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A Guide to the National Academy of Science Report on Cannabis: An Exclusive Discussion with Panel Members

Moderator: Daniele Piomelli,[1,*]
Participants: Ziva Cooper,[2,3] Donald Abrams,[4] Igor Grant,[5] and Sachin Patel[6]

Dr. Daniele Piomelli: Dr. Cooper, as a member of the committee summoned by the National Academies of Sciences, Engineering, and Medicine (NASEM) to draft the report, can you briefly describe its context and broad objectives?

Dr. Ziva Cooper: The NASEM report[1] was developed in response to the significant changes in policy regarding the legalization of medical and recreational cannabis. These changes are happening in the absence of a dialogue regarding the scientific evidence pertaining to both the potential therapeutic effects of cannabis and the health outcomes, both positive and negative, of use. The Health and Medicine Division of the NASEM was asked to convene a committee of experts from a range of fields to conduct a comprehensive review of the literature and develop a consensus report delineating evidence for both the therapeutic effects and health risks associated with cannabis and cannabinoid use. The committee was also charged with developing a research agenda to address the most critical areas to help guide future high-quality research on the effects of cannabis and cannabinoids. Research and recommendations associated with policy was beyond the scope of the report, yet the impact of policy on research was raised in a "Barriers to Research" section that highlighted the difficulty of doing both preclinical and clinical studies with cannabis and cannabinoids due to their Schedule I classification.

Dr. Piomelli: What challenges did the NASEM committee encounter in its work?

Dr. Donald Abrams: The committee held its first meeting in June, and we were asked to produce a comprehensive report in 4 to5 months. The task of reviewing the bulk of the cannabis literature published since 1999 was not trivial. There were thousands of abstracts to sift through to select the appropriate meta-analyses and systematic reviews, and more to find primary research on the topics chosen that were not available as reviews. For me, the learning curve was steep because I have read a lot of medical literature in my day, but never really graded the articles as meticulously as the committee did to make sure we were reporting on the best research available. Writing the draft of the findings was perhaps the easiest. The concept of writing conclusions with graded evidence was also new for me. Because the report was a consensus document, we worked collectively on crafting the language of our conclusions and recommendations so that the final product would be acceptable to all. That was less of a challenge than I expected it to be. I would have to say that the biggest challenge we faced was doing the large amount of work we had to do in such a short time, while also trying to do our day jobs!

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Dr. Cooper: One challenge was the volume of published work in this area and the paucity of high-quality data available to effectively address the topics of the study. Since the last Institute of Medicine (IOM) report on cannabis published in 1999,[2] 24,000 articles have been published in the field. The committee considered over 10,000 of these abstracts for inclusion in the report. Because of the large volume of literature that was reviewed, areas of research that were not directly related to the statement of task could not be included. These areas included preclinical studies addressing biological plausibility for cannabis and cannabinoid effects and controlled human laboratory "proof-of-concept" studies relevant to both cannabis and cannabinoid's therapeutic effects and health outcomes. Despite the large volume of reviewed literature, the existing data were only strong enough to support substantial conclusions for a handful of the over 100 associations outlined in the report.

Dr. Piomelli: Dr. Grant, you were not part of the NASEM committee, do you think that the report was worth the time and effort put into drafting it?

Dr. Igor Grant: Yes, I believe the report is very timely given the emerging science on cannabis as well as the shifts in state policies regarding both medicinal and recreational use. The report provides an authoritative updating of this complex area.

Dr. Piomelli: The NASEM report contains several important conclusions and recommendations. Dr. Abrams, what conclusions did the committee reach regarding the therapeutic uses of cannabis?

Dr. Abrams: The committee graded the strength of the evidence of the effectiveness of cannabis and cannabinoids in several therapeutic areas. We also explained in Chapter 15[1] the barriers to conducting research with cannabis, which are particularly relevant to a discussion of therapeutic effects. In truth, most of the literature we reviewed was not actually assessing the cannabis plant, but pharmaceutically derived compounds, especially tetrahydrocannabinol alone as dronabinol or nabilone. There are an increasing number of trials investigating nabiximols, which is a whole plant extract. Some studies looked at cannabidiol alone, but none of the studies on the pharmaceutical cannabidiol preparation, Epidiolex, was yet published in the literature we reviewed. This agent has shown promise in epilepsy patients. Studies of the whole plant, usually smoked or vaporized, were few. So, when you ask what conclusions we drew regarding the therapeutic uses of cannabis, it would probably be more correct to ask about the therapeutic uses of cannabinoids; and then recall the strength of the evidence that qualified our confidence in the validity of the conclusion.

I can say that the committee concluded there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults, nausea and vomiting related to cancer chemotherapy, and symptoms of spasticity associated with multiple sclerosis. Again, this means that we found strong evidence in good-quality systematic reviews or meta-analyses to support these conclusions. Interestingly, these were quite similar to the results reported in the IOM 1999 report.[2] We found moderate evidence that cannabinoids may be beneficial in sleep disorders associated with several chronic illnesses. Evidence supporting the use of cannabis or cannabinoids for appetite stimulation, improving anxiety, and symptoms of Tourette syndrome was felt to be limited by our review of existing literature. For all the other conditions or symptoms included in the analysis, we found only limited or no evidence to support or refute that cannabis or cannabinoids have benefit. Included in our list were conditions or diseases for which states allow patients to access cannabis. As mentioned, we also found no evidence of benefit in epilepsy, although recently completed and ongoing clinical trials are supporting the benefit of pharmaceutical-grade cannabidiol for refractory seizures.

One of my mantras on the committee was that the absence of evidence of effectiveness does not equate to evidence of the absence of effectiveness! We were quite selective and stringent in reviewing only the highest quality clinical trials and restricted our grading of evidence by using the careful criteria that the committee agreed upon. This coupled with the significant barriers that exist to conducting clinical trials of the potential therapeutic benefit of the plant material leave us with a handful of strong conclusions on therapeutic benefits of cannabis. Most of the conclusions are based on studies of approved pharmaceutical products or those under current clinical investigation. Hopefully, the future will allow for larger, longer, high-quality studies of plant-based medicine preparations to be conducted and provide us with much needed information.

As an oncologist, I am faced daily with patients asking me if they can forego conventional cancer therapies and treat their malignancy with cannabis. There is absolutely no data in the published literature to support

the use of cannabis or any cannabinoid as a treatment for cancer. The committee decided to veer from the mandate to only include clinical trials in the report to be able to say something about cannabinoids and cancer. So, a review of 34 preclinical studies of cannabinoids in brain tumors was included. Although there is an increasing and impressive body of evidence that cannabinoids may have some anticancer activity in cell culture and animal studies, the only clinical trial in cancer patients reported to date involved infusion of tetrahydrocannabinol by a catheter into brain tumor recurrences in nine patients. Hence, we concluded there was insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers.

Dr. Piomelli: Dr. Grant, what do you think of NASEM report's conclusions?

Dr. Grant: There are some specific areas that might have benefitted from more precision in the summary conclusions. For example, the substantial statistical association between cannabis use and schizophrenia might suggest a causal link association. In fact, there has been no increase in diagnosis of schizophrenia in western societies during the five decades since recreational cannabis use became prevalent. A more cautious interpretation of the cannabis–schizophrenia association may be that different elements of psychopathology travel together, perhaps reflecting influence of some common vulnerability factor or factors, with problematic substance use being one of those indicators.

Regarding cannabis and persisting brain injury, my view as someone who has looked at neurocognitive consequences of several substances of abuse, leads me to the conclusion that the evidence for lasting effect of cannabis on the brain is very inconclusive. The meta-analyses on neurocognitive performance in adult cannabis users that adjusted for recency of use basically found no associations, and similarly, the brain imaging reports have been contradictory. Even data on human neurodevelopmental consequences are quite fragmented. So, in that sense the report might have hewed closer to data by interpreting the strength of the associations more cautiously or explaining the pitfalls better.

Dr. Piomelli: The existence of a possible link between cannabis and schizophrenia, anxiety, or depression has been repeatedly suggested. Dr. Patel, what conclusions did the committee reach regarding the impact of cannabis on these three mental disorders?

Dr. Sachin Patel: Regarding schizophrenia, the report concluded that there was substantial evidence to support an association between cannabis use and development of psychotic disorders. This was one of the strongest conclusions in the report. The strength of this conclusion arose from the large number of studies examining this issue as well as evidence for a dose–response relationship in which more frequent cannabis use was associated with higher risk of developing a psychotic disorder. All of the studies reviewed found some degree of increased risk with no significant findings to the contrary. It is still not clear whether cannabis use causes schizophrenia and, as pointed out by Dr. Grant, alternate hypotheses could explain this strong and consistent association. Regarding anxiety disorders, the report concluded that there was moderate evidence for an association between cannabis use and an increased incidence of social anxiety disorder. There was limited evidence that daily cannabis use increases symptoms of anxiety. Also, the report concluded with moderate evidence that cannabis use is associated with a small increase in the risk of developing depressive disorders, but no evidence to support or refute an association between cannabis use and symptoms of depression. It is not clear whether cannabis use is causally linked to the development of social anxiety or depression.

Dr. Piomelli: What about cancer? Dr. Abrams, is there any evidence that cannabis use may lead to lung cancer or other forms of cancer?

Dr. Abrams: Several studies have investigated the possible association with cannabis and lung and upper aerodigestive malignancies over the years. It makes sense that an inhaled plant material that many equate with tobacco should raise a concern for the possibility of an increased risk of tobacco-related malignancies. We reviewed two publications each comprised of analysis of six studies that both failed to show a statistical association between the use of cannabis and the development of lung cancer. One could question how this could be so when there is such a clear link between tobacco smoking and pulmonary neoplasia. First, no one smokes 20 to 40 cannabis cigarettes a day. Second, cannabis has anti-inflammatory, antioxidant, and some believe antitumor qualities which tobacco does not. Many of the older studies suggesting a link between

cannabis smoking and lung cancers did not control for tobacco use. We also reviewed another analysis of nine case–control studies of head and neck cancers that also was suggestive of no increased association of cannabis use with those malignancies either. The only possible link that we noted was limited evidence of a statistical association between current, chronic, or frequent cannabis use and nonseminomatous germ cell testicular tumors. As an oncologist, I am not sure I see biologic plausibility in that association other than the fact that cannabis use and testicular cancer are two things common to young men.

Dr. Piomelli: Dr. Cooper, did the committee reach any conclusion on the impact of cannabis use on automobile driving?

Dr. Cooper: The committee concluded that there is substantial evidence for an association between cannabis use and increased risk of motor vehicle accidents. This conclusion was based primarily on a 2016 meta-analysis of 21 case–control or culpability studies across 12 countries and included an impressive sample of nearly 240,000 participants. The findings demonstrated that cannabis use, as assessed by self-report and the presence of tetrahydrocannabinol metabolites in blood, saliva, or urine, was associated with a 20% to 30% higher odds of a motor vehicle crash. In addition, the magnitude of the association was in the low to moderate range. An important aspect of the study was the magnitude of effect was weakened when accounting for alcohol intoxication. A limitation of these findings is the difficulty in determining the proximity of cannabis use relative to motor vehicle crashes based on the presence of tetrahydrocannabinol and its metabolites in biological samples, like urine or plasma, since they can be detected long after use in heavy cannabis users. However, studies by the Huestis laboratory investigating the effects of acute cannabis exposure on performance in a driving simulator agree with these findings.[3] These controlled studies demonstrate that smoking cannabis significantly impairs psychomotor skills needed for safe driving.

Dr. Piomelli: Finally, a question for the entire panel. What are the research priorities identified by the NASEM report? Should we add anything to that list?

Dr. Patel: From a mental health perspective, whether cannabis use is a potential treatment for post-traumatic stress disorder (PTSD) would be an important question to answer given the potential public health relevance of this issue, and the relatively widespread use of cannabis in patients with PTSD.

Dr. Cooper: Four recommendations were put forth to support and improve a cannabis research agenda. The first recommendation was to address research gaps. These gaps included prioritized research areas to assess the short- and long-term effects of cannabis and cannabinoids specifically related to clinical and observation research, health policy and economic research, and public health and public safety research. The second recommendation included suggestions to improve research quality by developing a set of research standards and benchmarks that can yield high-quality cannabis research. The third recommendation was to improve surveillance capacities to ensure that sufficient population-based data are available to query the health effects of cannabis. Finally, the fourth recommendation addressed the barriers that impede research on cannabis and cannabinoids. This recommendation highlighted significant obstacles for both preclinical and clinical researchers who are interested in studying cannabis and cannabinoids, but are hindered due to regulatory barriers associated with the Schedule I classification of these drugs and the lack of funding opportunities to support research, which needs to be done to address both the therapeutic and adverse effects of cannabis and cannabinoids.

Many important issues were included under the prioritized research areas, including addressing understudied health endpoints like epilepsy, PTSD symptoms, child and adult cancers, and the effects of cannabis and cannabinoids in under-researched and at-risk populations. An area that I would like to see added to the research agenda is long-term randomized, double-blind, placebo-controlled studies of cannabis and cannabinoids for their clinical utility. These studies should evaluate safety and tolerability, address potential issues of tolerance to their therapeutic effects, and systematically evaluate adverse effects, including abuse liability and psychomotor and cognitive function. Additionally, the clinical efficacy of cannabis and cannabinoids should be compared with other established pharmacotherapies for a therapeutic endpoint of interest for example opioids for pain. Another understudied area of research that needs to be addressed is the effect of lesser-studied phytocannabinoids, including tetrahydrocannabinolic

acid, cannabigerol, and tetrahydrocannabivarin, with hypothesized therapeutic utility.

Dr. Grant: The panel produced a comprehensive and well-considered set of priorities. I would add that longer term clinical trials on cannabis, variously administered, both botanical and pure compounds, to understand the long-term benefits or toxicities of medicinal cannabis.

More studies are needed on potential salutary or problematic combinations of cannabis and available drugs for various conditions. For example, is there a true "opioid-sparing effect" in pain management? That would be a major public health benefit. Is to possible that cannabinoids like cannabidiol are good anti-anxiety, antipsychotic, and antiepileptic drugs that reduce or even eliminate need for more toxic agents?

We need enhanced preclinical and translational research on physiologic and pathophysiologic alterations in the endocannabinoid system which may point to the development of novel therapeutic agents. This is especially relevant for neuropsychiatry which has been basically frozen in paradigms that seek to modify monoamine physiology.

Lastly, we need better outcome research that moves beyond cross-sectional association to longitudinal analysis of possible true causal–consequent links between cannabis and outcomes, such as motor vehicle accidents. At present, the suggestion that cannabis policies have led to more accidents rests on an association that cannabis is more frequently detected now in motor vehicle accident actors, but without demonstrating a significant and sustained rise in accidents in jurisdictions that have legalized medical or recreational use. The association might simply mean that more drivers are using cannabis or more are being tested, which would mean more drivers are indeed cannabis positive without necessarily establishing a causal link.

Dr. Abrams: I second Dr. Grant's proposal to investigate further the possibility that cannabis might have an impact on the ability to decrease or wean off opiates altogether. Also, it is really time for someone to do a trial in people with cancer to assess whether highly concentrated cannabinoid preparations have any antitumor effect.

References

1. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.
2. IOM (Institute of Medicine). Marijuana and medicine: assessing the science base. Washington, DC: The National Academies Press, 1999.
3. Hartman RL, Brown TL, Milavetz G, et al. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol Depend. 2015; 154:25–37.

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Abbreviations Used

IOM = Institute of Medicine
NASEM = National Academies of Sciences, Engineering, and Medicine
PTSD = post-traumatic stress disorder