civil Procedure, that this Declaration is true and correct.

Respectfully submitted this ____ day of February, 2019

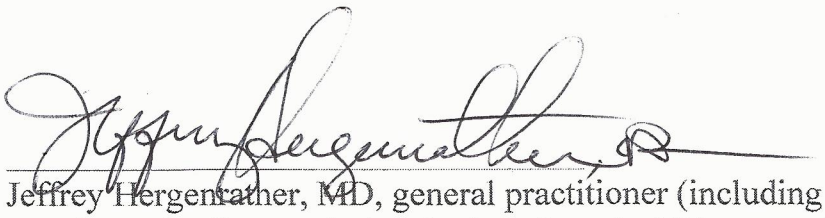
Bonni Goldstein, MD, Pediatrician, Medical Director, Canna-Centers and Member, Society of Cannabis Clinicians

Joe D. Goldstrich, MD

Joe D. Goldstrich, MD, FACC, Cardiologist and Member, Board of Directors, Society of Cannabis Clinicians



Benson A. Hausman, MD, MPH, Member, Board of Directors, Society of Cannabis Clinicians



Jeffrey Hergenrather, MD, general practitioner (including pediatrics, geriatric care, oncology, family practice), Member, Board of Directors, Society of Cannabis Clinicians

Stephen S. Robinson, MD, MPH,
Member, Board of Directors, Society of Cannabis Clinicians

Dustin Sulak, DO, general practice and integrative medicine, Member, Board of Directors, Society of Cannabis Clinicians

Genester Wilson-King, MD, FACOG, _____, Member, Board of Directors, Society of Cannabis Clinicians

Sherry Yafai, MD, _____, Member, Board of Directors, Society of Cannabis Clinicians

DECLARATION OF DAVID J. CASARETT, M.D., M.A.

I, David J. Casarett, M.D., M.A. declare pursuant to Rule 80(c), Ariz. R. Civ. P., under penalty of perjury that this Declaration is true and correct, as follows:

1. I submit this Declaration in support of the *Amicus Curiae* Brief filed by Gina Mecagni Berman, M.D. and Jeffrey A. Singer, M.D. with the Arizona Supreme Court seeking to reverse the Arizona Court of Appeals decision in *State v. Jones*, 245 Ariz. 46 (App. 2018).

2. I am a Medical Doctor and am Board certified in both Internal and Palliative Care Medicine. I am a Professor at the Department of Medicine at Duke University School of Medicine in Durham, North Carolina. I am also the Chief of Palliative Medicine and the Director of the Duke Center for Palliative Care.

3. I received my M.D. and M.A. from Case Western Reserve University, and then did a residency at the University of Iowa, in Iowa City, followed by a fellowship in Palliative Medicine at the University of Pennsylvania, in Philadelphia. A portion of my c.v. is attached.

4. I did not learn anything about medical marijuana in medical school or residency. I described on a TED Talk in 2016 how a 73-year-old retired English professor patient with pancreatic cancer asked me about medical marijuana and I

told her that as far as I knew, it had no benefits. She then pulled out a number of randomized controlled trials showing that medical marijuana has benefits for symptoms like nausea, pain and anxiety, and told me that she had been using it and it was helping with her pain. https://www.ted.com/talks/david_casarett_a_doctor_s_case_for_medical_marijuana/transcript?language=en

5. Until my visit with that patient, I always thought medical marijuana was a joke even though patients had told me they used it for symptoms like pain or nausea. I then realized I needed to learn more and started reading more medical articles, talking to researchers, talking to doctors, and listening to patients. As a result, I ended up writing a book about medical marijuana called "Stoned: A Doctor's Case for Medical Marijuana," published by Penguin Random House in 2015.

6. I researched the merits and issues involved with medical marijuana because I wanted to be able to decide, as a physician, what advice I should give my patients when they ask me whether they should use it. In my research, I attempted to look carefully – and critically – at the evidence, meaning that I subjected medical marijuana to the same scrutiny that I'd give to drugs that the pharmaceutical industry tries to sell to physicians like me.

7. During my research, I discovered that medical marijuana does have some medical benefits, particularly for neuropathic and some chronic pain,

chemotherapy-induced nausea, anorexia, insomnia, and seizures. It also has some risks, which I describe in the book, that can be minimized with education and appropriate measures. I also found that for palliative care patients, many of whom are facing illnesses that will end their lives, using medical marijuana on their own terms and schedule makes them feel more in control of their lives and health.

8. In my research, I explored different ways that people get medical marijuana into their systems. In my opinion, the route of administration needs to be individualized, because each route has unique advantages and disadvantages. Vaping, tinctures, edibles, capsules and sometimes smoking are all potentially beneficial routes of administration.

9. I also found that the better medical marijuana dispensaries will willingly spend an hour or more talking with patients about the nuances of different strains of marijuana, and about different forms of delivery (e.g., smoking versus vaporizing, edibles versus tinctures, etc.) and will tailor their products and delivery methods to the patient's medical needs and objectives.

10. After researching and writing the book, I believe that medical marijuana does offer medical benefits to some patients.

11. Given what we know now about the benefits of THC and CBD, marijuana should be reclassified to at most a Schedule II substance. In my opinion, it is no longer appropriate, given existing research and patient and doctor reports,

to say that marijuana deserves a Schedule I classification, reserved for drugs that offer no clinical use. In addition, I believe that change will make it easier to do controlled trials, producing more of the evidence we need to use medical marijuana correctly and safely.

EXECUTED this 7th day of February, 2019.

David Jonathan Casarett, M.D., M.A.

Signature: _____

Date: _____

DUKE UNIVERSITY – SCHOOL OF MEDICINE
Curriculum Vitae

Date: May, 2017

David Jonathan Casarett, M.D., M.A.

Home Address: 1001 Edith Street
Durham, NC 27705

Office Address: Duke University Hospital
2301 Erwin Road
CMO/EVP suite, Green Zone
Durham, NC 27710

Education:

1985-89	B.A.	With Honors, Swarthmore College (Anthropology)
1989-93	M.D.	Case Western Reserve University
1991-93	M.A.	Case Western Reserve University (Medical Anthropology)

Postgraduate Training and Fellowship Appointments:

1993-96	Resident Physician, University of Iowa Hospitals, Iowa City
1996-97	Ethics Fellow, MacLean Center for Clinical Medical Ethics, University of Chicago, Chicago
1997-98	Chief Resident, Department of Medicine, University of Iowa Hospitals, Iowa City
1998-99	Fellow, Palliative Medicine, University of Pennsylvania, Philadelphia

Military Service: None

Faculty Appointments:

1999-02	Instructor, Division of Geriatrics, Department of Medicine, University of Pennsylvania School of Medicine
2002-07	Assistant Professor, Division of Geriatrics, Department of Medicine, University of Pennsylvania School of Medicine
2007-2013	Associate Professor, Division of Geriatrics, Department of Medicine, University of Pennsylvania School of Medicine
2014-2016	Professor, Division of Geriatrics, Department of Medicine, University of Pennsylvania School of Medicine
2016-	Professor, Division of General Internal Medicine, Department of Medicine, Duke University School of Medicine

Hospital and Administrative Appointments:

1994-96	Staff Physician, Free Medical Clinic of Iowa City, University of Iowa Hospitals and Clinics
1996-97	Ethicist, St. Joseph Hospital, University of Chicago
1996-97	Staff Physician, Chicago Health Clinic (Free Clinic)
1998-99	Associate Medical Director, Wissahickon Hospice, University of Pennsylvania Health System
1999-2000	Staff physician and Medical Director, Palliative Care, Philadelphia Veterans Affairs Medical Center
2007-2010	Director of Research and Evaluation, University of Pennsylvania Hospice
2010-2016	Chief Medical Officer, Penn Hospice
2012-2016	Director of Hospice and Palliative Care, University of Pennsylvania Health System
2016-	Chief of Palliative Medicine, Duke Health
2016-	Director, Duke Center for Palliative Care

Other Appointments:

1999-present	Faculty, Center for Bioethics, University of Pennsylvania
1999-present	Fellow, University of Pennsylvania Institute on Aging
2000-present	Senior Fellow, Leonard Davis Institute of Health Economics, University of Pennsylvania
2002-2010	Faculty, Center for Health Equity Research and Promotion, Philadelphia VA Medical Center
2011-2016	Faculty, Department of Medical Ethics and Health Care Policy

Specialty Certification (recertification):

1996 (2006)	American Board of Internal Medicine (Internal Medicine)
2001 (2010)	American Board of Internal Medicine (Palliative Medicine)

Licensure: Pennsylvania, North Carolina

Awards, Honors, and Membership in Honorary Societies:

1988	Steven Polgar Prize for student research in Medical Anthropology, the American Society for Medical Anthropology
1989	John Snow Award for student research in rural health care delivery, awarded by the National Rural Health Association
1989	Sigma Xi
1999	Veterans Affairs Faculty Leader in End of Life Care

1999	Invited Participant, National Institute on Aging Summer Institute
2002	Undersecretary's Commendation for contribution to end-of-life care in the Veterans Health Administration
2002	Palliative Care representative, National Board of Directors, National Hospice and Palliative Care Organization
2003	Fellow, American Academy of Hospice and Palliative Medicine
2003	Best Poster Award at the American Academy of Hospice and Palliative Medicine Annual Meeting, for "All's well that ends well? Outcome of patients who withdraw from hospice," Kapo J, Galbraith L, Hirschman K, **Casarett D**
2003	Fellow, American Academy of Hospice and Palliative Medicine.
2004	Best Poster Award (Health Systems), American Geriatrics Society Annual Scientific Meeting "Needs of patients and caregivers discharged from hospice" Kapo J, Galbraith L, Hirschman K, **Casarett D**
2004	Outstanding Student Research Award, American Geriatrics Society Annual Scientific Meeting, for "Bereavement needs of long-term caregivers" Rickerson E, Strumpf N, Somers C, Allen C, Lewis B, **Casarett D**
2004	Commendation by the Undersecretary for Veterans Affairs: National VA Advisory Panel.
2005	Best Paper Award, American Academy of Hospice and Palliative Medicine, for "Effectiveness of a "case-finding" intervention to increase hospice referrals: Results of a randomized controlled trial" **Casarett D**, Karlawish J, Morales K, Asch D.
2005	William A. Nelson Award in Ethics Leadership, Department of Veterans Affairs.
2006	Outstanding Clinical Investigation Award, American Geriatrics Society
2006	Presidential Early Career Award for Scientists and Engineers
2006	Marjorie A. Bowman - New Investigator Research Award
2011	Rosenthal lectureship, Harvard University, Boston MA.
2012	Kaleidoscope lectureship, Trinity College, Dublin Ireland.
2014	Outstanding poster award (senior author) for L. Dingfield, Differences between adult and pediatric hospice patients, American Academy of Hospice and Palliative Medicine annual assembly.
2015	Outstanding paper awards (senior author) for M. Mendlik, Huntington's Disease case series, and N. O'Connor, Independent predictors of late hospice referrals, American

	Academy of Hospice and Palliative Medicine annual assembly.
2015	Distinguished Service Award, American Academy of Hospice and Palliative Medicine

Memberships in Committees and Professional and Scientific Societies:

International: None

National:

American Academy of Hospice and Palliative Medicine, member, 1998-.
American College of Physicians End of Life Consensus Panel, member 1998-2001.
American Geriatric Society, member, 1999-2006.
National Hospice and Palliative Care Organization Research Committee, 1999-2004.
American Thoracic Society Task Force on End of Life Care, member 1999-2001.
Hastings Center Access and Values Expert Advisory Panel, 1999-2002.
American Academy of Hospice and Palliative Care Ethics Committee, 1999-2003.
National Hospice and Palliative Care Organization Ethics Committee, 1999-2006.
Chair, National Hospice and Palliative Care Organization Task Force on Research Ethics, 2000-2001.
American College of Physicians End of Life Patient Education Task Force, 2000-2002.
American Geriatrics Society Task Force on Geriatric Pain Management, 2000-2002.
American Geriatrics Society Task Force on Priorities for Geriatric Pain Research, 2000-2002.
Veterans Affairs Task Force on the Ethics of Quality Improvement, 2001-2003.
Palliative Care representative, National Board of Directors, National Hospice and Palliative Care Organization, 2002-07.
Chair, Ethics Committee of the National Hospice and Palliative Care Organization, 2003-2006.
National Palliative Care Research Center, Review Committee, 2005-2007.
National Institutes of Health State of the Science conference on end-of-life care, Planning Committee, 2003-2004.
Department of Veterans Affairs Health Services Research and Development Quality Merit review study section, 2004-2009.
Chair, Ethics Committee, American Geriatrics Society, 2005-2008.
Chair, Research Committee, National Hospice and Palliative Care Organization, 2006-2007.

Member, American Academy of Hospice and Palliative Medicine Quality Task Force, 2009-present.
Member, CMS Technical Expert Panel on quality measurement in hospice, 2011.
Member, National Quality Forum palliative care expert panel, 2011.
Standing member, Nursing and Related Sciences Study Section, NIH, 2011-present.
Chair, American Academy of Hospice and Palliative Medicine Quality Task Force, 2012-present.
Co-Chair, American Academy of Hospice and Palliative Medicine and Hospice and Palliative Nurses Association Measuring What Matters program, 2013-present.
Member, TJC technical expert panel on quality measurement for advanced certification in palliative care, 2015-present.

Local:

Ethicist, Ryan White Title II Advisory Committee, State of Illinois Department of Public Health, Springfield, Illinois. 1996-1997

Editorial positions:

2003-2007	Associate Editor, Ethics and Legal section, Physicians Information and Education Resource, American College of Physicians
2003-present	Associate Editor, Journal of Palliative Medicine
2004-present	Editorial Board, Journal of Pain and Symptom Management
2004-2009	Associate Editor and Section Editor, Ethics, Law, and Public Policy, Journal of the American Geriatrics Society
2010-2012	Associate Editor, Journal of Pain and Symptom Management
2012-present	Senior Associate Editor, Journal of Pain and Symptom Management

Academic Committees at the University of Pennsylvania and Affiliated Hospitals:

1999-2003	Member, Philadelphia VA Medical Center Institutional Review Board
1999-2002	Member, Philadelphia VA Medical Center Pain Committee
1999-2009	Chair, Philadelphia VA Medical Center Ethics Committee
2011-present	UPHS CEQI committee
2011-present	Chair, UPHS palliative care steering committee

Major Teaching and Clinical Responsibilities at the University of Pennsylvania and Affiliated Hospitals:

1. Founding Medical Director, Philadelphia VAMC Palliative Care service
2. Lecturer and small group preceptor, "Ethics of Human Subjects Research"
3. Small group preceptor, ID 390 (Ethics), University of Pennsylvania
4. Chief Medical Officer, Penn-Wissahickon Hospice
5. UPHS Director of Hospice and Palliative Care

Lectures by Invitation (Selected from past 7 years; does not include presentations and posters and regional and national professional meetings):

May 12, 2007	"Is it time to redesign hospice? End-of-life care from the user's perspective" – Outstanding clinical investigation award plenary, American Geriatrics Society Annual Meeting, Chicago, IL.
June 14, 2007	"What should be included in an international minimum dataset to measure the quality of end-of-life care?" Invited plenary lecture, International Conference on End-of-life Care as a Public Health Priority, Amsterdam, The Netherlands.
July 17, 2007	"Opportunities to improve end-of-life care" University of Nebraska Medicine Grand Rounds.
December 6, 2007	"Measuring and improving the quality of end-of-life care." Geriatrics Grand Rounds, Brown University, Providence RI.
March 4, 2008	"The art and science of effective hospice discussions" (Medicine Grand Rounds) and "The appropriate use of artificial nutrition and hydration (Surgery Grand Rounds); Lehigh Valley Hospital, Allentown, PA.
June 22, 2008	"Improving palliative care for HIV/AIDS" Session chair, International Congress of Infectious Disease annual assembly, Kuala Lumpur, Malaysia.
October 24, 2008	"Improving hospice access" Plenary, National Hospice and Palliative Care Organization clinical conference, Dallas TX.
October 28, 2008	"Improving hospice access" Plenary, Colorado Hospice and Palliative Care Organization clinical conference, Breckenridge CO.

November 5, 2008	"Improving hospice access" Plenary, Ohio Hospice and Palliative Care Organization clinical conference, Columbus OH.
May 12, 2009	"Measuring palliative care quality." Plenary, National VA palliative care annual meeting. St. Louis, MO.
September 24, 2009	"Measuring hospice quality." NHPCO CTC, Denver, CO.
October 19, 2009	"Improving the quality of hospice care." Plenary, West Virginia Hospice Organization annual meeting. Morgantown WVa.
December 4, 2009	"Last Acts." Plenary, NHPCO Volunteers conference. Orlando, FL.
March 2, 2010	"Hospice decision-making." Medicine Grand Rounds, Brown University, Providence, RI.
July 15, 2010	"The optimal design of palliative care services" Plenary, Idaho state hospice/home care organization annual meeting. Boise ID.
March 9, 2011	"Opening the black box of hospice decisions." Palliative Care Grand Rounds. Massachusetts General Hospital, Boston MA.
March 11, 2011	"The illusion of control." Rosenthal lectureship, Harvard Medical School/Dana Farber Cancer Institute, Boston MA.
April 21, 2012	"Does hospice care work?" University of South Florida Medicine Grand Rounds, Tampa, FL
October 12, 2013	"Expanding the evidence base for palliative care" Plenary, Asia Pacific Hospice and Palliative Care Conference, Bangkok, Thailand.
November 5, 2013	"The future of palliative care" Christiana Value Institute annual conference, Newark, DE.
April 10, 2014	"Shocked: Adventures in the strange science of resuscitation" Coalition for Compassionate Care Annual conference, Santa Monica, California
April 4, 2014	"Palliative care and the Affordable Care Act" Association of Health Care Journalists, Denver, Colorado

June 8, 2014	Plenary, "Coalition of Hospices Organized to Investigate Comparative Effectiveness (CHOICE)," European Association of Palliative Care, Lleida, Spain.
September 13, 2014	"The moral hazards of resuscitation," Queens Hospital Grand Rounds, Honolulu HI.
October 12-14, 2014	"Cicely Sunders Institute Visiting Professorship series," Cicely Saunders Institute, Kings College London.
May 15, 2015	"Advances in CPR and moral conundrums," Oregon Health Sciences Center/Portland VA grand rounds, Portland OR.
June 10, 2015	"The future of home-based palliative care" Tufts University/Maine Medical Center Internal Medicine Grand Rounds, Portland ME.

Organizing Roles in Scientific Meetings:

October 2001	Moderator, National Institutes of Health consensus conference on palliative care research for the elderly, Bethesda, MD
September 2002	NIH working group on the ethics of end-of-life research, Co-PI, National Institutes of Health, Bethesda, MD
2003-2004	National Institutes of Health State of the Science conference on end-of-life care, Planning Committee
October 14, 2004	Designing clinical trials of therapeutic interventions for Malignant Bowel Obstruction, Planning Committee, National Cancer Institute, Pasadena, CA
December 6, 2004	State of the Science Conference on end-of-life research, Planning Committee, National Institutes of Health, Bethesda, MD
February 28, 2005	Defining a consensus about the ethics of artificial nutrition and hydration, Co-PI, University of Pennsylvania Center for Bioethics, Philadelphia, PA
March 18, 2005	Guidelines for global efforts to measure quality of end-of-life care, Co-PI, Rockefeller Foundation, Bellagio, Italy

December, 2005	Organizer, weeklong training course in palliative medicine for community health nurses in Botswana
June 2006	Organizer, Opportunities for international collaboration in measurement, Amsterdam
November, 2006	Organizer and co-chair, Intensive palliative medicine training, Salzburg, Austria
2006-2012	Organizer, Annual Community-wide symposium (The Future of Palliative Care) Philadelphia, PA
2007	Invited Chair, Scientific Subcommittee for the American Academy of Hospice and Palliative Medicine's annual meeting
February, 2009	Chair, Veterans Health Administration Advisory Panel meeting on end-of-life quality measurement, Philadelphia PA
February, 2010	Chair, Coalition of Hospices Organized to Investigate Comparative Effectiveness, Clearwater FL
April, 2012	Steering committee, African Palliative Care Association Research Network conference, Kampala Uganda

Bibliography:

Research publications, peer-reviewed:

1. Harris PS, Stalam T, Ache KA, et al. Can hospices predict which patients will die within six months? J Palliat Med. 2014;17(8):894-8. doi:10.1089/jpm.2013.0631
2. Kraynik SE, Casarett DJ, Corcoran AM. Implantable cardioverter defibrillator deactivation: a hospice quality improvement initiative. J Pain Symptom Manage. 2014;48(3):471-7. doi:10.1016/j.jpainsymman.2013.09.010
3. Powell RA, Harding R, Namisango E, et al. Palliative care research in Africa: consensus building for a prioritized agenda. J Pain Symptom Manage. 2014;47(2):315-24. doi:10.1016/j.jpainsymman.2013.03.022
4. Harrold J, Byhoff E, Harris P, et al. All hospice patients are not equal: development of a visit-based acuity index. J Palliat Med. 2014;17(2):135-40. doi:10.1089/jpm.2013.0109
5. Kelly L, Bender L, Harris P, Casarett D. The "comfortable dying" measure: how patient characteristics affect hospice pain management quality scores. J Palliat Med. 2014;17(6):721-4. doi:10.1089/jpm.2013.0571

DECLARATION OF JAMES B. ADAMS, Ph.D.

I, James B. Adams, Ph.D., declare pursuant to Rule 80(c), Ariz. R. Civ. P., under penalty of perjury that this Declaration is true and correct, as follows:

1. I submit this Declaration in support of the *Amicus Curiae* Brief filed on behalf of Gina Mecagni Berman, M.D., Jeffrey A. Singer, M.D., and other healthcare professionals, with the Arizona Supreme Court in support of reversing the Court of Appeals decision in *State v. Jones*, 245 Ariz. 46 (App. 2018).

2. I am the Director of the Autism/Asperger's Research Program at Arizona State University. I am also a co-leader of the Science Advisory Panel of the Autism Research Institute, one of the oldest autism research foundations in the world, and a chair of the Scientific Advisory Board of the Neurological Health Foundation, which is dedicated to preventing autism and other neurological disorders.

3. I have a B.S. in Physics and Computer Science from Duke University, and an M.S. and Ph.D. in Materials Science and Engineering from the University of Wisconsin at Madison, Wisconsin. I am a professor in the ASU School of Engineering and for many years I did research on computational quantum chemistry.

4. Since about 2000, I have conducted a number of studies on Autism Spectrum Disorder (Autism), and published more than 40 papers on Autism in peer-reviewed scientific journals. Autism is a developmental disorder that primarily involves deficits in communication and social skills and restricted/repetitive behaviors. People with Autism often have many other co-morbid conditions, including anxiety, depression, irritability, hyperactivity, intellectual disability, sensory sensitivity, and gastrointestinal disorders.

5. Autism affects about one in 59 children.

6. There are no FDA-approved medications for treating the core symptoms of Autism. Two FDA-approved medications, Risperdal and Abilify, only treat irritability, a common co-occurring symptom of Autism.

7. Starting in 2017, I and my colleagues began conducting a national survey (National Survey on Treatment Effectiveness for Autism) on the effectiveness of medications, nutritional supplements, diets, therapies and educational programs for treating people with Autism. This survey, taken by more than 3,000 respondents to date, ranked medical marijuana highly as an effective treatment to alleviate a number of the symptoms of Autism.[1]

[1] Adams JB, Anderson A. Frye RE, Rating of the Effectiveness of 26 Psychiatric and Seizure Medications for ASD: Results of a National Survey, accepted for publication in Journal of Child and Adolescent Psychopharmacology.

8. Research on marijuana has been greatly restricted because of the Federal Government's classification of cannabis as a Schedule I controlled substance. Given that a majority of states now allow medical marijuana, there is an urgent need to ramp up research, and further document and quantify its medicinal qualities.

9. Because the National Survey did not compare the effectiveness of medical marijuana, CBD alone and THC/CBD combinations, we created a new survey on the treatment effectiveness of those three products, called the Marijuana, THC/CBD, and CBD Study (MTCC). To date, we have received more than 100 responses.

10. As reported, the THC/CBD combination was given in oils (38%), gummies (17%), edibles (13%), tinctures (13%), vapes (8%) and other methods (8%). Straight CBD (with no THC) was administered by oils (53%), tinctures (25%), gummies (14%) and other methods (6%).

11. In my opinion, using oils or other extracts is better than smoking because the dosages can be more standardized and because of the adverse health effects of smoking. In addition, sublingual forms (drops under the tongue) have higher absorption than gummies or other edibles.

12. For each product, the MTCC asks about the overall benefit of the medication (with 0 being no benefit and 4 being great benefit), the primary

symptoms benefitted, any adverse effects (with 1 being mild and 3 being severe), the specific adverse effects and the form of product being used (e.g., extract, oil, tincture, edibles, gummies, etc.).

13. The survey study found that all three products had overall benefits between "moderate" and "good." Respondents reported the greatest improvement in anxiety (58-79% of participants), irritability (49-65%), aggression/agitation (43-58%), sleep (26-58%), cognition (26-46%), and attention (26-42%). The reported improvements were similar for the three different products. The responses also reported some improvements in core Autism symptoms, including social interaction (26-42%), language (26-38%), and stimming/perseveration/desire for sameness (16-27%). An Overall Benefit Scale Table is attached, showing the scores for each product.

14. The overall Adverse Effect scores for all three products were generally low, ranging from 0.2 (CBD) to 0.7 (marijuana), so averaging between "no adverse effects" and "mild adverse effects." Decreased cognition, dry mouth, and fatigue/drowsiness were the most common symptoms, and were more common for marijuana (16-26% of participants) than for the other two treatment combinations (1-8% of participants). An Overall Adverse Effect Table is also attached.

15. Overall, all three cannabis products had higher overall benefit scores (2.7-2.8), than the average ratings for the 26 most commonly used psychiatric and seizure medications (1.0 to 2.1). The overall benefit scores for Risperdal and Abilify (used for treating irritability in Autism) are 1.6 and 1.6.

16. The three products had low adverse effect scores (0.7 for marijuana) or very low adverse effect scores (0.2-0.3 for CBD and THC/CBD). With Risperdal and Abilify, the adverse effect scores were higher, at 1.4 and 0.9 respectively.

17. Marijuana, THC/CBD and CBD products had higher overall benefit scores than traditional psychiatric and seizure medications, and comparable or lower adverse effect scores. Respondents reported a wide range of benefits for the three cannabis combinations, including both calming effects (improvements in anxiety, irritability, aggression/agitation, sleep and stimming/perseveration/desire for sameness) and cognitive benefits (improvements in cognition, attention, social interaction, and language).

18. This survey suggests that marijuana, THC/CBD, and CBD products may have a wide range of benefits, with minimal adverse effects for THC/CBD and CBD, and mild adverse effects for marijuana. More research is needed to confirm these preliminary survey results and to evaluate any placebo effect.

19. Last month, a study was published from Israel of treatment with Autism patients using CBD/THC oil, mainly drops under the patients' tongues. The study found that more than 80 percent of the patients reported significant or moderate improvement, with behavioral outbreaks improved in 61%, communication problems in 47%, anxiety in 39%, stress in 33% and disruptive behavior in 33%. The researchers concluded that cannabis in Autism patients "appears to be well tolerated, safe and effective" to relieve symptoms associated with Autism. See Study published January 17, 2019, attached.

20. Based on the initial results of our survey and the above study, I support additional research and making cannabis extracts (such as CBD and THC/CBD) available to benefit Autism patients.

EXECUTED this 12 day of February, 2019.

James B Adams

James B. Adams, Ph.D.

Overall Benefit Score Table

(no benefit=0, slight benefit=1, moderate benefit=2, good benefit=3, or great benefit=4) and percent of participants reporting improvement in a particular symptom. The number of respondents for each treatment is also listed.

Marijuana (n=19)		**CBD/THC Combination (n=26)**		**CBD Only (n=76)**	
Benefit Score	**2.68**	**Benefit Score**	**2.85**	**Benefit Score**	**2.75**
Anxiety	79%	Irritability	65%	Anxiety	71%
Aggression/Agitation	58%	Aggression/Agitation	58%	Irritability	49%
Depression	58%	Anxiety	58%	Aggression/Agitation	43%
Irritability	58%	Sleep (falling asleep)	58%	Hyperactivity	39%
Sleep (falling asleep)	53%	Sleep (staying asleep)	50%	Cognition (ability to think)	32%
Sleep (staying asleep)	53%	Cognition (ability to think)	46%	Sensory Sensitivity	32%
Health (fewer illnesses and/or less severe illnesses)	37%	Attention	42%	Sleep (falling asleep)	30%
Social Interaction and Understanding	37%	Social Interaction and Understanding	42%	Attention	26%
Attention	32%	Health (fewer illnesses and/or less severe illnesses)	38%	Language/ Communication	26%
Language/ Communication	32%	Hyperactivity	38%	OCD	26%
OCD	32%	Language/ Communication	38%	Sleep (staying asleep)	26%
Sensory Sensitivity	32%	Depression	35%	Social Interaction and Understanding	26%
Cognition (ability to think)	26%	Sensory Sensitivity	31%	Stimming/Perseveration/ Desire for Sameness	26%
Stimming/Perseveration /Desire for Sameness	26%	Stimming/Perseveration/ Desire for Sameness	27%	Depression	16%
Hyperactivity	21%	Self-Injury	23%	Health (fewer illnesses and/or less severe illnesses)	16%
Reflux/Vomiting	21%	OCD	19%	Tics/Abnormal movements	16%
Self-Injury	21%	Reflux/Vomiting	19%	Self-Injury	14%
Tics/Abnormal movements	21%	General benefit, no one particular symptom	15%	General benefit, no one particular symptom	13%
Constipation	16%	Diarrhea	15%	Constipation	12%

General benefit, no one particular symptom	11%	Seizures	15%	Seizures	8%
Lethargy (easily tired)	11%	Tics/Abnormal movements	15%	Reflux/Vomiting	7%
Seizures	11%	Constipation	12%	Diarrhea	4%
Diarrhea	5%	Lethargy (easily tired)	12%	Eczema/Skin problem	4%
Eczema/Skin problem	5%	Eczema/Skin problem	4%	Lethargy (easily tired)	1%

Overall Adverse Effect Score Table

(no adverse effects=0, mild adverse effects=1, moderate adverse effects=2, or severe adverse effects=3) and percent of participants reporting a particular adverse effect. The number of respondents for each treatment is also listed.

Marijuana (n=19)		**CBD/THC Combination (n=26)**		**CBD Only (n=76)**	
Adverse Score	**0.68**	**Adverse Score**	**0.32**	**Adverse Score**	**0.21**
Decreased cognition (difficulty thinking/remembering)	26%	Dizziness/Unsteadiness	8%	Behavior problems	5%
Dry mouth	26%	Dry mouth	8%	Aggression/Agitation	4%
Anxiety	16%	Fatigue/Drowsiness	8%	Decreased cognition (difficulty thinking/remembering)	4%
Fatigue/Drowsiness	16%	Anxiety	4%	Fatigue/Drowsiness	4%
Weight loss	11%	Decreased cognition (difficulty thinking/remembering)	4%	Sleep Problems	3%
General worsening, no one specific symptom	5%	Nausea	4%	General worsening, no one specific symptom	1%
Aggression/Agitation	5%	General worsening, no one specific symptom	0%	Bedwetting/Bladder Control	1%
Behavior problems	5%	Aggression/Agitation	0%	Depression	1%
Dizziness/Unsteadiness	5%	Bedwetting/Bladder Control	0%	Dizziness/Unsteadiness	1%
Nausea	5%	Behavior problems	0%	Dry mouth	1%
Sleep Problems	5%	Depression	0%	Gastrointestinal problems	1%
Bedwetting/Bladder	0%	Gastrointestinal	0%	Irritability	1%

Control		problems			
Depression	0%	Headache/Migraine	0%	Nausea	1%
Gastrointestinal problems	0%	Stimming/Perseveration/Desire for Sameness	0%	Anxiety	0%
Headache/Migraine	0%	Irritability	0%	Headache/Migraine	0%
Stimming/Perseveration/Desire for Sameness	0%	Liver/Kidney problem	0%	Stimming/Perseveration/Desire for Sameness	0%
Irritability	0%	Loss of appetite	0%	Liver/Kidney problem	0%
Liver/Kidney problem	0%	Rash	0%	Loss of appetite	0%
Loss of appetite	0%	Seizures	0%	Rash	0%
Rash	0%	Self-injury	0%	Seizures	0%
Seizures	0%	Sleep Problems	0%	Self-injury	0%
Self-injury	0%	Tics/Abnormal movements	0%	Tics/Abnormal movements	0%
Tics/Abnormal movements	0%	Weight gain	0%	Weight gain	0%
Weight gain	0%	Weight loss	0%	Weight loss	0%

SCIENTIFIC REPORTS

OPEN

Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy

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There has been a dramatic increase in the number of children diagnosed with autism spectrum disorders (ASD) worldwide. Recently anecdotal evidence of possible therapeutic effects of cannabis products has emerged. The aim of this study is to characterize the epidemiology of ASD patients receiving medical cannabis treatment and to describe its safety and efficacy. We analysed the data prospectively collected as part of the treatment program of 188 ASD patients treated with medical cannabis between 2015 and 2017. The treatment in majority of the patients was based on cannabis oil containing 30% CBD and 1.5% THC. Symptoms inventory, patient global assessment and side effects at 6 months were primary outcomes of interest and were assessed by structured questionnaires. After six months of treatment 82.4% of patients (155) were in active treatment and 60.0% (93) have been assessed; 28 patients (30.1%) reported a significant improvement, 50 (53.7%) moderate, 6 (6.4%) slight and 8 (8.6%) had no change in their condition. Twenty-three patients (25.2%) experienced at least one side effect; the most common was restlessness (6.6%). Cannabis in ASD patients appears to be well tolerated, safe and effective option to relieve symptoms associated with ASD.

There has been a 3-fold increase during the last 3 decades in the number of children diagnosed with autism spectrum disorders worldwide[1–5]. No specific treatments are currently available and interventions are focussing on lessening of the disruptive behaviors, training and teaching self-help skills for a greater independence[6].

Recently, CBD enriched cannabis has been shown to be beneficial for children with autism[7]. In this retrospective study on 60 children, behavioural outbreaks were improved in 61% of patients, communication problems in 47%, anxiety in 39%, stress in 33% and disruptive behaviour in 33% of the patients. The rationale for this treatment is based on the previous observations and theory that cannabidiol effects might include alleviation of psychosis, anxiety, facilitation of REM sleep and suppressing seizure activity[8]. A prospective single-case-study of Dronabinol (a THC-based drug) showed significant improvements in hyperactivity, lethargy, irritability, stereotypy and inappropriate speech at 6 month follow-up[9]. Furthermore, Dronabinol treatment of 10 adolescent patients with intellectual disability resulted in 8 patients showing improvement in the management of treatment-resistant self-injurious behaviour[10].

In 2007, The Israel Ministry of Health began providing approvals for medical cannabis, mainly for symptoms palliation. In 2014, The Ministry of Health began providing licenses for the treatment of children with epilepsy. After seeing the results of cannabis treatment on symptoms like anxiety, aggression, panic, tantrums and self-injurious behaviour, in children with epilepsy, parents of severely autistic children turned to medical cannabis for relief.

Although many with autism are being treated today with medical cannabis, there is a significant lack of knowledge regarding the safety profile and the specific symptoms that are most likely to improve under cannabis treatment. Therefore, the aim of this study was to characterize the patient population receiving medical cannabis treatment for autism and to evaluate the safety and efficacy of this therapy.

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APP-066

	Total (188)
Mean age (SD)	12.9 (7.0)
Gender (male), No. (%)	154 (81.9)
Mean body mass index (SD)	29.0 (5.3)
Previous experience with cannabis (Yes), No. (%)	19 (10.1)
Comorbidities:	
Epilepsy, No. (%)	27 (14.4)
Attention Deficit Hyperactivity Disorder, No. (%)	7 (3.7)
Tourette syndrome, No. (%)	4 (2.1)
Celiac Disease, No. (%)	3 (1.6)
Anxiety Disorder, No. (%)	3 (1.6)

Table 1. Demographic and clinical characteristics of patients at intake.

		Change at six months		
	Intake prevalence Total (188)	Symptom disappeared	Improvement	No change or deterioration
Restlessness, No. (%)	170 (90.4)	1 (1.2)	71 (89.8)	7 (8.8)
Rage attacks, No. (%)	150 (79.8)	1 (1.3)	65 (89.0)	7 (9.5)
Agitation, No. (%)	148 (78.7)	1 (1.4)	57 (83.8)	10 (14.7)
Sleep problems, No. (%)	113 (60.1)	9 (19.5)	27 (58.6)	10 (21.7)
Speech Impairment, No. (%)	113 (60.1)	—	15 (30)	35 (70)
Cognitive impairment, No. (%)	91 (48.4)	—	15 (27.2)	40 (72.7)
Anxiety, No. (%)	69 (36.7)	—	24 (88.8)	3 (11.1)
Incontinence, No. (%)	51 (27.1)	2 (9.0)	7 (31.8)	13 (59.0)
Seizures, No. (%)	23 (12.2)	2 (15.3)	11 (84.6)	—
Limited Mobility, No. (%)	17 (9.0)	2 (18.1)	—	9 (81.8)
Constipation, No. (%)	15 (8.0)	1 (12.5)	6 (62.5)	2 (25)
Tics, No. (%)	15 (8.0)	1 (20.0)	4 (80.0)	—
Digestion Problems, No. (%)	14 (7.4)	1 (12.5)	5 (62.5)	2 (25.0)
Increased Appetite, No. (%)	14 (7.4)	1 (33.3)	1 (33.3)	1 (33.3)
Lack of Appetite, No. (%)	14 (7.4)	2 (40.0)	1 (20.0)	2 (40.0)
Depression, No. (%)	10 (5.3)	—	5 (100.0)	—

Table 2. Symptom prevalence and change. Symptom prevalence at intake in 188 patients assessed at intake and change at six months in patients responding to the six-month questionnaire.

Results

Patient population. During the study period, 188 ASD patients initiated the treatment. Diagnosis of ASD was established in accordance with the accepted practice in Israel; six board certified paediatric psychiatrists and neurologists were responsible for treatment of 125 patients (80.6%), the remaining 30 children were referred by 22 other physicians. Table 1 shows demographic characteristics of the patient population. The mean age was 12.9 ± 7.0 years, with 14 (7.4%) patients being younger than the age of 5, 70 patients (37.2%) between 6 to 10 years and 72 (38.2%) aged 11 to 18. Most of the patients were males (81.9%). Twenty-seven patients (14.4%) suffered from epilepsy and 7 patients (3.7%) from Attention Deficit Hyperactivity Disorder (ADHD).

At baseline parents of 188 patients reported on average of 6.3 ± 3.2 symptoms. Table 2 shows the prevalence of symptoms with most common being restlessness (90.4%), rage attacks (79.8%) and agitation 78.7%.

Cannabis products recommended to the patients were mainly oil applied under the tong (94.7%). Seven patients (3.7%) received a license to purchase oil and inflorescence and three patients (1.5%) received a license to purchase only inflorescence. Most patients consumed oil with 30% CBD and 1.5% THC, on average 79.5 ± 61.5 mg CBD and 4.0 ± 3.0 mg THC, three times a day (for a more detailed distribution of CBD/THC consumptions see Supplementary Fig. S1). Insomnia recorded in 46 patients (24.4%) was treated with an evening does of 3% THC oil with on average additional 5.0 ± 4.5 mg THC daily. All the products content was validated by HPLC (High Performance Liquid Chromatography) in each production cycle. The cannabis dose was not significantly associated with weight (r correlation coefficient $= -0.13$, $p = 0.30$), age (r correlation coefficient $= -0.10$, $p = 0.38$), or gender ($p = 0.38$).

Follow-up, one month. After one month, out of 188 patients, 8 (4.2%) stopped treatment, 1 (0.5%) switched to a different cannabis supplier, and 179 patients (94.6%) continued active treatment (Fig. 1). Of the latter group, 119 (66.4%) responded to the questionnaire with 58 patients (48.7%) reporting significant improvement, 37

APP-067

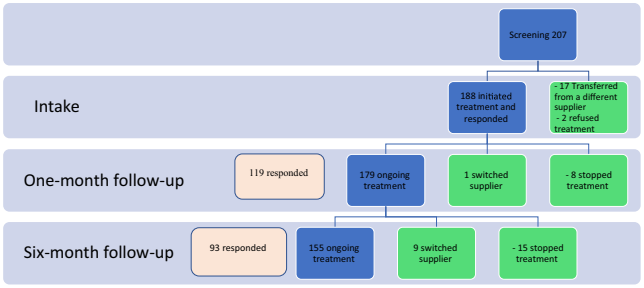

Figure 1. The study population in the three follow-up periods, at intake, after one month and after six months of medical cannabis treatment.

(31.1%) moderate improvement; 7 patients (5.9%) experienced side effects and 17 (14.3%) reported that the cannabis did not help them.

The reported side effects at one month were: sleepiness (1.6%), bad taste and smell of the oil (1.6%), restlessness (0.8%), reflux (0.8%) and lack of appetite (0.8%).

Follow-up, six months. After six months, of the 179 patients assessed in the one-month follow-up, 15 patients (8.3%) stopped treatment, 9 (4.9%) switched to a different cannabis supplier and 155 patients (86.6%) continued treatment (Fig. 1). Of the latter group, 93 (60.0%) responded to the questionnaire with 28 patients (30.1%) reporting a significant improvement, 50 patients (53.7%) moderate improvement, 6 patients (6.4%) slight improvement and 8 (8.6%) having no change in their condition. None of the variables entered to the multivariate analysis to predict treatment success was statistically significant.

To assess the potential response bias, we have compared baseline characteristics between 93 respondents and 62 non-respondents to the 6-month questionnaire. The former group was slightly older (13.7 ± 0.8 vs. 10.8 ± 0.5, $p = 0.004$).

Quality of Life. Quality of life, mood and ability to perform activities of daily living were assessed before the treatment and at six months. Good quality of life was reported by 31.3% of patients prior to treatment initiation while at 6 months good quality of life was reported by 66.8% ($p < 0.001$, Supplementary Fig. S2). Positive mood was reported by the parents on 42% before treatment and 63.5% after 6 months of treatment ($p < 0.001$). The ability to dress and shower independently was significantly improved from 26.4% reported no difficulty in these activities prior to the treatment to 42.9% at six months ($p < 0.001$). Similarly, good sleep and good concentration were reported by 3.3% and 0.0% (respectively) before the treatment and on 24.7% ($p < 0.001$) and 14.0% ($p < 0.001$) during an active treatment (Table 3).

The improved symptoms at 6 months included seizures, of the 13 patients on an active treatment at six months 11 patients (84.6%) reported disappearances of the symptoms and two patients reported improvement; restlessness and rage attacks were improved in 72 patients (91.0%) and 66 (90.3%) respectively (Table 2).

Medications Use. The most common concomitant chronic medications on the intake were antipsychotics (56.9%), antiepileptics (26.0%), hypnotics and sedatives (14.9%) and antidepressants (10.6%). Out of 93 patients responding to the follow-up questionnaire, 67 reported use of chronic medications at intake. Overall, six patients (8.9%) reported an increase in their drugs consumption, in 38 patients (56.7%) drugs consumption remained the same and 23 patients (34.3%) reported a decrease, mainly of the following families: antipsychotics, antiepileptics antidepressants and hypnotics and sedatives (Table 4). Antipsychotics, the most prevalent class of medications taken at intake (55 patients, 33.9%); at 6 months it was taken at the same dosage by 41 of them (75%), 3 patients (5.4%) decreased dosage and 11 patients (20%) stopped taking this medication (Table 4).

Side Effects. The most common side effects, reported at six months by 23 patients (25.2%, with at least one side effect) were: restlessness (6 patients, 6.6%), sleepiness (3, 3.2%), psychoactive effect (3, 3.2%), increased appetite (3, 3.2%), digestion problems (3, 3.2%), dry mouth (2, 2.2%) and lack of appetite (2, 2.2%).

Out of 23 patients who discontinued the treatment, 17 (73.9%) had responded to the follow-up questionnaire at six months. The reasons for the treatment discontinuation were: no therapeutic effect (70.6%, twelve patients) and side effects (29.4%, five patients). However, 41.2% (seven patients) of the patients who discontinued the treatment had reported on intentions to return to the treatment.

Discussion

Cannabis as a treatment for autism spectrum disorders patients appears to be well-tolerated, safe and seemingly effective option to relieve symptoms, mainly: seizures, tics, depression, restlessness and rage attacks. The compliance with the treatment regimen appears to be high with less than 15% stopping the treatment at six months follow-up. Overall, more than 80% of the parents reported at significant or moderate improvement in the child global assessment.

APP-068

	Sleep			Eating with Appetite			Concentration on daily tasks			Bowel Activity		
	Before	During	p value	Before	During	p value	Before	During	p value	Before	During	p value
Severe difficulty	44 (47.3)	2 (2.2)		2 (2.2)	1 (1.1)		75 (80.6)	21 (22.6)		3 (3.2)	2 (2.2)	
Moderate difficulty	18 (19.4)	27 (29.0)		6 (6.5)	13 (14.0)		11 (11.8)	41 (44.1)		13 (14.0)	17 (18.3)	
No difficulty	28 (30.1)	39 (41.9)	<0.001	59 (63.4)	47 (50.5)	0.751	2 (2.2)	11 (11.8)	<0.001	71 (76.3)	54 (58.1)	0.242
Good	2 (2.2)	15 (16.1)		10 (10.8)	16 (17.2)		0	10 (10.8)		5 (5.4)	13 (14.0)	
Very Good	1 (1.1)	8 (8.6)		16 (17.2)	14 (15.1)		0	3 (3.2)		1 (1.1)	4 (4.3)	

Table 3. Assessment of daily activities. Ability to perform activities of daily living was assessed prior to and six months after initiation of cannabis treatment. Numbers in parenthesis represent the % of patients.

	Intake	Change at six months follow-up				
Medication family	Total	Stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	New medication
Antipsychotics, n (%)	55	11 (20)	3 (5)	41 (75)	0	0
Antiepileptics, n (%)	46	6 (13)	0	35 (76)	2 (4.5)	3 (6.5)
Antidepressants, n (%)	10	3 (30)	0	4 (40)	1 (10)	2 (20)
Hypnotics and sedatives, n (%)	10	2 (20)	1 (10)	7 (70)	0	0
Anxiolytics, n (%)	7	2 (28)	0	5 (72)	0	0

Table 4. Concomitant medications. Concomitant medications use at the baseline and six months follow up in patients responding to the six-month questionnaire.

The exact mechanism of the cannabis effects in patients with ASD is not fully elucidated. Findings from ASD animal models indicate a possible dysregulation of the endocannabinoid (EC) system[11–16] signalling behaviours, a dysregulation that was suggested to be also present in ASD patients[17]. Mechanism of action for the effect of cannabis on ASD may possibly involve GABA and glutamate transmission regulation. ASD is characterized by an excitation and inhibition imbalance of GABAergic and glutamatergic signalling in different brain structures[18]. The EC system is involved in modulating imbalanced GABAergic[19] and glutamatergic transmission[20].

Other mechanism of action can be through oxytocin and vasopressin, neurotransmitters that act as important modulators of social behaviours[21]. Administration of oxytocin to patients with ASD has been shown to facilitate processing of social information, improve emotional recognition, strengthen social interactions, reduce repetitive behaviours[22] and increase eye gaze[23]. Cannabidiol was found to enhance oxytocin and vasopressin release during activities involving social interaction[16].

Two main active ingredients (THC and CBD) can have different psychoactive action mechanisms. THC was previously shown to improve symptoms characteristic to ASD patients in other treated populations. For example, patients reported lower frequency of anxiety, distress and depression[24], following THC administration, as well as improved mood and better quality of life in general[25]. In patients suffering from anxiety, THC led to improved anxiety levels compared to placebo[26] and in dementia patients, it led to reduction in nocturnal motor activity,violence[27,28] behavioural and severity of behavioural disorders[29]. Moreover, cannabis was shown to enhances interpersonal communication[30] and decrease hostile feelings within small social groups[31].

In our study we have shown that a CBD enriched treatment of ASD patients can potentially lead to an improvement of behavioural symptoms. These findings are consistent with the findings of two double-blind, placebo-controlled crossover studies demonstrating the anxiolytics properties of CBD in patients with anxiety disorder[32,33]. In one, CBD had a significant effect on increased brain activity in the right posterior cingulate cortex, which is thought to be involved in the processing of emotional information[32], and in the other, simulated public speaking test was evaluated in 24 patients with social anxiety disorder. The CBD treated group had significantly lower anxiety scores than the placebo group during simulated speech, indicating reduction in anxiety, cognitive impairment, and discomfort factors[33].

The cannabis treatment appears to be safe and side effects reported by the patients and parents were moderate and relatively easy to cope with. The most prevalent side effects reported at six months was restlessness, appearing in less than 6.6% of patients. Moreover, the compliance with the treatment was high and only less than 5% have stopped the treatment due to the side effects. We believe that the careful titration schedule especially in the ASD paediatric population is important for maintaining a low side effects rate and increase of the success rate. Furthermore, we believe that a professional instruction and detailed parents' training sessions are highly important for the increasing of effect to adverse events ratio.

The present findings should be interpreted with caution for several reasons. Firstly, this is an observational study with no control group and therefore no causality between cannabis therapy and improvement in patients' wellbeing can be established. Children of parents seeking cannabis therapy might not constitute a representative sample of the patient with the specific disease (self-selection bias). We have not formally confirmed the ASD diagnosis, however all the children included in the study were previously diagnosed with ASD by certified neurologist or psychiatrist, as required by Ministry of Health prior to the initiation of the cannabis-based treatment.

This study was based on a subjective self-report of the patient's parent's observation and not by the patients themselves. These reports, with subjective variables such as quality of life, mood, and general effects, may be

biased by the parent's opinion of the treatment. Moreover, even though the effect was assessed at six months, the possibility of the inflated expectations of the novel treatment "miracle" effect cannot be excluded. The questionnaire response rate at 6 months was 60%, thus the estimates of the efficacy and safety of the treatment can be biased. However, high compliance (above 80%) with the treatment provides a good evidence of the patients and parents satisfaction with the treatment.

While this study suggest that cannabis treatment is safe and can improve ASD symptoms and improve ASD patient's quality of life, we believe that double blind placebo-controlled trials are crucial for a better understanding of the cannabis effect on ASD patients.

Methods

Study Population. There are currently over 35,000 patients approved for medical cannabis use in Israel and 15,000 (~42.8%) of them receive treatment at Tikun-Olam Ltd. (TO), the largest national provider of medical cannabis. This study included all patients receiving cannabis license at TO with the diagnosis of autism in the years 2015–2017.

During the routine treatment process at the cannabis clinic, all willing patients underwent an extensive initial evaluation and their health status was periodically assessed by the treating team. At the intake session, the nurse assessed a complete medical history. The patient's parents were interviewed by the nurse and filled a medical questionnaire, which included the following domains: demographics, comorbidities, habits, concomitant medications, measurements of quality of life and a detailed symptoms check-list. Following intake, the nurse advised on the treatment plan.

Treatment Regiment. The treatment in majority of the patients was based on cannabis oil (an extract of a high CBD strain dissolve in olive oil in a ratio THC:CBD of 1:20, 30% CBD and 1.5% THC), and underwent an individualized titration. The starting dose was one sublingual drop three times a day with one oil drop (0.05 ml) containing 15 mg CBD and 0.75 mg Δ9-THC. Oil contained 45% olive oil, 30% CBD, 1.5% THC, <1.5% CBC, 0.5% CBG, <0.5% CBDV and <0.1% CBN. The remaining ingredients were terpenes, flavonoids, waxes and chlorophyll

In patients who reported high sensitivity to previously used medications, the treatment started with oil containing 1:20 15% CBD and 0.75% THC. In patients with severe sleep disturbances, following the initial treatment phase, 3% THC oil was added to the evening dose. In cases with a significant aggressive or violent behaviour, 3% THC oil was added.

The dose was increased gradually for each patient depending on the effect of the cannabis oil on the targeted symptoms according to the treatment plan and the tolerability of each patient. Finding of the optimal dose could take up to two months and dosage range is wide: from one drop three times a day to up to 20 drops three times a day of the same product.

After one month, the treating team contacted the parents to follow-up on the treatment progression. At six months patients underwent an additional assessment of the symptom intensity, side effects and quality of life.

Study outcomes. For safety analysis we have assessed the frequency of the following side effects at one and at six months: physiological effects – headaches, dizziness, nausea, vomiting, stomach ache, heart palpitation, drop in blood pressure, drop in sugar, sleepiness, weakness, chills, itching, red/irritated eyes, dry mouth, cough, increased appetite, blurred vision, slurred speech; cognitive side effects – restlessness, fear, psycho-active effect, hallucinations, confusion and disorientation, decreased concentration, decreased memory or other. The patient parents were asked to provide details of the incidence, duration and severity of the reported side effect.

For the efficacy analysis we used the global assessment approach where the patient parents were asked: "How would you rate the general effect of cannabis on your child condition?" the options were: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration and significant deterioration. Autism symptoms severity assessment included the following items: restlessness, rage attacks, agitation, speech impairment, cognitive impairment, anxiety, incontinence, depression and more. Quality of life was assessed on a Likert scale ranging from very poor to poor, neither poor nor good and good to very good[34].

The study was approved by Soroka University Medical Centre Ethics Committee and due to the nature of the data analysis based on the routinely obtained clinical data, it was determined that no informed consent is required. All methods were performed in accordance with the relevant institutional and international research guidelines and regulations.

Statistical analysis. Continuous variables with normal distribution were presented as means with standard deviation. Ordinary variables or continuous variables with non-normal distribution were presented as medians with an interquartile range (IQR). Categorical variables were presented as counts and percent of the total.

We used t-test and paired t-test for the analysis of the continuous variables with normal distribution. The non-parametric Mann-Whitney U test and paired Wilcoxon test was used whenever parametric assumptions could not be satisfied.

We utilized logistic regression for the multivariate analysis of factors associated with treatment success. We have included the following variables into the models based on clinical considerations: age, gender, number of chronic medications, number of total symptoms, and the three most prevalent symptoms: restlessness, rage attacks and agitation (as a dichotomous variable- yes/no), as reflected in the intake form.

P value < 0.05 was considered to be statistically significant. All analyses were performed at the Clinical Research Centre, Soroka University Medical Centre, Beer-Sheva, Israel using IBM SPSS version 22 (SPSS, Chicago, IL).

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Declarations. The study was approved by Soroka University Medical Center Ethics Committee (study number: SCRC-0415-15) and the need for informed consent was waived due to the retrospective nature of the data analysis.

Availability of Data

The data set generated and/or analysed during the current study are not publicly available due to medical confidentiality but are available from the first author on reasonable request summarized form pending the approval of the IRB.

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Author Contributions

L.B.L.S., V.N. and R.M. planned the study; N.S. collected the data, L.B.L.S. and V.N. analysed the data, L.B.L.S. wrote the manuscript, V.N. and G.M. reviewed and approved the manuscript.

Additional Information

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Competing Interests: L.B.L.S. and N.S. are employees of Tikun-Olam Ltd. V.N. is a paid member of the Tikun Olam Ltd. scientific advisory board. R.M. and G.M. have no conflicts of interest pertaining to the current manuscript.

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