

REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1-5, were presented by Robert A. Gilchick, MD, MPH, Chair.

1. UNIVERSAL COLOR SCHEME FOR RESPIRATORY INHALERS (RESOLUTION 906-I-16)

Reference committee hearing: see report of Reference Committee K.

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
IN LIEU OF RESOLUTION 906-I-16
REMAINDER OF REPORT FILED
*See Policy H-100.949***

INTRODUCTION

Resolution 906-I-16, “Universal Color Scheme for Respiratory Inhalers,” introduced by the Resident and Fellow Section and referred by the House of Delegates asked:

That our American Medical Association work with leading respiratory inhaler manufacturing companies and health agencies such as the Federal Drug Administration and the American Pharmacists Association to develop consensus of a universal color scheme for short-acting beta-2 agonist respiratory inhalers that are used as “rescue inhalers” in the United States;

That our AMA work with leading respiratory inhaler manufacturing companies to ensure the universal color scheme for respiratory inhalers would allow for the least disruption possible to current inhaler colors, taking into account distribution of each brand and impact on current users if color were to change;

That our AMA work with leading respiratory inhaler manufacturing companies to ensure that universal color scheme for respiratory inhalers be designed for adherence and sustainability, including governance for future companies entering the respiratory inhaler market, and reserving colors for possible new drug classes in the future.

Traditionally, in the United Kingdom, Canada, and parts of Europe short-acting β_2 -adrenergic agonist (SABA) respiratory inhalers are colored blue and referred to as “relievers” or “rescuers,” while inhaled corticosteroids (ICS) are colored brown, orange, or red and are referred to as “preventers” or “controllers.” No convention exists in the United States for the coloration of respiratory inhalers.

CURRENT AMA POLICY

Policy H-115.980, “Distinctive Labeling of Vials and Ampules, Prefilled Syringes, Ophthalmic Solutions and Related Liquid Medications,” is somewhat related to this resolution, calling for the development of appropriate guidelines aimed at developing easily identifiable labeling to optimize the safe use of liquid medication. No current AMA policy related to color coding of respiratory inhalers exists.

METHODS

English-language articles were selected from a search of the PubMed database through July, 2017 using the search term “inhaler” coupled with “color” and “colour.” Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society and international, national, and local government agency websites were conducted to identify relevant clinical guidelines, position statements, and reports.

COLOR CODING

Color coding is the systematic, standard application of a color system to aid in the classification and identification of drug products. Conceptually, a color coding system allows users to associate a color with a function. Color coding as an aid to patient safety requires the use of consistent coloring schemes by all manufacturers.

Color Coding and Medication Errors

In a 2004 report, titled “The Role of Color Coding in Medication Error Reduction,” the Council on Scientific Affairs (CSA) (predecessor to the Council on Science and Public Health) noted controversy among experts and a variety of potential problems with color coding of pharmaceutical products, which suggest that a universal color scheme should not be universally adopted.¹ Several organizations involved in medication error prevention, including the American Society of Health-System Pharmacists (ASHP), Institute for Safe Medication Practices (ISMP), U.S. Food and Drug Administration (FDA), and the pharmaceutical industry either oppose color coding or recommend caution in its application.²⁻⁵ The report also noted a lack of evidence proving that color coding reduces medication errors; this lack of evidence still exists.^{1,6}

The result of the CSA report was a directive that was sunsetted in 2014 after AMA provided testimony to the FDA regarding the report’s findings, which identified potential problems associated with the color coding of pharmaceutical products.⁷ The FDA released a draft guidance in 2013, entitled “Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.”⁵ The draft guidance recommends avoiding color coding in most instances and goes on to note that “[c]olor coding schemes developed to decrease error may actually increase error when the color is relied upon as a shortcut to proper identification (i.e., not reading the label).”⁵ FDA intends to finalize this guidance.

FDA notes limited applications of color coding that are appropriate and were established before the 2013 guidance document, such as the caps of ophthalmic solutions that indicate the therapeutic class of a drug. These classifications, however, are generally not useful to end users outside of ophthalmology and these color classifications have caused problems with users having difficulty differentiating between drugs within the same therapeutic class.⁵ Additionally, the color-coding of surgical anesthesia syringes has been adopted with the intention of reducing the risk of accidental syringe swapping by surgical users, but limited evidence has not shown that drug errors have been eliminated.⁸ In both examples, the end user populations are limited groups, not a large outpatient patient population.

Additional Disadvantages of Color Coding of Pharmaceutical Products

In addition to the lack of scientific evidence that proves color coding reduces medication errors, experts in the field of medication errors also cite other reasons why the widespread adoption of color coding systems for pharmaceutical products should be done with great caution.^{1,3,5,6,9-12} Potential problems include:

- There is a limit to the number of discernable colors available for commercial use.
- Subtle distinctions in color are poorly discernable unless products are adjacent to one another.
- Color coding of drug classes can increase the chance of “intra-class” medication errors.
- Colors may fade when exposed to light.
- It is not always possible to exactly reproduce Pantone colors from batch to batch.
- Approximately 8% of men and fewer than 1% of women have some difficulty with color vision (colorblindness).
- Color coding can be error-prone if it is not applied consistently across the industry, or within a single manufacturer’s product line.
- Physicians and other health professionals may be unable to remember large or multiple-color coding systems.
- Color coding may offer a false sense of security and, in some instances, result in failure of the physician or other health professional to “read the label.”

COLOR CODING OF RESPIRATORY INHALERS

The coloring of outpatient SABA inhalers as blue and ICS as brown/red/orange in the United Kingdom and Canada is an informal convention that has been an accepted practice for several decades. No regulations have been issued by

the United Kingdom Medicines and Healthcare Products Regulatory Agency, the European Medicines Agency, or Health Canada, and no formal agreement exists for manufacturers, regarding a color convention for respiratory inhalers. As a general principle, the three health agencies recommend against color coding.^{9,13,14} The European Medicines Agency has stated that “there can be no substitute for carefully reading the label before any medicine is taken.”¹⁵ Color of inhalers is not addressed in guidelines for the management of asthma.^{16,17}

With the increasing diversity of inhaler devices, including combination products, entering the market in the United Kingdom and Canada, color coding is becoming more complex and inconsistent. The recent Health Canada approval of a long-acting β_2 -adrenergic agonist (LABA) and ICS combination inhaler in the color blue¹⁸ has raised concerns.¹⁹ The existence of a generic salbutamol (a SABA) inhaler in brown in the United Kingdom adds confusion to the color coding convention.¹⁵ Manufacturers have been called on to consider universal concepts such as color coded dots or bands that correspond to different types of medications.²⁰ However, the aforementioned disadvantages of color coding pharmaceutical products such as colorblindness and limited color availability persist and no formal action has been taken to ensure universal concepts.²¹

Color Coding Respiratory Inhalers and Patient Adherence

A small survey of health care professionals in the United Kingdom found that the existing color convention for inhalers appears to be helpful in aiding communication between health care professionals and patients and can be helpful for reinforcing the different roles of inhalers and aiding in medication adherence.¹³ However, it should be noted that this communication between patients and physicians regarding inhaler color in the United Kingdom is likely aided by the color convention that has existed and been known for decades. A parallel situation of familiarity with a color convention does not exist for patients in the United States. The authors of the survey also noted a lack of studies regarding color-standardization in general and specific issues surrounding color coding such as color blindness.

Poor adherence to maintenance therapy is common among asthma patients and a complex challenge to overcome.²² Individualized action plans developed in a collaborative fashion between asthma patients and their physicians that focus on self-management are typically employed to promote adherence and appropriate clinical use of different inhalers. Inhaler color was of little importance in action plan discussions; emphasis was placed on when to use medications, skills training for use of inhalers, and education for asthma symptom management.^{22,23}

CONCLUSION

Although looked to for simplicity, limited evidence exists that color coding systems reduce medication errors in outpatients. Disadvantages of using color coding systems have been cited and experts either oppose color coding or recommend caution in its application. The FDA, Health Canada, and health agencies in the United Kingdom emphasize the best course of action before administration of any medication is to read the label. Even though the health agencies of United Kingdom and Canada recommend against color coding, an informal respiratory inhaler color coding convention exists in these countries. However, because of continued development of new products, including combinations, this color coding convention is becoming inconsistent and more complex. Experts evaluating the adherence of patients using inhalers have suggested that individualized counseling with personalized action plans and inhaler skills training are the best approach for improving adherence. With the lack of evidence to support a color coding scheme for outpatient respiratory inhalers, there is no justification for urging manufacturers to change inhaler colors, the potential cost associated with such a change which may be passed along to patients, and disruption to the current market of familiar inhaler products.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 906-I-16, “Universal Color Scheme for Respiratory Inhalers,” and the remainder of the report be filed:

Our American Medical Association supports research into mechanisms to improve patient understanding of their respiratory inhaler medications with the aim of improving safety and reducing unintentional medication errors, such as inhaler skills training, individualized action plans and distinctive packaging features for rescue inhalers.

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2. TARGETED EDUCATION TO INCREASE ORGAN DONATION

Reference committee hearing: see report of Reference Committee K.

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
REMAINDER OF REPORT FILED**
See Policy H-370.959

INTRODUCTION

Policy D-370.984, “Targeted Education to Increase Organ Donation,” asked:

That our American Medical Association study potential educational efforts on the issue of organ donation tailored to demographic groups with low organ donation rates.

This report responds to Policy D-370.984 by reviewing current organ donation statistics, attitudes about donation, disproportion between those needing a transplant and the organs available, factors influencing the decision to designate oneself as a donor, and educational interventions targeted to segments of the population with historically low rates of organ donation. Other factors affecting organ donation rates, including mandated choice and presumed consent for donation of cadaver organs, as well as novel models for living donation, have been discussed in Board of Trustees Reports 13-A-15 and 15-A-12.^{1,2}

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2007 and 2017 using the search term “organ donation,” with the terms “minority,” “religion,” “education,” and “barriers.” A Google search was conducted using the same search terms. Additional articles were identified by manual review of the references cited in identified publications. The Health Resources and Services Administration Organ Donation and Transplantation and Organ Procurement and Transplantation Network websites and the United Network for Organ Sharing website also were consulted.

ORGAN DONATION STATISTICS AND ATTITUDES

Donated organs and tissues for transplantation are most often obtained from deceased donors, referred to as deceased organ donation. Deceased organ donors can donate kidneys, liver, lungs, heart, pancreas, and intestines.³ In addition to these organs, tissues such as heart valves, skin, bone, and tendons; corneas; and face and hands can be donated after death.³ Approximately 90% of organ donations are from deceased donors; the remaining donations are from living donors.⁴ Organs donated by living donors include one of two kidneys, one of two lobes of the liver, a lung or part of the lung, part of the pancreas, and part of the intestines. Tissues donated by living donors include skin, bone, bone marrow cells and umbilical cord blood cells, amnion (donated after childbirth), and blood.⁵ More than 33,000 transplants were performed in 2016.⁶ Kidney and liver transplants made up the vast majority of organs transplanted (approximately 58 and 23 percent, respectively). Less common transplants were heart (9 percent), lung (7 percent), kidney and pancreas (2 percent), pancreas (0.7 percent), intestine (0.5 percent), and heart and lung (0.05 percent).⁴

Organ and tissue donation in the United States is voluntary. Individuals wishing to donate their organs after death “opt in” by documenting their desire. Deceased organ donation registration is a state process; individuals can sign up online with the state registry or through a state’s Department of Motor Vehicles. When the person’s preferences are not documented or known, the next of kin may decide to allow organs to be harvested for transplantation after death.³ More than 130 million adults in the United States (approximately 54% of the population) are registered as organ and tissue donors.⁴

Living organ donation is not administered through state or other government programs. Rather, it most often occurs in the form of directed donation, in which the donor names a specific person to receive the organ or tissue, usually a biological relative or a biologically unrelated person with a personal or social connection (spouse, significant other, friend, or acquaintance).⁷ In non-directed donation, the living organ donor does not name a recipient. Those wishing to be non-directed donors can do so by contacting a designated Organ Procurement and Transplant Network (OPTN) transplant center, or by contacting the United Network for Organ Sharing (UNOS).⁷

A 2012 survey of a nationally representative sample of US adults, administered by the Health Resources and Services Administration (HRSA), examined organ donation attitudes and behaviors. More than 95 percent of respondents supported or strongly supported the donation of organs for transplantation.⁸ Small but significant differences in support exist among racial and ethnic groups. Approximately 95 percent of those categorizing themselves as White, Asian/Pacific Islander, or Hispanic support or strongly support donation, while approximately 92 percent of Native Americans and 87 percent of African Americans support or strongly support donation.⁸ Despite strong support for organ donation, the survey indicated that fewer people took steps to register as organ donors; only 60 percent of respondents with a driver’s license reported that they had granted permission for organ donation on their driver’s license.⁸ Racial and ethnic differences were apparent on this measure as well; 65 percent of White, 56 percent of Asian/Pacific Islander, 47 percent of Native American, 44 percent of Hispanic, and 39 percent of African-American respondents with a driver’s license reported that they had granted permission for organ donation on their license.⁸

ORGAN DONATION NEEDS

Although the number of both donors and transplants has been growing slowly over the last two decades, the need for donated organs far exceeds the number available for transplantation. Nearly 120,000 people are on the national transplant waiting list, with the vast majority (81 percent) waiting for a kidney.⁴ Only about three in 1,000 registered donors actually become donors after death. This is due to a number of criteria that must be met for a donor organ to be appropriate for an intended recipient (the “matching” process). These include blood and human leukocyte antigen (HLA) type, body size, severity of the recipient’s medical condition, severity of donor’s pre-death medical condition, length of time on the waiting list, distance between the donor’s and recipient’s hospitals, and the availability of the recipient.⁹

The proportion of racial and ethnic minority patients on the waiting list is higher than the corresponding proportion of racial and ethnic minorities who are donors.⁴ For example, African Americans make up nearly 30 percent of patients on the waiting list, but only approximately 16 percent of donors are African American.⁴ Hispanics and Asians make up nearly 20 and 8 percent, respectively, of patients on the waiting list, but only approximately 14 and 3 percent of donors are Hispanics and Asians, respectively.⁴ This disparate representation on the transplant waiting list exists partially because minority groups, specifically African Americans, are disproportionately impacted by chronic conditions such as diabetes, heart disease, and hypertension, which often are managed with transplants.^{10,11,12} Additionally, African Americans have more HLA polymorphisms and enhanced alloreactivity, making the chance of finding a matching donor, especially among a pool of donors that includes proportionally fewer African Americans, particularly difficult.^{10,12,13}

FACTORS INFLUENCING ORGAN DONATION

Irving et al.¹⁴ conducted a systematic review of studies that characterized factors influencing attitudes toward deceased and living organ donation, and categorized the factors into several broad themes:

- **Relational ties:** The needs of family members or friends appear to be more influential in the decision to become a donor than those of strangers. Many study participants were willing to donate an organ to a family member or friend even if they were not willing to donate to someone they did not know.
- **Religious beliefs:** While some believe that organ donation aligns with the altruistic tenets of their religion, others believe that donation is not consistent with their religion. For example, some Islamic study participants interpret the Qur’an and traditional Islamic literature as forbidding organ donation. Others believe that transplantation, and therefore the facilitation of transplantation through organ donation, is “playing God.” The most common religious objection to organ donation was the need to maintain body wholeness to enter the next life.
- **Cultural beliefs:** Cultural beliefs concerning health care and death and dying, often based on superstition, are associated with lack of support for organ donation. For example, study participants cited the belief among some cultures that discussing death could lead to one’s own death. Others believe that death is a private matter, that ancestral approval is needed before organ donation, and that grieving rituals are disrupted by organ donation.
- **Family influence:** Family members’ beliefs about organ donation often influence individual beliefs. Study participants with one or both parents who object to organ donation expressed reluctance to be donors themselves, and some participants believed that they should seek permission from family members if they wanted to be donors. Other participants believed that by designating themselves as organ donors, they were sparing their family members difficult decisions after their death.
- **Body integrity:** Apart from religion, body integrity after death appears to influence support for donation. Participants worried that family members would be traumatized about the thought of their bodies being “cut up,” and that organ donation would preclude an open coffin at their funeral.
- **Interaction with the health care system:** A distrust of the organ donation system and process, often based on negative experiences with the health care system, reduce support for organ donation. Participants questioned the concept of “brain death,” and were suspicious of health care providers making such a designation. Some believed that organ donors would not receive proper care since health care personnel would only be interested

in harvesting their organs, or that donor bodies would not be treated with dignity and respect. Opinions based on previous experience or interactions with the health care system were more prevalent among study participants belonging to minority groups that have historically experienced a sense of marginalization from the health care system.

- Knowledge about the organ donation process: A lack of knowledge about the organ donation process is a barrier to donation. Study participants expressed the need for more information before they could commit to donation, and a lack of awareness about where such information could be obtained.

Across a number of studies assessing characteristics of those willing to donate, individuals who are younger, are female, have higher educational levels and/or socioeconomic status, and have higher knowledge about organ donation are generally more likely to have positive attitudes toward donation and are more willing to donate.¹⁵ The HRSA organ donation attitudes and behaviors survey found that the following attitudes were predictors of designating oneself as an organ donor: placing low importance on body wholeness after death, family support for organ donation, being receptive to receiving a transplant as a life-saving measure, an understanding that many people die while on the transplant waiting list, and not believing the notion that physicians would be less likely to save the life of a person who is a donor.⁸

Some factors influencing support for organ donation are more pronounced in certain racial or ethnic groups than in others. For example, interviews with African Americans found the following as predominant barriers: religious beliefs and misperceptions, distrust of the medical establishment, fear of premature declaration of death if a donor card has been signed, and a preference among African American donors for assurance that the organs will be given preferentially to African American recipients.¹⁶ In Native Americans, the importance of traditional religious beliefs, including the need to be buried with an intact body, is a barrier to deceased organ donation.^{17,18,19} Among Hispanics, greater concern over body disfigurement and greater doubt that physicians do all they can to preserve life before pursuing organ donation exist compared to non-Hispanic whites.^{20,21,22}

It is unclear that religion itself is a consistent barrier to organ donation.^{10,20} The role of religion in support for organ donation is often confounded by community and cultural norms.²⁰ In international studies, Buddhists have reported objection to deceased organ donation based on the religious belief that a person's spirit remains in the body as long as the heart is still beating, even though brain death has occurred.^{20,23} This is despite a central Buddhist tenet that honors persons who donate their organs to save a life. Studies of Muslims have indicated that religious beliefs are a barrier to organ donation, and in the United States, Muslims who demonstrate negative aspects of religious coping (a psychological state in which individuals express an insecure relationship with God and an ominous view of the world) are more likely to hold negative attitudes toward organ donation.²⁴ However, other measures of Muslim religiosity are not correlated with organ donation attitude, and many Muslims in the United States believe that donation is justified.²⁴ Among Christians, non-Catholic Christians are more likely to report willingness to be organ donors than are Catholic Christians.²⁰

TARGETED EDUCATIONAL INTERVENTIONS TO INCREASE DONATION

Given the significant need to increase the number of organs available for donation, educational interventions are needed to improve willingness to donate. Ideal interventions include those that address perceptions that influence the decision to donate and target populations most likely to hold such perceptions.¹⁴ A systematic review of interventions to improve organ donor registration among minorities found that educational interventions alone or combined with mass media approaches (as opposed to mass media alone) were most effective.²⁵ Those that included strong interpersonal components, were delivered by members of the local community in familiar environments, and included immediate opportunities to register were important for improving outcomes.²⁵ Others have emphasized culturally appropriate strategies to engage minority groups, and comprehensive information about organ donation that can be easily obtained.¹⁴ A recent study examining factors that may facilitate the willingness of African Americans to become organ donors determined that improving knowledge about organ donation, particularly with regard to donor involvement and donation-related risks, may be successful in increasing organ donation.²⁶

Examples of national, church-based, and community-based targeted educational interventions are summarized below. It is important to note that although some interventions appear to have been successful in improving knowledge and attitudes about organ donation, discussion of organ donation with family members, and changing organ donor status, it is generally difficult to measure intervention success because of concurrent programs that

directly or indirectly affect organ donation.²⁷ For example, policies aimed at motorcycle helmet use, health system transformation, public health spending, smoking rates, and chronic disease affect the health of the donor pool, which in turn could affect the number of organs available for donation.²⁷

Nationally Targeted Interventions

The National Minority Organ Tissue Transplant Education Program (MOTTEP) was created in 1991 with a mission to decrease the number of ethnic minority Americans on transplant waiting lists.^{17,28,29,30} Fifteen national sites were funded to carry out community-based programs that centered on approaches including community participation and direction to target specific community differences; face-to-face presentations, especially to smaller audiences to foster discussion; collaboration and partnerships with religious, social, and civic organizations; media promotion of MOTTEP's message; dissemination of culturally sensitive and informative brochures, videos, public service announcements, and other information; and comprehensive evaluation to gauge effectiveness of the program.^{17,29,31} The number of organs recovered for transplantation from African Americans increased more than 3-fold between 1991 and 2016, with some suggesting the success is partially due to MOTTEP efforts.^{29,31,32}

Church-Based Targeted Interventions

Another educational program targeting African Americans, Project ACTS (About Choices in Transplantation and Sharing), was a self-administered donation education intervention developed with a focus on addressing religious barriers to donation and encouraging family discussion.³³ The program consisted of materials distributed at churches that are taken home and reviewed individually. The materials included a video hosted by a gospel choir with excerpts from individual and family conversations about beliefs, attitudes, myths, misconceptions, and fears about organ donation/transplantation; an educational pamphlet; a donor card; a National Donor Sabbath pendant; and several additional items embossed with the project name and logo. Participants in the program were 1.6 times more likely to have discussed, or be in discussion, with family members about their organ donation wishes than those who had not participated in the program.³³ A revised program, Project ACTS II, was designed to improve uptake by testing the intervention in individual and group settings.³⁴ Participants in the revised program who viewed the video in a group setting had a significantly greater increase in positive attitudes toward donation and beliefs than those who were given the video to view at home.³⁴ It is thought that the group dynamic provided an opportunity for active contemplation of donation-related beliefs, attitudes, and the act of registration, and engaged people in a way that could not be attained by reviewing materials individually.³⁴

A church-based intervention targeted to Hispanics entailed a 45-60 minute educational program, created specifically for religious organizations, administered to participants in four Catholic churches whose membership was predominantly Hispanic.³⁵ The program, led by a local organ procurement organization and conducted in both English and Spanish, included factual information about the need for organ and tissue transplantation, how the organ donation and allocation process serves such a need, and discussion of religious misconceptions regarding organ donation. After the intervention, significant increases in organ donation knowledge and positive perceptions regarding organ donation were observed.³⁵ However, no change in intent to donate was observed. Interestingly, both before and after the intervention, those whose families supported organ donation were more likely to indicate intent to donate than those whose families did not support donation. The study authors therefore suggest that education focused on family support is important in improving intent to donate.³⁵

Other church-based education programs have not been successful. A peer-led program at predominantly African American churches, in which a church member was trained to provide educational sessions within the church, included the viewing of a video and discussions about organ donation and the provision of brochures and flyers containing the web address of the donor registry.³⁶ No statistically significant differences in organ donation attitudes or intent to donate were observed following the intervention.³⁶ The study concluded that lack of pastoral support may have influenced outcomes, and that participants misinterpreted the consent form to be involved in the study as an affirmative indication that they wished to be organ donors.³⁶

Community-Based Targeted Interventions

A 2007-2012 community-based intervention targeting Hispanics resulted in an increase in consent for organ donation.³⁷ Media messages were conveyed on television and radio, and culturally sensitive educational programs were held at high schools, churches, and medical clinics in four Southern California neighborhoods with a high

percentage of Hispanic residents. Among those targeted by the intervention, the consent rate for organ donation increased significantly from 56 percent before the intervention to 83 percent after the intervention.³⁷

A different approach has been to use peer-to-peer techniques to deliver health education messages. This technique was employed in several Michigan hair salons, with hair stylists acting as lay health advisors to improve organ donation among their African-American clients.³⁸ Stylists delivering the intervention were asked to discuss organ donation at least twice with their clients. Following the intervention, clients in the intervention group were 1.7 times more likely than those in the control group (in which general health topics, but not organ donation specifically, were discussed) to report positive donation status.³⁸

CURRENT AMA POLICY

The AMA has a number of policies related to improving organ donation. Regarding education, AMA policy supports “state of the art” educational materials for the medical community and the public that address the importance of organ donation and the need for organ donors (H-370.995, H-370.996), development of effective methods for meaningful exchange of information to educate the public about donating organs (H-370.959), implementation of UNOS recommendations for organ donation (H-370.983), and the provision of educational materials by states and local organ procurement organizations to attendees of driver education and safety classes (H-370.984).

AMA policy also encourages research on methods for increasing the number of organ donors in the United States, including studies that evaluate the effectiveness of mandated choice and presumed consent models for increasing organ donation (H-370.959); studies evaluating the use of incentives, including valuable considerations, to increase living and deceased organ donation rates (H-370.958); and pilot studies on promotional efforts that stimulate each adult to respond “yes” or “no” to the option of signing a donor card. Ethical Opinion 6.1.4, “Presumed Consent and Mandated Choice for Organs from Deceased Donors,” describes the ethical challenges of presumed consent and mandated choice models and emphasizes the need for education about organ donation.

CONCLUSIONS

Although the numbers of organ donors and transplants have grown over the last two decades, the need for donated organs still far exceeds the number available for transplantation. This disparity is especially true for certain racial and ethnic minorities that make up a larger proportion of the transplant waiting list compared to their relative proportion among organ donors. Educational programs that address identified factors influencing attitudes toward organ donation and targeted to populations with historically low organ donation rates have been developed to improve donation. Some have been successful at improving knowledge about organ donation, comfort in discussing organ donation wishes with family members, and intent to donate; however, it is difficult to determine the impact of the programs on donation because they do not occur in isolation from other factors that may influence organ donation rates.

Non-targeted educational approaches have had success as well. For example, an organ donation registration campaign in California consisting of intense public awareness using public service announcements; news conferences; and community outreach in federal buildings, universities, and libraries; combined with an online organ donor registration process at the Department of Motor Vehicles, improved consent for donation from 47.5 percent before the campaign to 51 percent after the campaign.³⁹ And direct mail campaigns, in which information about organ donation and a request to join the state organ donor registry are mailed to residents, have been successful in prompting both young adults and older adults to join organ donation registries.^{40,41}

Additionally, other approaches to improving organ donation rates should be explored. A 2015 analysis examined a number of state policies on organ donation, including first-person consent laws, donor registries, dedicated revenue streams for donor recruitment activities, population education programs, paid leave for donation, and tax incentives, and found that only revenue policies to promote organ donation had any effect on organ donation and transplantation.²⁷ These revenues can be used on funding for outreach campaigns and educational programs that incorporate elements that appear to be most successful in increasing intent to donate. Others have proposed that financial incentives in the form of a contribution to a donor’s retirement fund, an income tax credit, a tuition voucher, or a posthumous funeral benefit would be far more effective at increasing the donor pool than educational approaches.⁴²

The Council on Science and Public Health supports continued implementation of targeted educational programs that have shown promise in increasing intent to donate, and encourages further study of other approaches that may be successful.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and remainder of report filed.

1. That Policy H-370.959, “Methods to Increase the US Organ Donor Pool,” be amended by addition to read as follows:

In order to encourage increased levels of organ donation in the United States, our American Medical Association: (1) supports studies that evaluate the effectiveness of mandated choice and presumed consent models for increasing organ donation; (2) urges development of effective methods for meaningful exchange of information to educate the public and support well-informed consent about donating organs, including educational programs that address identified factors influencing attitudes toward organ donation and targeted to populations with historically low organ donation rates; and (3) encourages continued study of ways to enhance the allocation of donated organs and tissues.

2. That Policy D-370.984 be rescinded, having been accomplished through this report.

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3. NEUROPATHIC PAIN AS A DISEASE (RESOLUTION 912-I-16)

Reference committee hearing: see report of Reference Committee K.

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
IN LIEU OF RESOLUTION 912-I-16
REMAINDER OF REPORT FILED
See Policy D-160.922**

Resolution 912-I-16, “Neuropathic Pain as a Disease,” introduced by the American Academy of Pain Medicine at the 2016 Interim Meeting and referred to the Board of Trustees, asked:

That our American Medical Association recognize neuropathic pain as a disease state with multiple pathophysiological aspects requiring a range of interventions to advance neuropathic pain treatment and prevention.

METHODS

English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 2005 to August 2017 using the search terms “neuropath*,” in combination with “pain,” and “pathophysiology,” “chronic,” and “pain as a disease.” A total of 103 articles were retrieved for analysis based on their ability to supply new information about the pathogenesis of chronic and neuropathic pain, as well as viewpoints on whether chronic (including neuropathic) pain can or should be considered as a disease in its own right. Medical dictionaries were consulted for definitions of disease and related terms.

BACKGROUND

The Council previously examined the issue of neuropathic pain on two occasions. In 2005, the Council reviewed the neurobiology of nociceptive and neuropathic pain, and the definition, classification, common causes, diagnostic approach, and pharmacologic management of neuropathic pain.¹ In 2010, the Council reviewed more recent findings about how neural damage, which is the signature precipitating event for the development of neuropathic pain, provokes multiple responses in nociceptive pathways that generate and amplify pain.² Such responses include peripheral and central sensitization, ectopic activity in pain carrying fibers, neuronal cell death, disinhibition, altered gene expression, neuron sprouting, neuronal plasticity and modified neural connectivity.² Some discussion was devoted to whether such changes, which can eventually persist in the absence of ongoing noxious stimuli, should be considered maladaptive and warrant consideration as a disease. The Council did not specifically endorse that viewpoint, concluding in part, that the clinical value of viewing chronic or neuropathic pain as a disease was not established. This report responds to the specific request that our AMA, through Council evaluation and deliberation by the House of Delegates, recognize neuropathic pain as a disease state. It is already established that neuropathic pain is characterized by “multiple pathophysiologic aspects” and requires a treatment approach that differs from that applied to chronic nociceptive and inflammatory pain.

RELEVANT DEFINITIONS

Pain Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”³ This definition acknowledges that pain is a conscious experience involving interpretation of (painful) sensory input that is influenced by emotional, pathological, and cognitive factors, as well as previous pain experiences.

Nociceptive Pain Nociceptive pain is caused by tissue injury generating pain through the primary somatosensory nervous system via a process involving activation of peripheral nociceptors, transduction, transmission, modulation and perception of noxious stimuli. Nociceptive pain can be acute, subacute or chronic, may be complicated by inflammation, and may be visceral or referred in origin.

Chronic Pain Chronic pain has been variously defined. The definition used by the Centers for Disease Control and Prevention in developing its guideline on the use of opioids in chronic noncancer pain is based on the International Association for the Study of Pain (IASP) definition:

Ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury healing, more than 3 to 6 months, and which adversely affects the individual’s well-being⁴

Neuropathic Pain Neuropathic pain was re-defined by the IASP in 2012 as “pain initiated or caused by a lesion or disease of the somatosensory system.”⁵ The basis for this definition is that “neuropathic pain is not a single disease, but a syndrome caused by a range of different diseases and lesions, which manifests as an array of symptoms and signs.”

Disease

- An interruption, cessation, or disorder of body function, system, or organ OR a morbid entity characterized usually by at least two of these criteria: recognized etiologic agent(s), identifiable group of signs and symptoms, or consistent anatomic alterations.⁶

- Any deviation from or interruption of the normal structure or function of any body part, organ, or system that is manifested by a characteristic set of symptoms and signs whose etiology, pathology, and prognosis may be known or unknown.⁷

Syndrome The aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease.⁷

Disorder An illness that disrupts normal physical or mental functions.⁶

EVOLUTION OF PAIN THEORY

Initial investigation and understanding of pain focused on describing the specific somatosensory pathways involved in pain processing.⁸ Nociception is the perception of noxious stimuli and represents an alarm signal mediated by specialized primary afferent (sensory) neurons that respond to sufficiently intense thermal, mechanical, or chemical stimuli, transduce these stimuli into electrical activity, and transmit signals via well-defined pathways in the central nervous system. Cell bodies of the primary afferent neurons are located in dorsal root ganglia and the spinal sensory nucleus of cranial nerve V; bifurcated axonal processes are distributed to the periphery for detection, and to the spinal cord to transmit information centrally. A δ fibers (thinly myelinated) carry a well-localized “first” pain of sharp, pricking quality. C fibers (unmyelinated) carry a poorly localized “second” pain of dull and persistent or burning quality. Muscle and deep tissue nociceptor stimulation produce aching or cramping type pain. There are several sub-populations of primary afferents that differ in their axon diameter, response to stimuli, neurophysiologic and neurochemical characteristics and targets in the dorsal horn of the spinal cord.⁹ When local inflammation ensues, certain features of the nociceptive response are modified and magnified to aid healing and repair.

In the spinal cord, peripheral pain-carrying primary afferent terminals synapse on (second order) neurons within the superficial lamina of the dorsal horn, which ascends to form the spinothalamic tract and spinoreticular system. The former transmits information about acute pain (location, intensity, quality) through the thalamus to the somatosensory cortex and the latter is involved with autonomic and affective reactions to pain. The dorsal horn is not a simple relay station but is subject to “gating” by local interneurons with inhibitory and excitatory influences, as well as descending influences from the midbrain and higher centers.¹⁰

Secondary spinal projection neurons transmit nociceptive information to brainstem regions, including the rostral ventral medulla and periaqueductal gray (PAG); this information is further modulated in the brainstem, relayed to the thalamus, and then transmitted to the cortex where it is interpreted as pain. Several cortical regions are involved in pain processing, including the primary somatosensory cortex, secondary somatosensory cortex, insular cortex, prefrontal cortex, and motor cortex.¹¹

The Pain Matrix

Although a detailed understanding of the neuroanatomy of nociception exists, neuroimaging studies have identified several brain regions that are activated during the “pain experience.” This pattern of neural activation has been posited to represent an array of interrelated brain regions integral to human pain perception and response or colloquially representing the “neurosignature of pain.”¹²⁻¹⁵ An extensive neural network (dubbed the “pain matrix”) is accessed during the processing of nociceptive input including the primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices and the thalamus; subcortical areas (e.g., brain stem, PAG, hypothalamus, amygdala, hippocampus, and even the cerebellum) also are involved in the pain experience.¹⁵⁻¹⁹ Thus, modulation of the primary nociceptive stimulus occurs within the spinal cord where noxious stimuli are just part of the overall sensory input, in response to descending neuronal influences, and at numerous supraspinal levels affecting the discriminative, emotional, and cognitive aspects of pain.^{4,10,20}

Neuroimaging studies have shown that many brain regions activated by nociceptive stimuli also are activated during various emotional and behavioral responses, and that non-nociceptive events or inputs (e.g., loss of a loved one, social exclusion) can produce pain-like experiences.²¹⁻²³ These types of findings have informed a conceptual three-tiered hierarchical model of the human pain experience based on nociception (1st tier), conscious perception subject to cognitive and attentional modulation and the triggering of somatic reactions (perceptive-attentional, 2nd tier), and consideration of how individual factors and characteristics (including psychological factors and emotional context)

influence pain and the memory of that experience (reappraisal-emotional, 3rd tier).²⁴ Brains regions involved in the second and thirds tiers can either inhibit or facilitate nociception in a descending fashion.

The Biopsychosocial Model of Chronic Pain

Pain is an individual and subjective experience, recognized as an integrative sum of nociceptive input and factors related to cognition, mood, and context, as well as individual variables such as genetics and sex. Chronic pain and patient outcomes are influenced by individual biologic, psychologic and social factors and various common comorbidities (Figure 1).^{25,26} Brain regions involved in the pain matrix are involved in many other sensory, motor, cognitive, and emotional functions and a reciprocal relationship exists between chronic pain and mental health disorders. Neural pathways that involve pain, depression and anxiety overlap and likely have important biological interactions that are not well understood.²⁷ Chronic pain induces disturbances in mood (reactive depression or anxiety), impaired coping (often with catastrophization), and other processes which can worsen pain and pain-related distress and lead to fear-avoidance behaviors. Pain patients also have much higher premorbid or comorbid psychosocial concerns, mental health disorders and cognitive distortions that influence the pain experience and drive pain-related distress. Individuals who observe other people's suffering often experience a subjective enhancement of their own pain suffering.²⁸ Thus, the pain experience is influenced by various cognitive, emotional, and environmental factors affecting brain function.²⁹ Chronic pain is a multidimensional experience that, like other chronic conditions has multiple contributors, including psycho-behavioral ones. Effective management often demands a multidisciplinary assessment and treatment plan that identifies and addresses all the components of the individual's pain experience.

IS CHRONIC (OR NEUROPATHIC) PAIN A DISEASE?

Many "diseases" are accompanied by persistent pain including cancer, human immunodeficiency virus infection, osteoarthritis/rheumatoid arthritis, lower back injury, headache, degenerative spine disease, fibromyalgia, diabetes, post herpetic neuralgia, etc. However, when considering whether neuropathic pain is a disease, it is important to note that the question of whether chronic pain should be considered a disease is not a new concept.

In 2001, the IASP and the European Federation of IASP Chapters adopted the following declaration:

Pain is a major healthcare problem worldwide. Although acute pain may reasonably be considered a symptom of disease or injury, chronic and recurrent pain is a specific healthcare problem, a disease in its own right.

The landmark 2011 report by the Institute of Medicine on Relieving Pain in America concluded that:

Chronic pain can be a disease in itself. Chronic pain has a distinct pathology, causing changes throughout the nervous system that often worsen over time. It has significant psychological and cognitive correlates and can constitute a serious, separate disease entity.³⁰

In 2016 Vardeh et al noted:

The past few decades have witnessed a huge leap forward in our understanding of the mechanistic underpinnings of pain, in normal states where it helps protect from injury, and also in pathological states where pain evolves from a symptom reflecting tissue injury to become the disease itself.³¹

Neuropathic Pain

With respect to neuropathic pain, many different types of neural lesions and systemic diseases trigger neuropathic pain symptoms (e.g., diabetes, post-herpetic neuralgia, radiculopathies, stroke, spinal cord injury, chemotherapy, certain surgeries, alcohol misuse, vitamin deficiencies, heavy metal toxicity, and many other causes and triggers).³² Signs and symptoms characteristic of neuropathic pain include spontaneous "positive" (gain of function) signs (e.g., paresthesias, burning, shooting or shock-like pains), "negative" (loss of function) signs (e.g., numbness, weakness, hypoalgesia, decreased tendon reflexes) and certain stimulus-dependent or evoked signs (e.g., allodynia, hyperalgesia) (Figure 2).³³ Diseases causing neuropathic pain vary substantially in terms of anatomical location and cause; depending on the cause, individual patients exhibit similar clinical characteristics, but not all symptoms that are commonly associated with neuropathic pain. Two prominent neuropathic pain symptoms across causes are allodynia (pain induced by normally innocuous stimuli) and hyperalgesia (increased pain in response to noxious stimuli) (see below).

Debate on Chronic Pain as a Disease

The field of pain medicine, the Institute of Medicine and some clinicians and researchers have proposed that chronic pain should be considered a disease; others continue to see pain primarily as a symptom of disease.^{30,34-39} Much of the thinking about chronic pain as a disease has been driven by neuroimaging studies, and structural/functional changes observed in animal models of chronic pain and/or neural injury. It has been proposed that because some unique changes accompany neural injury, chronic pain with a neuropathic component should be considered in a distinct fashion.⁴⁰

Neuroimaging. An extensive literature base exists on using various brain imaging techniques in patients with chronic pain, including neuropathic pain; most studies have been cross-sectional. A comprehensive review is beyond the scope of this report. A critical review of more than 100 brain neuroimaging reports identified neural correlates of chronic pain associated with various diseases (i.e., osteoarthritis, irritable bowel syndrome, back pain, fibromyalgia) and demonstrated distinctions from images associated with acute nociceptive pain.⁴¹ Patients suffering from chronic pain also exhibit dysfunction in descending inhibition of pain, less gray matter in the thalamus and prefrontal cortex with more gray matter loss in patients with neuropathic components; differences in various measures of brain neurochemistry also have been demonstrated.⁴¹ Subsequent studies extended these findings to other chronic pain conditions (pelvic pain, complex regional pain syndrome, diabetic peripheral neuropathy, phantom limb pain) demonstrating changes in gray matter density in multiple cortical regions, as well as the amygdala and hippocampus.¹⁴ What remains unresolved is to what extent altered structure, function and neurochemistry represents a “disease” or are simply neuroplastic adaptive processes in response to ongoing nociceptive input, or reflect the consequences of pain, common co-morbid conditions, medications, or altered lifestyles in patients with chronic pain.⁴²

Cellular and Functional Changes. Adaptive and persistent cellular and functional modifications also have been used to support the concept that neuropathic pain, in particular, is a chronic disease. As described in the previous Council report, neural injury provokes a host of neuroplastic and neuroimmune responses which become drivers of neuropathic pain, some of which also are common to persistent nociceptive/inflammatory pain.^{2,43-46} These include:

- peripheral sensitization of nociceptors related to altered trafficking of ion channels. Peripheral sensitization decreases the threshold for activation and augments normally painful stimuli (primary hyperalgesia) and triggers the development of spontaneous (ectopic) activity in primary afferent neurons;
- central sensitization, characterized by increased spontaneous activity, expansion of receptive fields, and a decreased threshold to primary afferent inputs into the dorsal horn. This ultimately enhances the function of neurons and circuits in nociceptive pathways via increased membrane excitability, increased synaptic efficacy, and reduced inhibition. It manifests as mechanical allodynia and secondary hyperalgesia;
- changes in the phenotype of low threshold sensory fibers (A β) that are normally activated by touch, pressure, and vibration, to one whereby they can generate sensations of pain or tenderness;
- a pathological triad of reciprocal interactions among neurons, immune cells, and glial cells with glia activation and release of proinflammatory mediators that contributes to both peripheral and central sensitization; and
- disinhibition resulting from an imbalance of excitatory and inhibitory influences at the spinal cord level, and descending facilitation from the brain stem and higher centers.

DISCUSSION AND COMMENT

Recognition of chronic pain as a disease may lead to increases in resources, education, and priority, but considerable attention has already been devoted to the burden of chronic pain in the United States, and a National Pain Strategy has been developed.⁴⁷

A disease, by definition, requires a set of “characteristic signs and symptoms.” Chronic pain is:

complex, affecting individuals physically, mentally, socially and spiritually. This results in a common symptomatic and functional spectrum of physical, cognitive, psychological and behavioral effects. Decreased physical functioning coupled with little hope for effective treatment often results in a downward spiral of depression, distress, anxiety, and sleep problems, which lead to impaired social functioning and family relationship that all increase perceived pain.⁴⁸

Some of these consequences may be explained by common neural substrates or reciprocal interactions and may not be considered unique to chronic pain because they can accompany any chronic condition that causes substantial distress.

With neural injury or repetitive nociceptive stimuli, remodeling of the nervous system and alteration in gene expression occurs. Such changes reflect neuroplasticity that impacts pain in the peripheral and central nervous system, leading to increased excitability within pain circuits and generating peripheral and central sensitization, which underlie the phenomena of hyperalgesia, allodynia, and the spread of pain to adjacent uninjured regions (secondary hyperalgesia). Based on neuroimaging research, cross sectional studies of structural and functional changes accompanying chronic pain, including neuropathic pain, support clear differences compared with both normal conditions and the presence of acute nociceptive pain, but it remains unclear what the cause and effect relationships might be, or whether such brain alterations should be viewed primarily as an adaptive response to continuing nociceptive input. Do these phenomena fulfill the requirement for the presence of “characteristic signs and symptoms?” Does it make sense to consider an altered pain response as a symptom that can logically define pain as a disease?

With respect to pain management and relieving the burden of suffering among patients with chronic pain, it would seem that wider adoption of the biopsychosocial model of pain management should be the most important goal, with attention to reducing pain, restoring function, cultivating well-being and improving quality of life. This requires identifying and addressing psychosocial contributors and emphasizing active over passive modalities. For neuropathic pain, diagnostic and management approaches are different; preferred initial pharmacological interventions are antiepileptic and antidepressant drugs. Several interventional approaches are available but psychobehavioral approaches can be more challenging in patients with neural injury.²

CONCLUSION

The topic of neuropathic pain as disease would be best deliberated by a multi-specialty group of experts involved in the evaluation and treatment of pain that could more deeply focus on the topic and consider all of its ramifications. At the 2016 Interim Meeting the House of Delegates adopted a resolution directing the AMA to convene a Federation-based pain care task force (Policy D-160.922). This task force is in the process of being formed and the Council believes that it is a more appropriate body to address this issue in a comprehensive manner.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 912-I-16 and the remainder of this report be filed:

That the Federation Task Force on Pain Care evaluate the relative merits of declaring neuropathic pain as a distinct disease state, and provide a recommendation to the Council on Science and Public Health.

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Figure 1. Biopsychosocial Context of Pain

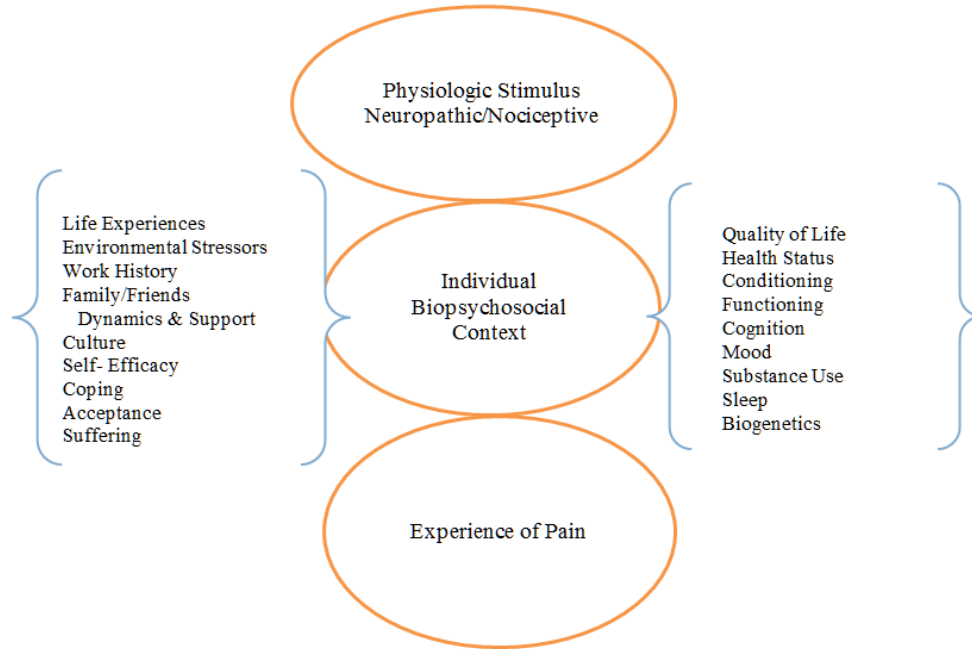
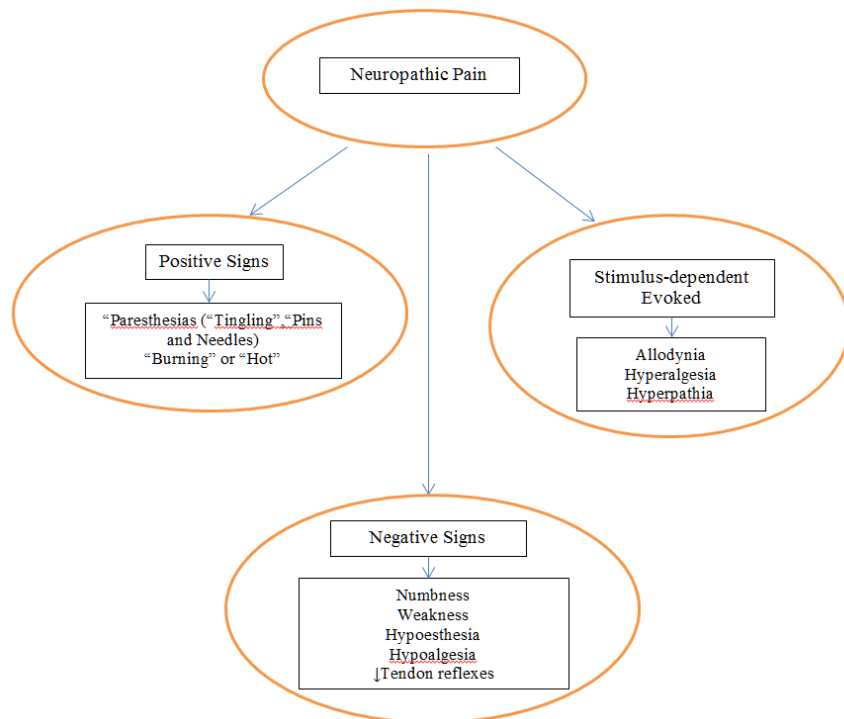


Figure 2. Signs and Symptoms Characteristic of Neuropathic Pain



4. NATIONAL DRUG SHORTAGES: UPDATE

Reference committee hearing: see report of Reference Committee K.

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
REMAINDER OF REPORT FILED**
See Policy H-100.956

INTRODUCTION

Policy H-100.956, “National Drug Shortages,” directs the Council on Science and Public Health (CSAPH) to continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates (HOD) on progress made in addressing drug shortages in the United States. This informational report provides an update on continuing trends in national drug shortages and ongoing efforts to further evaluate and address this critical public health issue.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from September 2016 to August 2017, using the text term “drug shortages” combined with “impact,” “crisis,” “oncology,” “chemotherapy,” “antibacterial,” “pediatric(s),” “nutrition,” and “parenteral.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the US Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), Pew Charitable Trusts, the Association for Accessible Medicines, the Pharmaceutical and Research Manufacturers of America (PhRMA) and by direct contact with key FDA, ASHP, and Utah Drug Information Service staff who monitor drug shortages and related issues on a daily basis.

BACKGROUND

The Council has issued seven reports on drug shortages.¹⁻⁷ The findings and conclusions of the first five reports are summarized in CSAPH Report 2-I-15.⁶ The remainder of this report will update information on drug shortages since the 2016 report was developed.

CURRENT TRENDS IN DRUG SHORTAGES

The two primary data sources for information on drug shortages in the United States continue to be the Drug Shortage Resource Center maintained by ASHP in cooperation with the University of Utah Drug Information Service and the Drug Shortage Program at the FDA.^{8,9} Table 1 summarizes how the ASHP’s and FDA’s information and statistics on drug shortages are developed. The ASHP defines a drug shortage as “a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.”

The FDA defines shortages as “a period of time when the demand or projected demand for a medically necessary drug in the United States exceeds its supply.” Medically necessary drugs are defined by FDA as “any drug product used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other drug that is judged to be an appropriate substitute or there is an inadequate supply of an acceptable alternative.”

Because their criteria differ (the main distinction being the FDA’s definition of a “medically necessary drug”), the ASHP site lists more drug shortages than the FDA site.

American Society of Health-System Pharmacists

As of August 7, 2017, ASHP’s Drug Shortage Resource Center identified 133 drugs in shortage, approximately the same number as at the corresponding time in 2016 (135). In addition, 14 products are not commercially available at all.⁹ Seventy-one manufactured drugs have been discontinued since 2010, an increase of two from a year ago. Nearly 85% of drug shortages are generic sterile injectable formulations. The top active shortages by drug class remain antimicrobials, electrolytes and nutritional components, central nervous system agents, chemotherapeutic

agents and cardiovascular/autonomic drugs. For a longitudinal view of new drug shortages on an annual basis, and the number of active drug shortages quarterly, see the Appendix. Active shortages include both new and unresolved drug shortages. According to ASHP, the number of new shortages is currently on a par with 2016, and the number of active shortages has stabilized.

US Food and Drug Administration

As of August 7, 2017, the FDA reported that 46 drugs were currently in shortage (compared with 61 one year ago), and 13 other shortages had been resolved.⁹ The latter are closely monitored because they may be at risk for falling back into shortage. Based on passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, companies are required to notify the FDA of a permanent discontinuance or an interruption in manufacturing of certain drug products six months in advance, or if that is not possible, as soon as practicable. The shortage notification requirement has apparently reduced the number of new shortages by allowing FDA additional time to work with manufacturers to prevent shortages. The FDA's drug shortages website lists drugs that meet these criteria, reflecting shortage information supplied by manufacturers.⁸ A Final Rule published on July 27, 2015, provides further guidance on the notification process and adds biologic products to the requirements for notification about potential supply disruptions.⁹

Drug Shortages Metrics Reported by FDA. The FDA's fourth annual report on drug shortages (required by FDASIA) noted the following metrics during the first three quarters of calendar year 2016.¹⁰

- FDA was notified of 186 potential shortage situations by 67 different manufacturers, a 35% increase over the number of potential shortages reported in 2015.
- 64 new drug shortages were prevented in the first three quarters of 2016, a 50% decrease over the comparable time period for 2015.
- The review of 102 generic abbreviated new drug or supplemental applications was expedited, exactly the same as the number reported in 2015.
- 10 inspections were prioritized to address a drug shortage, comparable to the number reported in 2015.
- Three fewer new drug shortages occurred in 2016 (23) compared with 2015 (26); currently, FDA is working to resolve 24 ongoing shortages that began prior to 2016, which is a decrease from the 64 ongoing shortages tracked at the end of 2015 (Personal Communication, Valerie Jensen, RPh, FDA).
- FDA exercised regulatory flexibility and discretion in 25 instances affecting 15 medically necessary products.¹⁰ Most of these involved measures to mitigate risks such as the use of filters to remove particulate matter, extra testing for quality, third-party oversight of production, provision of special instructions to prescribers and/or patients, approval of foreign sources, and expanded access to investigational drugs for treatment use. With respect to approval of new foreign sources, the FDA now conducts regular virtual meetings with their international regulatory counterparts to share information on drug shortages and mitigation strategies impacting patients in other countries.

The FDA continues its work to improve its system for data tracking and drug shortage analysis. The FDA released a new technology platform in 2017 for drug manufacturers/applicants to send drug shortage and supply notifications. The "Direct NextGen" platform allows users to login, enter their shortage information, and submit to the FDA. This approach is intended to "streamline day-to-day work to identify and mitigate shortages, including research, data entry, and data management."¹⁰

The FDA also has developed apps for both the iPhone and Android operating systems that provide access to drug shortage information as well as notifications about new and resolved drug shortages. Physicians can directly report a drug shortage via the app, the ASHP drug shortage [website](#), or to the Center for Drug Evaluation and Research via email (drugshortages@fda.hhs.gov) or by phone at 240-402-7770.

In late June 2017, the FDA took additional steps to increase competition in the market for prescription drugs and facilitate entry of lower-cost alternatives. The agency published a list of off-patent, off-exclusivity branded drugs without approved generics, and also implemented, for the first time, a new policy to expedite the review of generic drug applications where competition is limited.^{11,12}

STATE OF THE INDUSTRY

Report from Pew Charitable Trusts

Potential economic drivers of drug shortages were previously evaluated by the Council.^{2,5,7} A new report from Pew Charitable Trusts and the International Society for Pharmaceutical Engineering took a closer look at shortages of sterile injectable pharmaceutical products based on interviews with company executives; the main focus areas were market forces, business continuity planning, and supply chain management.¹³

The report confirmed that quality issues continue to be a driving force behind shortages. Examples included FDA-inspection-related delays, delays in active pharmaceutical ingredient acquisition, failure of final product quality to meet good manufacturing practices, and problems arising from transferring the product from development (or in transferring new technology for a legacy product) to commercial manufacturing site. Factors cited by companies that contributed to drug shortages other than quality included market withdrawals, supply chain design, lack of business continuity elements needed to protect against shortages, limited purchaser-manufacturer incentives, limited insight into future market demands, and regulatory challenges impacting facility expansion or upgrading equipment; the latter is especially pertinent for legacy products.

CURRENT PERSPECTIVE

Based on analysis by the Utah Drug Information Service, during the past 2 years, the number of new drug shortages affecting clinicians and patients has been declining, and the number of active and ongoing drug shortages has remained similar (Appendix, Personal Communication, Erin Fox, PharmD). Shortages have stabilized, but even though the number remains elevated, it is significantly lower than 3 to 4 years ago. The fact that a high number of shortages continues to exist has obscured to a certain degree the progress that has been made, largely attributable to manufacturer notification requirements and proactive steps taken by the FDA. These changes have substantially decreased the actual number of shortages by preventing a large number of new ones. Significant progress has been made overall, but this progress has remained largely unnoticed by hospital pharmacists and practicing physicians who continue to experience the effects of ongoing shortages on a daily basis.

Additionally, it is apparent that some difficult challenges to continued progress exist. As previously noted, most drug shortages involve generic sterile injectable formulations and the cause of these shortages is typically manufacturing and quality problems. The 2016 report from the Government Accountability Office (discussed in the 2016 Council report) identified a decline in the number of suppliers, failure of a supplier to comply with manufacturing standards resulting in a warning letter, and manufacturers operating at low profit margins for generic drugs as primary contributing factors.¹⁴ A major contributing factor to this trend was the failure of Boehringer Ingelheim's BenVenue manufacturing facility in Bedford, Ohio, in 2013, which at the time was one of the largest suppliers of sterile injectable drugs, including many cancer chemotherapy products. The failure occurred despite the investment of \$350 million to upgrade the facility; facing projected deficits of at least \$750 million, the facility was not profitable and was closed.¹⁵

Currently, the majority of sterile injectables for the US market are produced by Pfizer (Hospira), Fresenius Kabi (Akorn), Teva and Baxter; other contributors are American Regent (Luitpold), Sandoz, and Mylan. Pfizer completed its acquisition of Hospira, at the time the largest manufacturer of sterile injectable in the United States, in September 2015. Recent events have created a climate of worsening drug shortages for critical care and emergency medications as well as some of what would be considered "basic products" emanating from the Hospira portfolio. In April 2017, Pfizer notified clinicians about a shortage of pre-packaged emergency drug syringes including atropine, dextrose, epinephrine, and sodium bicarbonate. In June, Pfizer recalled 42 lots of sodium bicarbonate vials (approximately half of supplies) due to concerns that the product may not be sterile; succinylcholine was also impacted by this recall.¹⁶ Most recently, Pfizer had to halt production of 30 different Carpuject™ products (morphine, hydromorphone, etc.) due to problems at a specific manufacturing facility. Vial substitutes exist for most of the Carpuject™ products, but there may be shortages later this year. In response, the FDA extended expiration dating for emergency syringes, approved another supplier of sodium bicarbonate, and also allowed imported sodium bicarbonate.¹⁷

Although attention remains focused on injectable products, shortages of some solid dosage forms, including atenolol, furosemide, and methylphenidate tablets also have created problems for clinical management this year.

CONCLUSION

The generic sterile injectable drug industry is fragile and some drug supplies for acutely and critically ill patients in the United States remain vulnerable despite industry and federal efforts. Until new and reliable production capacity for sterile injectables is developed, the situation will not appreciably improve. Some progress is being made, but permanent solutions remain elusive and beyond the control of individual practitioners and the health care system. As long as a free market economy exists and no one entity, including the FDA can mandate that a company produce a specific product, drug shortages will exist into the foreseeable future as the industry continues to merge and contract (except for high cost specialty drugs), the number of drugs emerging off patent increases each year, and the profit margin for legacy products disappears. This dynamic is occurring at the same time that pharmaceutical companies are under increasing pressure to reduce drug costs. The recent acquisition of Hospira by Pfizer and the resulting shortages raises the issue of how such acquisitions or mergers might impact the likelihood of such shortages.

RECOMMENDATION

The Council recommends that Policy H-100.956 be amended by addition to read as follows:

National Drug Shortages

1. Our AMA supports recommendations that have been developed by multiple stakeholders to improve manufacturing quality systems, identify efficiencies in regulatory review that can mitigate drug shortages, and explore measures designed to drive greater investment in production capacity for products that experience drug shortages, and will work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.
2. Our AMA supports authorizing the Secretary of Health and Human Services to expedite facility inspections and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage.
3. Our AMA will advocate that the US Food and Drug Administration (FDA) and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. This plan should include establishing the necessary resiliency and redundancy in manufacturing capability to minimize disruptions of supplies in foreseeable circumstances including the possibility of a disaster affecting a plant.
4. The Council on Science and Public Health shall continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates on progress made in addressing drug shortages.
5. Our AMA urges the development of a comprehensive independent report on the root causes of drug shortages. Such an analysis should consider federal actions, the number of manufacturers, economic factors including federal reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing. In particular, further transparent analysis of economic drivers is warranted. The Centers for Medicare & Medicaid Services should review and evaluate its 2003 Medicare reimbursement formula of average sales price plus 6% for unintended consequences including serving as a root cause of drug shortages.
6. Our AMA urges regulatory relief designed to improve the availability of prescription drugs by ensuring that such products are not removed from the market due to compliance issues unless such removal is clearly required for significant and obvious safety reasons.
7. Our AMA supports the view that wholesalers should routinely institute an allocation system that attempts to fairly distribute drugs in short supply based on remaining inventory and considering the customer's purchase history.
8. Our AMA will collaborate with medical specialty partners in identifying and supporting legislative remedies to allow for more reasonable and sustainable payment rates for prescription drugs.
9. Our AMA urges that during the evaluation of potential mergers and acquisitions involving pharmaceutical manufacturers, the Federal Trade Commission consult with the FDA to determine whether such an activity has the potential to worsen drug shortages.

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Table 1. Contrasting the FDA (CDER) and ASHP Drug Shortage Websites

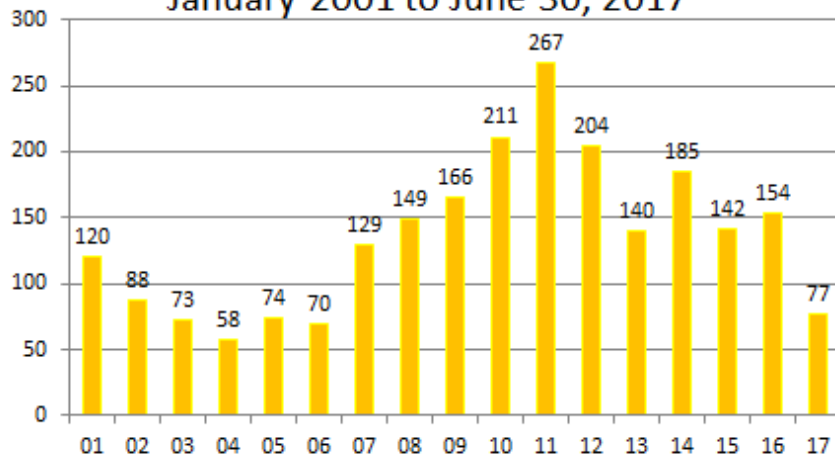
	FDA	ASHP
Purpose	Provides information obtained from manufacturers about current shortages, estimated duration, and discontinuations and provides information about FDA’s and other stakeholders’ roles in addressing and preventing shortages	Notification of new shortages and status of ongoing shortages; drug shortage management resources
Audience	Public	Healthcare practitioners
Scope of shortage list	All drugs are listed that are confirmed to be a national shortage by FDA. A shortage is considered to be the period of time when the demand for the drug within the United States exceeds the supply of the drug.*	All drug and biologic shortages reported and confirmed with manufacturer that are national in impact.
Source of shortage report	Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports are also received from ASHP and from public via drugshortages@cder.fda.gov Note: Manufacturer-provided information represents shortage status at drug firm level.	Voluntary reports from practitioners, patients, pharmaceutical industry representatives and others Note 1: Information is updated based on release dates from manufacturers. Note 2: Reports reflect status at healthcare provider level.
Criteria for inclusion on list	Manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research. Drug listed are defined as “medically necessary.”	(1) Shortage is verified with manufacturers and (2) affects how pharmacy prepares or dispenses a product, or (3) requires use of alternative drugs, which may affect patient care.

Criteria for resolving shortage	One or more manufacturers are in production and able to meet full market demand.	All manufacturers of the drug restore all formulations and dosage sizes to full availability. Note: Products are listed despite partial or restricted availability as supply chain disruptions can result in intermittent shortages at the provider or patient level.
Reason for shortage	Provided by manufacturers using reasons required by legislation. † FDA encourages firms to provide additional information about reasons and other information which, if proprietary, is nondisclosable without the firm’s permission.	Provided by manufacturer, if willing to disclose. Note: May differ from FDA’s due to different sources of information and legislation requiring FDA to use specified reasons
Other information	Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters	Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives
<p>* Note: A separate shortage webpage for vaccines and some biologics is maintained by the Center for Biologics Evaluation and Research. † Categories include (a) requirement related to complying with good manufacturing practices; (b) regulatory delay; (c) shortage of an active ingredient.</p>		

APPENDIX

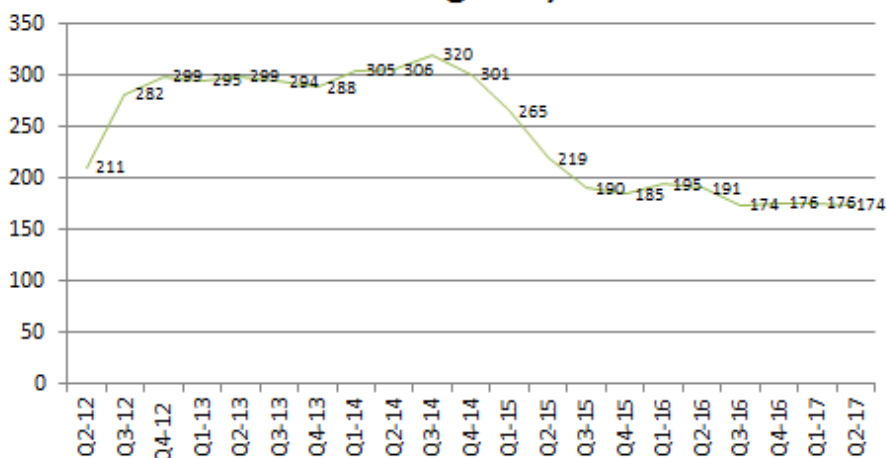
National Drug Shortages New Shortages by Year

January 2001 to June 30, 2017



Note: Each column represents the number of new shortages identified during that year.
 University of Utah Drug Information Service
Erin.Fox@hsc.utah.edu, @foxerinr

National Drug Shortages – Active Shortages by Quarter



Note: Each column represents the number of active shortages at the end of each quarter.
 University of Utah Drug Information Service
Erin.Fox@hsc.utah.edu, @foxerinr

5. CLINICAL IMPLICATIONS AND POLICY CONSIDERATIONS OF CANNABIS USE (RESOLUTION 907-I-16)

Reference committee hearing: see report of Reference Committee K.

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
 IN LIEU OF RESOLUTIONS 907-I-16 AND 915
 REMAINDER OF REPORT FILED**

See Policies H-95.923, H-95.924, H-95.936, H-95.952 and D-95.969

INTRODUCTION

Resolution 907-I-16, “Clinical Implications and Policy Considerations of Cannabis Use,” introduced by the Resident and Fellow Section and referred by the House of Delegates, asked that our AMA amend Policy H-95.998 by addition and deletion to read as follows:

H-95.998 AMA Policy Statement on Cannabis

Our AMA believes that (1) cannabis is a dangerous drug and as such is a public health concern; (2) ~~sale of cannabis should not be legalized;~~ (3) public health based strategies, rather than incarceration, should be utilized in the handling of individuals possessing cannabis for personal use; and (4) (3) additional research should be encouraged,

and amend Policy D-95.976 by deletion to read as follows:

D-95.976 Cannabis - Expanded AMA Advocacy

1. Our AMA will educate the media and legislators as to the health effects of cannabis use as elucidated in CSAPH Report 2-I-13, A Contemporary View of National Drug Control Policy, and CSAPH Report 3-I-09, Use of Cannabis for Medicinal Purposes, and as additional scientific evidence becomes available. 2. Our AMA urges legislatures to delay initiating full legalization of any cannabis product until further research is completed on the public health, medical, economic and social consequences of use of cannabis and, instead, support the expansion of such research. 3. Our AMA will also increase its efforts to educate the press, legislators and the public regarding its policy position that stresses a “public health”, as contrasted with a

“criminal,” approach to cannabis. 4. Our AMA shall encourage model legislation that would require placing the following warning on all cannabis products not approved by the U.S. Food and Drug Administration: “Marijuana has a high potential for abuse. ~~It has no scientifically proven, currently accepted medical use for preventing or treating any disease process in the United States.~~”

The Council on Science and Public Health (Council) has issued four previous reports on cannabis (1997, 2001, 2009, and 2013) establishing a broad policy base.¹⁻⁴ This report focuses on the health effects (both therapeutic and harmful) of cannabis and reviews available data on the impact of legalization. While the AMA prefers to use the scientific term “cannabis,” the colloquial term “marijuana” is used interchangeably in this report, for example, when quoting a source or identifying the official name of a committee.

METHODS

English language reports were selected from searches of the PubMed, Google Scholar, and Cochrane Library databases from March 2013 to July 2017 using the search terms “marijuana or cannabis” in combination with “health,” “mental health,” “health effects,” “therapeutic use,” “therapeutic benefits,” “legalization,” “youth or adolescents,” “edibles,” “driving,” “taxes,” and “treatment.” Additional articles were identified by manual review of the reference lists of pertinent publications. Websites managed by federal and state agencies and applicable regulatory and advocacy organizations were reviewed for relevant information.

CURRENT AMA AND FEDERATION POLICY

Existing AMA policy on cannabis states that it is a dangerous drug and as such is a public health concern (H-95.998). The AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy (D-95.952). The AMA also urges that marijuana’s status as a federal schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines (D-95.952). The AMA also believes that public health based strategies, rather than incarceration, should be utilized in the handling of individuals possessing cannabis for personal use (H-95.998).

The AMA believes that the sale of cannabis should not be legalized (H-95.998) and urges legislatures to delay initiating full legalization of any cannabis product until further research is completed on the public health, medical, economic, and social consequences of recreational use (D-95.976). The AMA supports requiring the following warning on all cannabis products not approved by the U.S. Food and Drug Administration, “Marijuana has a high potential for abuse. It has no scientifically proven, currently accepted medical use for preventing or treating any disease process in the United States” (D-95.976). The AMA also advocates for regulations requiring point-of-sale warnings and product labeling for cannabis and cannabis-based products regarding the potential dangers of use during pregnancy and breastfeeding (H-95.936). The AMA supports increased educational programs relating to use and abuse of alcohol, marijuana, and controlled substances (H-170.992). (see Appendix A)

Many medical societies in the Federation have taken positions that are consistent with AMA policy. The California Medical Association (CMA) is one exception. It is on record as urging the legalization and regulation of cannabis to allow for greater clinical research, oversight, accountability, and quality control.⁵ CMA believes that the most effective way to protect the public’s health is to tightly control, track, and regulate cannabis and to comprehensively research and educate the public on its health impacts, not through ineffective prohibition.⁵

STATE LAWS ON CANNABIS

At the state level, trends in law have moved from decriminalization, to the legalization of medical use of cannabis, to cannabis regulated for adult recreational use.⁶ California was the first jurisdiction in the United States (U.S.) to legalize the medical use of cannabis. Today, 29 states, the District of Columbia (D.C.), Guam, and Puerto Rico have legalized the medical use of cannabis through either the legislative process or ballot measures.⁷ These laws vary greatly by jurisdiction from how patients access the product (home cultivated or dispensary), to qualifying conditions, product safety and testing requirements, packaging and labeling requirements, and consumption method (some states prohibit smoking the product). In jurisdictions that have legalized cannabis for medicinal use, physicians can “certify” or “recommend” a qualifying patient for the medicinal use of cannabis, but physicians cannot prescribe cannabis for medical purposes because it is illegal under federal law. In recent years, an additional

17 states have enacted laws allowing access to low delta-9-tetrahydrocannabinol (THC)/high cannabidiol (CBD) products for children with epilepsy.⁷

In 2012, Colorado (CO) and Washington (WA) were the first U.S. jurisdictions to legalize the adult use of cannabis for recreational purposes.^{8,9} Today, a total of 8 states and D.C. have legalized cannabis for recreational purposes, all through the ballot measure process.⁷ (Figure 1) Most of these jurisdictions have created for-profit, commercial cannabis production and distribution markets where the product is sold and taxed. D.C. is the exception; they have adopted a “grow and give” model whereby residents are permitted to possess, use, grow, and give away cannabis, but they cannot sell it.¹⁰ In 2017, legislatures in 20 states introduced legislation to legalize cannabis for recreational use. Vermont’s legislature was the first in the country to vote in favor of legalizing cannabis for recreational use.¹¹ The bill was ultimately vetoed by the governor due to the lack of provisions to protect public health and safety. Specifically, he called on policymakers to hold off on moving forward with commercialization until the state could:

...detect and measure impairment on our roadways, fund and implement additional substance abuse prevention education, keep our children safe and penalize those who do not, [and] measure how legalization impacts mental health and substance abuse issues our communities are already facing.¹²

RELEVANT FEDERAL LAW AND POLICY

Under the U.S. Controlled Substances Act (CSA) of 1970, cannabis is classified as a Schedule I controlled substance, meaning it has no currently accepted medical use in treatment in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.¹³ In 2011, the governors of Washington and Rhode Island petitioned the Drug Enforcement Administration (DEA) asking it to change cannabis from a Schedule I to a Schedule II drug under the CSA. In August of 2016, the DEA announced that cannabis would remain a Schedule I controlled substance.¹⁴ The notice stated that:

The DEA and FDA continue to believe that scientifically valid and well-controlled clinical trials conducted under investigational new drug applications are the proper way to research all potential new medicines, including marijuana. Furthermore, we believe that the drug approval process is the proper way to assess whether a product derived from marijuana or its constituent parts is safe and effective for medical use.¹⁴

Cannabis is not FDA-approved as a safe and effective drug for any indication. However, the agency has approved three drug products containing synthetic versions of the main psychoactive ingredient of cannabis, THC. Marinol[®] and Syndros[™], which include the active ingredient dronabinol, are indicated for nausea and vomiting associated with cancer chemotherapy and anorexia associated with weight loss in patients with AIDS.¹⁵ Cesamet[®], which contains the active ingredient nabilone, also is indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy.¹⁵ Clinical investigations are underway for one CBD-based product, Epidiolex[®] for Lennox-Gastaut syndrome and Dravet syndrome and the THC/CBD combination product Sativex[®] for cancer pain.^{15,16}

In 2016, the DEA announced a change in policy designed to increase the number of DEA-registered cannabis manufacturers. Currently the University of Mississippi is the only entity authorized to produce cannabis for research purposes in the United States. The new policy will allow additional entities to submit applications and become registered with the DEA to grow and distribute cannabis for FDA-authorized research purposes.¹⁷

Under the Obama Administration, a memorandum to all U.S. Attorneys outlined cannabis enforcement priorities for the federal government. The memo explained that jurisdictions enacting laws legalizing cannabis that also have strong regulatory enforcement systems would be less likely to be threatened with federal enforcement.¹⁸ Federal priorities include preventing: (1) the distribution of cannabis to minors; (2) revenue from the sale of cannabis from going to criminal enterprises, gangs, and cartels; (3) the diversion of cannabis from states where it is legal under state law in some form to other states; (4) state-authorized cannabis activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity; (5) violence and the use of firearms in the cultivation and distribution of cannabis; (6) drugged driving and the exacerbation of other adverse public health consequences associated with cannabis use; (7) the growing of cannabis on public lands and the attendant public safety and environmental dangers posed by cannabis production on public lands; and, (8) cannabis possession or use on federal property.¹⁸ Accordingly, if particular conduct threatens federal priorities, that person or entity would be subject to federal enforcement actions.

While the Obama Administration tolerated state laws legalizing cannabis, it is still unclear how the Trump Administration will handle the issue.¹⁹ In July of 2017, the Attorney General sent letters to four governors warning them that he had “serious concerns” about the effects of cannabis legalization, raising questions as to whether the current compromise on enforcement with the Justice Department may be under reconsideration.²⁰

THE HEALTH EFFECTS OF CANNABIS

The National Academies of Sciences, Engineering, and Medicine (National Academies) published a comprehensive report in January 2017 commissioned by federal, state, philanthropic, and nongovernmental organizations, entitled “The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and the Recommendations for Research.”⁶ The report’s recommendations outline priorities for a research agenda and highlight the potential for improvements in data collection efforts and enhanced surveillance capacity.⁶ The report also contained 98 conclusions based on the accumulated evidence related to cannabis or cannabinoid use and health.⁶ (see Appendix B)

The report examined a broad range of possible health effects of cannabis and cannabinoids. Health effects examined included those related to cancer; cardiometabolic risk; respiratory disease; immunity; injury and death; prenatal, perinatal, and neonatal exposure; psychosocial and mental health; problem cannabis use; and cannabis use and the misuse of other substances. The findings are organized into 5 evidence categories: conclusive, substantial, moderate, limited, and no/insufficient evidence. The report found conclusive or substantial evidence that cannabis or cannabinoids are effective: (1) for the treatment of chronic pain in adults (cannabis); (2) as antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids); and (3) for improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids).⁶ The report also found substantial evidence of a statistical association between cannabis smoking and: (1) more frequent chronic bronchitis episodes (long-term cannabis smoking); (2) increased risk of motor vehicle crashes; (3) lower birth weight of offspring (maternal cannabis smoking); and (4) the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.⁶

A systematic review published subsequent to the National Academies report examined 27 clinical trials involving patients with chronic pain and found limited evidence that cannabis may alleviate neuropathic pain in some patients, but that insufficient evidence exists to demonstrate analgesic effects in patients with other types of chronic pain.²¹ This conclusion contradicts the finding of the National Academies report and is an example of how research findings on the therapeutic effects of cannabis remain inconsistent, leading to confusion among physicians, patients, the media, policy makers, and others.

IMPACT OF STATE LEGALIZATION OF CANNABIS

In 2012, CO and WA were the first states to legalize cannabis for recreational use. As jurisdictions continue to follow in their footsteps, many are looking at data from these states to determine the impact of legalization on public health and safety. Issues being examined include the impact of legalization on patterns of use by adults, children and adolescents, and pregnant women; cannabis-related exposures; cannabis-related hospital or emergency department visits; cannabis-related treatment admissions; impaired driving; crime; opioid use; and governmental costs and revenue. Since regulatory structures governing cannabis vary by jurisdiction and continue to evolve, the impact on health and safety is difficult to discern. It is also worth noting that although recreational use of cannabis was first legalized in 2012, cannabis products for recreational use were not commercially available for sale in CO or WA until 2014. Alaska (AK), D.C., and Oregon (OR) voted to legalize recreational use in 2014. While OR allowed limited sales of cannabis through medical dispensaries in 2015, cannabis dispensaries for recreational users did not open in AK or OR until 2016 (Figure 2). As a result, limited data are currently available to determine the overall impact of legalizing recreational cannabis use on specific outcome measures.

The Colorado Department of Public Health and Environment (CDPHE) appointed a Retail Marijuana Public Health Advisory Committee (RMPHAC), to review scientific literature on the health effects of cannabis and state-specific health outcomes and patterns of use.²² The RMPHAC report was informed by state-based data and national surveys such as the Substance Abuse and Mental Health Services Administration’s (SAMHSA) National Survey on Drug Use and Health (NSDUH) and the Center for Disease Control and Prevention’s (CDC) Behavioral Risk Factor Surveillance System (BRFSS) and Pregnancy Risk Assessment Monitoring System (PRAMS). The Washington State Institute for Public Policy (WSIPP) has conducted a benefit-cost analysis of the implementation of WA

Initiative 502 as required by law.²³ The Northwest High Intensity Drug Trafficking Area (NWHIDTA) and the Rocky Mountain High Intensity Drug Trafficking Area (RMHIDTA) have also issued reports on the impacts of the legalization of cannabis in WA and CO, respectively.^{24,25} The results from these reports were utilized in examining the impact of cannabis legalization on public health and safety.

Use among Adults

In the United States, cannabis is the most commonly used illicit drug.²⁶ Overall, from 2002-2014, the prevalence of cannabis use during the past month, past year, and daily or almost daily increased among persons aged 18 years and older.²⁷ In 2016, the percentage of young adults (18-25 years) who were current marijuana users (past month) was similar to the percentages in 2014 and 2015, while the percentage of older adults (≥ 26 years) who were current users continued to increase.²⁸

The percentage of young Coloradan adults aged 18 to 25 years reporting cannabis use within the past year increased significantly after “medical” cannabis legalization (35 percent in 2007 to 2008 to 43 percent in 2010 to 2011).²⁹ The latest data available suggest cannabis use has remained fairly constant in CO (45 percent in 2013-2014). In 2015, based on the BRFSS data, 13 percent of CO adults ages 18 and up had used cannabis in the past-month.²² The NSDUH estimate for past-month use is higher, at 17 percent.²² However, neither survey showed a statistical change from 2014 to 2015.²² According to NSDUH data, adult use of cannabis in CO has continued to be higher than the national average, which was 8 percent.²² In WA, young adults’ (18-25 years) past-year cannabis use was 6 percent higher than the nation’s in 2012-2013, and adults’ use (≥ 26 years) was 5 percent higher.²⁴ Past month use of cannabis was 5 percent higher than the nation’s average for young adults and adults in 2012-2013.²⁴ Statewide BRFSS data indicate that since the legalization of recreational cannabis in WA, use has increased among adults.²³

Use among Pregnant Women

Cannabis is the most commonly used illicit drug during pregnancy.³⁰ The movement toward the legalization of cannabis may result in more women using cannabis during pregnancy.³¹ Cannabis crosses the placenta and is found in breast milk.³⁰ It may have adverse effects on both perinatal outcomes and fetal neurodevelopment, though evidence is limited.³¹ In 2015, the American College of Obstetricians and Gynecologists issued a committee opinion discouraging physicians from suggesting the use of marijuana during preconception, pregnancy, and lactation.³⁰

Overall, cannabis use during pregnancy is increasing with 3.85 percent of pregnant women between the ages of 18 and 44 years reporting past-month cannabis use in 2014, compared with 2.37 percent in 2002.³² PRAMS data for CO showed that among new mothers, 11.2 percent used cannabis prior to pregnancy, 5.7 percent used cannabis during pregnancy, and 4.5 percent of breastfeeding mothers used cannabis after delivery.²² Cannabis use during pregnancy was statistically higher among women with an unintended pregnancy (9.1 percent) than among women who intended to become pregnant (4.0 percent).²² When cannabis use during pregnancy was compared among different demographics, both education and age showed statistical differences, whereas race and ethnicity did not.²²

Use among Adolescents

Adolescents are of particular interest in cannabis-policy discussions because the negative health effects of the drug are heightened when use begins in adolescence.³³ In addition to the health effects, including the increased risk of addiction, evidence also suggests that cannabis use in adolescence and early adulthood is associated with poor social outcomes, including unemployment, lower income, and lower levels of life and relationship satisfaction.³³⁻³⁵ Changes in the legal status of cannabis may affect use among adolescents by decreasing the perceived risk of harm or through the marketing of legal cannabis. Studies examining the impact of “medical” cannabis laws found no measurable effect on the patterns of adolescent cannabis use.³⁶⁻³⁸ States with recreational or adult use cannabis laws also have not experienced an increase in adolescent use in the short term.^{22,23} However, further surveillance is necessary to determine long-term results.

NSDUH data for 2016 suggest that 6.5 percent or 1.6 million adolescents (12-17 years) were current (past month) users of cannabis.²⁸ The percentage of adolescents who were current cannabis users in 2016 was lower than the percentages in most years from 2009 to 2014, but was similar to the percentage in 2015.²⁸ In CO, estimates of current cannabis use (2002-2015) among high school students have fluctuated between approximately 20 percent and 25 percent.²² Survey results from 2015 indicate that approximately 38 percent of CO high school students

reported having ever used cannabis and 21 percent reported use in the past 30 days.²² These estimates are similar to national estimates of ever and current cannabis use among high school students. Among CO middle school students in 2015, an estimated 7.6 percent had ever used cannabis and an estimated 4.4 percent reported currently using cannabis.²² In WA, the Healthy Youth Survey, found that cannabis use indicators across grades 6, 8, 10, and 12, have been stable or fallen slightly since the legalization of recreational cannabis.²³

Cannabis-Related Exposures

Cannabis-related exposures generally refer to the number of human exposures related to accidental or excessive consumption or inhalation of cannabis and cannabis edibles. Early data from states that have legalized cannabis have shown an increase in calls to poison control centers related to cannabis exposures. According to the WA State Poison Control Center (WAPC), calls related to cannabis exposure nearly doubled from 2011 (n=146) to 2016 (n=286).³⁹ In 2016, over 42 percent (n=120) of the total cannabis-related calls involved individuals 13-29 years of age who had been exposed to some form of cannabis.³⁹ Over 70 percent (n=226) of patients were exposed to cannabis through ingestion.³⁹

In CO, 7.9 percent of adults with children 1-14 years old in the home reported having cannabis or cannabis products in or around the home (2015).²² It was estimated that approximately 14,000 homes in CO with children 1-14 years old had cannabis in the home with potentially unsafe storage.²² Cannabis-related exposures in CO increased 100 percent in the three-year average (2013-2015) since CO legalized recreational use of cannabis compared to the three-year average (2010-2012) prior to legalization.²⁵ In children (≤ 5 years old), cannabis-related exposures increased 169 percent after legalization of recreational cannabis in CO.²⁵ However, overall human exposures reported to Rocky Mountain Poison Center involving cannabis were marginally lower in 2016 (n=224) compared with 2015 (n=231).²²

A retrospective cohort study of CO children's hospital admissions and regional poison control (RPC) cases for cannabis exposures between January 1, 2009, and December 31, 2015, found that hospital visits and RPC case rates for cannabis exposures in patients under 10 years of age increased between the 2 years prior to and the 2 years after legalization.⁴⁰ During this time period, RPC calls increased at a significantly higher rate in CO than in the rest of the U.S. (34 percent vs. 19 percent per year).⁴⁰ In CO, edible products were responsible for more than half of the exposures.⁴⁰

Cannabis Secondhand Smoke Exposure

For 2014 and 2015 together, 3.2 percent of adults with children 1-14 years old reported cannabis being used inside the home in CO.²² Of these, 83.2 percent reported the cannabis was smoked, vaporized, or dabbed (dabs are a highly concentrated extract of THC).²² It is estimated that approximately 16,000 homes in CO had children 1-14 years old with possible exposure to secondhand cannabis smoke or vapor in the home.²²

Cannabis-Related Emergency Department Visits and Hospital Admissions

In addition to hospitalizations for unexpected pediatric exposure to cannabis, increased cannabis use after legalization has resulted in an increase in the number of ED visits and hospitalizations related to acute marijuana intoxication.²⁹ Retrospective data from the CO Hospital Association has shown that the prevalence of hospitalizations for cannabis exposure in patients aged 9 years and older essentially doubled after the legalization of medical cannabis (15 per 100,000 hospitalizations in 2001 to 2009 versus 28 per 100,000 hospitalizations from 2010 to 2013) and that cannabis-related ED visits nearly doubled after the legalization of recreational cannabis (22 per 100,000 ED visits in 2010 to 2013 versus 38 per 100,000 ED visits from January to June of 2014).²⁹

Cannabis legalization may also eventually contribute to increased ED visits for the sequelae of chronic cannabis use, including cannabinoid hyperemesis syndrome.²⁹ Patients with cannabinoid hyperemesis present to the ED with periodic bouts of intractable vomiting that are unresponsive to traditional antiemetics. CO saw a doubling of ED visits for cyclic vomiting after the legalization of medical cannabis in CO in 2009, although the total number of visits remained small.²⁹

Cannabis-Related Treatment Admissions

Limited data is available regarding the impact of laws legalizing the recreational use of cannabis on cannabis-related treatment admissions,¹ though the early data suggests a decline in treatment admissions. A study of cannabis-related treatment admissions in Denver from 2001-2013 found that such admissions increased from 2005 (2,694) to 2008 (3,295) and then declined by 10.6 percent to 2,887 in 2011.⁴¹ Significant decreases in treatment entries after 2009, a time when access to cannabis through CO's medical cannabis program was increasing, have been hypothesized to be a reflection of an accepting public opinion of cannabis use resulting in fewer individuals seeking treatment.⁴¹ In WA, cannabis-related treatment admissions fell in the three years following legalization of recreational use dropping from 7,843 in 2012, to 7,374 in 2013, 6,885 in 2014, and 6,142 in 2015.²³ Youth treatment admissions for cannabis have remained between 66 percent and 70 percent of overall admissions in WA state since 2010.²⁴

Impaired Driving

A potential unintended consequence of legalizing cannabis use for medical or recreational purposes is increased cannabis-related driving impairment. While the effects of alcohol on driving performance and crash risk are well understood, less is known regarding the effects of cannabis on driving. Research, including direct observations made in a driving simulator, has demonstrated the potential of cannabis to impair driving related skills.⁴²⁻⁴⁴ Individuals driving under the influence of cannabis seem to exhibit a general reckless driving style and cannabis smoking increases the risk of involvement in a motor vehicle accident approximately 2-fold.⁴⁴ Cannabis use is associated with slower driving, an increased tendency to drive below the speed limit, increased following distance, increased lane weaving, and increased mean distance headway to the preceding vehicle.⁴³ These behaviors suggest that those driving under the influence of cannabis are aware of their impairment and decrease their speed to compensate.⁴⁴

Unlike alcohol, THC is not water soluble, but is stored in fatty tissues and released over time. A clear relationship between THC levels and impairment has been difficult to establish, in part, because a urine or even serum level of THC could reflect cannabis used quite remotely from the date of the specimen collection.⁴⁵ Peak THC level can occur when low impairment is measured, and high impairment can be measured when THC level is low.⁴⁵ Additionally, some individuals may demonstrate little or no impairment at a THC level that impairs someone else.⁴⁵

The most recent data from CO show that cannabis-related traffic deaths increased 48 percent in the three-year average (2013-2015) after recreational use of cannabis was legalized compared with the three-year average (2010-2012) prior to legalization.²⁵ Similarly, the WA State Traffic Safety Commission found that the number of drivers with THC in their blood involved in fatal driving accidents increased more than 120 percent from 2010 to 2014.²⁴ Despite data from these individual states, another study found that three years after recreational cannabis legalization, motor vehicle crash fatality rates overall for WA and CO were not statistically different from those in similar states without recreational cannabis legalization.⁴⁶

Criminal Justice

Legalizing cannabis for recreational use could have variable impacts on crime. Some have argued that legalization could result in a decrease in drug-trafficking and possession charges; others contend that the increased use of cannabis could result in increases in violent crime.

Data from WA's Administrative Office of the Courts demonstrated that among adult offenders, misdemeanor cannabis possession convictions declined from 297 convictions in January 2012 to 0 by January 2013.²³ Among youth offenders, misdemeanor cannabis convictions dropped from 1,015 in the first three months of 2012 to 722 in the first quarter of 2013.²³ WA reports that from 2012 through 2014, cannabis seizure offenses reported to the National Incident-Based Reporting System decreased by nearly 62 percent.²⁴ Despite the overall decline in seizures in the state, youth cannabis seizure offenses have not followed this trend. In 2010, youth twelve to seventeen years old represented 28.9 percent (n=855) of all seizures.²⁴ In 2012 (legalization), they represented 37.5 percent (n=2,378) of seizures, and in 2013 they represented 68.6 percent (n=1,840) of total seizures.²⁴ By the end of 2014 (commercialization), 74 percent (n=1,791) of seizures involved youth aged twelve to seventeen years.²⁴

¹ Treatment admissions data as reported by substance abuse treatment facilities for inclusion in the national Treatment Episode Data Set.

Crime in Denver and Colorado has increased from 2013 to 2015.²⁵ Since 2014, there has been an increase in organized, large-scale home grows for trafficking to states where cannabis is not legalized.²⁵ Seizures of Colorado marijuana in the U.S. mail increased 471 percent from an average of 129 pounds (2010-2012) to 736 pounds (2013-2015) over the three-year period after recreational use was legalized.²⁵ In addition, in Colorado, property crime increased 6.2 percent, violent crime increased 6.7 percent, and all crime increased 6.2 percent from 2014 to 2015.²⁵

Opioid Use

According to the Centers for Disease Control and Prevention, increases in unintentional overdoses and deaths due to prescription opioids and heroin are the biggest driver of the drug overdose epidemic. Studies have found a decrease in the use of opioids among pain patients provided with medical cannabis.⁴⁷ Furthermore, medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates.⁴⁷ Additional research is necessary to determine how cannabis laws may impact opioid use, morbidity, and mortality.

Governmental Costs and Revenue

Cannabis tax collections in CO and WA have continued to increase, and, on a national basis, legalization and associated taxation of cannabis could result in billions of dollars per year of tax revenue for states.⁴⁸ In WA, I-502 required the WA State Liquor and Cannabis Board to oversee the recreational cannabis market and imposed a 25% excise tax on producers, processors, and retailers, which was later replaced with a 37% excise tax on retail sales.²³ The Dedicated Marijuana Account was created for cannabis revenues and expenditures.²³ Voters were told legalization could bring in as much as \$1.9 billion over five years, with 40 percent going to the state general fund and local budgets and the remaining 60 percent intended for substance abuse prevention, research, education, and health care. As of April 2016, state sales average over \$2 million a day, which translates into mean excise tax revenue approaching \$270 million per year.⁴⁸

In CO, voters were initially told cannabis excise taxes would boost state revenues by \$70 million per year, with the first \$40 million each year to be allocated to school construction, leaving \$30 million for enforcement and general state funds.⁴⁸ Revenues in calendar year 2016 reached nearly \$200 million. The CO legislature established a Marijuana Tax Cash Fund (MTCF) in 2014, which collects tax revenue from both medical and recreational cannabis sales. Funds in the MTCF have been appropriated to government agencies to address the possible health and safety consequences of legalization such as monitoring the health effects of cannabis, conducting health education campaigns, and providing substance abuse prevention and treatment programs.

The legalization and commercialization of cannabis results in revenue for states through taxes and fees, but it also comes with costs, both in regulating and enforcement actions and in protecting public health and safety. For example, in Colorado, the Marijuana Enforcement Division (MED) is responsible for regulating both medical and recreational cannabis businesses in the state. The MED's four offices and 55 employees are responsible for rulemaking, licensing and inspecting cannabis-related businesses, and taking enforcement actions. The annual budget for the MED is approximately \$10.5 million.

MINIMIZING HEALTH RISKS OF LEGALIZATION

As jurisdictions continue to understand the impact of legalization on health and other outcomes, the regulatory structure governing cannabis will continue to evolve. In CO, CDPHE continues to assess the knowledge gaps related to cannabis and develop policies to protect vulnerable populations.⁴⁹ For example, the issue of child cannabis exposure from edibles has been concerning. In CO, confusion surrounding the serving size for edible products and the delayed onset of the effects of THC are thought to have contributed to overconsumption.⁴⁹ Regulations were changed to ensure easier identification of average serving size in a single edible product.⁴⁹ CO, OR and WA now require a universal symbol to be affixed to edibles. Four states (Alaska, CO, OR, and WA) prohibit the manufacture or packaging of edibles that appeal to youth.⁵⁰ Concerns remain regarding the regulatory gaps that exist in each of these states and whether these regulations are actually informing consumers and keeping the public safe.⁵⁰

To address motor vehicle crashes due to driving under the influence of cannabis, some states have established *per se* limits for driving under the influence of cannabis. For example, CO and WA have established 5 ng/ml of THC as the legal limit for cannabis-impaired driving.⁴⁹ However, little evidence exists to support the enactment of specific *per*

se limits for cannabis.²⁴ As a first step, states are being encouraged to conduct prevalence studies on the number and proportion of drivers testing positive for THC.²⁴

The Vermont Department of Health has conducted a health impact assessment to determine the potential impact of legislation to regulate and tax cannabis for recreational use on the health of Vermonters and to recommend ways to mitigate the adverse health impacts of such legislation. The recommendations include expanding all current tobacco laws to include cannabis, prohibiting the use of cannabis in public places, standardizing and testing packaging and potency, funding prevention and education, restricting advertising, prohibiting infused products on the regulated market, setting a blood level operating limit for THC, expanding screening for substance use disorders in primary care, training health care providers on the health impacts of cannabis, and funding surveillance and research.⁵¹

CONCLUSION

Although the National Academies found conclusive or substantial evidence that cannabis or cannabinoids have some therapeutic benefits, they also found substantial or conclusive evidence of a statistical association between cannabis smoking and health harms. Furthermore, the findings of a systematic review on the analgesic effects of cannabis released subsequent to the National Academies report were inconsistent with the National Academies report, which highlights the lack of agreement on this issue, and serves as a source of confusion among physicians, patients, and the public and demonstrates the need for additional research.

Legalizing the recreational use of cannabis may result in its increased use over time due to changes in perceptions of safety and health risks. Existing data, although limited, have yet to confirm this expectation for children and adolescents. However, cannabis use has increased in adults and pregnant women. Data from jurisdictions that have legalized cannabis demonstrate concerns particularly around unintentional pediatric exposures resulting in increased calls to poison control centers and ED visits as well as an increase in traffic deaths due to cannabis-related impaired driving. Limited data also show a decrease in cannabis-related treatment admissions as well as a possible decrease in the use of opioids for chronic pain. In terms of crime, convictions for the possession of cannabis may decline in states that legalize cannabis. While states have seen an increase in revenue through sales and excise taxes on retail cannabis, the administrative and enforcement costs as well as the costs to society in terms of public health and safety should not be minimized.

Ongoing surveillance to determine the impact of cannabis legalization and commercialization on public health and safety will be critical. Surveillance should include, but not be limited to, the issues covered in this report – impact on patterns of use, traffic fatalities and injuries, emergency department visits and hospitalizations, unintentional exposures, exposure to second-hand smoke, and cannabis-related treatment admissions. There should also be a focus on at-risk populations including pregnant women and children. Continued evaluation of the effectiveness of regulations developed to ensure public health and safety in states that have legalized the medical and/or recreational use of cannabis is necessary. Jurisdictions that have legalized cannabis should allocate a substantial portion of their cannabis tax revenue for public health purposes, including substance abuse prevention and treatment programs, cannabis-related educational campaigns, scientifically rigorous research on the health effects of cannabis, and public health surveillance efforts.

For physicians, legalization may require practice modifications, particularly regarding patient-provider conversations about use and risk. Additional education on counseling patients about the danger of second hand smoke exposure, underage use, safe storage, impaired driving, and the over-consumption of edibles may be warranted.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted in lieu of Resolution 907-I-16 and the remainder of this report be filed:

1. That portions of Policies H-95.998, “AMA Policy Statement on Cannabis,” H-95.995 “Cannabis Use,” H-95.938 “Immunity from Federal Prosecution for Physicians Recommending Cannabis,” and D-95-976 “Cannabis – Expanded AMA Advocacy,” be retained and used, in part, to establish the following new policies:

Cannabis Legalization for Recreational Use

Our AMA: (1) believes that cannabis is a dangerous drug and as such is a serious public health concern; (2) believes that the sale of cannabis for recreational use should not be legalized; (3) discourages cannabis use, especially by persons vulnerable to the drug's effects and in high-risk populations such as youth, pregnant women, and women who are breastfeeding; (4) believes states that have already legalized cannabis (for medical or recreational use or both) should be required to take steps to regulate the product effectively in order to protect public health and safety and that laws and regulations related to legalized cannabis use should consistently be evaluated to determine their effectiveness; (5) encourages local, state, and federal public health agencies to improve surveillance efforts to ensure data is available on the short- and long-term health effects of cannabis use; (6) supports public health based strategies, rather than incarceration, in the handling of individuals possessing cannabis for personal use.

Cannabis Legalization for Medicinal Use

Our AMA: (1) believes that scientifically valid and well-controlled clinical trials conducted under federal investigational new drug applications are necessary to assess the safety and effectiveness of all new drugs, including potential cannabis products for medical use; (2) believes that cannabis for medicinal use should not be legalized through the state legislative, ballot initiative, or referendum process; (3) will develop model legislation requiring the following warning on all cannabis products not approved by the U.S. Food and Drug Administration: "Marijuana has a high potential for abuse. This product has not been approved by the Food and Drug Administration for preventing or treating any disease process."; (4) supports legislation ensuring or providing immunity against federal prosecution for physicians who certify that a patient has an approved medical condition or recommend cannabis in accordance with their state's laws; and (5) believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between physicians and patients should not subject either party to criminal sanctions.

2. That the following new policy be adopted:

Taxes on Cannabis Products

Our AMA encourages states and territories to allocate a substantial portion of their cannabis tax revenue for public health purposes, including: substance abuse prevention and treatment programs, cannabis-related educational campaigns, scientifically rigorous research on the health effects of cannabis, and public health surveillance efforts.

3. That Policy H-95.952, "Cannabis for Medicinal Use," be amended by addition and deletion to read as follows:

H-95.952, "Cannabis and Cannabinoid Research for Medicinal Use"

(1) Our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease. (2) Our AMA urges that marijuana's status as a federal schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product. (3) Our AMA urges the National Institutes of Health (NIH), the Drug Enforcement Administration (DEA), and the Food and Drug Administration (FDA) to develop a special schedule and implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research involving cannabis and its potential medical utility. This effort should include: a) disseminating specific information for researchers on the development of safeguards for cannabis clinical research protocols and the development of a model informed consent form for institutional review board evaluation; b) sufficient funding to support such clinical research and access for qualified investigators to adequate supplies of cannabis for clinical research purposes; c) confirming that cannabis of various and consistent strengths and/or placebo will be supplied by the National Institute on Drug Abuse to investigators registered with the DEA who are conducting bona fide clinical research studies that receive FDA approval, regardless of whether or not the NIH is the primary source of grant support. (4) ~~Our AMA believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between physicians and patients should not subject either party to criminal sanctions.~~ Our AMA supports research to

determine the consequences of long-term cannabis use, especially among youth, adolescents, pregnant women, and women who are breastfeeding. (5) Our AMA urges legislatures to delay initiating the legalization of cannabis for recreational use until further research is completed on the public health, medical, economic, and social consequences of its use.

4. That Policy H-95.936, “Cannabis Warnings for Pregnant and Breastfeeding Women,” be reaffirmed.
5. That Policies H-95.998, “AMA Policy Statement on Cannabis,” H-95.995, “Cannabis Use,” H-95.938, “Immunity from Federal Prosecution for Physicians Recommending Cannabis,” and D-95.976, “Cannabis – Expanded AMA Advocacy,” be rescinded since they have been implemented, were duplicative of another policy, or portions were incorporated into new policies proposed in this report.

FIGURE 1. Status of State Laws on Cannabis Legalization (Source: ASTHO)

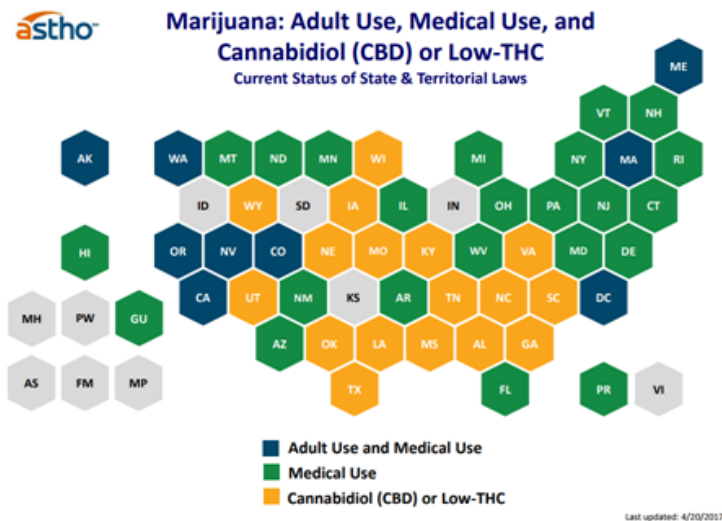
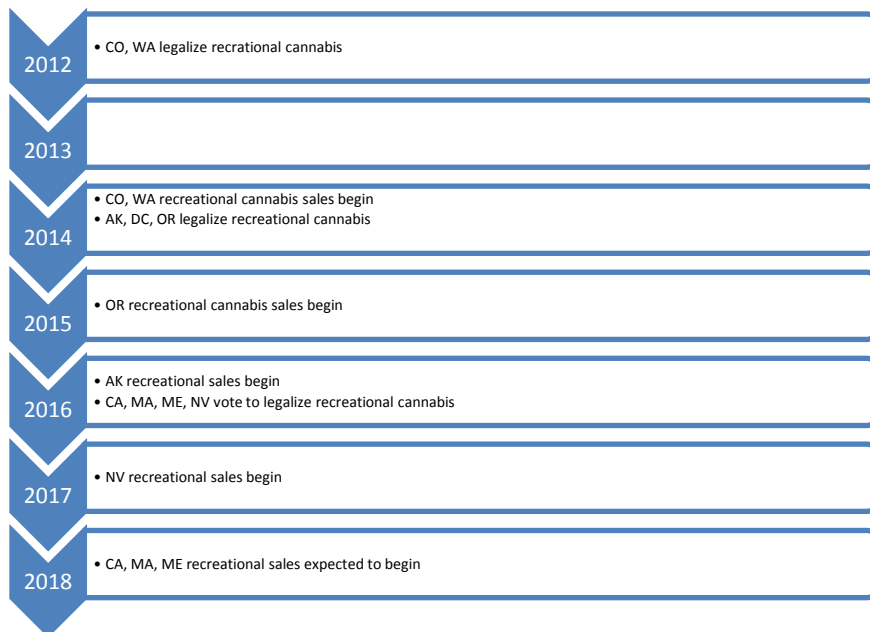


FIGURE 2. Timeline of State Recreational Cannabis Laws



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APPENDIX A - Existing AMA Policies Related to Cannabis

D-95.976, "Cannabis - Expanded AMA Advocacy"

1. Our AMA will educate the media and legislators as to the health effects of cannabis use as elucidated in CSAPH Report 2, I-13, A Contemporary View of National Drug Control Policy, and CSAPH Report 3, I-09, Use of Cannabis for Medicinal Purposes, and as additional scientific evidence becomes available. 2. Our AMA urges legislatures to delay initiating full legalization of any cannabis product until further research is completed on the public health, medical, economic and social consequences of use of cannabis and, instead, support the expansion of such research. 3. Our AMA will also increase its efforts to educate the press, legislators and the public regarding its policy position that stresses a "public health", as contrasted with a "criminal," approach to cannabis. 4. Our AMA shall encourage model legislation that would require placing the following warning on all cannabis products not approved by the U.S. Food and Drug Administration: "Marijuana has a high potential for abuse. It has no scientifically proven, currently accepted medical use for preventing or treating any disease process in the United States." Res 213, I-14.

H-95.952, "Cannabis for Medicinal Use"

(1) Our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease. (2) Our AMA urges that marijuana's status as a federal schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product. (3) Our AMA urges the National Institutes of Health (NIH), the Drug Enforcement Administration (DEA), and the Food and Drug Administration (FDA) to develop a special schedule and implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research involving cannabis and its potential medical utility. This effort should include: a) disseminating specific information for researchers on the

development of safeguards for cannabis clinical research protocols and the development of a model informed consent form for institutional review board evaluation; b) sufficient funding to support such clinical research and access for qualified investigators to adequate supplies of cannabis for clinical research purposes; c) confirming that cannabis of various and consistent strengths and/or placebo will be supplied by the National Institute on Drug Abuse to investigators registered with the DEA who are conducting bona fide clinical research studies that receive FDA approval, regardless of whether or not the NIH is the primary source of grant support. (4) Our AMA believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between physicians and patients should not subject either party to criminal sanctions. CSA Rep. 10, I-97, Modified: CSA Rep. 6, A-01, Modified: CSAPH Rep. 3, I-09, Modified in lieu of Res. 902, I-10, Reaffirmed in lieu of Res. 523, A-11, Reaffirmed in lieu of Res. 202, I-12, Reaffirmed: CSAPH Rep. 2, I-13.

H-95.998, “AMA Policy Statement on Cannabis”

Our AMA believes that (1) cannabis is a dangerous drug and as such is a public health concern; (2) sale of cannabis should not be legalized; (3) public health based strategies, rather than incarceration, should be utilized in the handling of individuals possessing cannabis for personal use; and (4) additional research should be encouraged. BOT Rep. K, I-69, Reaffirmed: CLRPD Rep. C, A-89, Reaffirmed: Sunset Report, A-00, Reaffirmed: CSAPH Rep. 1, A-10, Reaffirmed in lieu of Res. 202, I-12, Modified: CSAPH Rep. 2, I-13.

H-95.995, “Cannabis Use”

Our AMA (1) discourages cannabis use, especially by persons vulnerable to the drug's effects and in high-risk situations; (2) supports the determination of the consequences of long-term cannabis use through concentrated research, especially among youth and adolescents; and (3) supports the modification of state and federal laws to emphasize public health based strategies to address and reduce cannabis use. CSA Rep. D, I-77, Reaffirmed: CLRPD Rep. C, A-89, Reaffirmed: Sunset Report, A-00, Reaffirmed: CSAPH Rep. 1, A-10, Modified: CSAPH Rep. 2, I-13.

H-95.936, “Cannabis Warnings for Pregnant and Breastfeeding Women”

Our AMA advocates for regulations requiring point-of-sale warnings and product labeling for cannabis and cannabis-based products regarding the potential dangers of use during pregnancy and breastfeeding wherever these products are sold or distributed. Res. 922, I-15.

H-95.938, “Immunity from Federal Prosecution for Physicians Recommending Cannabis”

Our American Medical Association supports legislation ensuring or providing immunity against federal prosecution for physicians who certify that a patient has an approved medical condition or recommend cannabis in accordance with their state's laws. Res. 233, A-15.

H-95.997, “Cannabis Intoxication as a Criminal Defense”

Our AMA believes a plea of cannabis intoxication not be a defense in any criminal proceedings.

BOT Rep. J, A-72 Reaffirmed: CLRPD Rep. C, A-89 Reaffirmed: Sunset Report, A-00 Reaffirmed: CSAPH Rep. 1, A-10 Modified: CSAPH Rep. 2, I-13.

H-170.992, “Alcohol and Drug Abuse Education”

Our AMA: (1) supports continued encouragement for increased educational programs relating to use and abuse of alcohol, marijuana and controlled substances; (2) supports the implementation of alcohol and marijuana education in comprehensive health education curricula, kindergarten through grade twelve; and (3) encourages state medical societies to work with the appropriate agencies to develop a state-funded educational campaign to counteract pressures on young people to use alcohol. Sub. Res. 63, I-80 Reaffirmed: CLRPD Rep. B, I-90 Reaffirmation and Reaffirmed: Sunset Report, I-00 Appended: Res. 415, I-01 Reaffirmed: CSAPH Rep. 1, A-11.

APPENDIX B - The National Academies of Sciences, Engineering, and Medicine

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017)

EVIDENCE	CONCLUSIONS FOR THERAPEUTIC EFFECTS
There is conclusive or substantial evidence that cannabis or cannabinoids are effective:	<ul style="list-style-type: none"> • For the treatment for chronic pain in adults (cannabis) • Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) • For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)
There is moderate evidence that cannabis or cannabinoids are effective for:	<ul style="list-style-type: none"> • Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)

There is limited evidence that cannabis or cannabinoids are effective for:	<ul style="list-style-type: none"> • Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) • Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) • Improving symptoms of Tourette syndrome (THC capsules) • Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) • Improving symptoms of posttraumatic stress disorder (nabilone)
There is limited evidence of a statistical association between cannabinoids and:	<ul style="list-style-type: none"> • Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage.
There is limited evidence that cannabis or cannabinoids are ineffective for:	<ul style="list-style-type: none"> • Improving symptoms associated with dementia (cannabinoids) • Improving intraocular pressure associated with glaucoma (cannabinoids) • Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone)
There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:	<ul style="list-style-type: none"> • Cancers, including glioma (cannabinoids) • Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) • Symptoms of irritable bowel syndrome (dronabinol) • Epilepsy (cannabinoids) • Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) • Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) • Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) • Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) • Dystonia (nabilone and dronabinol) • Achieving abstinence in the use of addictive substances (cannabinoids) • Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol)
EVIDENCE	CONCLUSIONS FOR CANCER
There is moderate evidence of no statistical association between cannabis use and:	<ul style="list-style-type: none"> • Incidence of lung cancer (cannabis smoking) • Incidence of head and neck cancers
There is limited evidence of a statistical association between cannabis smoking and:	<ul style="list-style-type: none"> • Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking)
There is no or insufficient evidence to support or refute a statistical association between cannabis use and:	<ul style="list-style-type: none"> • Incidence of esophageal cancer (cannabis smoking) • Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer • Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use)
EVIDENCE	CONCLUSIONS FOR CARDIOMETABOLIC RISK
There is limited evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • The triggering of acute myocardial infarction (cannabis smoking) • Ischemic stroke or subarachnoid hemorrhage • Decreased risk of metabolic syndrome and diabetes • Increased risk of prediabetes
There is no evidence to support or refute a statistical association between <i>chronic effects</i> of cannabis use and:	<ul style="list-style-type: none"> • The increased risk of acute myocardial infarction
EVIDENCE	CONCLUSIONS FOR RESPIRATORY DISEASE
There is substantial evidence of a statistical association between cannabis smoking and:	<ul style="list-style-type: none"> • Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)
There is moderate evidence of a statistical association between cannabis smoking and:	<ul style="list-style-type: none"> • Improved airway dynamics with acute use, but not with chronic use • Higher forced vital capacity (FVC)
There is moderate evidence of a statistical association between <i>the cessation</i> of cannabis smoking and:	<ul style="list-style-type: none"> • Improvements in respiratory symptoms.

There is limited evidence of a statistical association between cannabis smoking and:	<ul style="list-style-type: none"> • An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking)
There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:	<ul style="list-style-type: none"> • Hospital admissions for COPD • Asthma development or asthma exacerbation
EVIDENCE	CONCLUSIONS FOR IMMUNITY
There is limited evidence of a statistical association between cannabis smoking and:	<ul style="list-style-type: none"> • A decrease in the production of several inflammatory cytokines in healthy individuals
There is limited evidence of <i>no</i> statistical association between cannabis use and:	<ul style="list-style-type: none"> • The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use)
There is no or insufficient evidence to support or refute a statistical association between cannabis use and:	<ul style="list-style-type: none"> • Other adverse immune cell responses in healthy individuals (cannabis smoking) • Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) • Increased incidence of oral human papilloma virus (HPV) (regular cannabis use)
EVIDENCE	ConclusionS FOR Injury and Death
There is substantial evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • Increased risk of motor vehicle crashes
There is moderate evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal
There is no or insufficient evidence to support or refute a statistical association between cannabis use and:	<ul style="list-style-type: none"> • All-cause mortality (self-reported cannabis use) • Occupational accidents or injuries (general, nonmedical cannabis use) • Death due to cannabis overdose
EVIDENCE	Conclusions FOR Prenatal, Perinatal, and Neonatal Exposure
There is substantial evidence of a statistical association between maternal cannabis smoking and:	<ul style="list-style-type: none"> • Lower birth weight of the offspring
There is limited evidence of a statistical association between maternal cannabis smoking and:	<ul style="list-style-type: none"> • Pregnancy complications for the mother • Admission of the infant to the neonatal intensive care unit (NICU)
There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:	<ul style="list-style-type: none"> • Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use)
EVIDENCE	Conclusions FOR Psychosocial
There is moderate evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use)
There is limited evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • Impaired academic achievement and education outcomes • Increased rates of unemployment and/or low income • Impaired social functioning or engagement in developmentally appropriate social roles
There is limited evidence of a statistical association between <i>sustained abstinence from</i> cannabis use and:	<ul style="list-style-type: none"> • Impairments in the cognitive domains of learning, memory, and attention
EVIDENCE	Conclusions FOR Mental Health
There is substantial evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • The development of schizophrenia or other psychoses, with the highest risk among the most frequent users
There is moderate evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> • Better cognitive performance among individuals with psychotic disorders and a history of cannabis use • Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) • A small increased risk for the development of depressive disorders • Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users • Increased incidence of suicide completion • Increased incidence of social anxiety disorder (regular cannabis use)

There is moderate evidence of <i>no</i> statistical association between cannabis use and:	<ul style="list-style-type: none"> Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders
There is limited evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders The likelihood of developing bipolar disorder, particularly among regular or daily users The development of any type of anxiety disorder, except social anxiety disorder Increased symptoms of anxiety (near daily cannabis use) Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder
There is no evidence to support or refute a statistical association between cannabis use and:	<ul style="list-style-type: none"> Changes in the course or symptoms of depressive disorders The development of posttraumatic stress disorder
EVIDENCE	Conclusions FOR Problem Cannabis Use
There is substantial evidence that:	<ul style="list-style-type: none"> Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is <i>not</i> a risk factor for the development of problem cannabis use Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use
There is substantial evidence of a statistical association between:	<ul style="list-style-type: none"> Increases in cannabis use frequency and the progression to developing problem cannabis use Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does <i>not</i> differ between males and females
There is moderate evidence that:	<ul style="list-style-type: none"> Anxiety, personality disorders, and bipolar disorders are <i>not</i> risk factors for the development of problem cannabis use Major depressive disorder is a risk factor for the development of problem cannabis use Adolescent ADHD is <i>not</i> a risk factor for the development of problem cannabis use Being male is a risk factor for the development of problem cannabis use Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use
There is moderate evidence of a statistical association between:	<ul style="list-style-type: none"> A persistence of problem cannabis use and a history of psychiatric treatment Problem cannabis use and increased severity of posttraumatic stress disorder symptoms
There is limited evidence that:	<ul style="list-style-type: none"> Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use
EVIDENCE	Conclusions FOR Cannabis Use and the Abuse of Other Substances
There is moderate evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs
There is limited evidence of a statistical association between cannabis use and:	<ul style="list-style-type: none"> The initiation of tobacco use Changes in the rates and use patterns of other licit and illicit substances
EVIDENCE	Conclusions FOR Challenges and Barriers in Conducting Cannabis Research
There are several challenges and barriers in conducting cannabis and cannabinoid research, including:	<ul style="list-style-type: none"> There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed