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Review Article

The therapeutic effects of *Cannabis* and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report

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A B S T R A C T

The National Academies of Sciences, Engineering and Medicine conducted a rapid turn-around comprehensive review of recent medical literature on **The Health Effects of *Cannabis* and Cannabinoids**. The 16-member committee adopted the key features of a systematic review process, conducting an extensive search of relevant databases and considered 10,000 recent abstracts to determine their relevance. Primacy was given to recently published systematic reviews and primary research that studied one of the committee's 11 prioritized health endpoints- therapeutic effects; cancer incidence; cardiometabolic risk; respiratory disease; immune function; injury and death; prenatal, perinatal and postnatal outcomes; psychosocial outcomes; mental health; problem *Cannabis* use; and *Cannabis* use and abuse of other substances. The committee developed standard language to categorize the weight of evidence regarding whether *Cannabis* or cannabinoids use for therapeutic purposes are an effective or ineffective treatment for the prioritized health endpoints of interest. In the Therapeutics chapter reviewed here, the report concluded that there was conclusive or substantial evidence that *Cannabis* or cannabinoids are effective for the treatment of pain in adults; chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis. Moderate evidence was found for secondary sleep disturbances. The evidence supporting improvement in appetite, Tourette syndrome, anxiety, posttraumatic stress disorder, cancer, irritable bowel syndrome, epilepsy and a variety of neurodegenerative disorders was described as limited, insufficient or absent. A chapter of the NASEM report enumerated multiple barriers to conducting research on *Cannabis* in the US that may explain the paucity of positive therapeutic benefits in the published literature to date.

1. Introduction

The United States' Institute of Medicine published a comprehensive volume entitled **Marijuana and Medicine** in 1999 [1]. At that time, California was the only state that allowed patients to access *Cannabis* for medicinal purposes. By 2016, there were twenty-four states where *Cannabis* was available as a therapeutic agent and three that had approved *Cannabis* for recreational use. With more states voting on ballot measures in the November 2016 elections, the National Academies of Sciences, Engineering and Medicine (NASEM) was approached by a consortium of federal, state and independent agencies to update the 1999 report. The lead sponsor was the US Centers for Disease Control and Prevention. Additional federal agencies involved included the Food and Drug Administration, the National Institute on Drug Abuse, the National Cancer Institute and the National Highway Traffic Safety Administration. Stakeholders from states where *Cannabis* was approved for recreational use or likely to be so were also study sponsors including the Alaska Mental Health Trust Authority, the Arizona Department of Health Services, the California Department of Public Health, the Oregon Health Authority, the Colorado Health Foundation and the Washington State Department of Health. The summary of the statement of task to NASEM was to develop a comprehensive, in-depth review of existing evidence regarding the health effects – both benefits and harms- of *Cannabis* and cannabinoid use. An additional charge was to make short- and long-term recommendations regarding a research agenda to identify the most critical research questions to advance the *Cannabis* and cannabinoid research agenda [2].

To accomplish this mission, NASEM assembled a 16-member committee to produce a rapid turnaround report. The committee was nominated and underwent a vetting period during which open public comment was invited on the membership. The final composition of the writing committee included experts in substance abuse, cardiovascular health, epidemiology, immunology, pharmacology, pulmonary health, neurodevelopment, oncology, pediatrics, public health and systematic review methodology. Between June and December 2016, the committee held 5 in-person meetings at the NASEM headquarters in Washington,

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DC and one virtual meeting. The meetings were closed except for two meetings where open sessions occurred involving input from individuals outside of the core committee.

An early task of the committee was to determine what areas to focus on in a rather large field. In an effort to stay on mission, the committee elected to prioritize their investigations to include the following health endpoints: therapeutic effects; cancer incidence; cardiometabolic risk; respiratory disease; immune function; injury and death; prenatal, perinatal and postnatal outcomes; psychosocial outcomes; mental health; problem *Cannabis* use; and *Cannabis* use and abuse of other substances. Key words were generated and the committee adopted key features of a systematic review process. An extensive search of the relevant databases was conducted. The initial search of Medline, Embase, the Cochrane Database of Systematic Reviews and PsycINFO resulted in > 24,000 articles. Case reports, commentaries, conference abstracts, editorials and articles written by "Anonymous" or not written in English were deleted. The committee considered > 10,700 abstracts to determine their relevance to the report. At least two committee members evaluated each abstract to determine whether the article should be accessed for further review. Primacy was given to systematic reviews published after 2011. Primary research published after the systematic review was also evaluated. For topics of interest that had no available systematic reviews, the committee searched for high quality primary research studies published between January 1, 1999 and August 1, 2016. Each systematic review and primary research article was graded for quality by two committee members using established criteria. Only fair and good quality publications were included. If two reviewers disagreed, a third adjudicated.

The publications selected as fair or good quality were assimilated by topic authors and summarized. The full committee had numerous opportunities to review the work as it was being written. After the summary paragraphs had been written for each of the prioritized health endpoint chapters, the committee was asked to state conclusions and use standardized language to categorize the weight of the evidence as conclusive, substantial, moderate, limited or no or insufficient (definitions below). The full committee reviewed and discussed all of the chapter conclusions to establish consensus. This article will focus on the conclusions reported in the Therapeutic Effects chapter, organized by the assigned weight of the evidence. It is critical to note that there is a paucity of published literature investing the therapeutic utility of the *Cannabis* plant. The difficulties in conducting research to investigate the benefits of *Cannabis* are discussed in Chapter 15 of the report. Most of the literature evaluated in primary research studies as well as systematic reviews involved trials of isolated cannabinoids, most frequently pharmaceutical preparations of delta-9-tetrahydrocannabinol (THC) and, less frequently, cannabidiol (CBD). Increasingly an oromucosal whole plant extract, nabiximols, is also being investigated and generating published results. Data on inhaled *Cannabis* is rare and there were no published reports found that utilized any of the increasingly available oral edibles, tinctures and oils that US patients currently have access to in dispensaries across the nation.

1.1. Conclusive or substantial evidence of effect

Conclusive denotes that there is strong evidence from randomized controlled trials to support the conclusion that *Cannabis* or cannabinoids are an effective or ineffective treatment for the health endpoint of interest. Substantial suggests that there is strong evidence to support the conclusion that *Cannabis* or cannabinoids are an effective or ineffective treatment for the health endpoint of interest. For these levels of evidence, there are many (or several for substantial) supportive findings from good-quality studies with no (or few for substantial) credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

1.1.1. Chronic pain

Chronic pain is one of the most often cited reasons that patients are accessing medicinal *Cannabis* in states where it is available [3]. There were five fair-to-good quality systematic reviews that contributed to the conclusion that there is substantial evidence that *Cannabis* is an effective treatment for chronic pain in adults. The comprehensive review by Whiting et al. published in 2015 provided the basis for many of the conclusions reached in the NASEM report and included 28 randomized controlled trials in patients with chronic pain involving 2454 patients [4]. Neuropathic pain was the condition studied in 17 of the trials. Only five of the trials evaluated smoked or vaporized *Cannabis* plant material with most [13] investigating the whole plant extract oromucosal spray, nabiximols. An analysis that included seven trials of nabiximols and one of smoked *Cannabis* found that the plant-derived cannabinoids were 40% more likely to reduce pain than the control agent (OR 1.41, 95% confidence interval = 0.99–2.00). The effect size for the reduction of neuropathic pain with inhaled *Cannabis* compared to placebo was estimated at 3.22 (95% CI = 1.59–7.24) from a Bayesian pooled effect analysis of five published trials [5]. Of note, a more recent study from US Veteran's Administration investigators analyzing essentially the same cluster of published clinical trials of *Cannabis* plant-based medicines concluded with less conviction that pain was effectively treated [6].

1.1.2. Chemotherapy-induced nausea and vomiting

The delta-9-THC pharmaceutical agents, dronabinol and nabilone, were both initially approved in 1985 for use in treating nausea and vomiting associated with cytotoxic chemotherapy. Whiting et al. summarized 28 trials reporting on nausea and vomiting due to chemotherapy, most published before 1984, involving 1772 participants [4]. These are the studies that ultimately lead to the approval of dronabinol and nabilone. They were either placebo controlled or used the antiemetics available at the time- mostly prochlorperazine or chlorpromazine- as comparators. Whiting concluded that all trials suggested a greater benefit for cannabinoids than for both active agents and for the placebo, although the differences did not reach statistical significance in all trials. A Cochrane review summarized 23 trials, most of which were included in the Whiting analysis [7]. In this review the investigators conclude that cannabinoids were highly effective, being more efficacious than the placebo and similar to conventional antiemetics in treating chemotherapy-induced nausea and vomiting. Although the cannabinoids caused more adverse events, they were still preferred by patients over the both placebo and the other antiemetics. Three of 28 studies in a systematic review of antiemetics in children with chemotherapy-induced nausea and vomiting investigated either nabilone or oral THC [8]. The results in the pediatric population were less conclusive.

It is worth noting that despite an abundance of anecdotal reports and accumulated clinical experience of the benefits of the *Cannabis* plant in reducing chemotherapy-related nausea and vomiting, there are no good quality studies reported in the medical literature. Nor have any of the published trials investigated the utility of cannabidiol or cannabidiol-enriched products for combating nausea and vomiting, a question often asked by cancer patients seeking to avoid the psychoactive effects associated with THC. As CBD does not complex with the cannabinoid receptor in the brain as THC does, it is conceivable that it may not have the same therapeutic effect for this condition.

The American Society for Clinical Oncology Expert Panel on Antiemetics recently issued updated guidelines and recommended "FDA-approved cannabinoids dronabinol or nabilone to treat nausea and vomiting that is resistant to standard antiemetic therapies. Evidence remains insufficient to recommend marijuana in this setting" [9]. Some of the reluctance to be more enthusiastic in support of cannabinoids likely stems from the fact that most of the published literature compares dronabinol or nabilone to antiemetics that are no longer considered to be first line therapies. A more recent trial, however, did

suggest that dronabinol compared favorably with ondansetron in treatment of patients with delayed chemotherapy-induced nausea and vomiting [10].

1.1.3. Spasticity associated with multiple sclerosis

Nabiximols was initially approved in 2010 in the United Kingdom for the treatment of spasticity associated with multiple sclerosis [11]. The Whiting systematic review included 11 studies of multiple sclerosis [4]. In a pooled analysis of three trials investigating nabiximols or nabilone, they found that the cannabinoids decreased the patient self-reported spasticity score by − 0.76 (95% CI: − 1.38 to − 0.14) on a 0 to 10 scale that was statistically greater than placebo. The pooled odds of patient-reported improvement of a global impression of change score also favored nabiximols over placebo. An earlier systematic review focused on spasticity associated with MS concluded that nabiximols and oral THC were "probably effective" and oral *Cannabis* extract was "established as effective" in reducing patient reported spasticity scores [12]. Hence the NASEM report concluded that there is substantial evidence that oral cannabinoids are effective for improving patient-reported multiple sclerosis spasticity symptoms.

The Ashworth scale is a commonly used objective rating used by physicians for grading spasticity associated with MS. Whiting reported on a pooled analysis from 5 studies that utilized the Ashworth scale and concluded oral cannabinoids were associated with a greater improvement on the scale than placebo but the results were not statistically significant. Koeppel found that oral cannabinoids were "probably ineffective" for reducing objective measures of spasticity at 6 to 15 weeks of follow up, but that oral *Cannabis* extract and oral THC were "possibly effective" with regard to objective measures at one year. An additional placebo-controlled crossover trial of nabiximols in MS-related spasticity was published after the Whiting systematic review [13]. This trial demonstrated that a statistically significant improvement in objective spasticity was seen with nabiximols compared to placebo. Despite these findings, the conclusion was that the evidence for impact of cannabinoids on clinician-measured spasticity was limited.

1.2. Moderate evidence of effect

For this level of evidence, there are several findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence. For this level of evidence, NASEM found only one condition that met the criterion.

1.2.1. Sleep disturbance

It is estimated that 50 to 70 million adults in the United States suffer from a sleep disorder necessitating millions of physician visits annually. It has been hypothesized that the endocannabinoid system may have a role in sleep and it has been recognized that *Cannabis* may have effects on sleep latency. Many patients accessing *Cannabis* from dispensaries report that it helps with sleep. Some claim that *Cannabis indica* strains are particularly soporific. Users maintain that cannabidiol is a potent sedative-hypnotic, while the science suggests that it is actually more of a stimulant [14]. The Whiting review included two randomized trials investigating cannabinoids for sleep problems [4]. A 22 patient study with a high risk of bias found that dronabinol was better than placebo in patients with obstructive sleep apnea. A cross-over trial in 32 patients with fibromyalgia comparing nabilone to amitriptyline reported that nabilone was more effective in treating insomnia and producing greater sleep restfulness. Nineteen additional trials in the systematic review reported on sleep outcomes with cannabinoids. Meta-analysis revealed greater improvement in sleep quality in 8 trials and sleep disturbance in 3 trials, but the improvements were deemed to be small. No studies were found in the NASEM search that investigated the use of *Cannabis* or cannabinoids in primary insomnia. The conclusion was that there is moderate evidence that cannabinoids, predominantly nabiximols, are effective in improving the short-term sleep outcomes in individuals with sleep disturbances associated with obstructive sleep apnea, fibromyalgia, chronic pain and multiple sclerosis.

1.3. Limited evidence of effect

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

1.3.1. Appetite and weight gain

There are a number of conditions in the limited evidence category of the NASEM report. Of note, the 1999 Institute of Medicine report **Marijuana and Medicine** concluded that *Cannabis* was effective for pain, nausea and vomiting and spasticity associated with multiple sclerosis [1]. They also felt that the evidence supported *Cannabis* and cannabinoids in the treatment of anorexia associated with HIV infection. The more recent review of **The Health Effects of *Cannabis* and Cannabinoids** graded the evidence for increasing appetite and decreasing weight loss in HIV to be only limited. Similarly, studies of single cannabinoids in cancer cachexia and weight loss associated with anorexia nervosa have not yet provided convincing evidence of effectiveness. It is worth noting again that studies involving the *Cannabis* plant in these conditions are lacking. One randomized trial in HIV patients did show weight gain in the *Cannabis* smoking and dronabinol recipient groups compared to placebo, but the study was not powered for weight gain as an endpoint [15]. In patients with cancer-related weight loss, however, the progestational agent, megestrol, was superior to dronabinol in increasing both appetite and weight and the combination of the two was inferior to megestrol alone [16].

1.3.2. Post-traumatic stress disorder

There is much interest in the potential utility of *Cannabis* in individuals with post-tramautic stress disorder (PTSD). There are frequent anecdotal reports of remarkable success and in some states where it is an eligible indication for patients to receive *Cannabis* it ranks near or at the top of the list of conditions for which treatment is sought. A long-awaited controlled clinical trial of *Cannabis* is currently underway. In the meantime, the published literature contains a single fair-quality crossover trial of nabilone in ten Canadian male military personnel with trauma-related nightmares despite standard treatment for PTSD [17]. Nabilone was statistically better than placebo for improving nightmares, global clinical state and general well-being ($p < 0.05$). A subsequent systematic review confirmed the NASEM conclusions [18]. Ongoing clinical trials will hopefully provide more evidence on the effect of *Cannabis* and cannabinoids in the future. The NASEM report also noted that there was limited evidence of an association between smoked *Cannabis* and increased symptoms in patients with post-traumatic stress disorder. Epidemiologic evidence leading to this conclusion included large studies of veterans who were asked about their use of substances. The report did mention that PTSD patients often cite symptom-coping motives for use of *Cannabis* so that those with the most severe symptoms may be using more *Cannabis* in an attempt to self-medicate making it more challenging to attribute a causal relationship.

1.3.3. Anxiety

Another condition for which many have been utilizing *Cannabis* is anxiety. The Whiting review included one 24-participant trial of cannabidiol in individuals with social anxiety disorder [4]. Each subject received either a single dose of cannabidiol 600 mg or placebo prior to a simulated public speaking test. The cannabidiol was associated with a significantly greater improvement in the anxiety factor of a 100-point visual analogue mood scale compared to placebo ($p = 0.01$). No other studies were identified addressing the condition leading to the

conclusion of limited evidence.

1.3.4. Tourette syndrome

Two clinical trials evaluating oral THC in Tourette syndrome were identified in two systematic reviews. Thirty-six patients received either THC 10 mg or placebo for two days in one study (12 patients) and six weeks in the other (24 patients) [19]. Tic severity and global clinical outcome scores were improved in the treatment groups, but the tic severity improved by less than one point on a zero to six point scale and the studies were felt to have high risk of bias. A case report of a patient with refractory Tourette syndrome responding to nabiximols has also been recently published following the release of the NASEM report, but single case reports were not deemed eligible to include in that analysis [20].

1.4. No or insufficient evidence

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

1.4.1. Cancer

The committee veered from the charge to include only human clinical trials in the report when it came to discussing the evidence as to whether *Cannabis* or cannabinoids have any antitumor activity. This is because there is really only one published clinical trial investigating *Cannabis* as an anticancer agent. The bulk of the substantial literature is preclinical and heavily focused on the effect of cannabinoids on gliomas. The NASEM report focused on the systematic review of Machado Rocha et al. that included 34 in vitro and animal studies of this topic [21]. All but one of the studies reviewed showed that cannabinoids selectively killed the glioma cells while leaving normal brain cells unharmed. The various reports concluded that cannabinoids have direct antiproliferative effects inducing cell cycle arrest and inducing tumor cell death by way of toxicity, apoptosis, necrosis and autophagy. In addition to direct antitumor effect, investigators also demonstrated that cannabinoids exert antiangiogenic effects and inhibit matrix metalloproteinase activity leading to decreased cell migration and metastases.

Included in the Machado Rocha review was the lone human trial that investigated intratumoral THC delivered by way of a catheter into the recurrent glioblastoma multiforme tumors of nine patients who were also receiving chemotherapy [22]. Although the treatment was well-tolerated, there was no clinical benefit above that provided by chemotherapy alone. In vitro, however, THC inhibited the proliferation and decreased the viability of the glioblastoma cells from the tumor specimens. It was later demonstrated that CBD enhanced the inhibitory effects of THC on glioblastoma multiforme cell proliferation and survival [23]. Since the publication of the NASEM report, a randomized placebo-controlled pilot study of the safety of the oromucosal whole plant extract nabiximols with dose dense temozolomide in 21 patients with recurrent glioblastoma multiforme has been completed. Although the results of the trial have not yet been published, a press release indicated a survival benefit with the addition of nabiximols to standard therapy [24].

Increased expression of CB1 and CB2 receptors have been found in a wide array of malignant tissues [25]. In some situations, increased expression of one or the other receptor is correlated with a worse prognosis, while in others they portend a more favorable outcome. Clearly there is preclinical evidence that cannabinoids may have antitumor activity. However, at this point the data suggesting a clinical benefit in people with cancer is entirely lacking. The US Food and Drug Administration issued a warning in November 2017 to companies promoting *Cannabis*-derived products that claim to cure cancer [26]. Increasing numbers of patients in states where medicinal *Cannabis* is available are seeking highly concentrated THC or CBD preparations or elixirs with mysterious and magical ratios of THC:CBD in an effort to cure their cancers. When patients forego conventional cancer care in hopes that this unproven intervention will have therapeutic benefit, the results are often horribly disappointing with previously curable malignancies progressing to metastatic disease.

1.4.2. Epilepsy

Two systematic reviews assessing the effect of cannabinoids or *Cannabis* for reducing seizures in patients with epilepsy were included in the NASEM report. Gloss and Vickrey identified four randomized controlled trials of low quality that involved a total of 48 patients [27]. None of the trials assessed the pre-specified endpoint of freedom from seizures for 12 months or three times the previous seizure free interval so the authors reported that no reliable conclusion could be drawn. A systematic review of cannabinoids in neurologic conditions found no high quality randomized trials in epilepsy and concluded that the evidence was insufficient to support or refute the use of cannabinoids in epilepsy [12]. Three studies were found in the primary literature published after the systematic reviews. Two of the reports covered the same group of children with refractory seizures receiving a cannabidiol preparation in an expanded access program [28–29]. The third was an unblinded report of an oral formulation of CBD:THC of 20:1 in Israeli children with pediatric epilepsy [30]. Although the studies all reported benefit of the cannabinoid preparations utilized, the lack of blinding and control groups were deemed to make the evidence insufficient to support a benefit for cannabinoids in the treatment of seizures at this time.

1.4.3. Neurodegenerative disorders

The NASEM report found no or insufficient evidence to support the use of *Cannabis* or cannabinoids in the treatment of amyotrophic lateral sclerosis, chorea and certain neuropsychiatric symptoms associated with Huntington's disease, motor symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia. Additional neurologic conditions for which no or insufficient evidence of effectiveness was found include spasticity associated with paralysis in patients with spinal cord injury and dystonia.

1.4.4. Irritable bowel syndrome

There were no systematic reviews located in the literature on the use of *Cannabis* or cannabinoids for the treatment of symptoms related to irritable bowel syndrome. A single randomized trial of two doses of dronabinol versus placebo in adults with diarrhea related to irritable bowel syndrome was identified [31]. No effect of dronabinol on gastric, small bowel or colonic transit as measured by radioscintigraphy was seen. NASEM concluded that there was insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of irritable bowel syndrome.

The NASEM committee did not include inflammatory bowel disease as one of the priority conditions to investigate. An increasing number of patients with Crohn's disease and ulcerative colitis are seeking *Cannabis* and cannabinoid products to treat their symptoms. A small Israeli study assessed the effect of cannabidiol in 20 patients with moderately active Crohn's disease [32]. After 8 weeks of treatment, there was no apparent beneficial effect of CBD on the Crohn's Disease Activity Index compared to placebo. Additional ongoing trials are investigating *Cannabis* and cannabinoids in both irritable and inflammatory bowel syndromes.

1.4.5. Addiction

As the opiate epidemic runs rampant, it has been hypothesized that *Cannabis* may be a useful alternative to narcotics [33]. The NASEM report concluded that there is no evidence to support or refute the conclusion that cannabinoids are an effective treatment for achieving abstinence in the use of addictive substances. The committee's conclusion, however, was based on a literature that included two studies of

cannabinoids in the treatment of *Cannabis* use disorder and one in people who wished to quit smoking cigarettes. In this trial, inhalation of cannabidiol decreased the number of cigarettes smoked compared to placebo, but the difference was not significant [34]. No published trials have investigated cannabinoids in patients with opiate dependence although there is a physiologic basis to hypothesize that this may be effective and trials are certainly warranted.

2. Summary

The 2017 National Academies of Sciences, Engineering and Medicine report, like the 1999 Institute of Medicine publication before it, did conclude that there is evidence to support the therapeutic effect of *Cannabis* and cannabinoids in a number of conditions. Most of the evidence relates to the pharmaceutical cannabinoids – dronabinol, nabilone and increasingly nabiximols. This is due, in part, to the difficulty of obtaining *Cannabis* to research for its potential therapeutic benefit in the United States. NASEM recommended that committees be convened to address research gaps, improve research quality and address research barriers. In the meantime, more states and nations are making *Cannabis* available for medicinal purposes and more patients are extolling the health benefits of *Cannabis*-based medicines. Although it is well appreciated that the plural of anecdote is not evidence, it must also be remembered that in the case of evaluating the therapeutic effects of *Cannabis* as published in the medical literature, the absence of evidence is not necessarily indicative of evidence of the absence of effectiveness. Investigators must rise to the challenge and undertake further additional trials so that clinicians can be informed on how to best use this versatile medicine.

Disclosures

Dr. Abrams is currently a Scientific Advisor to ABcann, AXIM Biotechnologies, Inc., Maui Grown Therapies, Scriptyx and Tikun Olam although none of these relationships were active while he was a member of the committee of the National Academies of Sciences, Engineering and Medicine.

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