Reference Committee E

CSAPH Report(s)

01 Drug Shortages: 2020 Update
02 Neuropathic Pain as a Disease Update
03 Dietary Supplements: Update on Regulation, Industry, and Product Trends
04 Public Health Impacts of Cannabis Legalization

Resolution(s)

501 CBD Oil Use and the Marketing of CBD Oil
502 Drug Manufacturing Safety
503 Federal Initiative to Treat Cannabis Dependence
504 Supplemental Resources for Inflight Medical Kit
505 Regulation and Control of Self-Service Labs
506 Education for Patients on Opiate Replacement Therapy
507 Pharmacy Benefit Managers and Drug Shortages
508 Home Infusion of Hazardous Drugs
509* Hydroxychloroquine and Combination Therapies – Off-Label Use
510* Access to Opioid Agonist Treatment for Incarcerated Persons

**** contained in the Handbook Addendum***

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 1, November 2020

Subject: Drug Shortages: 2020 Update

Presented by: Kira A. Geraci-Ciardullo, MD, MPH, Chair

Referred to: Reference Committee E

INTRODUCTION

American Medical Association (AMA) 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 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 2017 to August 2020, using the text term "drug shortages." 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), National Academies of Sciences, Engineering, and Medicine (NASEM), U.S. Department of Health and Human Services (HHS), American Society of Health-System Pharmacists (ASHP), Duke Margolis Center for Health Policy, and by direct contact with key FDA, ASHP, and University of Utah Drug Information Service (UUDIS) staff who monitor drug shortages and related issues daily.

BACKGROUND

The CSAPH has issued ten reports on drug shortages.[1-10] The findings and conclusions of the first five reports are summarized in CSAPH Report 2-I-15, "National Drug Shortages: Update."[4] The remainder of this report will update information on drug shortages since the 2019 report was developed, specifically commenting on the drug shortage situation during the COVID-19 pandemic as well as issues associated with the drug supply chain that lead to drug shortages.

CURRENT TRENDS IN DRUG SHORTAGES

Drug shortages remain an ongoing public health concern in the United States and the AMA continues to monitor the situation and take action when appropriate. The rate of new shortages is increasing and common shortages are severely impacting patient care and pharmacy operations. Hospitals were already experiencing shortages of key injectable drugs prior to COVID-19 and unprecedented demand due to large numbers of critically ill patients with COVID-19 is worsening shortages.

The two primary data sources for information on drug shortages in the United States continue to be the Drug Shortage Program at the FDA and the Drug Shortage Resource Center maintained by

ASHP in cooperation with the UUDIS.[11,12] According to the most recent data compiled by ASHP and UUDIS, in 2019 there were 166 new shortages. Each quarter since the third quarter of 2017 until second quarter 2019 saw an increase in drug shortages. A spike in shortages occurred again in the first quarter of 2020, in conjunction with the emergence of the COVID-19 pandemic. In 2018 55 percent of shortages were injectable; this decreased to 39 percent in 2019. The top five classes of drugs implicated in active drug shortages include CNS medications (51); antimicrobials (37); cardiovascular medications (29); chemotherapy agents; and ophthalmics (19). The reasons for drug shortages vary and unknown/unreported reasons account for 82 percent of drug shortages, up from 51 percent in 2018 (See Appendix for ASHP/UUDIS data).[13] In the past year, significantly more suppliers did not provide a reason for shortages and FDA's Drug Shortage Task Force Report notes that more than 60 percent of shortages are due to manufacturer quality issues.[14]

The seventh annual report on drug shortages from the FDA to Congress published in April 2020 summarizes the major actions the FDA took in calendar year 2019 related to drug shortages.[15] Notably, using a range of available tools, the FDA worked with manufacturers to successfully prevent 154 shortages during 2019.

The FDA continues to utilize a mobile app to provide up-to-date access to information about drugs in shortage as well as notifications about new and resolved drug shortages and gives physicians the ability to report a drug shortage. The FDA Drug Shortages webpage includes a current shortages list, mobile app, and additional information (Box 1).[12] The ASHP Shortage Resource Center provides a list of shortages, guidance on managing critical shortages, as well as shortage metrics (Box 1).[11]

DRUG SHORTAGES AND COVID-19

As noted, hospitals were already experiencing shortages of injectable drugs prior to the COVID-19 pandemic. Unprecedented demand due to large numbers of critically ill patients with COVID-19 is worsening shortages, especially analgesics, sedatives, and paralytics because of the need to put many patients on ventilators.

Advocacy efforts are successfully creating changes that may improve the current situation. In response to shortages of medications for some chronic diseases, AMA, ASHP, and the American Pharmacists Association (APhA) made a Joint Statement on Ordering, Prescribing or Dispensing COVID-19 Medications.[16] The AMA also signed onto a letter to the U.S. Drug Enforcement Administration (DEA) regarding shortages of injectable Schedule II Controlled Substances that are increasingly needed for ventilation of patients.[17] After receiving the letter, the DEA immediately responded and increased annual production quotas and established regular communication with the AMA and the other letter signatories to identify controlled substances that are in shortage and monitor the rapidly changing situation.[18] DEA also issued two exceptions to regulations for DEA-registered hospital/clinics to facilitate continuous patient care during quickly changing scenarios.[19] FDA is working diligently on their COVID-19 drug shortage response and the Agency has clarified existing compounding guidance to provide flexibility for drugs in shortage.[20] Drug shortages vary by region and situations change rapidly, reporting any shortages experienced to FDA is recommended.

Dexamethasone

Shortages of dexamethasone, which is a generic drug and produced by many manufacturers, are ongoing. The FDA drug shortage website reports that a dexamethasone shortage was first posted February 2019. This was, however, just one supplier and that shortage is now resolved. Additional

suppliers have indicated shortages starting in May 2020, with the reason provided as "demand increase for the drug." All shortages listed note that "intermittent availability expected" with varying timeframes for resolution. The list is constantly changing with additional manufacturers, formulations, vial sizes, and doses.[12] In mid-July, dexamethasone sodium phosphate was added to the lists of drugs for temporary compounding by outsourcing facilities and pharmacy compounders during the COVID-19 public health emergency.[21]

Remdesivir

The FDA first issued an Emergency Use Authorization (EUA) for the new drug, remdesivir (Veklury), in May 2020 for the treatment of hospitalized adult and pediatric patients with severe COVID-19. The EUA was expanded in August 2020 to include treatment of all hospitalized adult and pediatric patients with suspected or laboratory-confirmed COVID-19, irrespective of their severity of disease.[22]

In May Gilead Sciences, Inc. donated 2 separate supplies of remdesivir to the U.S. Government. On June 28, 2020, a Memorandum of Agreement was signed between HHS and Gilead for HHS to receive 100% of the July production supply of the drug and 90% of the August and September production supplies.[23,24] To distribute the limited doses of available remdesivir in a fair and equitable manner, the HHS Office of the Assistant Secretary for Preparedness and Response (HHS/ASPR) is overseeing the allocation of the commercially available drug with a defined process (Figure 1).[25] ASPR has also been holding frequent calls to update stakeholders on the allocation process.

DRUG SUPPLY CHAIN AND DRUG SHORTAGES

The COVID-19 pandemic has exposed vulnerabilities in the global medicine supply chain leading to uncertainty, an increasing number of drug shortages, and potential quality issues. Inspections of foreign and domestic drug manufacturing facilities have been on hold, deficiencies in the drug supply chain have been amplified, and clinical trials have been disrupted.[26]

In a recent letter to the FDA related to Reauthorization of the Prescription Drug User Fee Act (PDUFA), the AMA noted that "[d]rug shortages remain an ongoing public health concern in the United States and strengthening the supply chain to ensure an uninterrupted supply of essential medicines that are safe, meet standards for quality, and are beneficial to health should be a public health priority."[27]

The AMA further stated that "[t]o maintain a strong and safe supply chain, regulators must know where medicines and their ingredients are manufactured and how they pass through the supply chain. The recently passed Coronavirus Aid, Relief, and Economic Security (CARES) Act took some steps to address supply chain issues, but more can be done, including expanding global reporting requirements for indicators of drug shortages, requiring drug manufacturers and ingredient suppliers to monitor and report on their capacity and ingredient quality, and providing incentives to manufacturers for manufacturing innovation and developing shortage mitigation plans."[27]

Your Council on Science and Public Health remains very concerned about medication quality issues and currently has this topic under study for report back to the HOD in 2021.

CURRENT DRUG SHORTAGE ACTIVITIES

American Medical Association

AMA staff continues to remain engaged in drug shortage activities. Notably, AMA co-convened a summit with ASHP, the American Hospital Association (AHA), and the United States Pharmacopeia (USP) on the topic of Safe, Effective, and Accessible High-Quality Medicines as a Matter of National Security on July 27-31, 2020.[28] The summit covered a broad range of topics related to supply chain resilience and opportunities to strengthen the U.S. and global regulatory systems were discussed. A comprehensive report detailing the summit and resulting recommendations is currently in development.

In April 2020, AMA staff provided a webinar for CME credit on the topic of drug shortages. The webinar was sponsored by the Organized Medical Staff Section (OMSS) and was open to interested individuals. The webinar is currently posted on the AMA Ed Hub™.[29]

AMA staff has also contributed to the document, *Coping with and Mitigating the Effects of Shortages of Emergency Medical Products: Strategies for Healthcare and Public Health*, which is an update to a 2012 publication from the Association of State and Territorial Health Officials (ASTHO). In 2012, ASTHO was funded by ASPR to convene a group of stakeholders from national Emergency Medical Services (EMS), emergency/trauma care associations, and select federal agencies to identify approaches for healthcare and EMS to cope with and lessen the impacts of drug shortages on patient care. Expert recommendations were compiled into a report, *Coping with and Mitigating the Effects of Shortages of Emergency Medications*.[30] In 2017 ASTHO was again funded by ASPR to convene experts to identify additional coping and mitigation strategies, with a focus on healthcare and public health. The report, which highlights the challenges, strategies, and recommendations identified by stakeholders, is being finalized for publication.

U.S. Food and Drug Administration

Inter-agency Drug Shortages Task Force. Last year, the FDA convened an inter-agency Drug Shortages Task Force to study the problem of drug shortages, determine the root causes of drug shortages, and make recommendations for enduring solutions.[31] This effort was designed to help address the number of drug shortages that continue to occur. The Task Force has released a report, *Drug Shortages: Root Causes and Potential Solutions*, that attempts to identify root causes and offer recommendations for government and industry based on insights gleaned from stakeholders in the private and public sectors. These recommendations are intended to help prevent and mitigate future drug shortages.[14,32]

The Task Force found that the number of ongoing drug shortages has been rising, and that their impact is likely underappreciated. Drugs in shortage were more likely to be relatively low-price and financially unattractive drugs and were more likely to be sterile injectables. Shortages often occurred as a result of disruption in supply due to a variety of factors. Importantly, prices rarely rose after shortages began, and, during shortages, production typically did not increase enough to restore supply to pre-shortage levels. Many manufacturers reported discontinuing the production of drugs before a shortage for commercial reasons (e.g., loss of profitability). These results suggest a broken marketplace, where scarcity of drugs in shortage or at risk of shortage does not result in the price increases predicted by basic economic principles.[14,32]

The Task Force offered three key recommendations to address the root causes of shortages (see Figure 2 for a summary). The first recommendation is to take steps to increase understanding of the

impacts of drug shortages and companies' contracting practices that may contribute to them. The report encourages more systematic and transparent study of current contracting practices to support development of model contracts designed to promote reliable access to safe, effective, and affordable drugs. The second recommendation is to develop a system to measure and rate a facility's quality management maturity. The rating would evaluate the robustness of a manufacturing facility's quality system and its ability to deliver high-quality products reliably and without disruption. This effort would introduce transparency into the market, and provide companies committed to quality management maturity with a competitive advantage, potentially enabling them to obtain sustainable prices as well as grow market share. The third recommendation is to consider new contracting approaches that help ensure a reliable supply of drugs. This may include providing financial incentives to make certain that manufacturers, especially of older generic drugs, earn sustainable returns on their products.[14,32]

The report also highlights the need for international action. Global implementation of guidelines related to pharmaceutical product supply chains, quality systems, and management of product lifecycles, as well as expansion and standardization of global reporting requirements for indicators of drug shortages could assist in drug shortage mitigation efforts of manufacturers for the international market. In addition, the report described legislative proposals in the President's FY2020 Budget and planned FDA initiatives to prevent and mitigate shortages that look at improved data sharing, risk management, and lengthened expiration dates for drugs.[14,32]

Manufacturing Modernization. As noted in the previous drug shortage report, CSAPH Report 2-A-19, the FDA is continuing their initiative to encourage manufacturers to adopt advanced manufacturing technologies, such as continuous manufacturing, that increase production reliability and capacity and can assist in medical product shortage mitigation.[33,34]

SUMMARY

The rate of new medical product shortages is increasing and shortages of essential medications are severely impacting patient care and pharmacy operations. The ongoing supply challenges of mostly generic medications, typically injectable products, that are off-patent persist. However, numerous organizations, the FDA, and our AMA remain involved in conversations with myriad stakeholders with a continued commitment to addressing this critical issue.

The recent report from the FDA Inter-agency Drug Shortages Task Force Report highlighting the root causes and potential solutions of drug shortages underscored topics that have been discussed for several years by the AMA and your Council. Many of the Task Force report topics are already adequately addressed in AMA drug shortage policy, including improvement quality systems; expedited facility inspections; necessary resiliency and redundancy in manufacturing capability; evaluation of root causes of drug shortages; transparent analysis of economic drivers and reasonable and sustainable payment rates for prescription drugs; greater transparency of the manufacturing process; and including drug manufacturing sites as part of the nation's critical infrastructure plan. However, your Council feels that some amendments to the policy related to manufacturing innovations, global supply chain harmonization and transparency, manufacturer incentives, and general updating are warranted at this time.

RECOMMENDATIONS

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

That Policy H-100.956, "National Drug Shortages" be amended by addition and deletion to read as follows:

1. Our AMA considers drug shortages to be an urgent public health crisis, and recent shortages have had a dramatic and negative impact on the delivery and safety of appropriate health care to patients.

2. 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 are in short supply, and will work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.

3. Our AMA supports authorizing the Secretary of the U.S. Department of Health and Human Services (DHHS) to expedite facility inspections and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage.

4. 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.

5. The Council on Science and Public Health shall continue to evaluate the drug shortage issue, including the impact of group purchasing organizations on drug shortages, and report back ~~at least annually~~ to the House of Delegates when warranted on progress made in addressing drug shortages.

6. Our AMA urges continued analysis of ~~the development of a comprehensive independent report on~~ the root causes of drug shortages that includes consideration of~~. Such an analysis should consider~~ federal actions, ~~the number of~~ evaluation of manufacturer,s~~-~~ Group Purchasing Organization (GPO), and distributor practices, ~~as well as~~ contracting practices by market participants on competition, access to drugs, ~~and~~ pricing, and ~~. In particular, further transparent~~ In particular, a further analysis of economic drivers~~-is warranted~~. ~~is warranted~~. ~~The federal Centers for Medicare & Medicaid Services (CMS) 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.~~

7. 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.

8. 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.

9. Our AMA will collaborate with medical specialty society partners and other stakeholders in identifying and supporting legislative remedies to allow for more reasonable and sustainable payment rates for prescription drugs.

10. 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.

11. Our AMA urges the FDA to require manufacturers to provide greater transparency regarding the pharmaceutical product supply chain, including production locations of drugs, and provide more detailed information regarding the causes and anticipated duration of drug shortages.

12. Our AMA supports the collection and standardization of pharmaceutical supply chain data in order to determine the data indicators to identify potential supply chain issues, such as drug shortages.

13. Our AMA encourages global implementation of guidelines related to pharmaceutical product supply chains, quality systems, and management of product lifecycles, as well as expansion of global reporting requirements for indicators of drug shortages.

14. Our AMA urges drug manufacturers to accelerate the adoption of advanced manufacturing technologies such as continuous pharmaceutical manufacturing.

15. Our AMA supports the concept of creating a rating system to provide information about the quality management maturity, resiliency and redundancy, and shortage mitigation plans, of pharmaceutical manufacturing facilities to increase visibility and transparency and provide incentive to manufacturers. Additionally, our AMA encourages GPOs and purchasers to contractually require manufacturers to disclose their quality rating, when available, on product labeling.

16. Our AMA encourages electronic health records (EHR) vendors to make changes to their systems to ease the burden of making drug product changes.

17. Our AMA urges the FDA to evaluate and provide current information regarding the quality of outsourcer compounding facilities.

18. Our AMA urges DHHS and the U.S. Department of Homeland Security (DHS) to examine and consider drug shortages as a national security initiative and include vital drug production sites in the critical infrastructure plan. (Modify Current HOD Policy)

Fiscal Note: Less than $1000

REFERENCES

1. Council on Science and Public Health. *Drug Shortages: Update.* American Medical Association; November 2018. 2-A-18.
2. Council on Science and Public Health. *National Drug Shortages: Update.* American Medical Association; November 2017. 4-I-17.
3. Council on Science and Public Health. *National Drug Shortages: Update.* American Medical Association; November 2016. 2-I-16.
4. Council on Science and Public Health. *National Drug Shortages: Update.* American Medical Association; November 2015. 2-I-15.
5. Council on Science and Public Health. *National Drug Shortages: Update.* American Medical Association; June 2014. 3-A-14.
6. Council on Science and Public Health. *National Drug Shortages: Update.* American Medical Association; June 2013. 8-A-13.
7. Council on Science and Public Health. *National Drug Shortages: Update.* American Medical Association; November 2012. 2-I-12.
8. Council on Science and Public Health. *Drug Shortages Update.* American Medical Association; June 2012. 7-A-12.
9. Council on Science and Public Health. *National Drug Shortages.* American Medical Association; November 2011. 2-I-11.
10. Council on Science and Public Health. *Drug Shortages: 2019 Update.* American Medical Association; June 2019. 2-A-19.
11. American Society of Health-System Pharmacists. Shortage Resources. https://www.ashp.org/Drug-Shortages/Shortage-Resources. Published 2019. Accessed February 25, 2019.
12. U.S. Food and Drug Administration. Drug Shortages. https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm. Published 2019. Accessed February 25, 2019.
13. American Society of Health-System Pharmacists and the University of Utah Drug Information Service. https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics. Published 2018. Accessed February 18, 2019.
14. U.S. Food and Drug Administration. Drug Shortages: Root Causes and Potential Solutions. https://www.fda.gov/media/131130/download. Published 2019. Accessed March 10, 2020.
15. U.S. Food and Drug Administration. Report on Drug Shortages for Calendar Year 2019. https://www.fda.gov/media/139613/download. Published 2020. Updated June. Accessed July, 2020.
16. American Medical Association. Joint statement on ordering, prescribing or dispensing COVID-19 medications. https://www.ama-assn.org/delivering-care/public-health/joint-statement-ordering-prescribing-or-dispensing-covid-19. Published 2020. Accessed April 17, 2020.
17. American Medical Association. Letter to DEA RE: Request to Immediately Increase Allocation of Controlled Substances to Combat COVID-19. https://searchlf.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-3-31-Letter-to-Dhillon-at-DEA-re-CII-APQ-Allocation-COVID-19.pdf. Published 2020. Updated Mach 31. Accessed.
18. American Medical Association. AMA praises DEA allowing increase in controlled substance production. https://www.ama-assn.org/press-center/ama-statements/ama-praises-dea-allowing-increase-controlled-substance-production. Published 2020. Accessed April 7, 2020.
19. U.S. Drug Enforcement Administration. DEA Letter providing flexibility to hospitals/clinics during COVID-19 pandemic. In:2020.

20. U.S. Food and Drug Administration. *Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency (Revised) Guidance for Industry.* U.S. Food and Drug Administration; April 2020.
21. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: Daily Roundup July 14, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-july-14-2020. Published 2020. Accessed July, 2020.
22. U.S. Food and Drug Administration. COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklury (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/covid-19-update-fda-broadens-emergency-use-authorization-veklury-remdesivir-include-all-hospitalized. Published 2020. Accessed August, 2020.
23. U.S. Department of Health and Human Services Trump Administration Secures New Supplies of Remdesivir for the United States. https://www.hhs.gov/about/news/2020/06/29/trump-administration-secures-new-supplies-remdesivir-united-states.html. Published 2020. Accessed July, 2020.
24. U.S. Department of Health and Human Services ASPR's Portfolio of COVID-19 Medical Countermeasures under Investigation. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Pages/remdesivir.aspx. Published 2020. Accessed July, 2020.
25. U.S. Department of Health and Human Services Remdesivir for the Commercial Marketplace Fact Sheet. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Pages/factsheet.aspx. Published 2020. Accessed July, 2020.
26. U.S. Food and Drug Administration. COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process. https://www.fda.gov/news-events/congressional-testimony/covid-19-and-beyond-oversight-fdas-foreign-drug-manufacturing-inspection-process-06022020. Published 2020. Accessed June, 2020.
27. American Medical Association. Letter to FDA Re: Docket No. FDA-2010-N-0128, "Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments." https://searchlf.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-8-20-Letter-to-Hahn-re-PDUFA-Comments.pdf. Published 2020. Accessed August.
28. American Society of Health-System Pharmacists. Drug Safety Summit Examined National Security Implications of Global Manufacturing. https://www.ashp.org/news/2020/08/03/drug-safety-summit-examined-national-security-implications-global-manufacturing. Published 2020. Accessed August, 2020.
29. American Medical Association Ed Hub. National Drug Shortages: Reacting to Current Shortages and Proactively Anticipating the Future. https://edhub.ama-assn.org/interactive/18418612?resultClick=1&bypassSolrId=M_18418612. Published 2020. Accessed August, 2020.
30. Association of State and Territorial Health Officials. Coping with and Mitigating the Effects of Shortages of Emergency Medications. Association of State and Territorial Health Officials. https://www.ems.gov/pdf/ASTHO_Shortages_of_Emergency_Meds.pdf. Published 2012. Accessed2019.
31. U.S. Food and Drug Administration. Agency Drug Shortages Task Force. https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm620590.htm. Published 2019. Accessed February 25, 2019.
32. U.S. Food and Drug Administration. Statement on FDA's new report regarding root causes and potential solutions to drug shortages. https://www.fda.gov/news-events/press-announcements/statement-fdas-new-report-regarding-root-causes-and-potential-solutions-drug-shortages?utm_campaign=102919_Statement_Statement%20on%20FDA%E2%80%99s%20ne

w%20drug%20shortages%20report&utm_medium=email&utm_source=Eloqua. Published 2019. Accessed October, 2019.
33. U.S. Food and Drug Administration. Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing. https://www.fda.gov/Drugs/NewsEvents/ucm557448.htm. Published 2018. Accessed February 28, 2019.
34. National Academies of Sciences E, Medicine. *Continuous Manufacturing for the Modernization of Pharmaceutical Production: Proceedings of a Workshop.* Washington, DC: The National Academies Press; 2019.

Box 1. Resources available to assist in mitigation of drug shortages.

1. ASHP Resource Center
2. ASHP list of current shortages
3. ASHP and University of Utah guidance on small-volume parenteral solutions shortages
4. ASHP and University of Utah guidance on injectable opioid shortages
5. FDA Drug Shortages Page (includes current shortages list, mobile app, and additional information)

Figure 1. ASPR Allocation and Distribution Strategy for Remdesivir

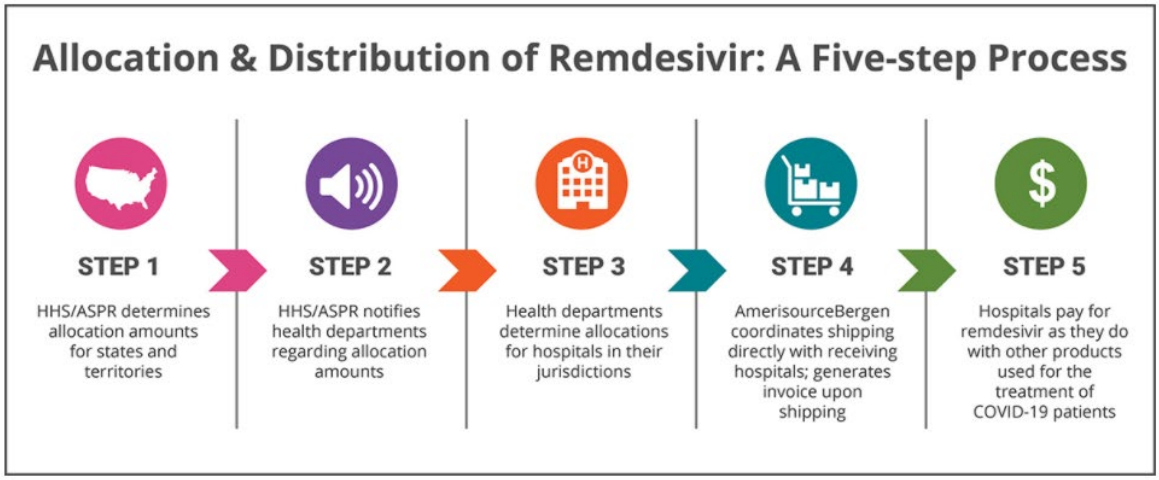
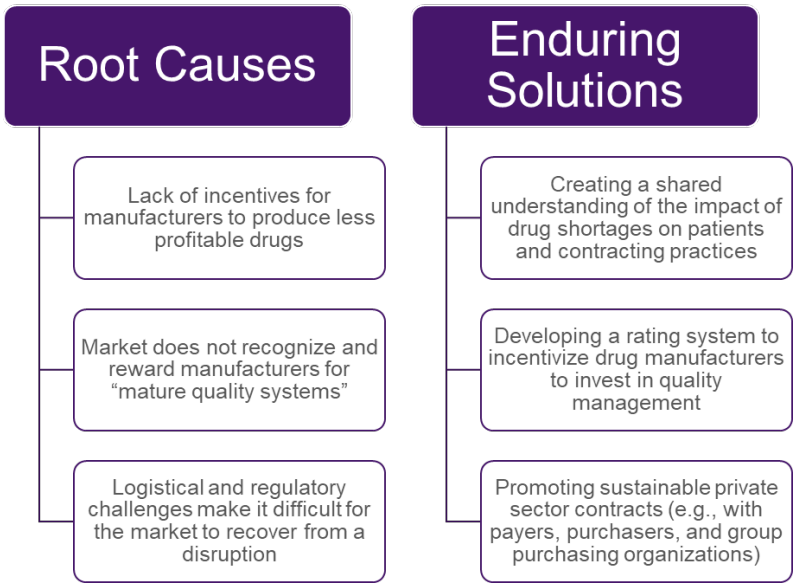


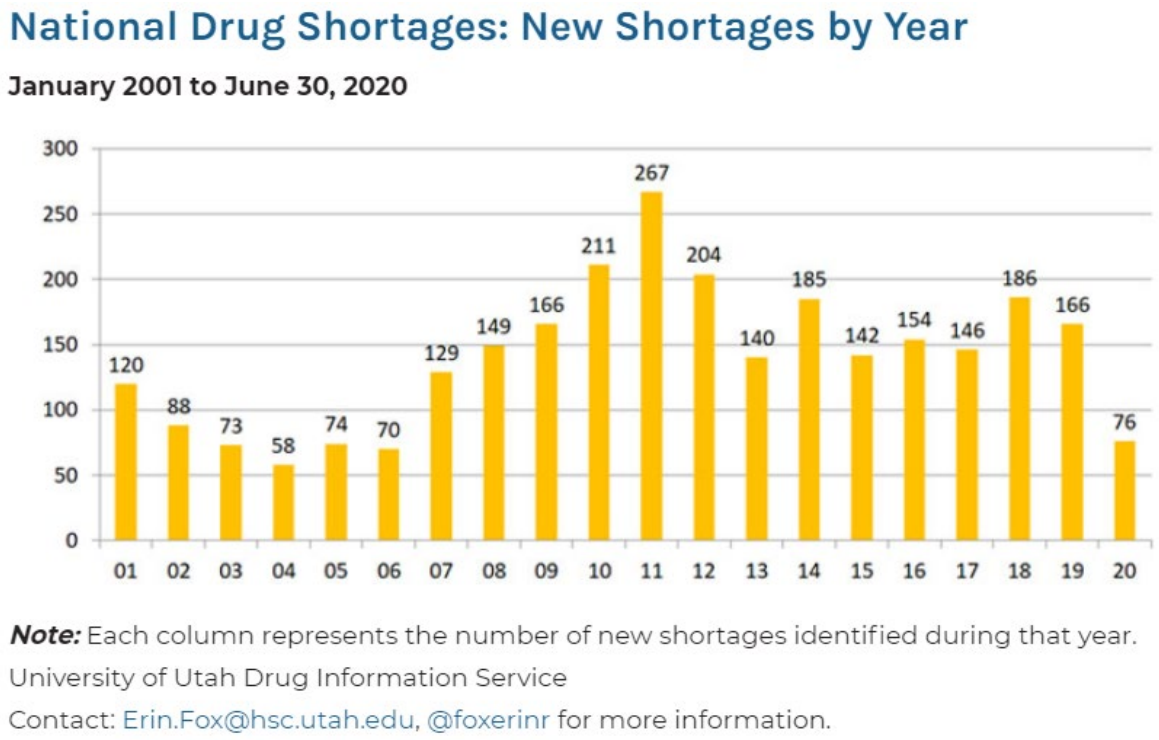
Figure 2. Root Causes and Potential Solutions from the FDA Inter-agency Drug Shortages Task Force Report



APPENDIX

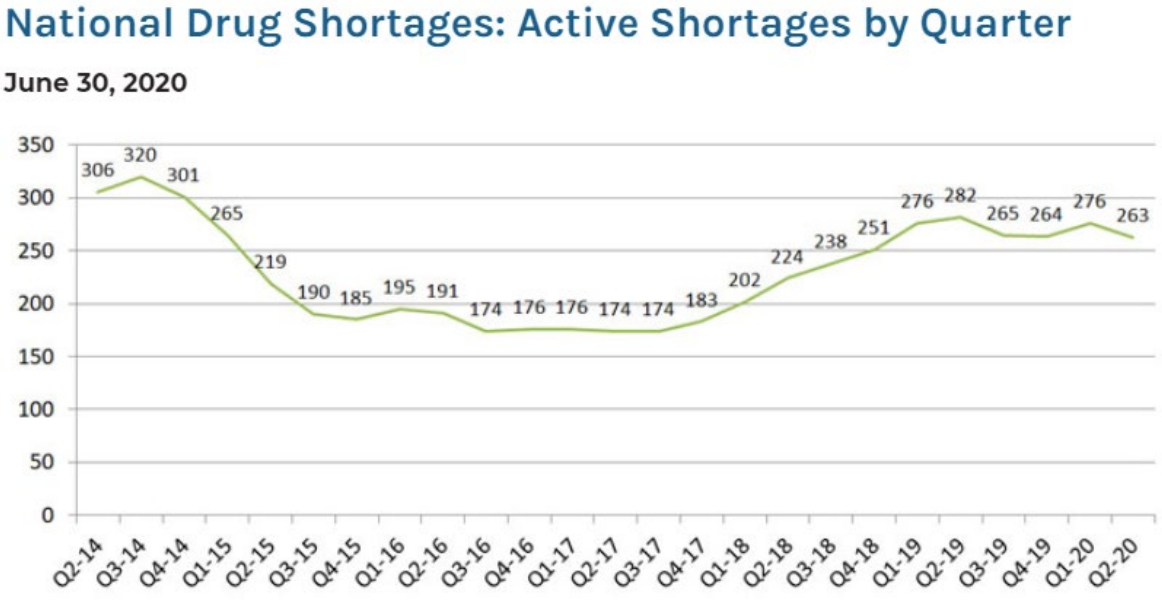
ASHP/University of Utah Drug Information Service Drug Shortage Data

Figure 1.



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

Figure 2.



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

Figure 3.

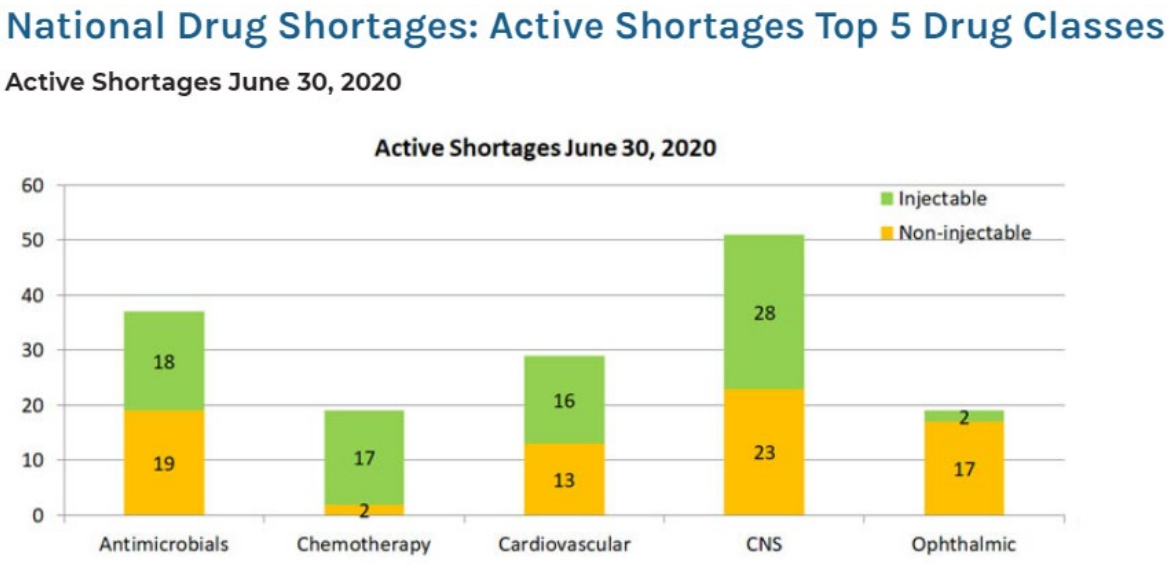
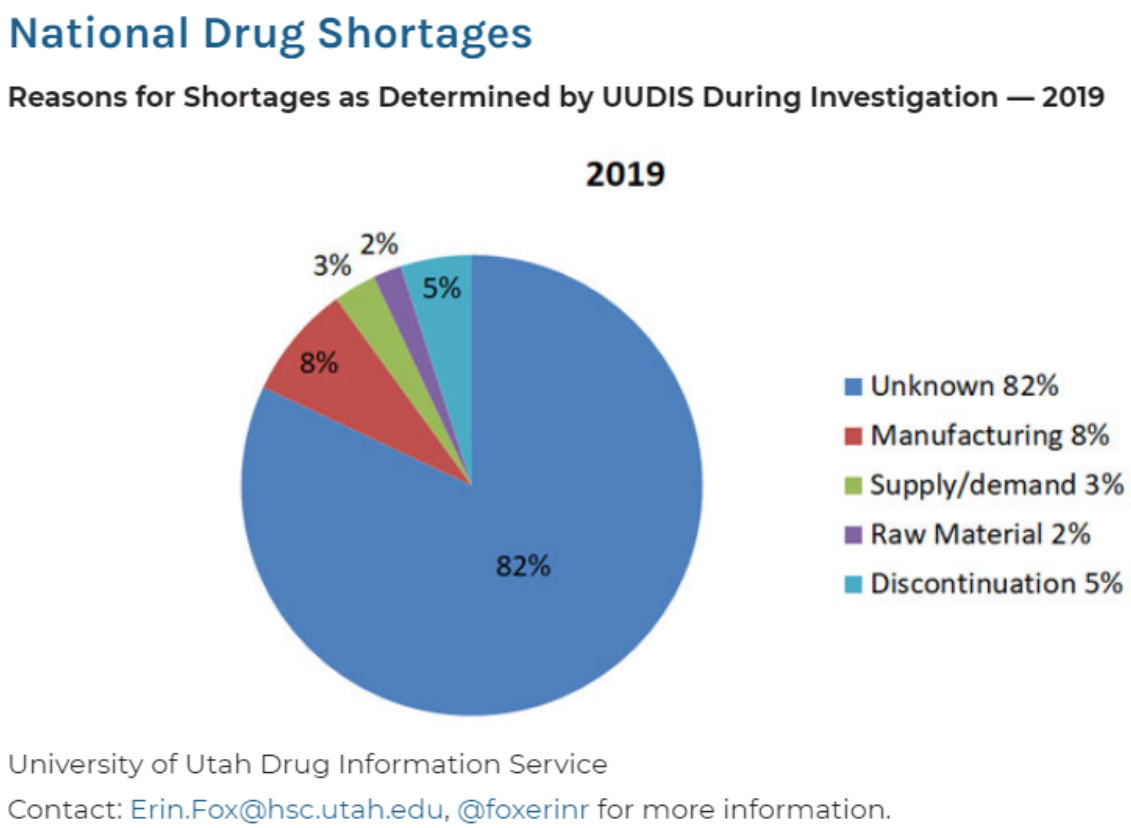


Figure 4.



REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2, November 2020

Subject: Neuropathic Pain as a Disease Update

Presented by: Kira A. Geraci-Ciardullo, MD, MPH, Chair

Referred to: Reference Committee E

INTRODUCTION

The AMA Council on Science and Public Health (CSPAH) presented Report 3-I-17, Neuropathic Pain as a Disease, to the AMA House of Delegates.[1] The adopted recommendation of the report states "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."

The AMA Pain Care Task Force (PCTF) deliberated this important issue at their November 25, 2019 meeting, came to a consensus opinion on the declaration of neuropathic pain as a disease, and communicated this opinion back to CSAPH. This report serves as CSAPH communicating the PCTF decision back to the AMA House of Delegates.

BACKGROUND

As noted in CSAPH Report 3-I-17, the "[u]nderstanding of the human pain experience has evolved over time. Although a detailed understanding of the neuroanatomy underlying the perception of noxious stimuli (nociception), exists, neuroimaging studies have identified several brain regions that are activated during the pain experience, dubbed the "pain matrix;" many of the same regions are also activated during various emotional and behavioral responses. Chronic pain is now recognized as an integrative sum of nociceptive input and factors related to cognition, mood, and context, as well as individual biologic, psychologic and social factors and various co-morbidities."[1]

CSAPH Report 3-I-17 defined nociceptive pain as follows: "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."[1] Information about pain is transmitted from the site of nociception through, for example, the spinothalamic tracts of the spinal cord to the midbrain and then onward, directly or indirectly, to the cerebral cortex, thus allowing the organism to adapt in a constructive way to the stimulus.

The definition of neuropathic pain used in CSAPH Report 3-I-17 is the 2012 definition of the International Association for the Study of Pain (IASP), which states that neuropathic pain is "pain initiated or caused by a lesion or disease of the somatosensory system."[2] The report stated that 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."[1] Classic examples of neuropathic pain are diabetic neuropathy and alcohol-related peripheral

neuropathy, where metabolic or toxic effects damage neurons, resulting in painful sensations. According to a study discussed in the 2017 report, "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)."[3]

CSAPH Report 3-I-17 report delved into the complexities of chronic pain, reviewing that, "[w]ith 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."[1]

CSAPH Report 3-I-17 points out that many diseases are accompanied by chronic pain, but it goes into some detail describing findings from neuroimaging studies that demonstrate differences in structure and functioning of the nervous system such that chronic pain differs from both normal states and states of acute nociceptive pain. It also describes that neuropathic pain "is characterized by adaptive cellular and functional changes which appear to persist after healing of the original injury."[1] CSAPH Report 3-I-17 drew also from a previous CSAPH report from 2010, "Maldynia: Pathophysiology and Nonpharmacologic Treatment," which later was published in a peer-reviewed journal.[4]

For the purposes of the current report, nociceptive pain, whether acute or chronic, is distinguished from neuropathic pain, whether acute or chronic. Nociceptive pain should be defined as it was in CSAPH Report 3-I-17. Neuropathic pain should be understood including the syndrome as the IASP defined it in 2012, but also encompassing the pain resulting from neuroadaptation associated with chronic pain. CSAPH Report 3-I-17 describes the cellular and functional changes in the nervous system in chronic pain, with "neuroplastic and neuroimmune responses which become drivers of chronic pain," including peripheral and central sensitization as well as "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."[1]

CORRESPONDANCE TO CSAPH FROM AMA PAIN CARE TASK FORCE

In a memo to CSAPH, the PCTF communicated its consensus opinion along with additional rationale and commentary to support their opinion. The AMA PCTF supports the designation of neuropathic pain as a distinct disease state.

The PCTF noted that members engaged in lengthy discussion of the consequences of this decision, which were not taken lightly. Although the IASP defines neuropathic pain as a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria, the PCTF is supportive of designating neuropathic pain a distinct disease state. The PCTF, however, cautions that a neuropathic pain disease designation should only be used when appropriate, and not overused. Additionally, the cause of the neuropathic pain should be carefully elucidated, and all underlying causes and/or types of neuropathy should be considered.

The PCTF understands that treating patients with neuropathic pain is complicated, challenging, and takes substantial time. Enhancing the scientific evidence base and successful treatment options for patients is critical. The PCTF is hopeful that support for the designation of neuropathic pain as a distinct disease state will allow for and encourage more research into the condition, payer coverage of treatment options, and improved resources for patients suffering with neuropathic pain.

Importantly, the PCTF also feels that the designation of neuropathic pain as a distinct disease state will validate patient experiences and provide a basis for their determination to move ahead without knowing the exact pathology causing their pain. Furthermore, this designation may assist in the alleviation of stigma patients with neuropathic pain face. The PCTF encourages physicians to engage in meaningful conversation about the pathology of complex pain and set appropriate expectations collaboratively with their patients. Encouraging patients to focus on function and quality of life can help reduce maladaptive changes in their condition.

CONSIDERATIONS OF THE COUNCIL

CSAPH appreciates the collaboration with the PCTF and thanks them for their response to the Council's request for guidance. The Council believes it is preferable, with our AMA recommending that neuropathic pain be designated as a distinct disease, that it be defined to the extent that its distinctions from nociceptive pain are clear to physicians, patients, researchers, and others. Hence, included in this report is the appropriate background material, with that material incorporated in the recommendations presented below.

RECOMMENDATIONS

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

1. That a new policy, Neuropathic Pain, be adopted:
   Our AMA:
   a. Supports the designation of neuropathic pain as a disease state distinct from nociceptive pain, encompassing metabolic, toxic, mechanical, and other injuries to nerve cells, as well as neuroplastic and neuroimmune adaptations to nerve cells in response to chronic pain.
   b. Encourages research related to neuropathic pain, payer coverage of treatment options for neuropathic pain, and improved resources for patients suffering with neuropathic pain.
   c. Encourages physicians to engage in meaningful conversation with their patients about what is known about the pathology of neuropathic pain and to set appropriate expectations collaboratively with their patients.
   d. Cautions that a neuropathic pain disease designation should only be used when appropriate, not overused, and that the cause of the neuropathic pain be carefully elucidated.

2. That part (d) of Policy D-160.922, "Future of Pain Care," which called for the AMA Pain Care Task Force to evaluate the merits of declaring neuropathic pain as a distinct disease state and provide a recommendation to the Council on Science and Public Health, be rescinded.

Fiscal Note: Less than $500

REFERENCES

1. Council on Science and Public Health. *Neuropathic Pain as a Disease.* American Medical Association;2017. 3-A-17.
2. International Association for the Study of Pain (IASP). ISAP taxonomy. http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576. Published 2012. Accessed August 25, 2017.
3. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers.* 2017;3:17002.
4. Dickinson BD, Head CA, Gitlow S, Osbahr AJ, 3rd. Maldynia: pathophysiology and management of neuropathic and maladaptive pain--a report of the AMA Council on Science and Public Health. *Pain medicine (Malden, Mass).* 2010;11(11):1635-1653.

APPENDIX: Member Organizations of the AMA Pain Care Task Force

American Medical Association
American Academy of Family Physicians
American Academy of Hospice and Palliative Medicine
American Academy of Neurology
American Academy of Orthopedic Surgeons
American Academy of Pain Medicine
American Academy of Pediatrics
American Academy of Physical Medicine and Rehabilitation
American Association of Neurological Surgeons and
Congress of Neurological Surgeons
American College of Occupational and Environmental Medicine
American College of Physicians
American Osteopathic Association
American Psychiatric Association
American Society of Addiction Medicine
American Society of Anesthesiologists
American Society of Clinical Oncology
Medical Association of the State of Alabama
California Medical Association
Maine Medical Association
Massachusetts Medical Society

REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (November 2020)
Dietary Supplements: Update on Regulation, Industry, and Product Trends
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. Patients and physicians expect the dietary supplements they purchase and recommend to be safe, quality products that are accurately labeled with their contents. Many dietary supplements, principally vitamins and minerals, are key components of modern evidence-based medicine for many conditions. However, illegal, fraudulent, adulterated and misbranded products can put patients at risk and adverse events (AEs) should be accurately collected. Additionally, confusion exists, for both patients and their caregivers, related to the regulation of dietary supplements and herbal products. The Council on Science and Public Health initiated this report to bring renewed attention to this important topic that affects many patients and to offer recommendations to strengthen AMA policy related to the dietary supplements.

Methods. English-language articles were selected from a search of the PubMed database through February 2020 using the search term "dietary supplement(s)." 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 clinical guidelines, position statements, and reports.

Results. While millions of patients use dietary supplements regularly, the current regulatory structure in place for dietary supplements does not offer adequate protection to the public. In the 26 years since the passage of the Dietary Supplement Health and Education Act (DSHEA), the dietary supplement industry has been reshaped by a complex global supply chain, the Internet, and newly discovered ingredients of unknown safety. An estimated 75,000 new supplement products have been introduced since 1994, and the U.S. Food and Drug Administration (FDA) has received adequate safety data for fewer than 250 new ingredients. The FDA also has no way to determine what ingredient are contained in the tens of thousands of products on the market. Furthermore, with violations identified in over half of inspected dietary supplement manufacturers, more effective enforcement tools are required to protect the health of patients. All patients would benefit from a regulatory framework that promotes product safety and provides appropriate tools and resources for the FDA to maintain appropriate oversight.

Conclusion. The advancement of a safe and transparent dietary supplement marketplace will require a trustworthy supply chain and will involve robust AE, drug interaction, and tainted product reporting. Unethical individuals and companies engage in the manufacture and distribution of intentionally adulterated, misbranded, and improperly labeled dietary supplement products and pose significant risks to patient health and safety. The reliance on an industry that self regulates is insufficient and ineffective at protecting the health of patients. As the dietary supplement industry continues to grow and patients continue to use dietary supplements, efforts to revise and modernize FDA oversight of the industry and the DSHEA itself are necessary. A mandatory product registry would be a simple, low-burden way for the FDA and patients to obtain a complete picture of the marketplace and better protect public health by providing greater transparency, enabling prioritization of limited agency resources, and enhancing efforts to respond to emerging safety concerns. Additionally, both physician and patient education are paramount to understand this industry and the risks associated with dietary supplement products.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3, November 2020

Subject: Dietary Supplements: Update on Regulation, Industry, and Product Trends

Presented by: Kira A. Geraci-Ciardullo, MD, MPH, Chair

Referred to: Reference Committee E

INTRODUCTION

Patients and physicians expect the dietary supplements they purchase and recommend to be safe, quality products that are accurately labeled with their contents. Many dietary supplements, principally vitamins and minerals, are key components of modern evidence-based medicine for many conditions. However, illegal, fraudulent, adulterated and misbranded products can put patients at risk. Adverse events (AEs) can occur with use of dietary supplements, and when they do, they should be accurately collected, tabulated and analyzed. Additionally, confusion exists, for both physicians and patients, related to the regulation of dietary supplements and herbal products.

The Council on Science and Public Health initiated this report to bring renewed attention to this important topic that affects many patients and to offer recommendations to strengthen American Medical Association (AMA) policy related to the dietary supplements.

BACKGROUND

The dietary supplement industry has grown from approximately 4,000 products in 1994 to as many as 90,000 in 2017, according to some estimates.[1,2] Surveys indicate that over half of Americans consume dietary supplement products.[3,4] Additionally, with the recent surge in the cannabidiol (CBD) market, which absent a clear regulatory pathway already includes a substantial number of products sold as dietary supplements, the number of products sold is expected to continue to increase. The economic value of the industry is projected to reach nearly $60 billion in the United States, and nearly $200 billion worldwide, by 2025.[5,6]

As the industry grows and more individuals are using dietary supplement products, a renewed focus on the risks associated with these products and the regulatory processes involved in bringing them to market is warranted. This report will provide an overview of the current regulatory framework for dietary supplements and comment on research-related activities, the dietary supplement industry, and product trends.

METHODS

English-language articles were selected from a search of the PubMed database through February 2020 using the search term “dietary supplement(s)” alone and coupled with “drug interactions” and “regulation.” 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 clinical guidelines, position statements, and reports.

DIETARY SUPPLEMENT REGULATION

Dietary Supplement Health and Education Act

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a dietary supplement as a product, taken orally, containing a dietary ingredient intended to supplement the diet.[7] Dietary ingredients include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates of the listed items.[8] Dietary supplements come in many forms, including tablets, capsules, powders, energy bars, and liquids and are available for purchase over-the-counter in stores throughout the United States and via the Internet. Herbal supplements are considered a type of dietary supplement and are included in this definition.

Since, by statutory definition, dietary supplements are only intended to supplement the diet, they are not therapeutic medications and are not intended to treat, diagnose, mitigate, prevent, or cure diseases. The U.S. Food and Drug Administration (FDA) oversees not only "conventional" food products and medications but also dietary supplements. Dietary supplements are regulated by the FDA differently from foods and differently from drugs. Whether a product is classified as a dietary supplement, conventional food, or drug is based on its intended use, and most often, classification as a dietary supplement is determined by the information that a manufacturer provides. Medications go through a rigorous FDA approval process before entering the market; drugs are considered unsafe until evidence shows they are safe. Dietary supplements do not undergo this approval process and are considered safe until proven unsafe.

FDA regulates the processing, manufacturing, labeling, and packaging of dietary supplements through the Dietary Supplement Health and Education Act (DSHEA), enacted as an amendment to the FD&C Act in 1994.[9] Dietary supplement companies are responsible for having evidence that their products are safe, and that the label claims are truthful and not misleading. As long as the product does not contain a "new dietary ingredient (NDI)," the company does not have to provide safety evidence to the FDA before the product is marketed. The term NDI means a dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994; however, no authoritative list of ingredients marketed before October 15, 1994 exists.[10] Therefore, manufacturers and distributors, and not federal regulators, are responsible for determining if an ingredient is an NDI.

Under DSHEA, manufacturers and distributors of dietary supplements and dietary ingredients are prohibited from marketing products that are adulterated or misbranded. Manufacturers are responsible for labeling their products before marketing to ensure that they meet all the requirements of DSHEA and FDA regulations. The FDA is responsible for taking action against any adulterated or misbranded dietary supplement product only after it reaches the market and a violation is found. The FDA pursues enforcement actions on dietary supplement products for the following reasons:

- Safety: The presence of unsafe ingredients or composition is generally determined from postmarket surveillance, such as monitoring adverse event reports (AERs), to identify potential concerns.[11]
- Manufacturing violations: Manufacturers must follow current good manufacturing practice (cGMP) to ensure the identity, purity, strength, and composition of their products.
- Marketing and misbranding (shared authority with the Federal Trade Commission (FTC)): Once a dietary supplement is on the market, it is the responsibility of the FDA to monitor product labels and package insert information to make sure that the information is accurate

and that any claims made are truthful and not misleading. The FDA, however, has limited resources to effectively do this.

Some penalties and enforcement actions exist which the FDA is able to pursue in instances of safety and cGMP violations. These include administrative actions such as warning letters, civil penalties such as product recalls and injunctions, and criminal penalties including both misdemeanor offenses of up to 1 year in prison and $500,000 in fines, and felony offenses of up to 3 years in prison and $500,000 in fines. Enforcement of penalties for marketing and misbranding is a shared authority with FTC, and the FDA cannot impose penalties if the only violation is misbranding. Civil penalties under the FDA include injunctions and product recalls, and under FTC include administrative actions, injunctions, and fines for consumer relief and recovery of illegal profits.

Dietary Supplement Labeling

Dietary supplement marketing, labeling, and advertising are all covered by regulations enforced by both the FDA and the FTC. Unlike drugs, supplements are not intended to treat, diagnose, prevent, or cure diseases. The FTC acts as the primary regulator of dietary supplement advertising and the FDA possesses primary enforcement responsibility for dietary supplement claims made in "labeling."

The Nutrition Labeling and Education Act of 1990 gave the FDA the discretion to regulate health claims for foods and dietary supplements and DSHEA made manufacturers responsible for ensuring dietary supplements have appropriate labeling that reflects safety and efficacy. Three classes of claims can legally be used on the labels of dietary supplements:[12]

1. Health claims: Statements that relate the consumption of a dietary ingredient to a reduced risk of a disease or health-related condition. Health claims require authorization by the FDA, but once a claim has been approved, it may be used by all manufacturers according to the regulations established by the FDA (example: "Adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis.").
2. Nutrient content claims: Provide information on the level of a nutrient in a product in absolute terms or relative to another component and help ensure that descriptive terms, such as high or low, are used consistently for all types of dietary supplement products and are meaningful to consumers. Most nutrient content claim regulations apply only to those nutrients that have an established Daily Value (DV). Percentage claims for dietary supplements are used to describe the percentage level of a dietary ingredient in a dietary supplement and may refer to dietary ingredients for which there is no established DV. Nutrient content claims require FDA review before they can be used on a product (example: "40% omega-3 fatty acids, 10 mg per capsule").
3. Structure/function claims: Describe the effect a substance has on the structure or function of the body. These types of claims are not pre-approved by the FDA, but manufacturers must have substantiation that the claim is truthful and not misleading and must submit a notification with the text of the claim to FDA no later than 30 days after marketing the dietary supplement with the claim. If a dietary supplement label includes such a claim, it must state in a disclaimer (using wording that is specified in the DSHEA) that the FDA has not evaluated the claim. The disclaimer must also state that the dietary supplement product is not intended to "diagnose, treat, cure or prevent any disease," because only a drug can legally make such a claim. Structure/function claims may not explicitly or implicitly link the claimed effect of the nutrient or dietary ingredient to a disease or to a state of health leading to a disease (example: "Helps improve memory.").

Another class of claim, a disease claim, is a claim to diagnose, cure, mitigate, treat, or prevent disease; as noted, such claims are prohibited on dietary supplements and require FDA approval to be used on approved drug products (example: "Reduces the pain and stiffness associated with arthritis.").

Criteria for the rigor of evidence needed to support a claim have not been established; scientific evidence may be provided by just one article assessing a compound *in vitro* that has not achieved recognition or agreement.[13] Importantly, studies have shown consumers are generally unaware of, or ignore, DSHEA disclaimers; studies also note that these disclaimers fail to communicate that patients should use caution in interpreting the efficacy claims manufacturers make for their dietary supplement and they have little reliable impact on patients' beliefs about the risk and effectiveness of dietary supplements. Furthermore, there is evidence that consumers erroneously believe that the labels of dietary supplements will include warnings of adverse effects where appropriate.[13,14]

While DSHEA, via statutory authority granted to the FDA, applies exclusively to the labeling of dietary supplements, the FTC is primarily responsible for the regulation of dietary supplement advertisements. The FTC regulates "unfair methods of competition" in commerce and "unfair or deceptive" practices under Sections 5 and 12 of the Federal Trade Commission Act (FTCA). Two principles apply in FTC enforcement of advertisements: ads have to be (1) truthful and not misleading and (2) substantiated. Additionally, the FTC has the authority to compel manufacturers to submit their evidence in substantiation of the claims they make in advertisements. Cease and desist orders not only prohibit further deceptive practice but may require companies to pay a fine of $16,000 per ad per day in the instance of future violations. Cases have been rare; over the last decade, the FTC reports that is has filed 120 cases challenging health claims made for dietary supplements.[15]

Supplement Facts Panel

In May 2016, a final rule was published in the Federal Register detailing Revision of the Nutrition and Supplement Facts Labels.[16] The Supplement Facts label is the black and white box located on dietary supplement product containers that is intended to provide the chemical composition of a dietary supplement. Because of changes and evolution of the American diet and advancements in nutrition science, federal requirements for the label are being updated. Notable changes include updates to DV to reflect the current American diet; a change from reporting some vitamins in International Units (IU) to more commonly used measures of milligrams (mg) and micrograms (mcg); listing of folic acid as folate (measured in mcg of dietary folate equivalents); and listing of the amount of added sugar and percent DV. The deadline for large manufacturers to reflect the label changes was January 1, 2020. Smaller manufacturers have until January 1, 2021 to comply with these changes. A resource has been developed to educate consumers about the changes.[17]

The FDA requires manufacturers to list all of the ingredients in a dietary supplement on the Supplement Facts panel of the product, along with the amount of each by weight, except when the ingredients are part of a "proprietary blend."[18] A proprietary blend (or "complex," matrix," or "formulation") is a collection of ingredients often unique to a particular product and sometimes given a fanciful name. The specific amount of each individual ingredient in a proprietary blend does not have to be listed; however, the absence of a stated amount for each ingredient can have significant implications for patients and physicians, especially if the blend contains stimulant or stimulant-like ingredients or if the ingredient has a supplement-drug interaction with a patient's medication.

DSHEA Modernization and Product Registries

The FDA recently announced efforts to strengthen the regulation of dietary supplements by modernizing and reforming their oversight.[19] The Agency established a Dietary Supplement Working Group at the FDA to identify opportunities across the Agency to modernize the oversight of dietary supplements, develop a new rapid-response tool to alert the public of tainted or recalled products, foster the submission of NDI notifications so they can evaluate the safety of a new ingredient before it becomes available to consumers, update the compliance policy regarding NDIs, and engage in conversations to modernize DSHEA. A public meeting was held in May 2019, attended by a representative from the AMA, to discuss Responsible Innovation in Dietary Supplements; the stated purpose of the public meeting was to give interested parties an opportunity to present ideas for facilitating responsible innovation in the dietary supplement industry while preserving the FDA's ability to protect the public from unsafe, misbranded, or otherwise unlawful dietary supplements.[20] The FDA has not yet released any reports or guidance from the public meeting. Many stakeholders testified in support of appropriate enforcement tools and policies, which may include mandatory recall and related authorities over products that are marketed as dietary supplements but contain drugs or drug analogues; the utilization of risk-based inspections for dietary supplement manufacturing facilities; and strengthening of AER systems.

Of note, a recent survey conducted by the Pew Charitable Trusts found that most American adults believe the FDA should do more to ensure the safety of dietary supplements.[21,22] Experts in the field of dietary supplements and their regulatory structure support modernization and reform of DSHEA to include stronger safeguards resulting in access to quality products.[23]

Currently, the FDA has no mechanism to know what dietary supplement products are on the market. Because dietary supplement manufacturers are not required to submit product information, the FDA has limited knowledge about the products on the market, including their ingredients and the conditions under which they were manufactured. Several experts and organizations support the concept of an FDA product listing regime--if it can be effective at identifying and removing dangerous dietary supplement products from the marketplace.[24] Some features have been proposed for a mandatory product registry to safeguard the public and inform physicians, investigators, and regulators including linking each product to a unique identifier such as a stock keeping unit (SKU) barcode or QR code and the ability to flag all products produced by manufacturers who have received warning letters from the FDA.[23] Proponents of an FDA-managed, mandatory product registry also support giving the FDA additional authorities to decline to add labels to the registry if the label lists a prohibited ingredient as well as FDA-required investigations of products labeled as containing NDIs for which no evidence of safety exists or for products which have reports of undisclosed ingredients.

The Supplement OWL® (Online Wellness Library) dietary supplement product listing is an industry-wide initiative developed with the intent to create a more complete picture of the marketplace and is led by the Council for Responsible Nutrition, joined by the American Botanical Council, the American Herbal Products Association, the Consumer Healthcare Products Association, the Natural Products Association, and the United Natural Products Alliance. However, the Supplement OWL is voluntary for manufacturers and is only a list of products; it lacks all of the safety provisions recommended by experts and listed above to ensure a safer marketplace of dietary supplements.[25]

DIETARY SUPPLEMENT RESEARCH

DSHEA granted the authority to establish regulations regarding dietary supplement manufacturing, regulate health claims and labeling of dietary supplements, and create governmental bodies to encourage research on supplements, such as centers and offices at the National Institutes of Health (NIH). Additionally, the FDA created a Botanical Safety Consortium, a public-private partnership that will gather leading scientific minds from industry, academia, and government to promote scientific advances in evaluating the safety of botanical ingredients and mixtures in dietary supplements.

National Institutes of Health

The NIH supports research and provides educational materials on dietary supplements.[26] The NIH Office of Dietary Supplements (ODS) provides scientific information about dietary supplements with the stated mission to strengthen knowledge and understanding of dietary supplements.[27] ODS hosts a website containing information about dietary supplement ingredients and co-funds research grants with several other NIH centers, including the National Center for Complementary and Integrative Health (NCCIH). ODS also supports the Dietary Supplement Label Database (DSLD) which includes label derived information from dietary supplement products marketed in the U.S.[28] DSLD was developed to serve the research community and as a resource for health care providers and the public. It also contains archived labels from products that have been removed from the market. Research suggests that even these NIH resources do not provide accurate information about the contents of dietary supplements for researchers or clinicians.[29]

DIETARY SUPPLEMENT INDUSTRY

Product Supply Chain and Quality

Beyond oversight by FDA and related agencies, the dietary supplement industry, can, and should, play an active and influential role in addressing dietary supplement quality and the problems associated with bad actors within the industry. The FDA inspected 656 dietary supplement production facilities in fiscal year 2017 and found violations in over half of them. The most common violations include failing to establish the identity, purity, strength, or composition of the final product.[30] Many companies do follow cGMP, adequately self-regulate, and make every effort to produce quality products, yet it is well documented in literature that unethical individuals and companies continue to engage in the manufacture and distribution of low quality, intentionally adulterated, or misbranded products labeled as dietary supplements that pose significant threats to patient health and safety.[31-34]

The supply chain behind the manufacture and distribution of dietary supplements can involve multiple ingredient suppliers, brokers, and contract manufacturers, both inside and outside of the United States. Because the supply chain is long and involves many links, problems with dietary supplement products can arise at various points and it can be difficult to track the lineage of ingredients and the identities of parties involved in the production of a single product.

Within the industry supply chain, ingredient providers, brokers, product manufacturers, distributors and product marketers all have the responsibility to self-regulate through qualifying and validating their suppliers, ensuring a secure supply chain, testing ingredients and finished products, identifying and removing high-risk products from product assortments, and implementing other mechanisms to assure that ingredients and final products do not contain undisclosed illegal ingredients with the potential to harm patients. Makers of fraudulent products ignore legal

obligations and FDA lacks the resources for more frequent inspections, substantive surveillance, and enforcement of the law.[35]

A regulatory framework that helps promote safe, quality dietary supplement products is necessary. Experts have suggested efforts are needed from both the FDA and industry to increase manufacturer awareness of cGMP regulations and quality standards, including quality control specifications for the identity, purity, strength, and composition of finished dietary supplements as well as their ingredients. Wider use of the public standards developed by the United States Pharmacopeial Convention (USP) or other public compendial standards, along with following cGMP, has been recommended for dietary supplements.[36] USP has also developed a General Chapter, <2251> Adulteration of Dietary Supplements with Drugs and Drug Analogs to assist manufacturers.[37]

Product Testing

With the large increase in dietary supplement manufacturers and the subsequent rise in dietary supplement safety concerns, several companies have started independent product certification services to provide an additional level of security and risk minimization for consumers who rely on dietary supplement products. Many companies test products to verify they contain the labeled dose(s) of the active ingredient(s) and not to contain microbes, heavy metals, other toxins, and/or substances that are banned by athletic organizations.[38] Testing labs include ConsumerLab.com,[39] USPharmacopeia,[40] NSF International,[41] and UL.[42]

Additional resources exist for patients and physicians who are seeking more information about products, product ingredients, or products with reported violations (Box 1). USP provides a list of products they have independently verified for quality,[40] NSF has a listing of products that are NSF Certified for Sport®,[41] and the U.S. Antidoping Agency (USADA) hosts a resource for dietary supplement safety education and awareness, Supplement 411.[43] Additionally, other, more comprehensive resources exist, but may require a paid subscription. An example is the Natural Medicines Research Collaboration Natural Medicines database, which claims to contain over 1200 monographs on natural ingredients, including vitamins, herbs, minerals, non-herbal supplements, naturally sourced chemical compounds, and foods; Natural Medicines provides monographs that include information on a variety of topics including interactions for both health care professionals and patients.[44]

DIETARY SUPPLEMENT PRODUCT TRENDS

General Trends

Not all dietary supplements lack evidence of efficacy. Many products considered dietary supplements are an important part of patient health care, including products to treat vitamin and mineral deficiencies and supplementation during pregnancy. However, many products that have medical benefits are commonly overused among the general population in an attempt to improve or maintain health and use in these ways provides little benefit. Studies have noted that dietary supplement use was not associated with mortality benefits in a nationally representative sample of U.S. adults, that supplement use itself does not have direct health benefits, and in some cases excess intake might increase harmful effects, including cancer and mortality.[38,45] Only approximately a quarter of patients who are using dietary supplements are doing so based on the recommendation of their physician.[46] Additionally, a study commissioned by the FTC found that the majority of patients in the United States are overly optimistic about the results they can achieve[13]

Investigators have also commented on significant misperceptions of understanding related to the safety and efficacy of dietary supplements and FDA authorities. Investigators found that patients incorrectly believe that dietary supplements are approved by the government; that dietary supplements have been tested for safety and effectiveness; that the content of all dietary supplements are analyzed; and that manufacturers are required to disclose known adverse effects.[14] Each of these beliefs is a misconception.

Experts on the subject of dietary supplements note that patients may not be aware of the lack of efficacy of products and respond to advertisements, recommendations from friends and family, and longstanding habits of use. Consistently, mainstream media produces articles related to popular dietary supplements. At the beginning of each new year, it is common to see many lists about dietary supplement trends for the year ahead, whether based on evidence of efficacy or not. Lists of dietary supplement trends for 2020 include bone marrow, berberine, nootropic products, collagen peptides, and cannabidiol (CBD).[47,48] Brain enhancement (nootropic) dietary supplement products are an emerging and increasing problem, as many contain unapproved pharmaceutical products.[49] The Council on Science and Public Health recently commented on this emerging issue in CSAPH report 9-A-16, Increasing Awareness of Nootropic Use.[50]

Commonly Adulterated Products

Adulteration of dietary supplements is usually either economic adulteration, when a less expensive ingredient is used in place of a more expensive ingredient listed on the label, or pharmaceutical adulteration, when an active pharmaceutical is included in a product and not listed on the label.[34] Adding to the complexity and safety risks associated with adulteration, pharmaceutical adulteration includes the use of not only FDA-approved drugs, or drugs formerly approved by the FDA and withdrawn, but also drugs used in other countries (and never FDA-approved), and experimental drugs minimally or never tested in humans.[51,52]

Dietary supplements are associated with an estimated 23,000 emergency department visits each year, and many of these visits are due to products that are adulterated with pharmaceutical drugs. The most commonly adulterated dietary supplements are those marketed as weight loss, sexual enhancement, or sports supplements.[33,34,53-57] Many times, active pharmaceuticals are identified in dietary supplements even after FDA warnings to the manufacturer.[52,58] The drug ingredients in these dietary supplements have the potential to cause AEs related to accidental misuse, overuse, interaction with other medications, or with other pharmaceuticals within the supplement, and related to underlying health conditions in the user.[59]

Additionally, extensive efforts have been made to silence physician-researchers investigating adulterated dietary supplements.[60,61] Despite research being vetted through peer review and published in reputable journals, dietary supplement manufacturers have attempted to intimidate researchers with strategic lawsuits against public participation (SLAPP), which attempt to suggest research was biased, unethical, or vindictive, instead of publishing rebuttals to challenge the research. Although anti-SLAPP laws exist and are intended to prevent people from using courts, and even the threat of a lawsuit, to intimidate people who are exercising their First Amendment rights, some courts have allowed these lawsuits go to trial to not undermine a supplement company's constitutional right to a jury trial.

Cannabidiol

CBD is a major cannabinoid in marijuana and does not appear to have any psychoactive effects similar to those caused by Δ^9-tetrahydrocannabinol (THC). Most cannabinoid compounds are

derived from the plant genus cannabis. Various breeds or strains of cannabis for medicinal use have a significant variety in the ratios of CBD-to-THC and are known to contain other non-psychotropic cannabinoids. “Marijuana” is listed as a Schedule 1 controlled substance under the Controlled Substances Act (CSA); CBD and other components of cannabis are also Schedule 1 compounds by definition because they are considered “derivatives” or “components” of marijuana.

Hemp, however, is excluded from this rule since the Agricultural Improvement Act (the 2018 Farm Bill) removed hemp-derived products from Schedule I status under the CSA.[62] The Farm Bill defined hemp as a strain of the cannabis plant containing no more than 0.3% THC. The 2018 Farm Bill does not legalize CBD generally and CBD remains a Schedule 1 substance under the CSA. The 2018 Farm Bill does create exceptions to this Schedule 1 status in certain situations: any cannabinoid that is derived from hemp will be legal, if and only if that hemp is produced in a manner consistent with the Farm Bill, associated federal regulations, association state regulations, and is produced by a licensed grower. All other cannabinoids, produced in any other setting, remain a Schedule I substance under the CSA and are illegal. The one exception is pharmaceutical-grade CBD products that have been approved by the FDA, of which there is one. Epidiolex from GW Pharmaceuticals, a purified 98% oil-based CBD extract of known and constant composition, is FDA approved to treat rare forms of epilepsy, and is Schedule V.

The legal landscape of CBD remains complex. As states have legalized cannabis use for medical purposes and for any purpose, a variety of non-FDA approved or regulated products have become more mainstream. Among these products are CBD oils or other products rich in CBD. CBD products are used by the public for a variety of purported indications, including seizure reduction, as an anti-inflammatory, and for alleviating anxiety. Often, CBD products are (incorrectly) called CBD-only products; many states define “CBD-only” as containing less than 0.3% THC (the same as hemp). For many products, it is difficult to determine if the product is hemp-derived (Schedule 1 exempt) or not, and variability in CBD and THC content is common. Recently, an analysis of twenty popular CBD products and found that only three contained what was listed on the labels.[63]

The FDA has taken the position that CBD cannot be legally sold in either supplements or foods and has repeatedly said it needs more data to better understand the risks and benefits of CBD.[64,65] The FDA has estimated it could take between three and five years to complete a rulemaking process that would allow CBD to be added to food and dietary supplements. If it is eventually permitted, FDA will need to establish science-based standards for dosing, composition, nomenclature, product claims, and numerous other manufacturing and marketing issues to further the goals of protecting the public and providing more clarity to industry and the public.[66,67] To further progress the knowledge related to CBD, the FDA has re-opened a public docket indefinitely for the submission of scientific data related to CBD.[67]

The FDA has focused its limited enforcement resources on removing CBD products that make claims of curing or treating disease, leaving many CBD products on the market as both foods and dietary supplements available for sale. Some experts believe this is an opportunity for the FDA to reform and improve oversight of dietary supplements and ingredients to create clear, reasonable pathways for low-dose CBD and other new substances to be safely introduced into supplements and food.[65]

Widespread agreement exists that additional research is needed regarding CBD, both for efficacy and long-term safety. Currently, CBD and hemp oils remain a widely available but unproven therapeutic option for many patients. CBD became the top selling “dietary supplement” in the United States in 2018 according to a recent report from the American Botanical Council.[63] Experts note that physicians should remain open to the possible future role CBD products may play in the

management of a variety of difficult to treat diseases,[68] yet use caution and consider of the risks present in patients' use of CBD products and the possibility of product contamination.[69]

ADVERSE EVENT REPORTING, INTERACTIONS, AND PRODUCT REPORTING

Post-market surveillance is a key part of identifying safety problems associated with both pharmaceutical products and dietary supplement products. The FD&C Act defines a dietary supplement AE as "any health-related event associated with the use of a dietary supplement that is adverse" (e.g., headache, abdominal pain, allergic reaction, rash, and dizziness or lightheadedness). A serious adverse event (SAE) is defined as an AE that "results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or requires, based on a reasonable medical judgement, a medical or surgical intervention to prevent an outcome described above."[7]

While few of the many high-quality studies evaluating dietary supplements and ingredients looking for positive health benefits from their use have found such results, several studies have produced evidence of harm.[46] It has been reported that less than 40 percent of patients reveal use of dietary supplements to their health care professionals and no metrics could be located related to how many health care professionals directly ask patients about dietary supplement use. The US Government Accountability Office estimates that a small fraction of the estimated 50,000 adverse reactions each year from dietary supplements are reported to the FDA. The lack of reporting, along with the poor quality of the information received in the few reports make it nearly impossible for the FDA to find and remove dangerous supplements.[70,71]

Literature documents that concomitant use of dietary supplements and prescribed medications is common, problematic, and can result in life-threatening ADEs, hospitalizations, and fatalities.[72] Adding to the risk for patients, dietary supplements often contain multiple active ingredients and are often inaccurately labeled. Myriad products and ingredients have been implicated in interactions and ADEs, yet investigators note underreporting, lack of case reports, and incomplete reports.[23,72-76] In several instances, local public health departments, the Centers for Disease Control and Prevention (CDC), or the Department of Defense have been more successful at linking cases of illness to dietary supplement products than physician reporting and the FDA.[75]

Suspected supplement-related AEs should be reported to the FDA.[38] All reporting by physicians is voluntary and also strongly recommended; the FDA gives extra credence to physician reports and the voluntary system of passive surveillance is the only opportunity the FDA has to detect harmful dietary supplements. The Safety Reporting Portal (SRP)[77] streamlines the process of reporting product safety issues to the FDA and the NIH, formerly done through FDA's Adverse Event Reporting System (FAERS)[78] and MedWatch[79] Online Voluntary Reporting Form. The SRP can be used by manufacturers, health care professionals, researchers, public health officials, and patients.[80] Contaminated dietary supplement products can be also be reported via an FDA portal.[81] Box 2 provides a list of resources for reporting dietary supplement safety issues.

Some dietary supplements are known to cause clinically important interactions with drugs and should be avoided by most patients receiving any pharmacologic therapy. Many other dietary supplement products, however, are predicted to cause interactions based limited in vitro studies.[72,82] Additionally, some dietary supplements have the potential to interfere with laboratory results.[83] Risk-based and open conversation with patients is crucial in minimizing and appropriately identifying interactions.

PATIENT-PHYSICIAN INTERACTION

Physicians or their office staff should include discussion of dietary supplements when reviewing medications with all patients. Reporting suspected AEs related to dietary supplements is critical, and dietary supplements should also be considered as source of unexplained AEs. Risk-based patient counseling of patients should include discussion about the variable quality of dietary supplements, the presence of unreputable products in the marketplace, and information on which products are commonly adulterated; additionally, physicians can ask patients to bring dietary supplement products with them to appointments for review and discussion.[52] Physicians should also make an effort to evaluate any potential drug-supplement interactions based on the products patients are using or considering. Box 1 contains a list of resources for information about dietary supplement products.

When counseling patients about dietary supplements, it should be noted that supplementation is not a substitute for a healthful and balanced diet and, in most cases, provides little benefit. Targeted supplementation may be warranted for high-risk populations for whom nutritional requirements may not be met through diet alone, including people at certain life stages and those with specific risk factors.[38]

CURRENT AMA POLICY AND ACTIVITIES

AMA currently has policy related to dietary supplements. Policy H-150.954, "Dietary Supplements and Herbal Remedies," notes AMA's support of the FDA MedWatch program, encourages the reporting of adverse events associated with dietary supplements, and urges manufacturers to investigate and include on the label any adverse effects, contraindications, and possible drug interactions. Policy D-150.991, "Herbal Products and Drug Interactions," supports FDA efforts to create a publicly accessible database of adverse event and drug interaction information on dietary supplements. Policy H-150.954 also urges for modifications to strengthen DSHEA, supports FDA and FTC enforcement efforts, and supports appropriate dietary supplement labeling. This policy also notes the AMA's support of educating patients and physicians about the risks associated with dietary supplements. Policy H-150.946, "Advertising for Herbal Supplements," states that the naming, packaging, and advertising of dietary supplement products be such that they cannot be confused with pharmaceutical products. Policy H-115.988, "Qualitative Labeling of All Drugs," supports efforts to require both active and inactive ingredients of over-the-counter and prescription drugs and dietary supplements to be listed on the manufacturer's label or package insert. Policy D-120.982, "Illegal Online Prescribing Operations," supports efforts that help the Drug Enforcement Administration and the FDA to better regulate and control the illegal online sales and distributions of drugs, dietary supplements, and herbal remedies.

Additionally, the AMA is a member of the Dietary Supplement Quality Collaborative (DSQC), a group committed to the advancement of policies and initiatives designed to improve and maintain the quality and safety of products marketed as dietary supplements.[84] The DSQC supports policies and resources to advance innovation; help ensure safe, quality supplements; remove illegal and tainted products from the marketplace; and promote consumer education. To this end, through DSQC, AMA has contributed to the writing of a white paper seeking to educate stakeholders about the dangers of tainted dietary supplements and recommend solutions to aid in minimizing the risks associated with them.[35] The AMA has also been a signatory to letters requesting support for the FDA's Office of Dietary Supplement Programs.

SUMMARY

Millions of patients use dietary supplements yet today, the regulatory structure in place for dietary supplements does not adequately protect the public. In the 26 years since the passage of DSHEA, the dietary supplement industry has been reshaped by a complex global supply chain, the Internet, and newly discovered ingredients of unknown safety. An estimated 75,000 new supplement products have been introduced since 1994, and the FDA has received adequate safety data for fewer than 250 new ingredients. The FDA also has no way to determine what ingredients are present in the tens of thousands of products on the market.[23,24]

Furthermore, with violations in over half of inspected dietary supplement manufacturers,[30] more effective enforcement tools are required to protect the health of patients. All patients will benefit from a regulatory framework that promotes product safety and provides appropriate tools and resources for the FDA to maintain appropriate oversight.[34]

CONCLUSION

The advancement of a safe and transparent dietary supplement marketplace will require a trustworthy supply chain and will involve robust AE, drug interaction, and tainted product reporting. The reliance on an industry that self-regulates is insufficient and ineffective at protecting the health of patients. Unethical individuals and companies engage in the manufacture and distribution of intentionally adulterated, misbranded, and improperly labeled dietary supplement products and pose significant risks to patient health and safety. As the dietary supplement industry continues to grow and patients continue to use dietary supplement, efforts to revise and modernize the DSHEA and FDA oversight of the industry and are necessary. The FDA has no mechanism to know what dietary supplement products, containing what ingredients, are on the market. Some have suggested that a mandatory product registry would be a simple, low-burden way for the FDA and patients to obtain a complete picture of the marketplace and better protect public health by providing greater transparency, enabling prioritization of limited agency resources, and enhancing efforts to respond to emerging safety concerns. Additionally, both physician and patient education are paramount to understand this industry and the risks associated with dietary supplement products.

RECOMMENDATIONS

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

1. That Policy H-150.954, "Dietary Supplements and Herbal Remedies" be amended by addition and deletion to read as follows:

    (1) Our AMA supports efforts to enhance U.S. Food and Drug Administration (FDA) resources, particularly to the Office of Dietary Supplement Programs, to appropriately oversee the growing dietary supplement sector and adequately increase inspections of dietary supplement manufacturing facilities.

    (2) Our AMA supports the FDA having appropriate enforcement tools and policies related to dietary supplements, which may include mandatory recall and related authorities over products that are marketed as dietary supplements but contain drugs or drug analogues, the utilization of risk-based inspections for dietary

supplement manufacturing facilities, and the strengthening of adverse event reporting systems.

(3) Our AMA supports continued research related to the efficacy, safety, and long-term effects of dietary supplement products.

(4) Our AMA will work with the FDA to educate physicians and the public about FDA's ~~MedWatch program~~ Safety Reporting Portal (SRP) and to strongly encourage physicians and the public to report potential adverse events associated with dietary supplements and herbal remedies to help support FDA's efforts to create a database of adverse event information on these forms of alternative/complementary therapies.

(5) Our AMA strongly urges physicians to inquire about patients' use of dietary supplements and engage in risk-based conversations with them about dietary supplement product use.

(6) Our AMA continues to strongly urge Congress to modify and modernize the Dietary Supplement Health and Education Act to require that:

(a) dietary supplements and herbal remedies including the products already in the marketplace undergo FDA approval for evidence of safety and efficacy;

(b) dietary supplements meet standards established by the United States Pharmacopeia for identity, strength, quality, purity, packaging, and labeling;

(c) FDA establish a mandatory product listing regime that includes a unique identifier for each product (such as a QR code), the ability to identify and track all products produced by manufacturers who have received warning letters from the FDA, and FDA authorities to decline to add labels to the database if the label lists a prohibited ingredient or new dietary ingredient for which no evidence of safety exists or for products which have reports of undisclosed ingredients; and

(d) regulations related to new dietary ingredients (NDI) are clarified to foster the timely submission of NDI notifications and compliance regarding NDIs by manufacturers; and

(7) Our AMA supports FDA postmarketing requirements for manufacturers to report adverse events, including drug interactions; and legislation that declares metabolites and precursors of anabolic steroids to be drug substances that may not be used in a dietary supplement.

(8) Our AMA will work with the Federal Trade Commission (FTC) to support enforcement efforts based on the FTC Act and current FTC policy on expert endorsements and supports adequate funding and resources for FTC enforcement of violations of the the FTC Act.

(9) Our AMA strongly urges that criteria for the rigor of scientific evidence needed to support a structure/function claim on a dietary supplement be established by the FDA and minimally include requirements for robust human studies supporting the claim.

(10) Our AMA strongly urges dietary supplement manufacturers and distributors to clearly label all products with truthful and not misleading information and for ~~supports that~~ the product labeling ~~of dietary supplements and herbal remedies~~ to:

~~(a) that bear structure/function claims contain the following disclaimer as a minimum requirement: "This product has not been evaluated by the Food and Drug Administration and is not intended to diagnose, mitigate, treat, cure, or prevent disease." This product may have significant adverse side effects and/or interactions with medications and other dietary supplements; therefore it is important that you inform your doctor that you are using this product;~~

(a) not include structure/function claims that are not supported by evidence from robust human studies;

(b) ~~should~~ not contain prohibited disease claims~~.~~;

(c) eliminate "proprietary blends" and list and accurately quantify all ingredients contained in the product;

(d) require advisory statements regarding potential supplement-drug and supplement-laboratory interactions and risks associated with overuse and special populations; and

(e) include accurate and useful disclosure of ingredient measurement.

(11) Our AMA supports and encourages the FDA's regulation and enforcement of labeling violations and FTC's regulation and enforcement of advertisement violations of prohibited disease claims made on dietary supplements and herbal remedies.

(12) Our AMA urges that in order to protect the public, manufacturers be required to investigate and obtain data under conditions of normal use on adverse effects, contraindications, and possible drug interactions, and that such information be included on the label.

(13) Our AMA will continue its efforts to educate patients and physicians about the ~~possible ramifications~~ risks associated with the use of dietary supplements and herbal remedies~~.~~ and supports efforts to increase patient, healthcare practitioner, and retailer awareness of resources to help patients select quality supplements, including educational efforts to build label literacy.

2. That Policy H-120.926, "Expedited Prescription Cannabidiol Drug Rescheduling," be amended by addition and deletion to read as follows:

Regulation of Cannabidiol Products

Our AMA will: (1) encourage state controlled substance authorities, boards of pharmacy, and legislative bodies to take the necessary steps including regulation and legislation to reschedule U.S. Food and Drug Administration (FDA)-approved cannabidiol products, or make any other necessary regulatory or legislative change, as expeditiously as possible so that they will be available to patients immediately after approval by the FDA and rescheduling by the U.S. Drug Enforcement Administration; ~~and~~ (2) advocate that an FDA-approved cannabidiol medication should be governed only by the federal and state regulatory provisions that apply to other prescription-only products, such as dispensing through pharmacies, rather than by these various state laws applicable to unapproved cannabis products~~.~~; and (3) support comprehensive FDA regulation of cannabidiol products and practices necessary to ensure product quality, including identity, purity, and potency.

3. That policy D-150.991, "Herbal Products and Drug Interactions," that notes our AMA's support of FDA efforts to create a publicly accessible database of adverse event and drug interaction information on dietary supplements, be reaffirmed.

Fiscal Note: Less than $1000

REFERENCES

1. U.S. Government Accountability Office (GAO). *Memory Supplements: Clarifying FDA and FTC Roles Could Strengthen Oversight and Enhance Consumer Awareness.* May 2017.
2. Incze M. Vitamins and Nutritional Supplements: What Do I Need to Know?Vitamins and Nutritional SupplementsVitamins and Nutritional Supplements. 2019.
3. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in Dietary Supplement Use Among US Adults From 1999-2012. *Jama.* 2016;316(14):1464-1474.
4. Council for Responsible Nutrition. Annual CRN Consumer Survey on Dietary Supplements: Consumer Intelligence to Enhance Business Outcomes. https://www.crnusa.org/resources/annual-crn-consumer-survey-dietary-supplements-consumer-intelligence-enhance-business. Published 2019. Accessed February 17, 2020.
5. Mikulic M. Total U.S. dietary supplements market size 2016-2024. https://www.statista.com/statistics/828481/total-dietary-supplements-market-size-in-the-us/. Published 2019. Accessed February 17, 2020.
6. Grand View Research. Dietary Supplements Market Worth $194.63 Billion By 2025 | CAGR 7.8%. https://www.grandviewresearch.com/press-release/global-dietary-supplements-market. Published 2019. Accessed February 17, 2020.
7. 21 C.F.R. In.
8. U.S. Food and Drug Administration. FDA 101: Dietary Supplements. https://www.fda.gov/consumers/consumer-updates/fda-101-dietary-supplements. Published 2015. Accessed February 17, 2020.
9. 21 C.F.R. § 111. In.
10. U.S. Food and Drug Administration. New Dietary Ingredients in Dietary Supplements - Background for Industry. https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/new-dietary-ingredients-dietary-supplements-background-industry. Published 2019. Accessed February 19, 2020.
11. U.S. Food and Drug Administration. Dietary Supplements. https://www.fda.gov/food/dietary-supplements. Published 2019. Accessed February 19, 2020.
12. U.S. Food and Drug Administration. Label Claims for Conventional Foods and Dietary Supplements. https://www.fda.gov/food/food-labeling-nutrition/label-claims-conventional-foods-and-dietary-supplements. Published 2018. Accessed February 19, 2020.
13. Starr RR. Too little, too late: ineffective regulation of dietary supplements in the United States. *American journal of public health.* 2015;105(3):478-485.
14. Dodge T. Consumers' perceptions of the dietary supplement health and education act: implications and recommendations. *Drug testing and analysis.* 2016;8(3-4):407-409.
15. U.S. Federal Trade Commission. Health Claims. https://www.ftc.gov/news-events/media-resources/truth-advertising/health-claims. Published 2020. Accessed March 11, 2020.
16. Food Labeling: Revision of the Nutrition and Supplement Facts Labels. In. Vol 81. Federal Register2016.
17. Label Wise: A Guide to Understanding Supplement Facts. https://belabelwise.org/. Published 2020. Accessed February 24, 2020.
18. U.S. Food and Drug Administration. Dietary Supplement Labeling Guide: Chapter IV. Nutrition Labeling (#34). https://www.fda.gov/food/dietary-supplements-guidance-documents-

regulatory-information/dietary-supplement-labeling-guide-chapter-iv-nutrition-labeling#4-34. Published 2018. Accessed March 11, 2020.
19. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's new efforts to strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-new-efforts-strengthen-regulation-dietary. Published 2019. Accessed February 24, 2020.
20. U.S. Food and Drug Administration. Public Meeting to Discuss Responsible Innovation in Dietary Supplements. https://www.fda.gov/food/workshops-meetings-webinars-food-and-dietary-supplements/public-meeting-discuss-responsible-innovation-dietary-supplements. Published 2019. Accessed February 24, 2020.
21. Pew Charitable Trusts. Q1141 Perceptions of Dietary Supplements and the FDA. https://www.pewtrusts.org/-/media/assets/2019/10/dietary_supplement_survey_topline_results.pdf. Published 2020. Accessed March 5, 2020.
22. Pew Charitable Trusts. Most Supplement Users Back Enhanced FDA Oversight of These Products. https://www.pewtrusts.org/en/research-and-analysis/articles/2019/10/01/most-supplement-users-back-enhanced-fda-oversight-of-these-products. Published 2020. Accessed March 5, 2020.
23. Cohen PA, Bass S. Injecting Safety into Supplements — Modernizing the Dietary Supplement Law. *New England Journal of Medicine.* 2019;381(25):2387-2389.
24. Kapoor A, Sharfstein JM. Breaking the gridlock: Regulation of dietary supplements in the United States. *Drug testing and analysis.* 2016;8(3-4):424-430.
25. Council for Responsible Nutrition. The Supplement OWL®. https://www.supplementowl.org/index.html. Published 2020. Accessed March 2, 2020.
26. Kuszak AJ, Hopp DC, Williamson JS, Betz JM, Sorkin BC. Approaches by the US National Institutes of Health to support rigorous scientific research on dietary supplements and natural products. *Drug testing and analysis.* 2016;8(3-4):413-417.
27. National Institutes of Health. Office of Dietary Supplements. https://ods.od.nih.gov/. Published 2020. Accessed March 3, 2020.
28. National Institutes of Health. Dietary Supplement Label Database. http://dsld.nlm.nih.gov/dsld/. Published 2020. Accessed March 3, 2020.
29. Cohen PA, Sharfstein JM, Kamugisha BS, Vanhee C. Analysis of Ingredients of Supplements in the National Institutes of Health Supplement Database Marketed as Containing a Novel Alternative to Anabolic Steroids. *JAMA Network Open.* 2020(In press).
30. Cohen PA. Probiotic Safety—No Guarantees. *JAMA internal medicine.* 2018;178(12):1577-1578.
31. Cohen PA, Avula B, Khan IA. Variability in strength of red yeast rice supplements purchased from mainstream retailers. *European journal of preventive cardiology.* 2017:2047487317715714.
32. Lewis ZT, Shani G, Masarweh CF, et al. Validating bifidobacterial species and subspecies identity in commercial probiotic products. *Pediatric research.* 2016;79(3):445-452.
33. Geller AI, Shehab N, Weidle NJ, et al. Emergency Department Visits for Adverse Events Related to Dietary Supplements. *New England Journal of Medicine.* 2015;373(16):1531-1540.
34. Cohen PA. The fda and adulterated supplements—dereliction of duty. *JAMA Network Open.* 2018;1(6):e183329.
35. Dietary Supplement Quality Collaborative. Briefing Paper on Products Illegally Marketed as Dietary Supplements and Proposed Multi-Stakeholder Responses. https://www.dsqcollaborative.org/sites/default/files/dsqc/PDF/dsqc_tainted_products_briefing_document.pdf. Published 2017. Accessed February 19, 2020.

36. Sarma N, Giancaspro G, Venema J. Dietary supplements quality analysis tools from the United States Pharmacopeia. *Drug testing and analysis.* 2016;8(3-4):418-423.
37. United States Pharmacopeial Convention. <1225> Validation of Compendial Procedures. In. *USP 43–NF 38.* 2016.
38. Manson JE, Bassuk SS. Vitamin and mineral supplements: What clinicians need to know. *Jama.* 2018;319(9):859-860.
39. ConsumerLab.com. ConsumerLab.com. https://www.consumerlab.com/. Published 2020. Accessed March 5, 2020.
40. United States Pharmacopeia. USP Verified Dietary Supplements. https://www.quality-supplements.org/verified-products?fireglass_rsn=true#fireglass_params&tabid=ac62888d17482230&application_server_address=isolation1-us-east-1.wss.prod.fire.glass&popup=true&is_right_side_popup=false&start_with_session_counter=1. Published 2020. Accessed March 5, 2020.
41. NSF International. NSF International Certified for Sport® Online Directory. https://www.nsfsport.com/certified-products/?fireglass_rsn=true#fireglass_params&tabid=a8eedd9075ff3414&application_server_address=isolation1-us-east-1.wss.prod.fire.glass&popup=true&is_right_side_popup=false&start_with_session_counter=1. Published 2020. Accessed March 5, 2020.
42. UL. Dietary Supplements. https://crs.ul.com/en/industries/dietary-supplements/. Published 2020. Accessed March 5, 2020.
43. United States Antidoping Agency. Supplement 411. https://www.usada.org/athletes/substances/supplement-411/. Published 2020. Accessed March 5, 2020.
44. Therapeutic Reserach Center. Natural Medicines. https://naturalmedicines.therapeuticresearch.com/. Published 2020. Accessed March 26, 2020.
45. Chen F, Du M, Blumberg JB, et al. Association Among Dietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults: A Cohort StudyDietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults. 2019.
46. Cohen PA. The Supplement Paradox: Negligible Benefits, Robust Consumption. *Jama.* 2016;316(14):1453-1454.
47. Fullscript. 2020 Supplement Trends: 12 Products And Trends To Watch. https://fullscript.com/blog/2020-supplement-trends. Published 2020. Accessed March 5, 2020.
48. Tibbits A. The Biggest Supplement Trends Of 2020, According To Nutritionists. https://www.thezoereport.com/p/the-biggest-supplement-trends-of-2020-according-to-nutritionists-20514377. Published 2020. Updated January 15. Accessed March 5, 2020.
49. Cohen PA, Zakharevich I, Gerona R. Presence of Piracetam in Cognitive Enhancement Dietary Supplements. *JAMA internal medicine.* 2020;180(3):458-459.
50. Council on Science and Public Health. *Increasing Awareness of Nootropic Use.* American Medical Association;2016. 9-A-16.
51. Cohen PA, Travis JC, Keizers PHJ, Deuster P, Venhuis BJ. Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-DMBA). *Clinical toxicology (Philadelphia, Pa).* 2018;56(6):421-426.
52. Cohen PA, Wen A, Gerona R. Prohibited stimulants in dietary supplements after enforcement action by the us food and drug administration. *JAMA internal medicine.* 2018.
53. Magee CD, Witte S, Kwok RM, Deuster PA. Mission Compromised? Drug-Induced Liver Injury From Prohormone Supplements Containing Anabolic-Androgenic Steroids in Two Deployed U.S. Service Members. *Military medicine.* 2016;181(9):e1169-1171.

54. Cohen PA, Wang YH, Maller G, DeSouza R, Khan IA. Pharmaceutical quantities of yohimbine found in dietary supplements in the USA. *Drug testing and analysis.* 2016;8(3-4):357-369.
55. Cohen PA, Travis JC, Keizers PHJ, Boyer FE, Venhuis BJ. The stimulant higenamine in weight loss and sports supplements. *Clinical toxicology (Philadelphia, Pa).* 2018:1-6.
56. Marcus DM. Dietary supplements: What's in a name? What's in the bottle? *Drug testing and analysis.* 2016;8(3-4):410-412.
57. Or F, Kim Y, Simms J, Austin SB. Taking Stock of Dietary Supplements' Harmful Effects on Children, Adolescents, and Young Adults. *J Adolesc Health.* 2019;65(4):455-461.
58. Cohen PA, Maller G, DeSouza R, Neal-Kababick J. Presence of Banned Drugs in Dietary Supplements Following FDA Recalls. *Jama.* 2014;312(16):1691-1693.
59. Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. Unapproved pharmaceutical ingredients included in dietary supplements associated with us food and drug administration warnings. *JAMA Network Open.* 2018;1(6):e183337.
60. Bagley N, Carroll AE, Cohen PA. Scientific Trials—In the Laboratories, Not the Courts. *JAMA internal medicine.* 2018;178(1):7-8.
61. Carroll AE. Why a Lot of Important Research Is Not Being Done. New York Times Web site. https://www.nytimes.com/2017/12/04/upshot/health-research-lawsuits-chilling-effect.html. Published 2017. Accessed March 11, 2020.
62. Public Law 115-334. Agriculture Act of 2018. . In.
63. Rubin R. Cannabidiol Products Are Everywhere, but Should People Be Using Them? *Jama.* 2019.
64. U.S. Food and Drug Administration. FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD). https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd. Published 2020. Accessed March 5, 2020.
65. Cohen PA, Sharfstein J. The Opportunity of CBD — Reforming the Law. *New England Journal of Medicine.* 2019;381(4):297-299.
66. Wang B. Throckmorton: FDA Needs More Data, Not Authority, For CBD Regulation. Inside Health Policy Web site. https://insidehealthpolicy.com/daily-news/throckmorton-fda-needs-more-data-not-authority-cbd-regulation. Published 2020. Accessed January 21, 2020.
67. U.S. Food and Drug Administration. FDA Advances Work Related to Cannabidiol Products with Focus on Protecting Public Health, Providing Market Clarity. https://www.fda.gov/news-events/press-announcements/fda-advances-work-related-cannabidiol-products-focus-protecting-public-health-providing-market?utm_campaign=030520_PR_FDA%20Advances%20Work%20Related%20to%20Cannabidiol%20Products&utm_medium=email&utm_source=Eloqua. Published 2020. Accessed March 6, 2020.
68. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. *Mayo Clinic proceedings.* 2019;94(9):1840-1851.
69. Rianprakaisang T, Gerona R, Hendrickson RG. Commercial cannabidiol oil contaminated with the synthetic cannabinoid AB-FUBINACA given to a pediatric patient. *Clinical Toxicology.* 2020;58(3):215-216.
70. Cohen P. How America's Flawed Supplement Law Creates the Mirage of Weight Loss Cures. *Harvard Public Health Review.* 2014.
71. United States Government Accountabily Office. *Dietary Supplements: FDA Should Take Further Actions to Improve Oversight and Consumer Understanding.* January 29 2009.
72. Awortwe C, Makiwane M, Reuter H, Muller C, Louw J, Rosenkranz B. Critical evaluation of causality assessment of herb-drug interactions in patients. *British journal of clinical pharmacology.* 2018;84(4):679-693.
73. Qato DM, Alexander GC, Guadamuz JS, Lindau ST. Prevalence of Dietary Supplement Use in US Children and Adolescents, 2003-2014. *JAMA pediatrics.* 2018.

74. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. *JAMA internal medicine.* 2016;176(4):473-482.
75. Cohen PA. Hazards of Hindsight — Monitoring the Safety of Nutritional Supplements. *New England Journal of Medicine.* 2014;370(14):1277-1280.
76. Chatham-Stephens K, Taylor E, Chang A, et al. Hepatotoxicity associated with weight loss or sports dietary supplements, including OxyELITE Pro™ — United States, 2013. *Drug testing and analysis.* 2017;9(1):68-74.
77. U.S. Food and Drug Administration. The Safety Reporting Portal. https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=d89fee1e-3356-4140-b57f-c82ca1331472. Published 2020. Accessed March 5, 2020.
78. U.S. Food and Drug Administration. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Published 2020. Accessed March 5, 2020.
79. U.S. Food and Drug Administration. MedWatch Online Voluntary Reporting Form. https://www.accessdata.fda.gov/scripts/medwatch/index.cfm. Published 2020. Accessed March 5, 2020.
80. U.S. Food and Drug Administration. How to Report a Problem with Dietary Supplements. https://www.fda.gov/food/dietary-supplements/how-report-problem-dietary-supplements?fireglass_rsn=true#fireglass_params&tabid=a88e403e01278ee9&application_server_address=isolation1-us-east-1.wss.prod.fire.glass&popup=true&is_right_side_popup=false&start_with_session_counter=1. Published 2020. Accessed March 5, 2020.
81. U.S. Food and Drug Administration. Reporting Unlawful Sales of Medical Products on the Internet. https://www.fda.gov/safety/report-problem-fda/reporting-unlawful-sales-medical-products-internet?fireglass_rsn=true#fireglass_params&tabid=a6490c7daaafc331&application_server_address=isolation1-us-east-1.wss.prod.fire.glass&popup=true&is_right_side_popup=false&start_with_session_counter=1. Published 2020. Accessed March 5, 2020.
82. Asher GN, Corbett AH, Hawke RL. Common Herbal Dietary Supplement-Drug Interactions. *American family physician.* 2017;96(2):101-107.
83. Li D, Radulescu A, Shrestha RT, et al. Association of Biotin Ingestion With Performance of Hormone and Nonhormone Assays in Healthy Adults. *Jama.* 2017;318(12):1150-1160.
84. Dietary Supplement Quality Collaborative. Dietary Supplement Qualtiy Collaborative. https://www.dsqcollaborative.org/. Published 2020. Accessed February 19, 2020.

Box 1. Resources for dietary supplement product information.

1. USP verified products [40]
2. NSF Certified for Sport® products [41]
3. USADA Supplement 411 [43]
4. Natural Medicines Research Collaboration Natural Medicines database (paid subscription)[44]

Box 2. Resources for reporting dietary supplement safety issues.

1. The Safety Reporting Portal (SRP) [77]
2. Reporting Unlawful Sales of Medical Products on the Internet [81]
3. How to Report a Problem with Dietary Supplements [80]
4. FDA's Adverse Event Reporting System (FAERS) [78]
5. MedWatch Online Voluntary Reporting Form [79]

REPORT 4 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (November 2020)
(Resolutions 408-A-19, 411-A-19 and Alternate Resolution 913-I-19)
Public Health Impacts of Cannabis Legalization
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. To review developments in cannabinoid pharmacology, update relevant sections of Council Report 5-I-17, "Clinical Implications and Policy Considerations of Cannabis Use," and evaluate the public health impacts in states that have legalized cannabis for adult use to determine whether modifications to AMA are warranted.

Methods. English language reports were selected from searches of the PubMed, Google Scholar, and Cochrane Library databases from August 2017 to August 2020 using the (text or MeSh) search terms "marijuana or cannabis or cannabinoid or cannabidiol" in combination with "legalization or laws," and "health," "mental or public health," "addiction or cannabis use disorder," "health effects," "use," "benefits or harms," "youth or adolescents," "edibles," "driving," "taxes," "social equity or justice" and "treatment." Additional articles were identified through related article searches and by manual review of the reference lists of retrieved articles. Websites managed by federal and state agencies, and applicable regulatory and advocacy organizations also were consulted for relevant information.

Results. Thirty-three states have legalized medicinal use of cannabis. Eleven of these states have legalized cannabis for adult use. All 17 states that have not legalized medical use of cannabis allow the use of cannabidiol (CBD) in some way, as does the federal government for CBD products derived from hemp containing ≤0.3% Δ-9-tetrahydrocannabinol (THC). The health effects of cannabis and cannabinoids described in Council Report 5-I-17 remain valid; additionally, attention has been drawn to increased cardiovascular risks with cannabis use.

The overall prevalence of cannabis use in the U.S has increased steadily since 2011, mostly among young adults aged 18-25 years and adults 26 years of age and older. Adolescent use has declined during the same time period; findings from state-based surveys in states with legalized adult use contradict to a certain degree patterns reported by national surveys in individual states, but in the fastest growing demographic (18-25 years-old), prevalence of use is highest in states with legalized adult use. Legalization of cannabis for adult use also is associated with increased traffic fatalities, exposures reported to poison control centers (including infants and children), emergency department visits, and cannabis-related hospitalizations. Changes in methods and patterns/intensity of cannabis use in pregnant women are most concerning. Legalization has led to a large decrease in cannabis-related arrests for adults, less so for juveniles, and with limited effects on disparities in that population. States that have legalized cannabis for adult use have garnered increasing revenues on a quarterly/annual basis, with variable portions earmarked for public health measures or designed to address social equity concerns.

Conclusion. Developments in states' retail cannabis market have advanced more rapidly than public health frameworks to minimize harms. Amendments to current AMA policy are recommended to address these developments.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 4, November 2020

Subject: Public Health Impacts of Cannabis Legalization
(Resolutions 408-A-19, 411-A-19 and Alternate Resolution 913-I-19)

Presented by: Kira A. Geraci-Ciardullo, MD, MPH, Chair

Referred to: Reference Committee E

INTRODUCTION

This Council report responds to three referred resolutions on cannabis.

Resolution 408-A-19, "Banning Edible Cannabis Products," introduced by the Illinois Delegation and referred to the Board of Trustees, asked:

> That our American Medical Association adopt policy supporting a total ban on recreational edible cannabis products;

Resolution 411-A-19, "AMA to Analyze Benefits/Harms of Legalization of Marijuana," introduced by the New York Delegation and referred to the Board of Trustees, asked:

> That our American Medical Association review pertinent data from those states that have legalized marijuana; and,

Alternate Resolution 913-I-19, "Public Health Impacts and Unintended Consequences of Legalization and Decriminalization of Cannabis for Medicinal and Recreational Use," was adopted, but an additional proposed resolve, referred to the Board of Trustees, asked:

> That our AMA amend Policy H-95.924, "Cannabis Legalization for Recreational Use," by addition and deletion to read as follows:
>
> H-95.924, "~~Cannabis~~ Legalization of Cannabis Use for Medical or Any Other Purposes ~~for Recreational Use~~" Our AMA: (1) ~~believes~~ warns that cannabis is a dangerous drug and as such is a serious public health concern; (2) advocates that cannabis and cannabinoid use are a serious public health concern; (~~2~~ 3) warns against the legalized use and sale of cannabis and cannabinoids due to their potential negative impact on human health ~~believes that the sale of cannabis for recreational use should not be legalized~~; (~~3~~ 4) ~~discourages~~ warns against cannabis and cannabinoid use, ~~especially by persons vulnerable to the drug's effects and in high-risk populations such as youth,~~ by children, adolescents, pregnant women, and women who are breastfeeding; (4 5) ~~believes~~ strongly advocates that states that have already legalized cannabis for medical purposes or any other purposes ~~(for medical or recreational use or both)~~ should be required to take steps to regulate ~~the product~~ cannabis and cannabinoids 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~~ 6) strongly 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 and cannabinoid use; and (~~6~~ 7) supports decriminalization and public health based strategies, rather than incarceration, in the handling of individuals possessing cannabis or cannabinoids for personal use.

This report updates relevant sections of Council Report 5-I-17, "Clinical Implications and Policy Considerations of Cannabis Use," summarizes current state legislation legalizing adult cannabis and cannabinoid use, and reviews other pertinent information and developments in these jurisdictions to evaluate the public health impacts of legalization.[1] The term cannabis will be used throughout when referring to the *Cannabis sativa* plant rather than the slang term marijuana/marihuana, unless the latter is officially included in a title, policy, or otherwise official language.

METHODS

English language reports were selected from searches of the PubMed, Google Scholar, and Cochrane Library databases from August 2017 to August 2020 using the (text or MeSh) search terms "marijuana or cannabis or cannabinoid or cannabidiol" in combination with "legalization or laws," and "health," "mental or public health," "addiction or cannabis use disorder," "health effects," "use," "benefits or harms," "youth or adolescents," "edibles," "driving," "taxes," "social equity or justice" and "treatment." Additional articles were identified through related article searches and by manual review of the reference lists of retrieved articles. Websites managed by federal and state agencies, and applicable regulatory and advocacy organizations also were consulted for relevant information.

CURRENT AMA AND FEDERATION POLICY

The Council has issued six previous reports on cannabis covering: (1) aspects of research and investigational and therapeutic use (including in-hospital); (2) the juxtaposition of cannabis within the evolution of U.S. national drug control policy; and, (3) the broader clinical implications and policy considerations associated with the proliferation of state-based medicinal and legalized adult use programs.[1-6]

AMA policy categorizes cannabis as a dangerous drug and public health concern (Policy H-95.924). Accordingly, our AMA supports increased educational programs on the use and misuse of alcohol, marijuana, and controlled substances, including specific measures aimed at K-12 curricula (H-170.992).

With respect to criminal penalties, our AMA believes that public health-based strategies, rather than incarceration, should be utilized in the handling of individuals possessing cannabis for personal use (H-95.924). A plea of cannabis intoxication should not be a defense in any criminal proceedings (H-95.997).

With respect to research, 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 (H-95.952). To facilitate the conduct of clinical research and development of cannabinoid-based medicines, the status of marijuana as a federal schedule I controlled substance should be reviewed and relevant federal agencies should implement measures designed to streamline the clinical research process (H-95.952). The consequences of long-term cannabis use in youth, pregnant women and those who are breastfeeding are special concerns. Our AMA discourages cannabis use, especially in these populations (and in those who are otherwise vulnerable to the drug's effects), and supports specific

point of sale warnings and product labeling about the potential dangers of use during pregnancy and breastfeeding (H-95.924).

In order to promote public health and safety, research on the impact of cannabis legalization and decriminalization also is encouraged and information derived from such activities should be disseminated. Local, state, and federal public health agencies can assist by improving surveillance efforts to capture relevant data on both short-and long-term health effects of cannabis. Our AMA supports the development of resources on the human health effects of cannabis and on methods for counseling and educating patients on cannabis and cannabinoid use (H-95.924).

AMA policy otherwise separates cannabis legalization for medicinal (D-95.969) or recreational use (H-95.924). AMA policy opposes state-based legalization of cannabis for medical use (whether via legislative, ballot, or referendum processes) and supports the traditional federal drug approval process for assessing the safety and efficacy of cannabis-based products for medical use. U.S. Food and Drug Administration (FDA) approved cannabinoid products include:

- Dronabinol (Marinol®) is an oral formulation (capsules) containing synthetic delta-9-tetrahydrocannabinol (THC) approved for the treatment of HIV-wasting and chemotherapy-induced nausea and vomiting when conventional treatments are inadequate; a liquified formulation (Syndros®) also is available.

- Nabilone (Cesamet®), a synthetic THC analogue that activates the endogenous cannabinoid type 1 (CB_1) receptor, is an oral formulation approved for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

- Cannabidiol (CBD) oral solution (Epidiolex®) is approved for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex in patients one year of age and older. (Note: AMA Policy H-120.926, "Expedited Prescription Cannabidiol Drug Rescheduling," supports legislative and regulatory measures designed to expedite the availability of FDA-approved cannabidiol products and to reassert that patient access should be managed like other prescription-only products.)

- Nabiximols (Sativex®) is a 1:1 ratio of THC and CBD, extracted from specially bred cannabis plants and formulated as an oromucosal spray for the treatment of spasticity in patients with multiple sclerosis. This product is approved in 20 countries, including Canada, but remains investigational in the U.S.

Cannabis products that have not been approved by the FDA (but are marketed for human ingestion in many states) should carry the following warning label: "Marijuana has a high potential for abuse. This product has not been approved by the FDA for preventing or treating any disease process" (D-95.969). Hospitals and health systems also should not recommend the use of such products within their facilities and should educate medical staffs on cannabis use, its effects, and symptoms (withdrawal syndrome) that may appear in patients who abruptly discontinue use. AMA policy also recognizes that physicians may need to engage in a dialogue with their patients about cannabis/cannabinoid use, that such discussions are protected, and that physicians whose behavior conforms to state cannabis laws should not be subject to federal prosecution.

Our AMA also opposes legalizing the sale of cannabis for adult use and supports stronger public health messaging on the health effects of cannabis and cannabinoid inhalation and ingestion (H-95.924). States that have already legalized cannabis (for medical or legalized adult use or both)

should ensure that processes are in place to regulate the product to effectively protect public health and safety with an ongoing evaluation of their effectiveness. A "substantial portion" of tax revenues derived from state-based programs should be used for public health purposes including prevention and treatment of substance use disorders, the aforementioned cannabis-related educational programs, research on the health effects of cannabis use, and public health surveillance efforts.

The AMA also has policy on addressing synthetic cannabinoids and recognizing new psychoactive substances as a public health threat. The Council addressed these substances in detail in its 2017 report, Emerging Drugs of Abuse are a Public Health Threat. Synthetic cannabinoids are outside the scope of this report. Issues relevant to the regulation of CBD are covered in detail in the Council on Science and Health Report on dietary supplements (CSAPH Report 2) being considered at this meeting. As a result, issues related to CBD and are outside of the scope of this report.

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.[7] 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.[7] CMA policy also opposes policies of health plans, health systems, and hospitals with pain management programs that automatically eliminate patients who use therapeutic cannabis.

CANNABIS AND CANNABINOID PRIMER

In order to better understand certain issues surrounding cannabis, substances derived from the plant, their pharmacology, and implications for adult legalization, a brief review is provided.

Cannabis Plant

Cannabis sativa contains a complex array of chemical compounds, including more than 100 phytocannabinoids that are exclusively produced in cannabis, and more than 200 terpenoids (comprising "essential oils") which are responsible for the aroma of cannabis. Phytocannabinoids and terpenoids are synthesized in secretory cells inside glandular trichomes that are most highly concentrated in unfertilized female flowers.[8,9] THC is the most concentrated phytocannabinoid and the main psychoactive substance; delta-8-THC is similar in potency to THC, but is normally present in only trace amounts.[10] CBD, which possesses its own pharmacologic profile and lacks THC's intoxicating effects, and cannabinol are the other major phytocannabinoids; CBD is the most common phytocannabinoid in hemp (fiber) plants.

Other phytocannabinoids of pharmacologic interest include cannabichromene, cannabigerol, tetrahydrocannabaverin, and cannabidivarin.[11] These substances have their own pharmacologic profiles, effects of which are largely unstudied in humans.[11] Precursor acid forms of the neutral phytocannbinoids, that break down in the presence of heat, exist in the plant and may be available in concentrated forms in dispensaries in some states; other "secondary" phytocannabinoids isolates have become available as well.

Selective Mendelian breeding has created cannabis varieties (termed chemovars or chemotypes) with altered concentrations and ratios of phytocannabinoids and terpenes. General categories based on cannabinoid content have been described as THC-predominant (typical of legalized adult use marketplaces), "balanced" THC and CBD varietals, and CBD-predominant; some strains have been

created that are enriched in specific terpenes.[12] The average THC content of illicit cannabis samples confiscated in the U.S. increased from ~4% to 12% between 1995 and 2014.[13] The majority of advertised cannabis flower products with both state medicinal and legalized adult use programs now exceed 15% THC, and some exceed 20% in states with legalized adult use. Genetic engineering, either via genetic modification of plants or using recombinant DNA in microorganisms (yeast, bacteria, algae) also is being used to increase yields of THC or CBD, or of the lesser studied phytocannabinoids.[14] These developments have implications for both the traditional pharmaceutical industry and the legalized adult use marketplace, and for evaluating both the risks and harms of cannabis and cannabinoid use in the published literature over time.

Endocannabinoid System

Phytocannabinoids exert their effects, in part, via the endogenous cannabinoid (endocannabinoid) system. This system comprises two specific neuromodulators that are arachidonic acid derivatives [anandamide (AEA) and 2-arachidonoylglycerol (2-AG)], enzymes for their biosynthesis and inactivation, and two transmembrane, G-protein coupled cannabinoid receptors (CB_1, CB_2).[15,16] CB_1 receptors are enriched and widely distributed in the brain, and to a lesser extent in peripheral tissues, in a region specific manner.[17-20] See Figure 1 for a summary of the functions that have been associated with CB_1 receptors. Expressed mainly peripherally on circulating immune system cells, the spleen, macrophage derived cells, and the liver, CB_2 receptors are normally present in low concentrations in the brain (brainstem and hippocampus), but following injury or inflammation are upregulated in reactive microglia and astrocytes where they inhibit neuroinflammation.[15,18,20]

2-AG is an agonist at CB_1 and CB_2 receptors; AEA is a partial agonist at CB_1 receptors and largely inactive at CB_2 receptors. These substances act in a retrograde manner, being released from postsynaptic sites, migrating to presynaptic CB_1 receptors and inhibiting neurotransmitter release, dampening activity within discrete excitatory and inhibitory pathways.[19]

THC is a partial agonist at CB_1 and CB_2 receptors.[18,21] CBD is a partial agonist of the CB_2 receptor, although it also binds to and acts as an antagonist at other non-cannabinoid G-protein receptors. CBD also inhibits the uptake of AEA and its metabolism and activates TRPV receptors and $5HT_{1A}$ receptors. CBD has low affinity for CB_1 receptors, but in low concentrations is capable of functioning as an effective antagonist (or perhaps as a noncompetitive negative allosteric modulator) of THC and other 2-AG agonists.[22,23] Peripherally, activation of CB_2 receptors exerts anti-inflammatory and immunomodulatory effects, mobilizes hematopoietic stem cells, decreases gastrointestinal motility, and reduces visceral pain.

Disposition of THC and Cannabadiol Based on Route of Administration

Based on information obtained in pharmacokinetic studies of approved drug products, oral THC capsules (Marinol®) demonstrate low (6% to 20%) and variable bioavailability among test subjects. Gastric acidity causes some isomerization of THC to the delta-8-derivative and the drug is subject to a significant first pass effect. Peak plasma concentrations of THC are achieved within 1 to 6 hours, but may remain elevated for several hours.[24-27] Initially, THC is oxidized in the liver to 11-hydroxy-THC, a potent psychoactive metabolite, which undergoes further oxidation to the primary inactive (acidic) metabolite (THC-COOH). Although THC is cleared rapidly by the liver it has a very large volume of distribution (≈10 L/kg).[24] Thus, the terminal half-life of THC is on the order of 20 to 36 hours.[24,27] With chronic use, the limiting step for the terminal phase of elimination is redistribution from peripheral tissue storage sites.

Following inhalation, THC and CBD are rapidly absorbed into the blood stream and redistributed. Considerable amounts of the dose contained in one cigarette are lost in sidestream smoke and destroyed by pyrolysis.[24,28] Peak blood levels of THC and CBD are achieved at the end of smoking and then decline rapidly over the next 30 minutes.[24] The pharmacokinetics of vaporized and smoked cannabinoids are comparable; however, infrequent users report more pronounced effects with vaping than smoking.[29,30] Smoked or vaped cannabis is associated with much larger peak plasma THC concentrations, but a shorter duration of effect than orally administered THC. The time course of plasma concentrations after smoking or vaping marijuana is similar to that obtained after intravenous administration.[26]

Considerably smaller amounts of 11-OH-THC are formed when THC is inhaled, compared with the oral route.[24,31] After oral administration of THC, THC-containing edibles, or cannabis-based extracts, the concentrations of THC and 11-OH-THC are much lower than those found upon smoked administration, exhibit marked variability among various preparations, and are slower to reach a peak level; however, they are capable of causing comparable subjective effects and substantial impairment of cognitive/psychomotor functioning.[31-34]

RELEVANT FEDERAL LAW AND POLICY

Under the U.S. Controlled Substances Act (CSA) of 1970, marihuana remains classified as a Schedule I controlled substance, and the DEA and FDA have reinforced that interpretation, 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.[35,36] The term "marihuana" means all parts of the plant *Cannabis sativa*, whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.[37] As noted in the introduction, FDA has approved three cannabinoid-based prescription medicines

Council Report 5-I-17 discussed legal challenges, federal agency findings, and federal policy recommendations that were intended to manage the conflict between federal and state laws and emerging issues on medical or legalized adult use of cannabis. That discussion remains valid with a few notable exceptions and developments.

Early in the Trump administration, then-Attorney General Jeff Sessions rescinded existing Department of Justice guidance (the Cole Memorandum) that was intended to make clear that state-legalized cannabis was not an enforcement priority. In response, the House of Representatives approved spending bill amendments in both 2019 and 2020 to block the Department of Justice from using its funding to interfere with the implementation of state, territorial and tribal cannabis programs.

Also, in 2018, the Agricultural Improvement Act (the 2018 Farm Bill) was passed.[38] This law removed hemp from the definition of marihuana in Schedule I of the Controlled Substances Act, thereby legalizing the production of hemp under federal law. The bill defined hemp as any cannabis plant, including derivatives or extracts, that contains less than 0.3 percent of THC.[38]

STATE LAWS ON CANNABIS

At the state level, trends in law continue to move from legal prohibition, to decriminalization, to the legalization of medical use of cannabis, to cannabis legalized for adult use (commonly referred to as recreational use).[39-42] To varying degrees these trends have been shaped by arguments that cannabis is less harmful than alcohol and tobacco and may demonstrate certain health benefits; that

arrests and criminal convictions for cannabis possession are disproportionately harmful (including their effect on minoritized populations), and that legalization has the potential to eliminate the illicit market, enable regulation of use (including product potency and purity), reduce prison overcrowding, redistribute law enforcement activities, and raise government revenue.[43]

California (CA) was the first jurisdiction in the United States (U.S.) to legalize the use of cannabis for medical purposes in 1997. Today, 33 states, the District of Columbia (D.C.), Guam, and Puerto Rico have legalized the use of cannabis for medical purposes through either a legislative process or ballot measure.[39-42] As described in Council Report 5-I-17, 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, the retail marketplace, and consumption method. 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, as a Schedule I Controlled Substance, it is illegal under federal law. Eleven of these states (and four others without medical use of cannabis laws) have decriminalized and removed jail time for possession of small amounts of cannabis.[42]

In 2012, Colorado (CO) and Washington (WA) were the first U.S. jurisdictions to legalize the adult use of cannabis.[44,445] At this point, a total of 11 states and D.C. have legalized cannabis for adult use, ten through the ballot measure process, and two (Illinois [IL[and Vermont [VT]) via legislation.[39,41] As noted in the 2017 Council report, most of these jurisdictions have created for-profit, commercial cannabis production and distribution markets where the product is sold and taxed; Washington, DC (DC) and VT are exceptions. DC has adopted a "grow and give" model whereby residents are permitted to possess, use, grow, and give away cannabis, but they cannot sell it.[46] VT's adult use law, passed in 2018, also allows residents to possess recreational cannabis (1 oz) or grow up to six plants (only two mature at a time) but retail sales are currently not allowed.[47] Possession limits for adult use in other states range from 1 to 2.5 oz of usable cannabis flower, with most allowing variable numbers of plants, and limits on the amount of hash, solid or liquid infused products, or concentrates that can be possessed.[39] See Figure 2 for a timeline of legalization and actual implementation.

RETAIL MARKETPLACE: LEGALIZED CANNABIS FOR ADULT USE

As the marketplace for legalization of cannabis for adult use has grown dramatically, an expansive retail environment has developed with "novel cannabis products, formulations and methods of administration."[48] Different formulations (extracts, concentrates) of cannabis have emerged that can be smoked, vaporized, or used to create (infused) edibles (e.g., gummy bears, lozenges, candies, lollipops, brownies/cookies/other foods, and beverages), tinctures and oils for consumption , as well as topicals.[49,50] Extracts are a type of concentrate formed by using solvents to wash the cannabinoid-rich trichomes off the plant and remove phytocannabinoids and terpenes. Hydrocarbons (e.g., butane, propane), ethanol, or supercritical fluid extraction using CO_2 are the most common approaches.[50] Depending on the method, the resulting concentrate comes in various forms (e.g., waxes, shatter, resin), that can be further processed into various textures (e.g., budder, crumble, honeycomb). Concentrates made without the use of solvents are produced using mechanical or physical means to remove and gather trichomes (e.g., hash, kief, rosin). Some dispensaries also feature products enriched in other phytocannabinoids, most commonly CBD, cannabinol, cannabigerol, or tetrahydrocannabinolic acid (THCA) and products that are enriched in certain terpenes.[48] See Table 1 for a graphic display and description.

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

The National Academies of Sciences, Engineering, and Medicine (National Academies, NASEM) 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."[51] 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 contained 98 conclusions based on the accumulated evidence related to cannabis or cannabinoid use and health.[56] It 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 were organized into 5 evidence categories: conclusive, substantial, moderate, limited, and no/insufficient evidence.

Health Uses: The report found conclusive or substantial evidence that cannabis or cannabinoids are effective: (1) as antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids); and (2) for improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids); and (3) for the treatment of chronic pain in adults (cannabis).

The report found moderate evidence that use of cannabis or cannabinoids: (1) are effective in 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); (2) are associated with improved cognitive performance among individuals with psychotic disorders (history of use).

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); (4) the development of schizophrenia or other psychoses, with the highest risk among the most frequent users; and substantial evidence that initiating use at an earlier age and smoking cigarettes (males) as risk factors for progression to problematic cannabis use.

The report found moderate evidence of a statistical association between cannabis use and: (1) increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal; (2) impairment in the cognitive domains of learning, memory, and attention; (3) a number of mental health domains including increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use); 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; and increased incidence of social anxiety disorder (regular cannabis use).

In general, the findings and conclusions of this report remain valid. Two additional comprehensive systematic reviews have been published since the NASEM report. A review on cannabis-related harms was in substantial agreement with the NASEM report.[52] This study also called attention to increased cardiovascular risks associated with cannabis use, prenatal exposure and cognitive dysfunction/behavioral disturbances in offspring, and hyperemesis syndrome. Case studies have linked cannabis use to acute myocardial infarction, cardiac arrythmias, cardiomyopathies, stroke, and arteritis, mostly in younger men with few cardiovascular risk factors.[53] A scientific statement

issued by the American Heart Association in August 2020 warned that cannabis use may be linked to an increased risk of heart attacks, atrial fibrillation and heart failure.[54] A recent retrospective analysis of nationwide inpatient data found that cannabis use was an independent predictor for acute myocardial infarction-related hospitalization in adolescents and young adults.[55] The other review used evidence mapping and appraisal to evaluate published studies on the therapeutic benefits of cannabis and cannabinoids. This study also was in substantial alignment with the NASEM report.[56]

PUBLIC HEALTH IMPACTS OF STATE LEGALIZATION OF CANNABIS

Despite the fact that 11 states and D.C. have now legalized the adult use of cannabis, evaluation of the impacts of legalization on health and safety remain somewhat limited. Retail sales have not commenced in ME, and are not allowed in VT and D.C. Insufficient time has elapsed since retail sales commenced in some states (e.g., IL, Michigan [MI], Massachusetts [MA]) to get meaningful results and/or a state program for formal analysis of post-legalization effects has not been created. Importantly some states established a framework for future analysis by evaluating and compiling various baseline measures (pre-legalization) to be used for comparison (e.g., OR, MI, MA).

Otherwise, CO [through its Department of Public Health and Environment (CDPHE) and appointed Retail Marijuana Public Health Advisory Committee (RMPHAC)] and WA [in partnership with the Washington State Institute for Public Policy (WSIPP)], and two other states (OR and AK), lead the way on having examined state-specific health and safety outcomes and patterns of cannabis use since legalization. State-based data and surveys, as well as 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), Monitoring for the Future (MTF) and Pregnancy Risk Assessment Monitoring System (PRAMS) have been relied on. Where available larger, state representative surveys that have been implemented longitudinally may be more relevant on certain measures.[57]

General issues being examined include the impact of legalization for the adult use of cannabis on:

- patterns of use by children and adolescents, college and university students, other adults, and pregnant women. In youth, monitoring changes in the perceived risk and social acceptability of cannabis and cannabis advertising also has been emphasized;
- incidents of impaired driving and traffic fatalities;
- cannabis-related hospital or emergency department visits and other cannabis-related (toxic) exposures;
- changes in the incidence, costs and treatment for mental health disorders, including treatment admissions for cannabis use disorder;
- effects on the market for alcohol and other drugs;
- criminal behaviors (including civil penalties, arrests, prosecution and incarceration); and, government revenues and costs of implementing legalization.

Considerable attention also has been devoted to the association between medicinal and/or legalized adult use and opioid-related measures and outcomes.

CO has the most extensive state-based data. Their findings are emphasized for some topics, buttressed with comparable data, where available, from other states that have legalized cannabis for adult use.

General Age-Related Patterns Use

In the U.S., the most commonly used illicit drug (based on federal status) in the past year among those aged 12 or older was cannabis, totaling approximately 43.5 million people or 15.9% of the population; nearly 44% of this group are of past month users.[58] The overall prevalence of cannabis use in the U.S. has increased steadily since 2011 (38% increase), accounted for mostly by increased use among young adults aged 18-25, and adults 26 years of age and older. Annual cannabis use is at historic highs (42.5%) since 2013 among 19-22 year-olds (both college and non-college peers).[59] In 2016, 43% past-month cannabis users who were 18 years and older reported daily or near-daily cannabis use (20 or more days per month), a 30% increase since 2002. This pattern of use declined about 23% in adolescents over the same time period. According to the 2019 MTF survey, there has been an uptake in daily use among younger students (grades 8 and 10) since 2017.[60] Based on the BRFSS, daily use of cannabis in adults in CO has increased from 6% in 2014 to 9% in 2018, but the methods of use in CO adults have remained fairly constant.[61]

Adolescent use has declined nationally since 2011, remaining fairly steady from 2015 to 2018.[58] Combined NSDUH data for 2017-18 suggest that 6.5% or 1.6 million adolescents (12-17 years old) were current (past month) users of cannabis. The prevalence of past month use in this survey was higher than the national average in CO (9.36%) as well as all other states with legalized adult use; six of these states (WA, VT, OR, MA, Nevada, ME) and DC showed increased adolescent use according to NSDSUH, contrary to the national trend.[58,62]

A nationally representative survey of U.S. adults aged 18 years or older using KnowledgePanel concluded that prevalence of past-year use of any form of cannabis is more common among in states with legalized adult use (20.3%) compared with use in medically legal states (15.4%), and nonlegal states (11.9%).[63] Perceptions of risk from using cannabis also have continued to decrease. An analysis based on the National College Health Assessment survey also concluded that cannabis use has accelerated to a greater degree among students who attend colleges in states with legalization of cannabis for adult use.[64]

When examining high school students specifically, state surveys have found higher rates of use and different trends than national surveys. CDPHE in conjunction with the Departments of Human Services and Education conducts the statewide Health Kids Survey. In 2019, the overall current or past 30-day marijuana use prevalence among CO high school students was 20.6% (slightly lower than national estimates based on the Youth Risk Behavioral Survey) but not increasing.[65] Similarly, according to the Healthy Youth Survey, past month cannabis use across grades 10 and 12 in WA state has deceased since the legalization of the adult use of cannabis, but the prevalence (~18%) is higher than estimates from national surveys.[66] The OR Health Authority Survey found similar trends (reduced use since legalization) among students in grade 11.[67]

Although adolescents who use cannabis still prefer smoking, recent changes in the usual methods of marijuana consumption have been documented with the prevalence of dabbing and vaporizing of concentrates increasing in CO, a pattern reflected across other parts of the country.[68] Data from the online international cannabis policy study conducted in 2018 among 16-19 year-olds found that the prevalence of past 30-day vaping of cannabis was 13.8%. Nearly one-third of these users in the U.S. reported vaping cannabis oil and consuming THC solid concentrates such as wax and shatter.[69]

These reported increases in the vaping of THC oil as a method of consumption are concerning given the CDC's investigation on the national outbreak of lung injury associated with the use of vaping products.[70] Among the cases or deaths reported to CDC (in which substance use was

available), 82% reported using THC-containing products, 33% exclusively. Sixteen percent reported acquiring products only from commercial sources (recreational and/or medical dispensaries, vape or smoke shops, stores, and pop-up shops); most others were obtained from family/friends, dealers, online, or other sources.

Increases that have been reported in daily (or near daily) use and changes in consumption patterns with the use of more concentrated products also presents cause for concern. Respondents who report using cannabis daily consume almost twice as much per day compared with those reporting less frequent use.[71] In adolescents with no history of heavy cannabis use, the use of cannabis concentrates is associated with progression to persistent use, more so than the use of other cannabis products.[72] As noted in CSAPH Report 5-I-17, adolescents are of particular interest in cannabis-policy discussions because the negative health effects of the drug are heightened when use begins in adolescence. In addition to health effects, including the increased risk of cannabis use disorder, 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.[73-75]

Use among Pregnant Women

Cannabis is the most commonly used (illicit) drug during pregnancy, and THC crosses the placenta and is found in breast milk.[76] Endocannabinoids play an important role in fetal neurodevelopment and in postnatal synaptic plasticity. Preclinical and emerging human evidence suggests that prenatal exposure to cannabis may "lead to subtle, persistent changes in targeted aspects of higher-level cognition"[77] and neurobehavioral outcomes in children. However, real world evidence is limited to three longitudinal cohorts, with different designs and outcomes, all of which were initiated at a time of much lower (average) THC exposure from cannabis.[78-80] Additionally, epigenetic effects of THC have been described.[81]

The American College of Obstetricians and Gynecologists updated its committee opinion in 2017 reaffirming that prenatal exposure is associated with low birth weight and discouraging physicians from suggesting the use of marijuana during preconception, pregnancy, and lactation.[76,82-84] Effects on low birth weight are independent of maternal age, race, ethnicity, level of education and tobacco use during pregnancy.[82] Infants exposed to cannabis in utero also may be more likely to end up in the NICU or experience preterm birth.[83,85]

Overall, based on NSDUH, cannabis use during pregnancy has doubled over the last 15 years with 7.0% of pregnant women between the ages of 18 and 44 years reporting past-month cannabis use in 2017 compared with 3.4% in 2002; daily or near daily use more than tripled (0.9 to 3.4%).[86] The majority of use was described as "non-medical" and is most prevalent during the first trimester. Pregnant women may use cannabis to help with nausea or to improve mood, are more likely to perceive it as natural and safe, and are unsure or unaware if cannabis is addictive or if risks are associated with prenatal cannabis use.[87]

Compared with 2014, PRAMS data for CO showed that among new mothers in 2018, 16.5 percent used cannabis prior to pregnancy (47% increase), 8.2 percent used cannabis during pregnancy (44% increase), and 7.9 percent of breastfeeding mothers used cannabis after delivery (160% increase), all substantially higher than national averages.[88] Umbilical cord sampling for cannabis metabolites detected prenatal use at an even higher rate than self-reported values.[89] Cannabis use during pregnancy in CO was statistically higher among women with an unintended pregnancy (12.5%) than among women who intended to become pregnant (4.5%). When cannabis use during pregnancy was compared among different demographics, both education and age showed statistical

differences, whereas race and ethnicity did not.[88] Across three states (AK, CO, WA) that had legalized adult use by 2016, women were more likely to use cannabis during preconception, during the prenatal period, and postpartum, compared with states without legalized adult use.[90] Clinicians can "play a key role in preventing harms associated with cannabis use in pregnancy by educating patients about the potential risks of frequent use, advising all patients who are pregnant to quit cannabis use, and providing patients with safe and effective medically approved ways to improve mood and treat nausea and vomiting in pregnancy."[91]

Impaired Driving

A serious consequence of legalizing cannabis for adult use is an increase in traffic crashes and fatalities. Although it is well established that acute THC intoxication impairs driving, CSAPH Report 5-I-17 explained some of the complexities involved with correlating blood concentrations of THC with driving impairment and outcomes, and in establishing legal standards. Unlike alcohol, there is poor correlation between blood or other fluid concentrations of THC or its metabolites and when the cannabis product might have been consumed, and behavioral effects or field sobriety or functional tests for cannabis/THC have not been validated. In CO, about 1 in 5 adults with past month use report driving within 2-3 hours after consumption, a value that has not increased with legalization of cannabis for adult use.[92] In WA among those 18-25 years of age reporting past year cannabis use, more than 40% reported driving with 3 hours of use at last once, with 1 in 7 reporting such driving on at least 6 occasions.[93]

In CO and WA, the THC blood limit for an inference of driving impairment is 5 ng/ml in those 21 and older; any detectable amount is considered a violation in individuals less than 21 years of age. Between 2013 and 2018, there has been an increase in traffic deaths in CO in which drivers tested positive for cannabis and an increase in the percentage of all traffic deaths that were presumed to be cannabis related.[94]

Based on an analysis of traffic fatality rates through 2018 obtained from the most recent report of the National Highway Traffic Safety Administration's Fatality Analysis Reporting System, legalization was associated with an increase in traffic fatalities compared with the 5 years preceding legalization among the first 4 states to legalize adult cannabis use (CO, WA, OR, and AK).[95] These states are the only ones that have legalized adult use for which there are at least 2 full years of traffic fatality data available following the opening of retail stores. On a national scale, this rate would translate to an excess 6800 deaths. The calculated rate in this study was comparable to the rate reported after commercialization of retail sales in a previous study of traffic fatalities in CO and WA.[96] Another recent study that examined data through 2017 and extended the comparison period to 2005 found that traffic fatalities increased (at a lower rate than above) in CO but not WA.[97] A trend for increased fatalities also may exist in neighboring jurisdictions.[98]

Cannabis-Related Exposures

Cannabis-related exposures generally refer to the number of human exposures related to either accidental/unintentional or excessive/intentional consumption or inhalation of cannabis and cannabis edibles. Some of these may end up as calls or reports to Poison Control Centers, emergency department visits (which also may report to Poison Control), or hospitalizations.

Poison Control. The number of calls to Rocky Mountain Poison and Drug Safety (serving CO) with a cannabis mention increased five-fold from 2006 to 2017, stabilizing between 2014 and 2017, when 222 reports occurred, and then increasing somewhat again.[99] Between January 2017 and June 2020, 973 exposures were reported by healthcare facilities and residences, mostly edibles (44.9%),

followed by the cannabis plant (29.1%) and concentrates (10.7%). Reporting rates for these substances have remained mostly unchanged since the middle of 2018. Patients ≤5 years old accounted for one-third of these reports, and those 6 to 12 years of age accounted for 9%.[92] In CO, there has been a significant increase since 2014, from 6.9% to 11.2%, in the percentage of homes with children 1-14 years old that reported having cannabis or cannabis products in or around the home.[100] It is estimated that approximately 23,000 homes (or 22.4%) in CO with children 1-14 years old had cannabis in the home with potentially unsafe storage, a rate that has increased 60% since 2014.[100]

Since retail sales opened in WA in 2014, calls to the WA State Poison Control Center involving cannabis in 2018 have more than doubled from 245 to 497; reports in children ≤5 years of age tripled from 34 to 94 (18.9% of total), and those in children 6-12 years of age more than doubled to 31 (6.2% of total).[101] Thirty-two percent of cannabis exposure calls involved edibles. Because of these trends, particularly among young children, a new logo was required in 2017 on all cannabis edible packaging (Figure 3). After increasing from 2013-2016, calls reported to OR poison control decreased in 2017 and then started increasing again in 2018; approximately 20% of cannabis exposures in 2017 were in children aged 5 years and under.[102]

Finally, a recent analysis of all 50 states from 2010-2017 found that an increase in cannabis exposures reported to the U.S. National Poison Data System occurred after commercialization (retail sales) in states with legalized adult use.[103] The overall magnitude of the increase was 67-77% relative to the pre-legalization average, depending on the composition of comparison states. The relative increases were higher in minors, males, and among those who were classified as suffering medical consequences.

Cannabis-Related Emergency Department Visits and Hospital Admissions

In addition to emergency department visits and sometimes hospitalizations for unexpected pediatric exposures to cannabis, emergency department visits and hospitalizations can be prompted by acute intoxication leading to drowsiness/lethargy/confusion, dizziness/vertigo/ataxia, psychotic symptoms, agitation or anxiety, and extreme tachycardia or other cardiovascular events.[102] Chronic use, especially of high potency derivatives, can lead to hyperemesis syndrome, which may require treatment for intractable vomiting, dehydration, and electrolyte abnormalities.[104] In individuals with a *history* of recreational use, the most common reasons for hospitalization were alcohol and drug rehabilitation or detoxification and psychological/psychiatric evaluation.[105]

In an informative analysis, the CO Department of Public Health analyzed rates of cannabis exposures, diagnoses, and billing codes from 2000 to 2016 per 100,000 hospitalizations.[92] From a baseline rate of 575/100K, hospitalization rates increased steadily to 894/100K when medical cannabis was legalized but not commercialized (2001-2009), experiencing another significant jump to 1,440/100K during the commercialization of medical cannabis (2010-2013), and further increasing again to 2,696 possible cannabis-related hospitalizations per 100,000 during the initial commercial phase of legalized adult use (2014-Sept 2015). An updated analysis indicates that the yearly number of cannabis-related hospitalizations doubled after the initial year of legalized adult use (2013) compared to with 2017.[106] Similar trends were noted in a study of cannabis-related hospitalizations from 2002-2016, a time period covering major changes in WA state policies and marketplace for medical cannabis, legalization for adult use, and then the initial period of retail sales.[107]

Cannabis Use Disorder and Related Treatment Admissions

A proportion of people who initiate cannabis use eventually meet the criteria for cannabis use disorder (CUD), although the estimated prevalence varies widely depending on the diagnostic criteria and sampling methods that were used. Nevertheless, CUD influences key brain responses and functions relevant to substance use and it manifests as other substance use disorders based on the reinforcing properties of THC, regardless of method of use or formulation.[108]

Epidemiological data indicate that "the majority of those who use cannabis do not have problems related to their use, but a substantial subset of people (using cannabis/THC) do report experiencing symptoms and consequences consistent with a CUD."[109] Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study indicate that the past year prevalence of DSM-IV cannabis abuse and dependence doubled from 1.5% in 2001-02 to 2.9% in 2012-13.[110] A similar analysis of NSDUH data (DSM-IV criteria) concluded that past year prevalence was relatively unchanged over the same time period (1.6-1.5%).[111] The disparate findings likely reflect differences in sampling methods (live interview versus online survey) and changes in societal norms over time which may influence respondents.[112] Again, depending on the method, between 11% (NSDUH, 2016) and 30% (NESARC, 2013) past-year cannabis users met DSM-IV criteria for cannabis abuse or dependence.[110,112] A recent meta-analysis using DSM-IV or ICD-9 criteria estimated that individuals who use cannabis have a 1 in 5 risk of developing cannabis abuse or dependence and risks increase if cannabis is initiated early and used frequently.[113] Other data suggest that in individual populations, the prevalence of cannabis abuse or dependence roughly doubles for those who initiate use before 17 years of age, and is much higher for adolescents who use weekly or more often.[114] Among youth and emerging adults in the U.S., prevalence of cannabis use and dependence appears to increase with time since initiation of use. This increase appears to be steeper for youth than emerging adults. The adjusted 12-month prevalence among youth with lifetime cannabis use ranged from 10.9 in the first year after starting cannabis use, increasing in each year to 20.6% in the fourth year and beyond. Values for young adults (aged 18-25) were lower at all times and increased at a lower rate eventually reaching about 10% four years after initiaition.[115]

A few previous studies examining the effects of state medical cannabis laws on CUD found mixed results.[116,117] A study in CO, WA, OR, and AK based on NSDUH surveys from 2008 to 2016 found a small increase in past year cannabis abuse and dependence among respondents aged 12 to 17 years, and more significant increases in frequent use and abuse or dependence among adults 26 years or older.[118] One look back study of the 2012-2014 NESARC study using DSM-5 criteria for CUD estimated that the prevalence of 12-month and lifetime CUD were 2.5% and 6.3%, respectively.[119]

In summary, most of the published longitudinal trends on cannabis use disorder are based on DSM-IV criteria for cannabis abuse and dependence, which were combined into one set of diagnostic criteria for DSM-V. The DSM-V criteria for CUD perform similarly to other substance use disorders. Although little is known about how legalization of cannabis for adult use will impact CUD, the availability of high potency products, easy access (cost and proximity), methods of use that are more appealing than smoking, decreased perceptions of risk, and changes in social norms and marketing, all point to a need for vigilance in this area.

Treatment Admissions

Treatment-seeking for CUD comprises a substantial proportion of all substance use treatment admissions. In 2017, cannabis remains by far the most common substance in adolescents seeking treatment; more than 70% percent of publicly funded treatment admissions in individuals aged 12 to 17 years were for primary cannabis use.[120]

Total publicly funded substance use disorder treatment admissions in the U.S. declined about 0.7% from 2007-2017 (see the Treatment Episode Data Set [TEDS-A]).[120] The proportion of cannabis admissions aged 12 years or older increased from 16% in 2007 to 19% in 2010, before declining to 13% percent in 2017. The average age at admission was 27 years among admissions for primary use of cannabis. Non-Hispanic Whites represented 42 percent of admissions, 31 percent were non-Hispanic Blacks, and 20 percent were of Hispanic origin. Consistent with the national picture, cannabis-related treatment admissions in WA declined in the three years following legalization of adult use 2012-2015.[121] In AK, among the approximately 6,800 total people who received public-paid substance dependence treatment in 2018, about 8% (550) received primary treatment for cannabis use disorder, similar to the proportion from 2016-17.[122] In CO, the overall treatment admission rate for those reporting cannabis as the primary drug has decreased every year from 2012-2017, except for a brief uptake in 2014-15 in those 21 years and older.[94]

Opioid Use

Increases in unintentional overdoses and deaths due to illicit fentanyl, heroin and prescription opioids remain the biggest drivers of the unintentional overdose death epidemic.[123] Nearly 70% of the 67,367 deaths in 2018 involved an opioid.

Several ecological or epidemiological studies and convenience survey samples have reported population-level associations between the existence of state medicinal cannabis laws and reductions in opioid-related morbidity/mortality, reduced opioid prescribing in Medicaid and Medicare enrollees, as well as subsets of privately insured individuals, self-reported reductions in opioid use (and risks) among medical users (i.e., substitution of cannabis), and intersections between cannabis use and opioids among drivers, including fatalities.[124-132] Effects of medical cannabis laws on reducing opioid prescriptions and dampening increases in opioid-related deaths have been linked, in part of the presence and density of dispensary distribution within states.[126,132]

A review of 25 such studies concluded:[133]

- States that with medical cannabis laws have reported a slower rate of increase in opioid overdose deaths which has persisted over time. Findings are strengthened when controlling for operation of state prescription drug monitoring programs and demographics which also influence patterns of use. The relative contribution of treatment for opioid use disorder in such states is not understood.
- Some epidemiologic and ecological studies provide evidence that cannabis availability may reduce opioid use and/or harms. Some of these studies are "limited by selection bias, cross sectional designs and reliance on self-reported assessments of the opioid sparing effects of cannabis."

While cannabis availability may reduce opioid consumption, based on urine drug testing in patients on chronic opioid therapy, legalization of the adult use of cannabis led to a small increase in positive cannabinoid test results, but compliance with opioid therapy was unaffected.[134] Additionally, in a cross-sectional study of toxicological testing data of drivers from the 2011–2016 Fatality Analysis Reporting System (FARS) and the 2013–2014 National Roadside Survey of

Alcohol and Drug Use by Drivers (NRS), drivers who tested positive for marijuana were significantly more likely to test positive for prescription opioids.[135]

CO's legalization of the adult use of cannabis resulted in a significant slowing of the upward trend in opioid-related deaths in 2015 after retail sales were initiated.[136] This turned out to be a short-term effect as deaths accelerated again in 2016 and 2017. A more recent study of states with medical cannabis laws and with legalized adult use confirmed previous findings of lower prescription rates in Medicare Part D enrollees, with incremental additional deceases in opioid prescribing in states with legalized adult use.[137] In another study of Medicaid recipients from 2010-2017 among states and D.C., where adult use had been legalized, prescriptions for Schedule III, but not Schedule II opioids were significantly reduced.[138]

Overall, "it remains unclear whether the presumed benefit of legalizing marijuana in reducing opioid-related harms outweighs the policy's externalities, such as its impact on mental health and traffic safety."[132]

Social and Criminal Justice

AMA policy supports decriminalization of cannabis (i.e., reduction in the penalty associated with possession of a small amount of cannabis from a criminal offense subject to arrest to a civil infraction), a view also held by the American Academy of Pediatrics.[139] Legalization of adult use allows cannabis and cannabinoid products or their legal sale and the removal of all penalties for possession of small amount of cannabis.

Criminal arrest. One large multistate comparison found that between 2000 and 2016, decriminalization substantially reduced adult and youth arrest rates for cannabis possession (less so for youth), but adult legalization had little or no impact on youth arrest rates.[140] A related outcome that is highly relevant is "whether cannabis legalization can be used to promote social equity and help communities of color that have been and still are disproportionately affected by prohibition."[141]

Arrests for cannabis violations have decreased dramatically in states with legalized adult use, falling 90-99% in AK, WA, OR and D.C.[142] In WA, a study that included data only through the initial period of legal adult sales, found that cannabis arrest rates among both African American and White adults decreased significantly and stayed at a dramatically lower rate after the marijuana retail market opened. Cannabis accounted for nearly half (47%) of all criminal drug use cases processed in calendar year 2012 in WA, a number which dropped dramatically to about 12% of all drug cases handled by the police by 2016.[143]

However, relative disparities in cannabis arrest rates for Blacks increased for those of legal age, and remained unchanged for younger adults.[144] Another study in OR found that adult cannabis legalization was associated with an increase in juvenile cannabis allegations, although relative disparities decreased for Black compared with White youth.[145] AK also reported a modest increase in the number of youth who have been referred to juvenile justice systems for cannabis offenses since 2016.[146] Juvenile offenders engage in both cannabis use and polysubstance use at higher rates than the general adolescent population.[147]

Crime Rates. Cannabis laws more broadly, and the legalization of recreational marijuana more specifically, had minimal effects on violent or major crime in CO or WA or on property crime rates through 2015, except for a decline of burglary rates in WA.[148] This contrasts with reports from the CO Bureau of Investigation of modest upticks in property crimes and a more significant increase in

violent crimes beginning in 2016-2018.[94] Legalization for adult use was associated with increased resolution of serious crimes in WA even though crime rates were steady as policy devoted more resources to their clearance.[143]

Expungement of Prior Cannabis Related Arrests and Convictions. Even with legalization of cannabis for adult use, for those who have a cannabis-related criminal record for a minor offence, the damage persists. Eight states have created a pathway for expungement although it is usually limited to possession, and may have other limiting conditions (e.g., waiting period, no other criminal convictions, petition hurdles).[142] IL included automatic expungement for convictions of possessing 1 oz or less in its bill; individuals can initiate the process and cases are being identified by law enforcement searches; more than 11,000 have been pardoned.

Social Equity in the Legal Cannabis Business. Some states have established social equity programs to encourage and enable participation (based on a set of criteria) in the cannabis industry by people from communities that have previously been disproportionately harmed by cannabis prohibition and enforcement. MA provides free, statewide, technical assistance, and a training program that provides education, skill-based training, and tools for success in the cannabis industry to applicants; about 4% of cannabis applications in MA were from self-identified minorities.[149] IL offers technical assistance and support in creating a business plan and applying for a license, and also established lower thresholds for license approval, lower fees and access to low interest loans.[150] IL also has its "Restore, Renew, Reinvest" program for communities that have been adversely affected by past prohibition efforts. MI offers substantial discounts on applicant, license and permit fees while expanding eligibility to persons with prior cannabis infractions.[151] Certain other states (e.g., OR) also have eliminated prior cannabis convictions as a disqualification. CA established a "Community Reinvestment Fund" to support communities disproportionately affected by past federal and state drug policies.

Governmental Costs and Revenue

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. Of the 9 states with active retail sales, six employ cultivation levies on growers, while all but AK charge an excise tax specifically on cannabis sales. Seven states also charge a general sales tax and/or allow a local option. Once these laws are fully implemented, legalized adult-use cannabis programs have generated significant annual sales that continue to trend upward annually, yielding surpluses from taxes and fees after accounting for the costs to administer the program. States have implemented adult-use regulatory programs for as little as $1.8 million (AK) up to $60 million for CA (medical and adult use together). For a summary of state administrative agencies, possession limits for legalized adult use, tax rates, recent tax revenues, and administrative costs see Table 2. In some states (e.g., MA) dispensaries for legalized adult use were closed for a period of time during early phases of the COVID-19 pandemic. While the creation of legalized adult use programs leads to reductions in the number of authorized medical users, the number of medical marijuana patients increased by thousands in MA during COVID closures.

How states distribute their cannabis tax revenues also is of interest. Virtually all states allocate a portion of funds for various cannabis/substance use treatment and education efforts.[152]

DISCUSSION

The last 20 years have seen a evolution in state laws increasing access to cannabis and cannabis products to the point where two-thirds of the country now have medical cannabis laws, 11 states

among this group and D.C have legalized the adult use of cannabis, and the other one-third have passed laws allowing the use of CBD in some way; Federal regulations also are now permissive for the use and marketing of certain CBD products.

In trying to evaluate public health impacts in states that have legalized cannabis for adult use, it is important to understand that state retail markets are in different developmental phases to becoming fully established, a process measured in terms of years. All of these states had preexisting, established medical cannabis programs, some more robust than others, especially the states (CO, WA, OR, and to a lesser extent AK) that have provided the most evidence to date. Many studies of the public health impacts of medical cannabis laws exist (and over a longer time period), so it is relevant to question what the appropriate comparison "group" is, especially for states with more recent movement into legalized adult use. In most studies this has been the pre- and post-legalization periods. Some states have set up a process to accomplish this, aided by development of detailed baseline analyses. It is tempting, but premature, to infer that what has happened in the earlier adopter states will be generalizable to other states that have subsequently begun retail sales. One thing that is common is the expansive array of cannabis varietals and novel cannabinoid products and formulations that have been developed, some at very high concentrations, accompanied by an array of administration routes and methods, some posing more health risks to users than others.

As reviewed in this and other reports on this topic, use of cannabis and cannabinoids are associated with some therapeutic benefits, as well as a range of harms and risks of social consequences. In particular, research into the possible therapeutic uses of cannabidiol is in an expansive phase. Harms and risks of social consequences are much more prevalent in the subset of users with generally recognized risk factors including initiation of use at younger ages, high intensity (i.e., frequency and potency) and mode of use.[153] A major difficulty in understanding impacts, risks and benefits of these substances under the umbrella of legalization is the substantial change in potency of products that has occurred over the years, and the range of products now available.

Nationally, cannabis use has increased in the U.S. among 18-25 year-olds, and adults 26+ but decreased in adolescents. Legalization has not significantly impacted recent patterns of adolescent use, but in the fastest growing demographic (18-25 year-olds), the eight states with highest prevalence of past month use are among those that have legalized adult use (ranging from 30.44% in WA to 37.67% in VT).[57] Although not specific to states with legalized adult use, it will be important to monitor recent changes in products used, methods of consumption, and intensity of use, as these are predictors of several harmful outcomes.

Cannabis use in pregnant women has doubled, and women in states with legalized adult use (by 2016) were more likely to use cannabis during preconception, pregnancy, and postpartum. It also seems clear that individuals who use cannabis, particularly younger adults, are driving under the influence of cannabis or cannabis products at a fairly high rate, that such use is associated with traffic accidents and fatalities, and these occur in higher rates in states with legalized adult use.

A robust finding has been the association of legalized adult use with an increase in reported poison control exposures and cannabis-related hospitalizations. Depending on the state, ingestion is the most common route for these exposures, with 20-33% of these reports involving children under the age of 5. In WA, the median age of children (range 0-9 years) was 2 years (2010-2016).[154] In one study involving a children's hospital in CO, the median age also was 2 years with about half of the exposure due to edibles, usually obtained by the child either due to lack of child-resistant packaging (at the time), poor child supervision or inadequate storage.[155] All states should educate the public in this area and require packaging that is child proof, conveys a meaningful and easily

understood unit of consumption, and that clearly differentiates the cannabis edible from food. Incremental increases in cannabis-related hospitalizations have been associated with both medical cannabis laws and legalization of adult use.

Publicly reported trends in cannabis use disorder and treatment admissions have lagged behind changes in consumption patterns. One would expect increased intensity of use and administration of higher concentrations to eventually become evident. Substantial research into the intersections of cannabis laws and various measures of opioid use and harm has largely been limited to medical cannabis laws; the impact of legalization for adult use, over a sufficient time period is only now being examined. Any protective effects of cannabis availability in this area is probably more than offset by impacts on mental health, cannabis use disorder, driving accidents, and other consequences of cannabis use requiring healthcare and community resources.

Legalization of cannabis for adult use has led to a large decrease in cannabis-related arrests for adults, but racial disparities still exist, especially in youth, where possession and use are still illegal. Overall effects on crime rates appear to be neither protective nor provocative. Some states have set up processes for expungement of prior cannabis-related convictions, mostly with limited success because of cumbersome processes that may interfere with successful minority participation. Some states have also set up specific programs to advance participation in the cannabis industry by people from communities that have been disproportionately harmed by previous prohibition and enforcement, and some have created funding streams for community development and provision of services.

Ultimately, the full public health impacts of cannabis legalization will involve the intersection of a number of competing interests including; (1) the regulated marketplace, (i.e., product properties, availability/supply, access/price, preventing youth access, combining current medical and "recreational" markets); (2) impacts on still operating illicit markets; (3) similar to alcohol and tobacco, impacts of advertising, labeling, price and taxes on purchase; (4) effectiveness of public health surveillance and monitoring; and, (5) the extent to which education and community outreach can foster changes in risky behaviors that are subject to individual control.

With respect to behaviors that are subject to individual control, in addition to general abstinence, and avoidance of use in specific populations (e.g., pregnancy, preexisting mental health disorder), the following set of evidence-based measures for lower risk cannabis use have been previously identified:[156]

- avoid early age initiation of cannabis use (i.e., definitively before the age of 16 years);
- choose low-potency tetrahydrocannabinol (THC) or balanced THC-to-cannabidiol (CBD)–ratio cannabis products;
- avoid combusted cannabis inhalation and give preference to nonsmoking use methods (e.g., oral solutions/oils, tincture, edibles);
- avoid deep or other risky inhalation practices;
- avoid high-frequency (e.g., daily or near-daily) cannabis use;
- abstain from cannabis-impaired driving, and,
- avoid combining risk behaviors (e.g., early initiation and high-frequency use).

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 408-A-19, Resolution 411-A-19, and the additional proposed resolve from Alternate Resolution 913-I-19 and the remainder of the report be filed:

That Policy H-95.924, "Cannabis Legalization for Recreational Use," be amended by addition and deletion to read as follows:

Cannabis Legalization for ~~Recreational~~ Adult Use (commonly referred to as 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~~ adult 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~~ adult use or both) should be required to take steps to regulate the product effectively in order to protect public health and safety including but not limited to: regulating retail sales, marketing, and promotion intended to encourage use; limiting the potency of cannabis extracts and concentrates; requiring packaging to convey meaningful and easily understood units of consumption, and requiring that for commercially available edibles, packaging must be child-resistant and come with messaging about the hazards about unintentional ingestion in children and youth. (5) ~~that~~ laws and regulations related to legalized cannabis use should consistently be evaluated to determine their effectiveness; (~~5~~6) 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, especially emergency department visits and hospitalizations, impaired driving, and prevalence of psychiatric and addictive disorders, including cannabis use disorder; (~~6~~7) supports public health based strategies, rather than incarceration, in the handling of individuals possessing cannabis for personal use; (~~7~~,8) encourages research on the impact of legalization and decriminalization of cannabis in an effort to promote public health and public safety; (~~8~~,9) encourages dissemination of information on the public health impact of legalization and decriminalization of cannabis; (~~9~~,10) will advocate for stronger public health messaging on the health effects of cannabis and cannabinoid inhalation and ingestion, with an emphasis on reducing initiation and frequency of cannabis use among adolescents, especially high potency products; use among women who are pregnant or contemplating pregnancy; and avoiding cannabis-impaired driving; (11) supports social equity programs to address the impacts of cannabis prohibition and enforcement policies that have disproportionately impacted marginalized and minoritized communities, and (~~10~~12) will coordinate with other health organizations to develop resources on the impact of cannabis on human health and on methods for counseling and educating patients on the use cannabis and cannabinoids.

Fiscal note: Less than $500

REFERENCES

1. Council on Science and Public Health Report 5. Clinical Implications and Policy Considerations of Cannabis Use. American Medical Association, Interim Meeting of the House of Delegates, Honolulu, HI, November 2017.

2. Council on Scientific Affairs Report 10. Medical marijuana. American Medical Association, Interim Meeting of the House of Delegates, Dallas, TX, December 1997.

3. Council on Scientific Affairs Report 6. Medical marijuana. American Medical Association, Annual Meeting of the House of Delegates, Chicago, IL, June 2001.

4. Council on Science and Public Health Report 3. Use of Cannabis for Medicinal Purposes. American Medical Association, Interim Meeting of the House of Delegates, Houston, TX, November 2009.

5. Council on Science and Public Health Report 2. A Contemporary View of National Drug Control Policy. American Medical Association, Interim Meeting of the House of Delegates, National Harbor, MD, November 2013.

6. Council on Science and Public Health Report 3. Patient Use of Non-FDA Approved Cannabis and Cannabinoid Products in Hospitals. American Medical Association, Interim Meeting of the House of Delegates, November 2019.

7. California Medical Association. CA Medical Association announces support for responsible marijuana ballot initiative. February 1, 2016. https://www.cmadocs.org/newsroom/news/view/ArticleId/32200/-CA-Medical-Association-announces-support-for-responsible-marijuana-ballot-initiative

8. Ross S, ElSohly M. The volatile oil composition of fresh and air-dried buds of Cannabis sativa. *J Nat Prod.* 1996;59:49-51.

9. Brenneisen R. Chemistry and analysis of phytocannabinoids and other Cannabis constituents. In: Elsohly M (ed.). *Marijuana and the Cannabinoids*. Humana Press: Totowa, NY. 2007:17-49.

10. Razdan RK. Structure-activity relationships in cannabinoids. *Pharmacol Rev.* 1986;38:75-149.

11. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Brit J Pharmacol.* 2011;163:1344-64.

12. Lewis MA, Russo EB, Smith KM. Pharmacological foundations of cannabis chemovars. *Planta Med*. 2018;84:225-33.

13. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC: Changes in cannabis potency over the last 2 decades (1995- 2014): analysis of current data in the United States. *Biol Psychiatry.* 2016;79:613-19.

14. Dolgin E. A boosted crop. *Nature*. 2019;572;S5-7.

15. Bie B, Wu J, Foss JF, Naguib M. An overview of the cannabinoid type 2 receptor system and its therapeutic potential. *Curr Opin Anaesthesiol*. 2018;31:407-414.

16. Felder CC, Glass M. Cannabinoid receptors and their endogenous agonists. *Annu Rev Pharmacol Toxicol*. 1998;38:179-200.

17. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990;346:561-4.

18. Shahbazi F, Grandi V, Banerjee A, Trant JF. Cannabinoids and cannabinoid receptors: The story so far. *iScience*. 2020;23(7). doi.org/10.1016/j.isci.2020.101301.

19. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. *Int J Mol Sci*. 2018;19:833.

20. Mackie, K. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handb Exp Pharmacol*. 2005;168:299–325.

21. Howlett AC, Abood ME. CB1 & CB2 Receptor Pharmacology. *Adv Pharmacol*. 2017;80:169-206.

22. Thomas A, Baillie G, Phillips A, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB_1 and CB_2 receptor agonists *in vitro*. *Br J Pharmacol*. 2007;150:613-23.

23. Laprairie R., Bagher A, Kelly M, Denovan-Wright E. Cannabidiol is a negative allosteric modulator of the cannabinoid CB_1 receptor. *Br J Pharmacol*. 2015;172:4790-4805.

24. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *J Clin Pharmacol.* 1983;34:352-63.

25. Wall ME, Perez-Reyes M. The metabolism of delta^9-tetrahydrocannabinol and related cannabinoids in man. *J Clin Pharmacol.* 1981;21:178S-189S.

26. Ohlsson A, Lindgren JE, Wahlen A, et al. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther.* 1980;28:409-16.

27. Marinol® capsules (Dronabinol solution in sesame oil in soft gelatin capsules). Roxane Laboratories, Inc. Columbus, Ohio. Package Insert.

28. Davis KH, McDaniel IA, Caddel LW, et al. Some smoking characteristics of marijuana cigarettes. In: Agurell S, Dewey WL, Willette RE, eds. *The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects*. New York: Academic Press; 1984:97-109.

29. Newmeyer MN, Swortwood MJ, Barnes AJ, et al. Free and glucuronide whole blood cannabinoids' pharmacokinetics after controlled smoked, vaporized, and oral cannabis administration in frequent and occasional cannabis users: identification of recent cannabis intake. *Clin Chem*. 2016;62:1579–92.

30. Spindle TR, Cone EJ, Schlienz NJ, et al. Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis: a crossover trial. *JAMA Netw Open.* 2018; 1:e184841.

31. Huestis MA. Human Cannabinoid Pharmacokinetics. *Chem Biodivers*. 2007;4:1770-1804.

32. Spindle T, Cone E, Herrmann E, et al. Pharmacokinetics of cannabis brownies: A controlled examination of Δ9-tetrahydrocannabinol and metabolites in blood and oral fluid of healthy adult males and females. *J Anal Toxicol.* 2020 Jun 15;doi:10.1093/jat/bkaa067.

33. Poyatos L, Pérez-Acevedo A,1Papaseit E, et al. Oral administration of cannabis and Δ-9-tetrahydrocannabinol (THC) preparations: A systematic review. *Medicina*. 2020;56:309.

34. Vandrey R, Herrmann ES, Mitchell JM, et al. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. *J Anal Toxicol.* 2017;41:83-99.

35. 21 USC 812.

36. 81 FR 53687.

37. 21 USC 802(16)

38. Public Law 115-334. Agriculture Act of 2018.

39. Britannica ProCon.org. Legal recreational marijuana states and DC. https://marijuana.procon.org/legal-recreational-marijuana-states-and-dc/. Accessed August 5, 2020.

40. Britannica ProCon.org. States with legal cannabidiol (CBD). https://medicalmarijuana.procon.org/states-with-legal-cannabidiol-cbd/. Accessed August 5, 2020.

41. Investopedia. Marijuana laws by U.S. state. https://www.investopedia.com/marijuana-legality-by-state-4844504. Accessed August 6, 2020.

42. Marijuana Policy Project. State policy. https://www.mpp.org/states/. Accessed August 5, 2020.

43. Hall W, Lynskey M. Assessing the public health impacts of legalizing recreational cannabis use: the US experience. *World Psychiatry.* 2020;19:179-96.

44. CO Amendment 64. (2012).

45. WA I-502. (2012).

46. Washington, D.C. Initiative 71. (2014).

47. VT S. 22. (2017).

48. Spindle T, Bonn-Miller M, Vandrey R. Changing landscape of cannabis: novel products, formulations, and methods of administration. *Curr Opin Psychol*. 2019 Dec;30:98-102. doi: 10.1016/j.copsyc.2019.04.002. Epub 2019 Apr 9.

49. Gabrys R. Clearing the Smoke on Cannabis. Edible Cannabis Products, Cannabis Extracts and Cannabis Topicals. Canadian Centre on Substance Abuse, 2020. https://www.ccsa.ca/sites/default/files/2020-05/CCSA-Edible-Cannabis-Extracts-and-Topicals-Report-2020-en.pdf. Accessed August 27, 2020.

50. Cannabis concentrates. https://weedmaps.com/learn/products-and-how-to-consume/cannabis-concentrates/. Accessed August 26, 2020.

51. The National Academies of Sciences Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press. 2017.

52. Campenya E, López-Pelayoa H, Nutt D. The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. *Eur Neuropsychopharm*. 2020;33:1-35.

53. Latif Z, Garg N. The impact of marijuana on the cardiovascular system: A review of the most common cardiovascular events associated with marijuana use. *J Clin Med*. 2020;9:1925. doi:10.3390/jcm9061925.

54. Page R, Allen L, Kloner R, et al. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health. A Scientific Statement From the American Heart Association. Circulation. 2020;142:00–00. https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000883. Accessed August 27, 2020.

55. Patel R, Manocha P, Patel J, Patel R, Tankersley W. Cannabis use is an independent predictor for acute myocardial infarction related hospitalization in younger population. *J Adolesc Health*. 2020;66:79e-85.

56. Montero-Oleas N, Arevalo-Rodriguez I, Nuñez-González S, Viteri-García A, Simancas-Racines D. Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews. *BMC Complem Med Therap*. 2020;20:12.

57. Midgette G, Reuter P. Has cannabis use among your increased after changes in its legal status? A commentary on use of Monitoring the Future for analyses of changes in state cannabis laws. *Prev Sci.* 2020;21:137-45.

58. Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/. Accessed August 23, 2020.

59. 2018 Monitoring the Future: College Students and Young Adults. Drug use trends among college age adults (19-22). https://www.drugabuse.gov/drug-topics/trends-statistics/infographics/drug-alcohol-use-in-college-age-adults-in-2018. Accessed August 24, 2020.

60. 2019 Monitoring the Future Survey. High School and Youth Trends.

61. Behavioral Risk Factor Surveillance System (BRFSS) data. Colorado adult marijuana users. https://marijuanahealthinfo.colorado.gov/health-data/behavioral-risk-factor-surveillance-system-brfss-data.

62. Substance Abuse and Mental Health Services Administration. (2019). 2017-2018 National Surveys on Drug Use and Health: Model-Based Estimated Totals (in Thousands) (50 States and the District of Columbia). https://www.samhsa.gov/data/report/2017-2018-nsduh-state-prevalence-estimates. Accessed August 23, 2020.

63. Steigerwald S, Wong PO, Cohen BE, et al. Smoking, vaping, and use of edibles and other forms of marijuana among U.S. adults. *Ann Intern Med*. 2018;169:890-92.

64. Bae H, Kerr DC. Marijuana use trends among college students in state with and without legalization of recreational use: initial and longer-term changes from 2008 to 2018. *Addiction*. 2020;115:1115-24.

65. Prevalence of past 30-day cannabis use among high school and middle school students in Colorado and the United States. https://marijuanahealthinfo.colorado.gov/health-data/healthy-kids-colorado-survey-hkcs-data. Accessed August 26, 2020

66. Dilley J, Richardson S, Kilmer B, et al. Prevalence of cannabis use in youths After legalization in Washington state. *JAMA Ped*. 2019;173;192-93.

67. Oregon Health Authority. Youth marijuana use, attitudes and related behaviors in Oregon. https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/MARIJUANA/Documents/fact-sheet-marijuana-youth.pdf. Accessed August 26, 2020.

68. Method of marijuana use among high school student-Colorado 2015-2019. https://marijuanahealthinfo.colorado.gov/health-data/healthy-kids-colorado-survey-hkcs-data. Accessed August 26, 2020.

69. Hammond D, Goodman S, Wadsworth E, Rynard V, Boudreau C. Evaluating the impacts of cannabis legalization: The International Cannabis Policy Study. *Int J Drug Policy*. 2020;77: https://doi.org/10.1016/j.drugpo.2020.102698. Accessed August 27, 2020.

70. Centers for Disease Control and Prevention. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-information. Accessed August 31, 2020.

71. Caulkins J, Pardo B, Kilmer B. Intensity of cannabis use: Findings from three online surveys. *Int J Drug Policy*. 2020;79:102740. doi: 10.1016/j.drugpo.2020.102740. Online ahead of print. Accessed August 23, 2020.

72. Barrington-Trimis J, Cho J, Ewusi-Boisvert E. Risk of persistence and progression of use of 5 cannabis products after experimentation among adolescents. *JAMA Network Open*. 2020;3:e1919792. doi:10.1001/jamanetworkopen.2019.19792. Accessed August 24, 2020.

73. Volkow ND, Baler RD, Compton WM.et al. Adverse health effects of marijuana use. *N Engl J Med.* 2014;370:2219-2227.

74. Fergusson DM, Boden JM. Cannabis use and later life outcomes. *Addiction.* 2008;103:969-976.

75. Hall W, Lynesky M. Evaluating the public health impacts of legalizing recreational cannabis use in the United States. *Addiction.* 2016;111:1764-1773.

76. American College of Obstetricians and Gynecologists. Marijuana use during pregnancy and lactation. Committee Opinion No. 722. *Obstet Gynecol.* 2017;130:e205-09.

77. Grant K, Petroff R, Isoherranen N, Stella N, Burbacher T. Cannabis use during pregnancy: Pharmacokinetics and effects on child development. *Pharmacol Ther*. 2018;182:133-51.

78. Calvigioni D, Hurd Y, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. *Eur Child Adolesc Psychiatry*. 2014;23:931-41.

79. Jutras-Aswad D, DiNieri J, Harkany T, Hurd Y. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. *Eur Arch Psychiatry Clin Neurosci*. 2009;259:395-412.

80. McLemore G, Richardson K. Data from three prospective longitudinal human cohorts of prenatal marijuana exposure and offspring outcomes from the fetal period through young adulthood. *Data in Brief*. 2016;9:753-7.

81. Szutorisz H, Hurd Y. High times for cannabis: epigenetic imprint and its legacy on brain and behavior. *Neurosci Biobehav Rev*. 2018;85:93-101.

82. Crume TL, Juhl A, Brooks-Russell A, et al. Cannabis use during the perinatal period in a state with legalized recreational and medical marijuana. The association between maternal characteristics, breastfeeding patterns, and neonatal outcome. *J Pediatr*. 197:90-6, 2018.

83. Gunn J,1 Rosales C, Center K, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open.* 2016;6:e009986. doi:10.1136/bmjopen-2015-009986.

84. Conner SN, Bedell V, Lipsey K, et al. Maternal marijuana use and adverse neonatal outcomes: A systematic review and meta-analysis. *Obstet Gynecol*. 2016;128:713-23.

85. Corsi D, Walsh L, Weiss D. Association between self-reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes. *JAMA*. 2019;322:145-52.

86. Volkow ND, Han B, Compton WM, et al. Self-reported medical and nonmedical cannabis use among pregnant women in the United States. *JAMA* 2019;322:167-9.

87. Chang JC, Tarr JA, Holland CL, et al. Beliefs and attitudes regarding prenatal marijuana use: Perspectives of pregnant women who report use. *Drug Alcohol Depend*. 2019;196:14–20.

88. Colorado Pregnancy Risk Assessment Monitoring System. Marijuana use during pregnancy by pregnancy intention. Colorado 2014-2018. https://marijuanahealthinfo.colorado.gov/health-data/pregnancy-risk-assessment-monitoring-system-prams-data. Accessed August 28, 2020.

89. Metz T, Silver R, McMillin G. Prenatal marijuana use by self-report and umbilical cord sampling in a state with marijuana legalization. *Obstet Gynecol*. 2019;133: 98–104.

90. Skelton K, Hecht A, Benjamin-Neelon S. Recreational cannabis legalization in the US and maternal use during the preconception, prenatal, and postpartum periods. *Int J Environ Res Public Health*. 2020;17:909; doi:10.3390/ijerph17030909.

91. Young-Wolff KC, Sarovar V, Tucker L, et al. Self-reported Daily, Weekly, and Monthly Cannabis Use Among Women Before and During Pregnancy. *JAMA Netw Open*. 2019;2(7):e196471. doi:10.1001/jamanetworkopen.2019.6471.

92. Colorado Department of Public Health & Environment. THC Concentration in Colorado: Marijuana Health Effects and Public Health Concerns. July 31,2020. https://www.thenmi.org/wp-content/uploads/2020/08/THC-Concentration-in-Colorado-Marijuana-_CDPHE-8.3.2020.pdf. Accessed August 21, 2020.

93. Washington Young Adult Health Survey. Driving After Marijuana Use. 2014-16. https://www.dshs.wa.gov/sites/default/files/BHSIA/dbh/Research/Young%20adult%20MJ%20survey%206-26-2015.pdf.

94. Rocky Mountain High Intensity Drug Trafficking Area. The Legalization of Marijuana in Colorado: The Impact. Volume 6, September 2019.

95. Kamer R, Warshafsky S, Kamer G. *JAMA Int Med*. 180;8:1119-20.

96. Aydelotte JD, Mardock AL, Mancheski CA, et al. Fatal crashes in the 5 years after recreational marijuana legalization in Colorado and Washington. *Accid Anal Prev*. 2019;132:105284. doi:10.1016/j.aap.2019.105284.

97. Santaella-Tenorio J, Wheeler-Martin K, DiMaggio C, et al. Association of Recreational Cannabis Laws in Colorado and Washington State With Changes in Traffic Fatalities, 2005-2017. *JAMA Intern Med*. 2020;180(8):1061-1068.

98. Lane T, Hall W. Traffic fatalities within US states that have legalized recreational cannabis sales and their neighbors. *Addiction*. 2019;114:847-56.

99. Colorado Department of Public Safety. Division of Criminal Justice , Office of Research and Statistics. *Impacts of Marijuana Legalization in Colorado.* October 2018

100. Colorado Child Health Survey. https://marijuanahealthinfo.colorado.gov/health-data/child-health-survey-chs-data. Accessed August 21, 2020.

101. Washington Poison Center. 2018 Annual Data Report: Cannabis. https://www.wapc.org/wp-content/uploads/2018-Cannabis.pdf. Accessed August 21, 2020.

102. Oregon Poison Control. Annual Marijuana Cases 2014-2017 By Age. https://www.ohsu.edu/sites/default/files/2018-11/Cannabis-report-FINAL%20november%2018%20PDF.pdf.

103. Shi Y, Liang D. The association between recreational cannabis commercialization and cannabis exposures reported to the US National Poison Data System [published online ahead of print, 2020 Feb 20]. *Addiction*. 2020;10.1111/add.15019. doi:10.1111/add.15019.

104. Richards JR. Cannabinoid Hyperemesis Syndrome: Pathophysiology and Treatment in the Emergency Department. *J Emerg Med*. 2018;54(3):354-363. doi:10.1016/j.jemermed.2017.12.010

105. Desai R, Shamim S, Patel K, et al. Primary causes of hospitalizations and procedures, predictors of in-hospital mortality, and trends in cardiovascular and cerebrovascular events among recreational marijuana users: A five-year nationwide inpatient assessment in the United States. *Cureus.* 10(8):e3195. doi.7759/cureus.3195.

106. Colorado Hospital Association (CHA) data. Rates of hospitalizations with marijuana billing codes in Colorado, 2000-2017. https://marijuanahealthinfo.colorado.gov/health-data/colorado-hospital-association-cha-data. Accessed August 29, 2020.

107. Close NS. Adverse Health Effects of Marijuana Legalization. Doctoral Thesis. https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/44809/Close_washington_0250E_20573.pdf?sequence=1&isAllowed=y. Accessed August 29, 2020.

108. Zehra A, Burns J, Liu C, Wang G. Cannabis addiction and the brain: a review. *J Neuroimmune Pharmacol*. https://doi.org/10.1007/s11481-018-9782-9

109. Budney A, Sofis M, Borodovsky J. An update on cannabis use disorder with comment on the impact of policy related to therapeutic and recreational cannabis use. *Eur Arch Psychiatry Clin Neurosci.* 2019; 269:73–86.

110. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of marijuana use disorders in the United States Between 2001-2002 and 2012-2013. *JAMA Psychiatry*. 2015;72(12):1235–1242. doi:10.1001/jamapsychiatry.2015.1858

111. SAMHSA. Results from the 2016 national survey on drug use and health: detailed tables Prevalence estimates, standard Errors, P Values, and sample sizes. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, Rockville, 2017.

112. Grucza RA, Agrawal A, Krauss MJ, Cavazos-Rehg PA, Bierut LJ. Recent trends in the prevalence of marijuana use and associated disorders in the United States. *JAMA Psychiatry.* 2016;73:300-01.

113. Leung J, Chan G, Hides L, Hall W. What is the prevalence and risk of cannabis use disorders among people who use cannabis? a systematic review and meta-analysis. *Addictive Behaviors*. 2020;109:106479. https://doi.org/10.1016/j.addbeh.2020.106479. Accessed August 29, 2020.

114. Silins E, Horwood LJ, Patton GC, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry*. 2014;1:286-93.

115. Han B, Compton W, Blanco C, Jones CM. Time since first cannabis use and 12-month prevalence of cannabis use disorder among youth and emerging adults in the United States. *Addiction*. 2019;114: 698-707.

116. Smart R, Pacula R. Early evidence of the impact of cannabis legalization on cannabis use, cannabis use disorder, and the use of other substances: Findings from state policy evaluations. *Am J Drug Alcohol Abuse*. 2019;45:644-63.

117. Hasin D, Sarvet A, Cerdá M. US adult illicit cannabis use, cannabis use disorder, and medical marijuana laws 1991-1992 to 2012-2013. *JAMA Psychiatry*. 2017;74:579-88.

118. Cerdá M, Mauro C, Hamilton A, et al. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2019.3254 Published online November 13, 2019.

119. Hasin DS, Kerridge BT, Saha TD, et al. Prevalence and correlates of DSM-5 cannabis use disorder, 2012–2013: findings from the national epidemiologic survey on alcohol and related conditions–III. *Am J Psychiatry*. 2016;173:588-599.

120. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2017. Admissions to and Discharges from Publicly-Funded Substance Use Treatment. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2019. https://wwwdasis.samhsa.gov/dasis2/teds_pubs/TEDS-2017-R.pdf

121. Northwest High Intensity Drug Trafficking Area. Washington State Marijuana Impact Report. Volume 3. August 2017.

122. Department of Health and Social Services. Marijuana Use and Public Health in Alaska -2020. Anchorage, Alaska: Office of Substance Misuse and Addiction Prevention, Division of Public Health, Alaska Department of Health and Social Services; January 2020.

123. Centers for Disease Control and Prevention. Opioid Overdose. Understanding the Epidemic. https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed August 31, 2020.

124. Bachhuber M, Saloner B, Cunningham C, Barry C. Medical cannabis laws and opioid analgesic overdose. Mortality in the United States, 1999–2010. *JAMA Intern Med*. 2014; 174: 1668-73.

125. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med*. 2018;178:667-72.

126. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *J Pain*. 2016;17:739-44.

127. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: Patient self-report. *Cannabis Cannabin Res*. 2017;2.1 doi:10.1089/can.2017.0012.

128. Bradford A, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. *Health Affairs*. 2016;35:1230-36.

129. Raji M, Abara NO, Salameh H, et al. Association between cannabis laws and opioid prescriptions among privately insured adults in the US. *Prev Med*. 2019;125:62-8.

130. Shia Y, Lianga D, Baob Y, et al. Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug Alcohol Depend*. 2019;194:13-9.

131. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*. 2018;58:29-42.

132. Chihuri S, Li G. State marijuana laws and opioid overdose mortality. *Injury Epidemiol*. 2019;6:38 https://doi.org/10.1186/s40621-019-0213-z.

133. Campbell G, Hall W, Nielsen S. What does the ecological and epidemiological evidence indicate about the potential for cannabinoids to reduce opioid use and harms? A comprehensive review. *Int Rev Psychiatry*. 2018;30:91-106.

134. Lo SY, Winston-McPherson GN, Starosta AJ, et al. Cannabis legalization does not influence patient compliance with opioid therapy. *Am J Med*. 2019;132:347-53.

135. Li G, Chihuri S. Is marijuana use associated with decreased use of prescription opioids? Toxicological findings from two US national samples of drivers. *Sub Abuse Treat Prevent Policy*. 2020;15:12 doi.org/10.1186/s13011-020-00257-7.

136. Livingston M, Barnett T, Delcher C, Wagenaar A. Recreational cannabis legalization and opioid-related deaths in Colorado, 2000–2015. *Am J Public Health*. 2017;107:1827-29.

137. Wen H, Hockenberry JM. Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. *JAMA Intern Med*. 2018;178(5):673-79.

138. Shia Y, Lianga D, Bao Y. Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug Alcohol Depend*. 2019;194:13-19.

139. Committee on Substance Abuse, Committee on Adolescence; Committee on Substance Abuse Committee on Adolescence. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics*. 2015;135:584-7.

140. Plunk A, Peglow S, Harrell P, Grucza R. Youth and adult arrests for cannabis possession after decriminalization and legalization of cannabis. *JAMA Pediatr*. 2019;173:763-9. doi:10.1001/jamapediatrics.2019.1539.

141. Kilmer B1, Kilmer Neel E. Being thoughtful about cannabis legalization and social equity. *World Psychiatry*. 19:2 - June 2020;194-5.

142. Adinoff B, Reiman A. Implementing social justice in the transition from illicit to legal cannabis. *Am J Drug Alcohol Abuse*. 2019;45:673-88.

143. Effects of Marijuana Legalization on Law Enforcement and Crime: Final Report Author(s): Stohr M, Willits D, Makin D et al. Document Number: 255060: July 2020.

144. Firth CL, Mahera J, Dilleya J, Darnell A, Lovrich N. Did marijuana legalization in Washington State reduce racial disparities in adult marijuana arrests? *Subst Use Misuse*. 2019; 54:1582-7.

145. Firth CL, Hajat A, Dilley J, Braun M, Maher J. Implications of cannabis legalization on juvenile justice outcomes and racial disparities. *Am J Prev Med*. 2020;58:562-9.

146. Alaska Department of Health and Social Services. Marijuana Use and Public Health in Alaska - 2020. Anchorage, Alaska: Office of Substance Misuse and Addiction Prevention, Division of Public Health, Alaska Department of Health and Social Services; January 2020.

147. Banks DE, Hershberger AR, Pemberton T, et al. Poly-use of cannabis and other substances among juvenile-justice involved youth: variations in psychological and substance-related problems by typology. *Am J Drug Alcohol Abuse*. 2019;45:313-22.

148. Lu R, Willits D, Stohr M et al. The cannabis effect on crime: Time-series analysis of crime in Colorado and Washington State, *Justice Quarterly*. 2019. doi:10.1080/07418825.2019.1666903.

149. Massachusetts Equity Programs. https://mass-cannabis-control.com/equityprograms/

150. Illinois Adult Use Social Equity Program https://www2.illinois.gov/dceo/CannabisEquity/Pages/default.aspx

151. Michigan expands parameters of marijuana social equity program. https://mjbizdaily.com/michigan-expands-parameters-of-marijuana-social-equity-program/

152. State Cannabis Tax Revenue Distributions as of 2019. https://www.civicfed.org/civic-federation/blog/how-will-illinois-spend-cannabis-revenues.

153. Fischer B, Russell C, Rehm J, Leece P. Assessing the public health impact of cannabis legalization in Canada: core outcome indicators towards an 'index' for monitoring and evaluation. *J Public Health* (Oxf). 2019;41(2):412-421. doi:10.1093/pubmed/fdy090

154. Thomas A, Von Derau K, Bradford M, et al. Unintentional pediatric marijuana exposures to and after legalization and commercial availability of recreational marijuana in Washington state. *J Emerg Med*. 2019;56:398-404.

155. Wang GS, Le Lait MC, Deakyne SJ, Bronstein AC, Bajaj L, Roosevelt G. Unintentional Pediatric Exposures to Marijuana in Colorado, 2009-2015. *JAMA Pediatr*. 2016;170(9):e160971. doi:10.1001/jamapediatrics.2016.0971

156. Fischer B, Russell C, Sabioni P, et al. Lower-risk cannabis use guidelines: A comprehensive update of evidence and recommendations [published correction appears in Am J Public Health. 2018 May;108(5):e2]. *Am J Public Health*. 2017;107(8):e1-e12. doi:10.2105/AJPH.2017.303818

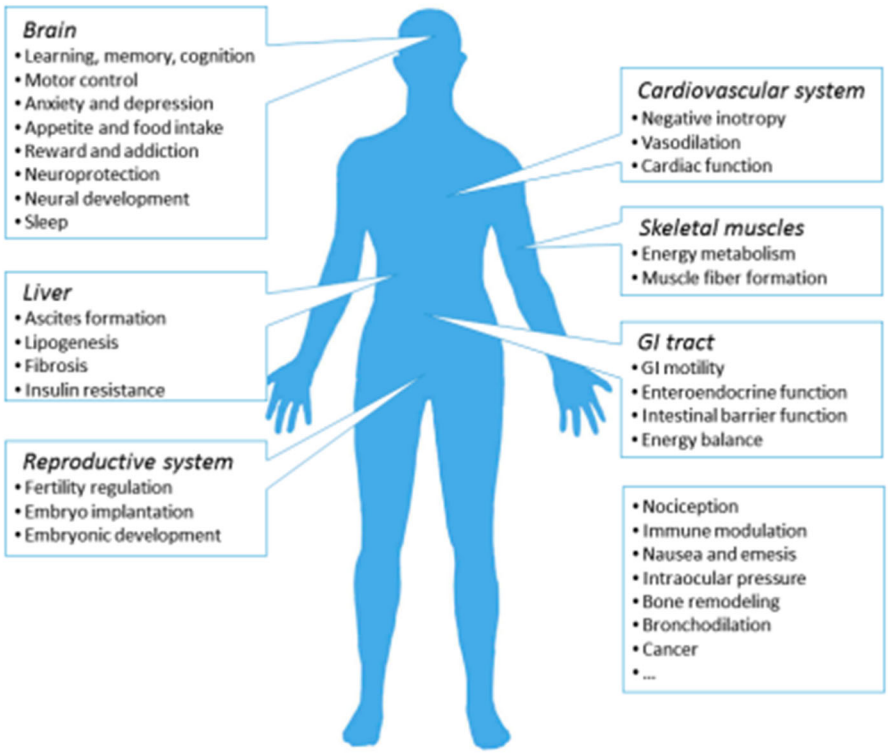


Figure 1. Major localization and associated functions of the CB1 receptor, the majority of which are expressed in the brain from: Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *Int J Mol Sci.* 2018 Mar 13;19(3):833. doi: 10.3390/ijms19030833. Open Access.

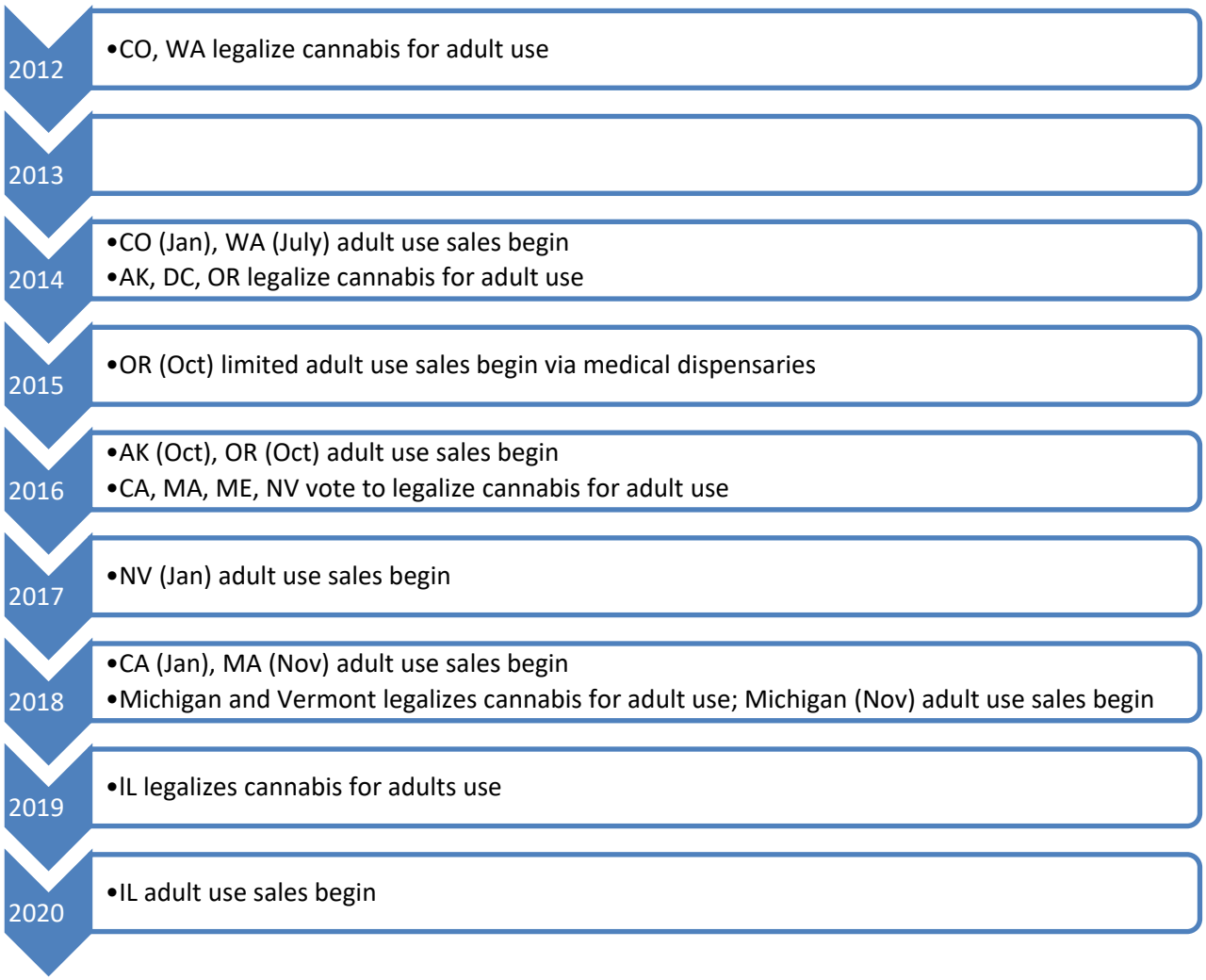


Figure 2. Timeline of legalization and implementation of cannabis for adult use. Constructed figure.

Figure 3. Washington State logo for cannabis edibles. Washington State Liquor and Cannabis Board

Table 1. Summary of cannabis extracts

Product	Description	Method of Use	Average Levels of THC and CBD[2]
Hash			
	Hash or hashish is the oldest and best-known type of cannabis extract. It is a light to dark brown substance composed of compressed or purified trichomes, which are the stalked resin glands that contain most of the cannabinoids present in the cannabis plant. Hash that has been pressed is usually solid, whereas water-purified hash develops a paste-like consistency and is often called "bubble melt hash" or "bubble hash."	- **Smoked** (either alone or mixed in with dried cannabis or tobacco) - **Vaped** - **Dabbed**	THC: 40–80% CBD: less than 5%
Kief			
	Kief refers to the collection of trichomes that accumulate when sifted from dried cannabis, often using a three-chamber grinder.	- **Smoked** (either alone or mixed in with dried cannabis or tobacco)	THC: 40–50% CBD: less than 5%
Wax (crumble, budder)			
	Wax is a solvent-based (e.g., butane[3]) extract that is named after its appearance and consistency. Wax varies in level of THC depending on quality, but can contain well over 50% THC. **Crumble** is the drier and more crumbly form of wax, whereas **budder** contains a higher moisture content.	- **Vaped** - **Dabbed**	THC: 26–70% CBD: --
Shatter			
	Shatter is amber and glass-like in appearance and consistency. It is generally high in THC and low in CBD. Compression following the extraction process turns shatter into a substance called "cookie crumble" or "honeycomb."	- **Vaped** - **Dabbed**	THC: ~ 70% CBD: --
Live Resin			
	Live resin is made the same way as wax, but with fresh cannabis plant material that has been immediately frozen after harvest. This is the reason for the term "live." This process gives live resin a "more intense and complex" smell and taste, so it is more expensive than typical wax and budder products. The moisture in this extract gives it a slightly different appearance from wax and budder.	- **Vaped** - **Dabbed**	THC: 40–50% CBD: --
Rosin			
	Rosin refers to cannabis extracts that were made using "rosin tech," which is essentially the application of heat and compression to the resinous sap from cannabis plant matter, most often flower (or bud), kief or hash. This extraction method results in a sappy and translucent cannabis extract that is similar in appearance and composition to **shatter.** It is believed that rosin can reach comparable THC concentrations to that in solvent-based extracts, but this has yet to be scientifically tested.	- **Vaped** - **Dabbed**	THC: ~ 70% CBD: --

Product	Description	Method of Use	Average Levels of THC and CBD[1]
Tinctures and Oil Sprays			
	Tinctures and oil sprays are products consisting of a cannabis extract, a carrier liquid, such as coconut-derived MCT (medium-chain triglycerides) oil, and sometimes terpenes. These products vary widely in their THC and CBD levels and reasons for use. Tinctures come in plastic or glass bottles with droppers and are administered under the tongue (sublingually). Oil sprays are similarly intended to be sprayed under the tongue.	- **Sublingual** - **Ingested**	**High THC:** THC: 20–30 mg/ml CBD: 0–1 mg/ml **High CBD:** THC: 0.7–2 mg/ml CBD: 15–55 mg/ml **Balanced:** THC: 1–12.5 mg/ml CBD: 1–12.5 mg/ml
Softgels and Capsules			
	Softgels and capsules are comprised of similar ingredients to that of tinctures and oil sprays: a cannabis extract, a carrier liquid (e.g., MCT) and, sometimes, terpenes. These products vary widely in their THC and CBD levels.	- **Ingested**	**High THC:** THC: 2.5–10 mg/capsule CBD: 0–1 mg/capsule Capsules on the illicit market appear to contain up to 100 mg of THC. **High CBD:** THC: 0–1 mg/capsule CBD: 9–25 mg/capsule **Balanced:** THC: 2–3 mg/capsule CBD: 2–3 mg/capsule
Vape Cartridges and Disposable Pens			
	Vape cartridges and pens contain high concentrated cannabis extracts and varying terpene (flavour) profiles. High THC vape products are the most commonly sold. However, it appears that high CBD and "balanced" vape products are becoming increasingly available.	- **Vaped**	**High THC:** THC: 70–95% CBD: 0–10% **High CBD:** THC: 0–5% CBD: 60–70% **Balanced:** THC: 40–60% CBD: 20–40%

Source: Gabrys R. Canadian Centre on Substance Use and Addiction. Clearing the Smoke on Cannabis Edible Cannabis Products, Cannabis Extracts and Cannabis Topicals. https://www.ccsa.ca/sites/default/files/2020-05/CCSA-Edible-Cannabis-Extracts-and-Topicals-Report-2020-en.pdf.

Table 2: Tax rates, recent tax revenues, and administrative cost (adult use)

State	Licensing & Tracking	Possession Limits	Taxes	Tax Revenue	Administrative Costs
Colorado	Colorado Dept. of Revenue	1 oz usable, 6 plants (no more than 3 mature), 8 g hash/concentrates; 800 mg edible	Cultivator excise tax of 15% sales to retail stores Retail tax of 15% Local option retail tax up to 8%	>1 billion in tax revenue from initiation to June 2019; $203 million for Jan-Jun 2020	$16 million
Washington	Washington State Liquor and Cannabis Board	1 oz usable, 16 oz solid cannabis-infused, 72 oz liquid infused, 7 g concentrates	37% tax on retail sales 6.5% retail sales tax (plus local tax)	$395 million in 2019; $248 million thru Jun 2020	$42 million
Oregon	Oregon Liquor Control Commission	1 oz usable in public, 8 oz homegrown, 4 plants, 16 oz solid, 72 oz liquid-infused, 1 oz hash/extract at home	17% retail sales tax Local option sales tax up to 3%	$133 million for FY 2020	$10 million
Alaska	Marijuana Control Board	1 oz usable, 6 plants (no more than 3 mature)	Cultivator excise tax of $50/oz flowers; $15/oz stems and leaves; $25/oz for immature flowers/buds; $1 per clone	$24.5 million FY 2020	$2 million
Nevada	Nevada Dept. of Taxation	1 oz usable, 6 plants, 3.5 g hash/concentrates	Cultivator wholesale excise tax 15% Retail tax 10% Sales tax 6.85% (plus local)	Jul 2019-May 2020, $95 million in tax revenue	$3.5 million
California	CalCannabis Cultivations Licensing (CA Dept. of Food & Agriculture	1 oz usable, 6 plants, 8 g hash/concentrates	Cultivator tax of $9.65/ounce for flowers; $2.87 ounce for leaves Fresh plant material $1.35/ounce Excise tax (15% of Retail Sales) Retail sales tax (7.25% plus local)	California passed $1 billion in cannabis tax revenue two years after launching legal market.	$61 million
Massachusetts	Massachusetts Cannabis Control Commission	1 oz usable (up to 10 oz secured), 6 plants, 5 g concentrates	10.75% Excise tax on retail sales 6.25% Retail sales tax Local option excise tax of up to 3%	$122 million in tax revenue collected in the FY 2019-2020	?
Michigan	Michigan Dept. of Licensing and Regulatory Affairs	2.5 oz usable, 12 plants, 15 g concentrates	10% Retail excise tax 6% State sales tax	Since Dec 2019, $35 million in excise/sales tax	?

Illinois	Illinois Dept. of Financial & Professional Regulation	1 oz usable, 5 g hash/concentrates	Cultivator excise tax (7%) on sales to dispensaries Retail Excise Taxes: 10% with THC level of <35%, 25% for THC>35%; 20% on cannabis-infused products; Local option tax up to 3%	$52.8 million Jan-Jun 2020 with further increase in July	?
Maine	Office of Marijuana Policys	2.5 oz usable, up to 15 plants (no more than 3 mature), 6 g hash/concentrates	Cultivator excise tax of $335 per pound/ $94 per pound trim/$1.50 per seedling/$0.35 per seed Retail sales tax of 10%	Sales on Hold	

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 501
(November 2020)

Introduced by: Illinois

Subject: CBD Oil Use and the Marketing of CBD Oil

Referred to: Reference Committee E

Whereas, Cannabidiol (CBD) oil is advertised in health clubs and convenience stores and online; and

Whereas, CBD oil is often marketed in ways that falsely imply medical doctor approval, verification or endorsement; and

Whereas, There is only one Food and Drug Administration (FDA)-approved drug in which CBD is the active ingredient for the indication of two rare types of epilepsy syndromes; and

Whereas, It is known that the side effects of CBD include elevated liver enzymes, diarrhea, somnolence and decreased appetite; and

Whereas, CBD oil is promoted for the treatment of a vast range of mental and physical ailments including: seizures, schizophrenia, depression, anxiety, Tourette syndrome, ADHD, pain reduction and sleep disorders; and

Whereas, CBD is one of more than 100 identified compounds in the cannabis plant, commonly known as marijuana and CBD is put into products including ingestible oils, bath salts and drinks; and

Whereas, CBD oil is not an FDA-approved product and is considered a dietary supplement and the composition and purity of the product generally extracted from hemp is not overseen by any U.S. regulatory body and adulteration, contamination with pesticides, herbicides and heavy metals and variable percentage of CBD product can and does occur; therefore be it

RESOLVED, That our American Medical Association support banning the advertising of cannabidiol (CBD) as a component of marijuana in places that children frequent (New HOD Policy); and be it further

RESOLVED, That our AMA support legislation to prohibit companies from selling CBD products if they make any unproven health and therapeutic claims, and to require companies to include a Food and Drug Administration-approved warning on CBD product labels. (New HOD Policy)

Fiscal Note: Minimal - less than $1,000

Received: 07/17/20

RELEVANT AMA POLICY

H-120.926 - Expedited Prescription Cannabidiol Drug Rescheduling
Our AMA will: (1) encourage state controlled substance authorities, boards of pharmacy, and legislative bodies to take the necessary steps including regulation and legislation to reschedule U.S. Food and Drug Administration (FDA)-approved cannabidiol products, or make any other necessary regulatory or legislative change, as expeditiously as possible so that they will be available to patients immediately after approval by the FDA and rescheduling by the U.S. Drug Enforcement Administration; and (2) advocate that an FDA-approved cannabidiol medication should be governed only by the federal and state regulatory provisions that apply to other prescription-only products, such as dispensing through pharmacies, rather than by these various state laws applicable to unapproved cannabis products. Res. 502, A-18

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 502
(November 2020)

Introduced by: Illinois

Subject: Drug Manufacturing Safety

Referred to: Reference Committee E

Whereas, It has recently been revealed in the media as well as written notifications from pharmacies informing the American public that certain medications produced outside but consumed inside the United States have contained carcinogenic substances; and

Whereas, Such tainted medications are widely consumed within the US and include, but are not limited to, Valsartan and Losartan; and

Whereas, Multiple medications are produced overseas and marketed broadly within the US; and

Whereas, Significant budgetary hurdles exist in empowering the U.S. Food and Drug Administration to inspect all foreign drug manufacturers on a frequent and rigorous basis; therefore be it

RESOLVED, That our American Medical Association support efforts to ensure that the U.S. Food and Drug Administration (FDA) resumes safety testing for all drug manufacturing facilities on a frequent and rigorous basis, as done in the past (Directive to Take Action); and be it further

RESOLVED, That our AMA call for the FDA to reaffirm the safety of the manufacture of drugs and the adequacy of volume in the pipeline. (Directive to Take Action)

Fiscal Note: Modest - between $1,000 - $5,000

Received: 07/17/20

The topic of this resolution is currently under study by the Council on Science and Public Health.

RELEVANT AMA POLICY

D-100.983 - Prescription Drug Importation and Patient Safety
Our AMA will: (1) support the legalized importation of prescription drug products by wholesalers and pharmacies only if: (a) all drug products are Food and Drug Administration (FDA)-approved and meet all other FDA regulatory requirements, pursuant to United States laws and regulations; (b) the drug distribution chain is "closed," and all drug products are subject to reliable, "electronic" track and trace technology; and (c) the Congress grants necessary additional authority and resources to the FDA to ensure the authenticity and integrity of prescription drugs that are imported; (2) oppose personal importation of prescription drugs via the Internet until patient safety can be assured; (3) review the recommendations of the forthcoming report of the Department of Health and Human Services (HHS) Task Force on Drug Importation and, as appropriate, revise its position on whether or how patient safety can be assured under legalized drug importation; (4) educate its members regarding the risks and benefits associated with drug importation and reimportation efforts;
(5) support the in-person purchase and importation of Health Canada-approved prescription drugs obtained directly from a licensed Canadian pharmacy when product integrity can be assured, provided such drugs are for personal use and of a limited quantity; (6) advocate for an increase in funding for the US Food and Drug Administration to administer and enforce a program that allows the in-person purchase and importation of prescription drugs from Canada, if the integrity of prescription drug products imported for personal use can be assured; and (7) support the personal importation of prescription drugs only if: (a) patient safety can be assured; (b) product quality, authenticity and integrity can be assured; (c) prescription drug products are subject to reliable, “electronic” track and trace technology; and (d) prescription drug products are obtained directly from a licensed foreign pharmacy, located in a country that has statutory and/or regulatory standards for the approval and sale of prescription drugs that are comparable to the standards in the United States. BOT Rep. 3, I-04 Reaffirmation A-09 Reaffirmed in lieu of: Res. 817, I-16 Appended: CMS Rep. 01, I-18 Appended: Res. 115, A-19

D-100.978 - FDA Drug Safety Policies
Our AMA will monitor and respond, as appropriate, to the implementation of the drug safety provisions of the Food and Drug Administration Amendments Act of 2007 (FDAAA; P.L. 110-85) so that the Food and Drug Administration can more effectively ensure the safety of drug products for our patients. Sub. Res. 505, A-08

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 503
(November 2020)

Introduced by: Illinois

Subject: Federal Initiative to Treat Cannabis Dependence

Referred to: Reference Committee E

Whereas, There is no effective medication for treating dependence on cannabis; and

Whereas, Many states are making cannabis available for recreational purposes; and

Whereas, It is well known the use of cannabis can lead to addiction; and

Whereas, Physicians have no Food and Drug Administration-approved, safe and effective medication to assist in treating cannabis addiction; therefore be it

RESOLVED, That our American Medical Association urge the National Institutes of Health to award appropriate incentive grants to universities, pharmaceutical companies and other capable entities to develop treatment options for cannabis dependence; and that the cost of these grants be financed by taxes on those who profit from selling cannabis. (Directive to Take Action)

Fiscal Note: Modest - between $1,000 - $5,000

Received: 07/17/20

Reference:

Lintzeris, N and associates, Nabiximois for the treatment of cannabis dependence: A randomized clinical trial, JAMA Intern Med, 2019; 179(9):1242-1253

RELEVANT AMA POLICY

H-95.924 - 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; (6) supports public health based strategies, rather than incarceration, in the handling of individuals possessing cannabis for personal use; (7) encourages research on the impact of legalization and decriminalization of cannabis in an effort to promote public health and public safety; (8) encourages dissemination of information on the public health impact of legalization and decriminalization of cannabis; (9) will advocate for stronger public health messaging on the health effects of cannabis and cannabinoid inhalation and ingestion; and (10) will coordinate with other health organizations to develop resources on the impact of cannabis on human health and on methods for counseling and educating patients on the use cannabis and cannabinoids. CSAPH Rep. 05, I-17 Appended: Res. 913, I-19

D-95.969 - 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; (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; (6) will, when necessary and prudent, seek clarification from the United States Justice Department (DOJ) about possible federal prosecution of physicians who participate in a state operated marijuana program for medical use and based on that clarification, ask the DOJ to provide federal guidance to physicians; and (7) encourages hospitals and health systems to: (a) not recommend patient use of non-FDA approved cannabis or cannabis derived products within healthcare facilities until such time as federal laws or regulations permit its use; and (b) educate medical staffs on cannabis use, effects and cannabis withdrawal syndrome. CSAPH Rep. 05, I-17 Appended: Res. 211, A-18 Appended: CSAPH Rep. 3, I-19

H-95.952 - Cannabis and Cannabinoid Research
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 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.
6. Our AMA will advocate for urgent regulatory and legislative changes necessary to fund and perform research related to cannabis and cannabinoids.
7. Our AMA will create a Cannabis Task Force to evaluate and disseminate relevant scientific evidence to health care providers and the public. 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 Modified: CSAPH Rep. 05, I-17 Reaffirmed in lieu of: Res. 434, A-19 Appended: Res. 913, I-19

H-95.923 - 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. CSAPH Rep. 05, I-17

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 504
(November 2020)

Introduced by: Illinois

Subject: Supplemental Resources for Inflight Medical Kit

Referred to: Reference Committee E

Whereas, According to the Bureau of Transportation Statistics, 770 million passengers boarded domestic flights in the United States in the year 2018 and 802 million passengers boarded domestic flights in the US in the year 2019; and

Whereas, Inflight medical emergencies (IMEs) are estimated to occur in approximately 1 in 604 flights, or 24 to 130 IMEs per 1 million passengers; and

Whereas, IMEs are common and occur in constrained areas with limited medical resources; and

Whereas, Inflight medical events are increasingly frequent because a growing number of individuals with pre-existing medical conditions travel by air; and

Whereas, The most common inflight emergency involves syncope or near syncope, which requires measurement of blood pressure and pulse for optimal assessment; and

Whereas, Travelers with diabetes may have altered dietary habits and medication dosing, so are at risk for hyper- or hypoglycemia; and

Whereas, Health care personnel are asked to assist affected passengers and have variable level of training and expertise in evaluating vital signs; and

Whereas, Efforts by health care volunteers are protected by Good Samaritan laws, there is an obligation and opportunity to optimize treatment in these situations; and

Whereas, The minimum requirements for the emergency medical kit do not include automated blood pressure cuff, pulse oximeter or glucose monitors; and

Whereas, The noise level of the airplane makes it difficult to auscultate for blood pressure, with cruising noise levels at around 85 dB but up to 105 dB during takeoff and landing; and

Whereas, Resources include automated external defibrillators, advanced life support injectables including epinephrine, atropine, lidocaine, analgesics, and first aid materials, but do not include pulse oximeters, automated blood pressure cuffs or glucose monitors; and

Whereas, Treatment and support decisions can be optimized with accurate vital signs, oxygen levels and blood sugar levels; and

Whereas, Blood glucose testing equipment is not required in the U.S.; and

Whereas, A pulse oximeter is a lightweight and inexpensive device that can determine heart rate as well as oxygen saturation; and

Whereas, An automated blood pressure cuff is a lightweight, inexpensive device that uses a pressure sensor and not sound to detect intraarterial systolic blood pressure; and

Whereas, A glucose monitor is a lightweight and relatively inexpensive device that can provide an accurate point of care blood sugar level; and

Whereas, A pulse oximeter, an automated blood pressure cuff and a glucose monitor are not among the standard supplies on a domestic U.S. flight; and

Whereas, The costs of these devices is minimal in comparison to the cost of diverting a flight for emergency medical attention due to inadequate evaluation on board; and

Whereas, In the absence of medical personnel during an inflight emergency, a pulse oximeter, automated blood pressure cuff and glucose monitor can be used to determine accurate data that can be shared with on ground medical support team; therefore be it

RESOLVED, That our American Medical Association advocate for U.S. passenger airlines to carry standard pulse oximeters, automated blood pressure cuffs and blood glucose monitoring devices in their emergency medical kits. (Directive to Take Action)

Fiscal Note: Modest - between $1,000 - $5,000

Received: 07/17/20

References:

American Speech-Language-Hearing Association (ASHA). Feb 25, 2014 Durden, Rick Pulse Oximeters: Too Cheap to Ignore. The Aviation Consumer, October 29, 2019
https://www.bts.gov/

Martin-Gill, C, Doyle, TJ Yealy, DM, In Flight Emergencies: A Review. JAMA 2018 Dec 25;320(24):2580-2590. doi: 10.1001/jama.2018.19842.

RELEVANT AMA POLICY

H-45.981- Improvement in US Airlines Aircraft Emergency Kits

1. Our AMA urges federal action to require all US air carriers to report data on in-flight medical emergencies, specific uses of in-flight medical kits and emergency lifesaving devices, and unscheduled diversions due to in-flight medical emergencies; this action should further require the Federal Aviation Administration to work with the airline industry and appropriate medical specialty societies to periodically review data on the incidence and outcomes of in-flight medical emergencies and issue recommendations regarding the contents of in-flight medical kits and the use of emergency lifesaving devices aboard commercial aircraft.
2. Our AMA will: (a) support the addition of naloxone to the airline medical kit; (b) encourage airlines to voluntarily include naloxone in their airline medical kits; and (c) encourage the addition of naloxone to the emergency medical kits of all US airlines (14CFR Appendix A to Part 121 - First Aid Kits and Emergency Medical Kits). Res. 507, A-97 Amended: CSA Rep. 3, I-99 Reaffirmed: CSAPH Rep. 1, A-09 Reaffirmed in lieu of: Res. 502, A-16 Appended: Res. 524, A-18

H-45.979 - Air Travel Safety
Our AMA: (1) encourages the ongoing efforts of the Federal Aviation Administration, the airline industry, the Aerospace Medical Association, the American College of Emergency Physicians, and other appropriate organizations to study and implement regulations and practices to meet the health needs of airline passengers and crews, with particular focus on the medical care and treatment of passengers during in-flight emergencies; (2) encourages physicians to inform themselves and their patients on the potential medical risks of air travel and how these risks can be prevented; and become knowledgeable of medical resources, supplies, and options that are available if asked to render assistance during an in-flight medical emergency; and (3) will support efforts to educate the flying physician public about in-flight medical emergencies (IFMEs) to help them participate more fully and effectively when an IFME occurs, and such educational course will be made available online as a webinar. CSA Rep. 5, I-98 Appended: CSA Rep. 3, I-99 Reaffirmed: CSAPH Rep. 1, A-09 Appended: Res. 718, A-14 Reaffirmation I-14 Reaffirmed in lieu of Res. 503, A-15 Reaffirmed in lieu of: Res. 502, A-16 Reaffirmed in lieu of: Res. 516, A-17 Reaffirmed: BOT Rep. 22, A-18 Reaffirmed: BOT Rep. 30, A-18

H-45.978 - In-flight Medical Emergencies
Our AMA urges: (1) urges that decisions to expand the contents of in-flight emergency medical kits and place emergency lifesaving devices onboard commercial passenger aircraft be based on empirical data and medical consensus; in-flight medical supplies and equipment should be tailored to the size and mission of the aircraft, with careful consideration of flight crew training requirements; and (2) the Federal Aviation Administration to work with appropriate medical specialty societies and the airline industry to develop and implement comprehensive in-flight emergency medical systems that ensure:
(a) rapid 24-hour access to qualified emergency medical personnel on the ground;
(b) at a minimum, voice communication with qualified ground-based emergency personnel;
(c) written protocols, guidelines, algorithms, and procedures for responding to in-flight medical emergencies;
(d) efficient mechanisms for data collection, reporting, and surveillance, including development of a standardized incident report form;
(e) adequate medical supplies and equipment aboard aircraft;
(f) routine flight crew safety training;
(g) periodic assessment of system quality and effectiveness; and
(h) direct supervision by physicians with appropriate training in emergency and aerospace medicine. CSA Rep. 3, I-99 Reaffirmed: CSAPH Rep. 1, A-09 Reaffirmation I-14 Reaffirmed in lieu of: Res. 502, A-16 Reaffirmed in lieu of: Res. 516, A-17

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 505
(November 2020)

Introduced by: Illinois

Subject: Regulation and Control of Self-Service Labs

Referred to: Reference Committee E

Whereas, In recent years the number of laboratories selling self-ordered tests to patients has increased significantly; and

Whereas, Laboratories advertise and promote their business on the Internet, and include companies like HealthOneLabs, Accesa Labs, Private MD Labs, Walk-In--Lab, HNL Lab Tests Direct, and several others; and

Whereas, Most laboratories selling self-ordered tests to patients state that their tests are run with high-quality controls and procedures, and that correct and validated results are emailed to the consumer directly; and

Whereas, Laboratories that sell self-ordered tests directly to patients clearly state that no medical referral is needed, and that their results are validated and reviewed by an “independent network of physicians,” of unspecified qualifications or licensures; and

Whereas, Many patients self-order tests out of fear or ignorance, and end up with results that they are unable to interpret or apply to their individual needs; and

Whereas, Many patients go to their physician with pages of results which they may not have needed in the first place and try to obtain a diagnostic interpretation and/or a therapeutic intervention based on said results, which places the physician at medical and legal jeopardy; therefore be it

RESOLVED, That our American Medical Association study issues with patient-directed self-service testing, including the accreditation and licensing of laboratories that sell self-ordered tests and physician liability related to non-physician-ordered tests. (Directive to Take Action)

Fiscal Note: Modest - between $1,000 - $5,000

Received: 07/17/20

RELEVANT AMA POLICY

H-480.941 - Direct-to-Consumer Laboratory Testing
Our AMA will: (1) advocate for vigilant oversight of direct-to-consumer (DTC) laboratory testing by relevant state and federal agencies; and (2) encourage physicians to educate their patients about the risks and benefits of DTC laboratory tests, as well as the risks associated with interpreting DTC test results without input from a physician or other qualified health care professional. Res. 526, A-18

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 506
(November 2020)

Introduced by: Oklahoma

Subject: Education for Patients on Opiate Replacement Therapy

Referred to: Reference Committee E

Whereas, We are in a time of potentially increased respiratory illness, given the threat of COVID-19 and flu season in the United States; and

Whereas, We are simultaneously in a time of increased use of opiate replacement therapy for the treatment of opiate use disorder and chronic pain; and

Whereas, Anecdotally, a death scenario occurs when patients in their 60s and 70s who are on relatively high dose maintenance opioid replacement therapy, take their usual dose after onset of a respiratory illness; and

Whereas, AMA Policy D-95.987, "Prevention of Opioid Overdose" is to educate physicians and at-risk patients, but it fails to specifically address the needs of older patients who are at risk of death from opiate maintenance therapy when the onset of respiratory illness occurs; therefore be it

RESOLVED, That our American Medical Association amend Policy D-95.987, "Prevention of Opioid Overdose," by addition to read as follows:

1. Our AMA: (A) recognizes the great burden that opioid addiction and prescription drug abuse places on patients and society alike and reaffirms its support for the compassionate treatment of such patients; (B) urges that community-based programs offering naloxone and other opioid overdose prevention services continue to be implemented in order to further develop best practices in this area; and (C) encourages the education of health care workers and opioid users about the use of naloxone in preventing opioid overdose fatalities; and (D) will continue to monitor the progress of such initiatives and respond as appropriate.
2. Our AMA will: (A) advocate for the appropriate education of at-risk patients and their caregivers in the signs and symptoms of opioid overdose; and (B) encourage the continued study and implementation of appropriate treatments and risk mitigation methods for patients at risk for opioid overdose.
3. Our AMA will support the development and implementation of appropriate education programs for persons in recovery from opioid addiction and their friends/families that address how a return to opioid use after a period of abstinence can, due to reduced opioid tolerance, result in overdose and death.
4. Our AMA will implement an education program for patients on opiate replacement therapy and their family/caregivers to increase understanding of their increased risk of death with concurrent opiate maintenance therapy and the onset of a serious respiratory illness such as SARS-CoV-2. (Modify Current HOD Policy)

Reference:
https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2020.20030348

Fiscal Note: Estimate cost of $72,000 to implement resolution.

Received: 08/17/2020

RELEVANT AMA POLICY

Prevention of Opioid Overdose D-95.987
1. Our AMA: (A) recognizes the great burden that opioid addiction and prescription drug abuse places on patients and society alike and reaffirms its support for the compassionate treatment of such patients; (B) urges that community-based programs offering naloxone and other opioid overdose prevention services continue to be implemented in order to further develop best practices in this area; and (C) encourages the education of health care workers and opioid users about the use of naloxone in preventing opioid overdose fatalities; and (D) will continue to monitor the progress of such initiatives and respond as appropriate.
2. Our AMA will: (A) advocate for the appropriate education of at-risk patients and their caregivers in the signs and symptoms of opioid overdose; and (B) encourage the continued study and implementation of appropriate treatments and risk mitigation methods for patients at risk for opioid overdose.
3. Our AMA will support the development and implementation of appropriate education programs for persons in recovery from opioid addiction and their friends/families that address how a return to opioid use after a period of abstinence can, due to reduced opioid tolerance, result in overdose and death.
Citation: Res. 526, A-06; Modified in lieu of Res. 503, A-12; Appended: Res. 909, I-12; Reaffirmed: BOT Rep. 22, A-16; Modified: Res. 511, A-18; Reaffirmed: Res. 235, I-18

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 507
(November 2020)

Introduced by: New York

Subject: Pharmacy Benefit Managers and Drug Shortages

Referred to: Reference Committee E

Whereas, Pharmacy Benefit Managers (PBMs) are poorly regulated entities which act as middlemen between health plans, pharmacies and drug manufacturers; and

Whereas, They have been associated with adverse business practices including opaque operations ‘spread pricing’, and skyrocketing drug costs; and

Whereas, PBM’s play an important part in the pharmaceutical supply chain--sometimes bankrupting pharmacies and making (and breaking) markets for pharmaceutical agents; and

Whereas, Drug manufacturers are legally obligated to report existing or pending drug shortages to the Food and Drug Administration, that requirement extends only to drug supply disruptions, not detailed information on their supply chain, in which PBMs play a key role; and

Whereas, Common retail prescription medications are frequently and chronically ‘backordered’ at a retail pharmacy, but often readily available at the hospital; therefore be it

RESOLVED, That our American Medical Association conduct a study which will investigate the role pharmacy benefit managers play in drug shortages. (Directive to Take Action)

Fiscal Note: Modest - between $1,000 - $5,000

Received: 10/08/20

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 508
(November 2020)

Introduced by: Association for Clinical Oncology, American College of Rheumatology

Subject: Home Infusion of Hazardous Drugs

Referred to: Reference Committee E

Whereas, AMA Policy H-55.986, "Home Chemotherapy and Antibiotic Infusions," was approved by our AMA in 1989 and has been reaffirmed during the 2000, 2010, and 2020 Annual Meetings without amendment; and

Whereas, Advances in infusion biologic drugs, chemotherapies, anti-neoplastics, and immunotherapies have significantly broadened access, variety, and utilization of infused drugs as front-line treatments for a number of diseases including cancers since the drafting of policy H-55.986; and

Whereas, The American Society of Clinical Oncology (ASCO) has a proven history of maintaining continuously updated standards on chemotherapy administration safety and standards for the safe workplace handling of hazardous oncology drugs.[1,2] These standards call for rigorous safeguards to ensure proper practitioner certification, patient education, treatment monitoring, accurate drug preparation/handling/administration, and related health care setting policies to protect both patients and staff when providing infusion therapy services; and

Whereas, The American College of Rheumatology (ACR) has a proven history of maintaining continuously updated guidance on both the complexity of biologic agents, patient access to biologic agents, and patient safety and site of service for infusible biologics.[3,4,5] This guidance emphasizes the highly complex nature of biologic agents particularly with respect to administration and monitoring, and stipulates the need for administration in a monitored healthcare setting with supervision by a provider appropriately trained in biologic administration; and

Whereas, While home infusions may be appropriate for patients in certain disease settings for certain infusion treatments as a result of informed, shared decision making between the physician and patient, they are not generally appropriate for the provision of biologic agents, hazardous drugs or anticancer therapy services in the absence of circumstances where the benefits of doing so outweigh the potential risks; and

Whereas, The Centers for Medicare & Medicaid Services (CMS) finalized a rule in 2019 for a home infusion therapy services benefit, to be implemented beginning in 2021. Additionally, CMS released numerous regulatory flexibilities to assist health care settings coping with the COVID-19 Public Health Emergency (PHE) including new provisions that opened the path for potential increases in use of home infusion for biologic agents and anticancer therapy; and

---

[1] https://www.asco.org/practice-policy/quality-standards/standards/chemotherapy-safety-standards
[2] https://www.asco.org/practice-policy/quality-standards/standards/standards-safe-handling-hazardous-drugs
[3] https://www.rheumatology.org/Portals/0/Files/Complexity%20of%20Biologics.pdf
[4] https://www.rheumatology.org/Portals/0/Files/Patient%20Access%20to%20Biologics%20aka%20Model%20Biologics.pdf
[5] https://www.rheumatology.org/Portals/0/Files/Biologics-Patient-Safety-and-site-of-Service.pdf

Whereas, The decision to administer biologic agents, hazardous drugs and anticancer therapies in a home setting should be made in exceptional circumstances by the treating physician in consultation with the patient, and after consideration of precautions necessary to protect medical staff, patients and caregivers from adverse events associated with drug infusion and disposal. While tradeoffs during a PHE could potentially indicate that access implications outweigh potential risks, these risks are not generally outweighed by the potential benefits of delivering biologic agents, hazardous drugs or anticancer therapy services in a home setting when the PHE is no longer in place; and

Whereas, Our AMA strives to maintain policies that meet with the most up to date standards of care across all medical specialties; therefore be it

RESOLVED, That our American Medical Association update its existing home infusion policy, H-55.986, "Home Chemotherapy and Antibiotic Infusions," by addition and deletion to read as follows:

"Our AMA (1) endorses the use of home injections and/or infusions of FDA approved drugs and group C drugs (including ~~chemotherapy and/or~~ antibiotic therapy) for appropriate patients under physicians' supervision if requested as a result of informed, shared decision making between the physician and patient; ~~and~~ (2) discourages the use of home infusions for biologic agents, immune modulating therapy, and anti-cancer therapy unless emergency circumstances are present where the benefits of doing so outweigh the potential risks; (3) encourages CMS and/or other insurers to provide adequate reimbursement for such treatment; ~~and~~ (4) supports educating legislators and administrators about the risks and benefits ~~of such~~ home infused antibiotics and supportive care treatments in terms of cost saving, increased quality of life and decreased morbidity, and about the need to ~~provide~~ emphasize patient and provider safety when considering emergency at home access to ~~such~~ ~~treatments~~ biologic, immune modulating, and anti-cancer therapy; and (5) advocates for ~~by~~ appropriate reimbursement policies when home infusion services are utilized. (Modify Current HOD Policy); and be it further

RESOLVED, That our AMA oppose extension of the temporary flexibility related to home infusion for Part B drugs, specifically biologics and anti-cancer drugs, that was approved as part of the response to the public health emergency (New HOD Policy); and be it further

RESOLVED, That our AMA oppose any requirement by insurers for home administration of drugs, if in the treating physician's clinical judgment it is not appropriate, or the precautions necessary to protect medical staff, patients and caregivers from adverse events associated with drug infusion and disposal are not in place; this includes withholding of payment for other settings. (New HOD Policy)

Fiscal Note: Minimal - less than $1,000

Received: 10/14/20

RELEVANT AMA POLICY

Home Chemotherapy and Antibiotic Infusions H-55.986
Our AMA (1) endorses the use of home injections and/or infusions of FDA approved drugs and group C drugs (including chemotherapy and/or antibiotic therapy) for appropriate patients under physicians' supervision, and encourages CMS and/or other insurers to provide adequate reimbursement for such treatment; and (2) supports educating legislators and administrators about the benefits of such treatments in terms of cost saving, increased quality of life and decreased morbidity, and about the need to provide access to such treatments by appropriate reimbursement policies.
Citation: Res. 186, I-89; Reaffirmed: Sunset Report and Reaffirmation A-00; Reaffirmed: CSAPH Rep. 1, A-10; Reaffirmed: CSAPH Rep. 01, A-20

Home Infusion Therapies D-210.997
Our AMA will: (1) work with the Centers for Medicare and Medicaid Services to develop a coordinated system among the various Medicare plans to ensure an expedited, seamless process for provision of home infusion therapies to reduce the need of the patient to remain in the hospital unnecessarily; and (2) work with home infusion stakeholders to seek a legislative remedy to Medicare's lack of coverage for the services, supplies and equipment necessary to provide infusions in the home setting.
Citation: Res. 718, A-08; Reaffirmed: CMS Rep. 01, A-18

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 509
(November 2020)

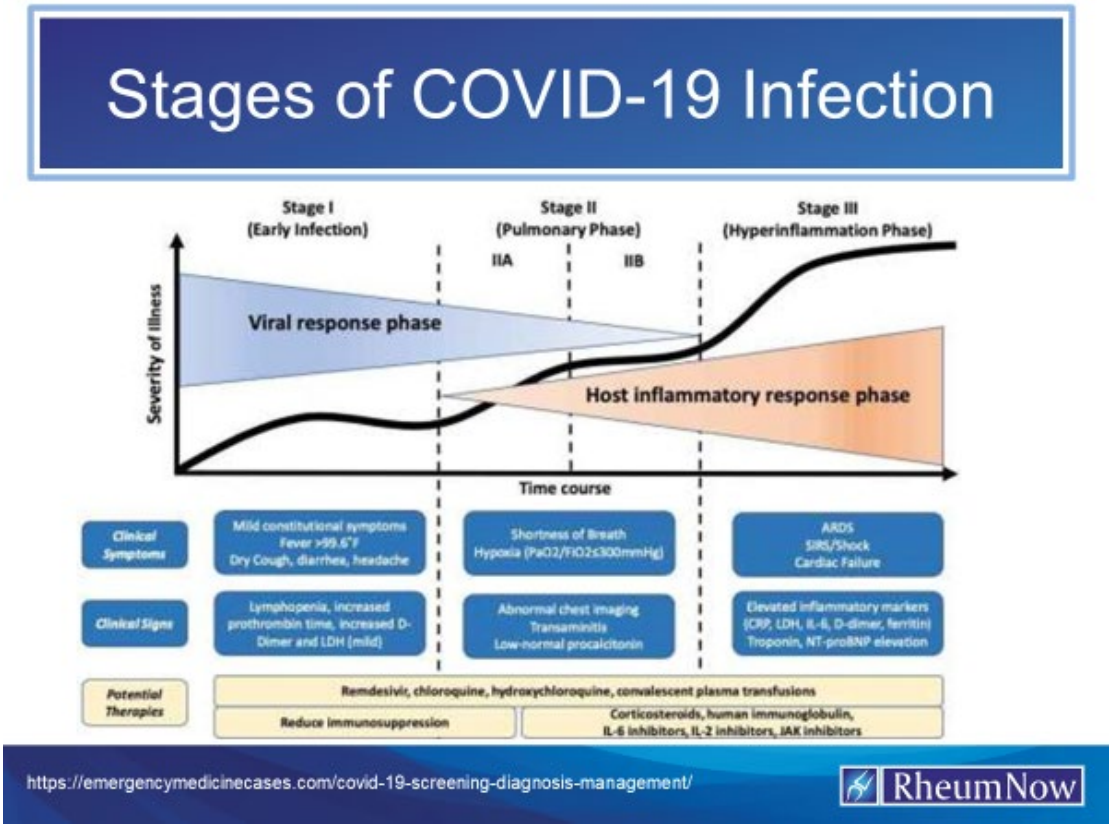
Introduced by: Georgia

Subject: Hydroxychloroquine and Combination Therapies – Off-Label Use

Referred to: Reference Committee E

Whereas, SARS-CoV-2 is the novel coronavirus that causes COVID-19; and

Whereas, Three distinct stages of COVID-19 infection have been observed in some people who test positive for the disease and have variable degrees of symptoms as noted (1); and



Whereas, During the early infection phase (Stage 1), the virus multiplies inside the body and is likely to cause mild symptoms that may be confused with a common cold or flu; and

Whereas, The second phase is the pulmonary phase (Stage 2), when the Immune System becomes strongly affected by infection and leads to primarily respiratory symptoms such as persistent cough, shortness of breath and low oxygen levels. Problems with blood clotting--especially with the formation of blood clots--may be predominant in Stage 2; and

Whereas, The third hyperinflammatory phase (Stage 3), occurs when a hyperactivated immune system may cause injury to the heart, kidneys, and other organs. A "cytokine storm"--where the body attacks its own tissues--may occur in this phase; and

Whereas, There is no current Federal Drug Administration (FDA) indication for the treatment of Early Coronavirus infection, but early emergency use authorization (EUA) originally approved the use of hydroxychloroquine and then rescinded it (2); and

Whereas, The FDA limited use of convalescence plasma but now has rescinded that limitation (3); and

Whereas, Hydroxychloroquine and Chloroquine are FDA approved medications for over 50 years, and these medications are safely prescribed long-term for other indications (2); and

Whereas, AMA President, Patrice A. Harris, MD, issued the following statement: “The AMA is calling for a stop to any inappropriate prescribing and ordering of medications, including chloroquine or hydroxychloroquine, and appealing to physicians and all health care professionals to follow the highest standards of professionalism and ethics” (4); and

Whereas, The AMA, American Pharmacists Association, and American Society of Health System Pharmacists issued a joint statement on March 25, 2020 on inappropriate ordering, prescribing, or dispensing of medications to treat COVID-19 (4); and

Whereas, Some states, pharmacy boards and institutions have forbidden the use of these medications for COVID-19 infection (4, 5); and

Whereas, A proposed regimen to treat COVID-19 for Stage 1, includes 10 days of hydroxychloroquine, Azithromycin, zinc, and on occasion Vitamin D (6); and

Whereas, This regimen is not being advocated for Stage 2 and Stage 3 COVID therapy; and

Whereas, The original studies published in *The Lancet* and T*he New England Journal of Medicine* (NEJM) initially citing harm due to hydroxychloroquine and chloroquine use were retracted by said journals due to dubious research methodology and incorrect conclusions (7, 8, 9); and

Whereas, AMA policy H-120.988, “Patient Access to Treatments Prescribed by Their Physicians,” supports a physician’s autonomy to prescribe medications the physician believes to be in the patient’s best interest, where the benefits outweigh risk and the patient consents; and

Whereas, Physicians have used off label medications for years and this use is supported by existing policy; and

Whereas, Data regarding harm have been limited due to poorly designed studies or studies usually in Stage 2 or later, or stopped without harm but no effect in phase 2 and hypothesis (7, 8, 9, 10, 11, 12); and

Whereas, There are many studies that indicate that the use of Hydroxychloroquine, Azithromycin is effective and front-line physicians are using the therapy where permissible (13, 14, 15); and

Whereas, The COVID-19 pandemic is a serious medical issue, people are dying, and physicians must be able to perform as sagacious prescribers; therefore be it

RESOLVED, That our American Medical Association rescind its statement calling for physicians to stop prescribing hydroxychloroquine and chloroquine until sufficient evidence becomes available to conclusively illustrate that the harm associated with use outweighs benefit early in the disease course. Implying that such treatment is inappropriate contradicts AMA Policy H-120.988, "Patient Access to Treatments Prescribed by Their Physicians," that addresses off label prescriptions as appropriate in the judgement of the prescribing physician (Directive to Take Action); and be it further

RESOLVED, That our AMA rescind its joint statement with the American Pharmacists Association and American Society of Health System Pharmacists, and update it with a joint statement notifying patients that further studies are ongoing to clarify any potential benefit of hydroxychloroquine and combination therapies for the treatment of COVID-19 (Directive to Take Action); and be it further

RESOLVED, That our AMA reassure the patients whose physicians are prescribing hydroxychloroquine and combination therapies for their early-stage COVID-19 diagnosis by issuing an updated statement clarifying our support for a physician's ability to prescribe an FDA-approved medication for off label use, if it is in her/his best clinical judgement, with specific reference to the use of hydroxychloroquine and combination therapies for the treatment of the earliest stage of COVID-19 (Directive to Take Action); and be it further

RESOLVED, That our AMA take the actions necessary to require local pharmacies to fill valid prescriptions that are issued by physicians and consistent with AMA principles articulated in AMA Policy H-120.988, "Patient Access to Treatments Prescribed by Their Physicians," including working with the American Pharmacists Association and American Society of Health System Pharmacists. (Directive to Take Action)

Fiscal Note: Modest - between $1,000 - $5,000

Received: 10/23/20

References:
1. Stages of COVID-19. https://emergencymedicinecases.com/covid-19-screening-diagnosis-management/
2. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and
3. Recommendations for Investigational COVID-19 Convalescent Plasma. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
4. "The A.M.A. is calling for a stop to any inappropriate prescribing and ordering of medications, including chloroquine or hydroxychloroquine, and appealing to physicians and all health care professionals to follow the highest standards of professionalism and ethics," said AMA President Patrice A. Harris, MD.
The American Medical Association, American Pharmacists Association, and American Society of Health System Pharmacists issued a j oint statement on March 25, 2020 on inappropriate ordering, prescribing or dispensing of medications to treat COVID-19. https://www.ama-assn.org/system/files/2020-04/board-of-pharmacy-covid-19-prescribing.pdf
5. Pharmacy Practice New. Rosenthal M. Hydroxychloroquine: Where Pharmacy, Medicine and Politics Intersect, Pharmacy Practice News August 8, 2020
6. Risch H. Opinion: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis Am J Epidemiol. 2020 May 27;kwaa093. doi: 10.1093/aje/kwaa093. Online ahead of print.
7. Piller C, Servick k. Two elite medical journals retract coronavirus papers over data integrity questions. https://www.sciencemag.org/news/2020/06/two-elite-medical-journals-retract-coronavirus-papers-over-data-integrity-questions# June 4, 2020
8. Lancet retraction website https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931180-6
9. NEJM Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.
11. NIH halts clinical trial of hydroxychloroquine https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine

12. Filippo Albani F, Fusina F , Giovannini A et al. Impact of Azithromycin and/or Hydroxychloroquine on Hospital Mortality in COVID-19. J. Clin. Med. 2020, 9, 2800; doi:10.3390/jcm9092800
13. Schwartz RA, Suskind RH DTH-9999-e13785 Azithromycin and COVID-19Prompt Early Use at First Signs of this Infection in Adults and Children an Approach Worthy of Consideration. DTH-999-e13785 doi 10.1111/dth.13785
14. Meo SA, Klonoff DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19 European Review for Medical and Pharmacological Sciences 2020; 24: 4539-4547
15. US 'frontline' doctors' website exposes 'criminal' campaign by tech giants, govt agencies to block COVID med file:///C:/Users/JGoldman/Documents/Corona%20Virus/critique%20of%20HCQ/US%20%E2%80%98frontline%E2%80%99%20doctors%E2%80%99%20website%20exposes%20%E2%80%98criminal%E2%80%99%20campaign%20by%20tech%20giants,%20govt%20agencies%20to%20block%20COVID%20med%20_%20Blogs%20_%20Lifesitenews.html

RELEVANT AMA POLICY

Patient Access to Treatments Prescribed by Their Physicians H-120.988

1. Our AMA confirms its strong support for the autonomous clinical decision-making authority of a physician and that a physician may lawfully use an FDA approved drug product or medical device for an off-label indication when such use is based upon sound scientific evidence or sound medical opinion; and affirms the position that, when the prescription of a drug or use of a device represents safe and effective therapy, third party payers, including Medicare, should consider the intervention as clinically appropriate medical care, irrespective of labeling, should fulfill their obligation to their beneficiaries by covering such therapy, and be required to cover appropriate 'off-label' uses of drugs on their formulary.
2. Our AMA strongly supports the important need for physicians to have access to accurate and unbiased information about off-label uses of drugs and devices, while ensuring that manufacturer-sponsored promotions remain under FDA regulation.
3. Our AMA supports the dissemination of generally available information about off-label uses by manufacturers to physicians. Such information should be independently derived, peer reviewed, scientifically sound, and truthful and not misleading. The information should be provided in its entirety, not be edited or altered by the manufacturer, and be clearly distinguished and not appended to manufacturer-sponsored materials. Such information may comprise journal articles, books, book chapters, or clinical practice guidelines. Books or book chapters should not focus on any particular drug. Dissemination of information by manufacturers to physicians about off-label uses should be accompanied by the approved product labeling and disclosures regarding the lack of FDA approval for such uses, and disclosure of the source of any financial support or author financial conflicts.
4. Physicians have the responsibility to interpret and put into context information received from any source, including pharmaceutical manufacturers, before making clinical decisions (e.g., prescribing a drug for an off-label use).
5. Our AMA strongly supports the addition to FDA-approved labeling those uses of drugs for which safety and efficacy have been demonstrated.
6. Our AMA supports the continued authorization, implementation, and coordination of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.
Citation: (Res. 30, A-88; Reaffirmed: BOT Rep. 53, A-94; Reaffirmed and Modified by CSA Rep. 3, A-97; Reaffirmed and Modified by Res. 528, A-99; Reaffirmed: CMS Rep. 8, A-02; Reaffirmed: CMS Rep. 6, A-03; Modified: Res. 517, A-04; Reaffirmation I-07; Reaffirmed: Res. 819, I-07; Reaffirmation A-09; Reaffirmation I-10; Modified: BOT Rep. 5, I-14; Reaffirmed: Res. 505, A-15)

Long-Term Care Prescribing of Atypical Antipsychotic Medications H-25.989

Our AMA: (1) will collaborate with appropriate national medical specialty societies to create educational tools and programs to promote the broad and appropriate implementation of non-pharmacological techniques to manage behavioral and psychological symptoms of dementia in nursing home residents and the cautious use of medications; (2) supports efforts to provide additional research on other medications and non-drug alternatives to address behavioral problems and other issues with patients with dementia; and (3) opposes the proposed requirement that physicians who prescribe medications with "black box warnings on an off-label basis certify in writing that the drug meets the minimum criteria for coverage and reimbursement by virtue of being listed in at least one of the authorized drug compendia used by Medicare."
Citation: (Res. 819, I-11)

Food and Drug Administration H-100.980
(1) AMA policy states that a strong and adequately funded FDA is essential to ensuring that safe and effective medical products are made available to the American public as efficiently as possible. (2) Our AMA: (a) continue to monitor and respond appropriately to legislation that affects the FDA and to regulations proposed by the FDA; (b) continue to work with the FDA on controversial issues concerning food, drugs, biologics, radioactive tracers and pharmaceuticals, and devices to try to resolve concerns of physicians and to support FDA initiatives of potential benefit to patients and physicians; and (c) continue to affirm its support of an adequate budget for the FDA so as to favor the agency's ability to function efficiently and effectively. (3) Our AMA will continue to monitor and evaluate proposed changes in the FDA and will respond as appropriate.
Citation: Sub. Res. 548, A-92; BOT Rep. 32, A-95; BOT Rep. 18, A-96; Reaffirmed: BOT Rep. 7, I-01; Reaffirmation I-07; Reaffirmed: Sub. Res. 504, A-10; Reaffirmation A-15; Reaffirmed: CMS Rep. 06, I-16; Reaffirmed: CMS Rep. 07, A-18;

FDA H-100.992
1. Our AMA reaffirms its support for the principles that: (a) an FDA decision to approve a new drug, to withdraw a drug's approval, or to change the indications for use of a drug must be based on sound scientific and medical evidence derived from controlled trials, real-world data (RWD) fit for regulatory purpose, and/or postmarket incident reports as provided by statute; (b) this evidence should be evaluated by the FDA, in consultation with its Advisory Committees and expert extramural advisory bodies; and (c) any risk/benefit analysis or relative safety or efficacy judgments should not be grounds for limiting access to or indications for use of a drug unless the weight of the evidence from clinical trials, RWD fit for regulatory purpose, and postmarket reports shows that the drug is unsafe and/or ineffective for its labeled indications.
2. The AMA believes that social and economic concerns and disputes per se should not be permitted to play a significant part in the FDA's decision-making process in the course of FDA devising either general or product specific drug regulation.
3. It is the position of our AMA that the Food and Drug Administration should not permit political considerations or conflicts of interest to overrule scientific evidence in making policy decisions; and our AMA urges the current administration and all future administrations to consider our best and brightest scientists for positions on advisory committees and councils regardless of their political affiliation and voting history.
Citation: Res. 119, A-80; Reaffirmed: CLRPD Rep. B, I-90; Reaffirmed: Sunset Report, I-00; Reaffirmation A-06; Appended: Sub. Res. 509, A-06; Reaffirmation I-07; Reaffirmation I-09; Reaffirmation I-10; Modified: CSAPH Rep. 02, I-18; Modified: CSAPH Rep. 02, I-19;

FDA Intrusion into the Practice of Medicine H-270.977
The AMA strongly opposes the FDA's intrusion into the practice of medicine by making decisions for individual care and mandated informed consent documents written without the input of specialists in the related field of medicine.
Citation: (Res. 544, A-92; Reaffirmed: BOT Rep. 28, A-03; Reaffirmed: CMS Rep. 4, A-13)

Code of Medical Ethics 7.3.10 Expanded Access to Investigational Therapies
Physicians who care for patients with serious, life-threatening illness for whom standard therapies have failed, are unlikely to be effective, or do not exist should determine whether questions about access to investigational therapy through the U.S. Food and Drug Administrations expanded access program are likely to arise in their clinical practice. If so, physicians should familiarize themselves with the program to be better able to engage in shared decision making with patients.
When a patient requests expanded access to an investigational therapy, physicians should:
(a) Assess the patients individual clinical situation to determine whether an investigational therapy would be appropriate, including:
(i) whether there is a satisfactory alternative therapy available to diagnose, monitor, or treat the patients disease or condition;
(ii) the nature of potential risks of the investigational therapy and whether those risks are not unreasonable in the context of the patients disease or condition;

(iii) whether the potential benefit to the patient justifies the risks of the investigational therapy;
(iv) whether the patient meets inclusion criteria for an existing clinical trial of the investigational therapy.
(b) As part of the informed consent process, advise the patient (or parent/guardian if the patient is a minor) that the investigational therapy has not yet been demonstrated to be effective in treating the patients condition and may pose as yet unknown risks. Physicians should explain the importance of clinical trials, encourage patients who meet inclusion criteria to participate in an existing trial rather than seek access to investigational therapy through the FDA expanded access program, and direct patients who wish to participate in research to appropriate resources.
(c) Decline to support an application for expanded access to an investigational therapy when:
(i) the physician judges the treatment with the investigational therapy not to be in the patients best interest, and explain why; or
(ii) the physician does not have appropriate resources and ability to safely supervise the patients care under expanded access.
In such cases, physicians should refer the patient to another physician with whom to discuss possible application for expanded access.
(d) Discuss the implications of expanded access for the patient and family and help them form realistic expectations about what it will mean to be treated with the investigational therapy outside a clinical trial. Physicians should alert patients:
(i) to the possibility of financial or other responsibilities associated with receiving an investigational therapy through expanded access;
(ii) to the lack of infrastructure to systematically monitor and evaluate the effects of the investigational therapy outside a clinical trial;
(iii) that they need information about how to contact the manufacturer for guidance if they seek emergency care from a health care professional who is not affiliated with a clinical trial of the investigational therapy;
(iv) that the physician has a responsibility to collect and share clinical information about the patients course of treatment with the investigational therapy, as well as to report any adverse events that may occur over the course of treatment;
(v) to the conditions under which the physician would recommend stopping treatment with the investigational therapy.
AMA Principles of Medical Ethics: V,VI
The Opinions in this chapter are offered as ethics guidance for physicians and are not intended to establish standards of clinical practice or rules of law.

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 510
(November 2020)

Introduced by: Michigan

Subject: Access to Opioid Agonist Treatment for Incarcerated Persons

Referred to: Reference Committee E

Whereas, An estimated 65 percent of the United States prison population has an active substance use disorder (SUD), and between 24 to 36 percent of persons with opioid use disorder (OUD) pass through U.S. prisons and jails each year; however, only five percent of people with OUD in jail and prison settings receive appropriate medication treatment; and

Whereas, The Centers for Disease Control and Prevention and World Health Organization guidelines recommend any opioid agonist treatment (OAT) during incarceration and upon release from prison; however, only approximately half of all U.S. prisons/jails provide treatment options to incarcerated individuals; and

Whereas, Most correctional institutions mandate withdrawal of any OAT upon entry into the criminal justice system, often preventing individuals from engaging in OAT outside of prison in fear of the abrupt cessation of their treatments; and

Whereas, Within one year of leaving prison, up to 10 percent of those who were formerly incarcerated die, and 15 percent of deaths of former inmates are due to opioid-related overdoses; and

Whereas, A 2013 study in Washington State determined that overdose was the leading cause of death of persons who were formerly incarcerated; and

Whereas, OAT, which includes the full agonist methadone and the partial agonist buprenorphine, is an evidence-based, effective treatment for OUD that lessens the harmful health and societal effects of such substance use disorders; and

Whereas, OAT has been studied within correctional facilities in numerous settings in the U.S. and worldwide and has been shown to decrease re-incarceration rates by 20 percent and reduce the hazard of death by 75 percent following release; and

Whereas, One study found that those in a prison who started OAT were less likely to report using heroin and sharing syringes during their incarceration than those on the waiting list for OAT; and

Whereas, Those who start OAT during incarceration have higher rates of successful re-entry into the community, reduced heroin use, and declining recidivism compared to those who do not; and

Whereas, The American Psychiatric Association (APA) policy states that "Jails and prisons should make available quality treatment for substance use disorders to all inmates who qualify for such treatment" and that whenever possible patients who are treated with medication (buprenorphine or methadone) for their OUD should be continued; and

Whereas, The 2017 Presidential Commission on "Combating Drug Addiction and the Opioid Crisis" recommended increased usage of OAT in corrections settings due to preliminary data suggesting OAT treatment reduces risk of overdose and improves outcomes for those with OUD; and

Whereas, The American Society of Addiction Medicine recommends pharmacotherapy (either methadone or buprenorphine) and psychosocial treatment for those with OUD in the criminal justice system and the initiation of pharmacotherapy a minimum of 30 days before release from prison; and

Whereas, Our AMA has endorsed the use of medication for OUD in prisons, encouraged public funding for such programs, and supported the establishment of post-incarceration programs to continue OUD; therefore be it

RESOLVED, That our American Medical Association amend policy H-430.987, "Opiate Replacement Therapy Programs in Correctional Facilities," by addition to read as follows:

H-430.987 Opiate Replacement Therapy Programs in Correctional Facilities

1. Our AMA endorses: (a) the medical treatment model of employing opiate replacement therapy (ORT) as an effective therapy in treating opiate-addicted persons who are incarcerated; and (b) ORT for opiate-addicted persons who are incarcerated, in collaboration with the National Commission on Correctional Health Care and the American Society of Addiction Medicine.
2. Our AMA advocates for legislation, standards, policies and funding that encourage correctional facilities to increase access to evidence-based treatment of opioid use disorder, including initiation and continuation of opioid replacement therapy in conjunction with counseling, in correctional facilities within the United States and that this apply to all incarcerated individuals including pregnant women.
3. Our AMA supports legislation, standards, policies, and funding that encourage correctional facilities within the United States to work in ongoing collaboration with addiction treatment physician-led teams, case managers, social workers, and pharmacies in the communities where patients, including pregnant women, are released to offer post-incarceration treatment plans for opioid use disorder, including education, medication for addiction treatment and counseling, and medication for preventing overdose deaths and help ensure post-incarceration medical coverage and accessibility to medication assisted therapy.
4. <u>Our AMA encourages all correctional facilities to use a validated screening tool to identify withdrawal and determine potential need for treatment for opioid use disorder for all incarcerated persons upon entry.</u> (Modify Current HOD Policy)

Fiscal Note: Minimal - less than $1,000

Received: 10/27/20

Sources:

1. National Institute on Drug Abuse (NIDA), “DrugFacts: Criminal Justice,” 2019. [Online]. Available: https://www.drugabuse.gov/publications/drugfacts/criminal-justice. [Accessed: 05-Jan-2020].
2. M. S. Gordon, T. W. Kinlock, R. P. Schwartz, and K. E. O’Grady, “A randomized clinical trial of methadone maintenance for prisoners: Findings at 6 months post-release,” Addiction, vol. 103, no. 8, pp. 1333-1342, Aug. 2008, doi: 10.1111/j.1360-0443.2008.002238.x.
3. L. Brinkley-Rubinstein et al., “Criminal justice continuum for opioid users at risk of overdose,” 2018, doi: 10.1016/j.addbeh.2018.02.024.
4. National Academy of Sciences, Engineering, “Medications for Opioid Use Disorder Save Lives,” 2019. [Online]. Available: http://www.nationalacademies.org/hmd/Reports/2019/medications-for-opioid-use-disorder-save-lives.aspx. [Accessed: 05-Jan-2020].
5. Nunn, N. Zaller, S. Dickman, C. Trimbur, A. Nijhawan, and J. D. Rich, “Methadone and buprenorphine prescribing and referral practices in US prison systems: Results from a Nationwide Survey,” Drug Alcohol Depend., vol. 105, no. 1-2, pp. 83-88, Nov. 2009, doi: 10.1016/j.drugalcdep.2009.06.015.
6. J. D. Rich et al., “Methadone continuation versus forced withdrawal on incarceration in a combined US prison and jail: A randomised, open-label trial,” Lancet, vol. 386, no. 9991, pp. 350-359, Jul. 2015, doi: 10.1016/S0140-6736(14)62338-2.
7. J. Hagan and H. Foster, “Imprisonment, opioids and health care reform: The failure to reach a high-risk population,” Prev. Med. (Baltim)., p. 105897, 2019, doi: 10.1016/j.ypmed.2019.105897.
8. D. Fox, J. Maradiaga, L. Weiss, J. Sanchez, J. L. Starrels, and C. O. Cunningham, “Release from incarceration, relapse to opioid use and the potential for buprenorphine maintenance treatment: a qualitative study of the perceptions of former inmates with opioid use disorder,” 2012, doi: 10.1186/s13722-014-0023-0.
9. W. Dick et al., “Growth In Buprenorphine Waivers For Physicians Increased Potential Access To Opioid Agonist Treatment, 2002-11,” Health Aff., vol. 34, no. 6, pp. 1028-1034, Jun. 2015, doi: 10.1377/hlthaff.2014.1205.
10. L. Stotts, C. L. Dodrill, and T. R. Kosten, “Opioid dependence treatment: Options in pharmacotherapy,” Expert Opinion on Pharmacotherapy, vol. 10, no. 11. pp. 1727-1740, Aug-2009, doi: 10.1517/14656560903037168.
11. S. Larney, B. Toson, L. Burns, and K. Dolan, “Effect of prison-based opioid substitution treatment and post-release retention in treatment on risk of re-incarceration,” Addiction, vol. 107, no. 2, pp. 372-380, Feb. 2012, doi: 10.1111/j.1360-0443.2011.03618.x.
12. L. Degenhardt et al., “The impact of opioid substitution therapy on mortality post-release from prison: Retrospective data linkage study,” Addiction, vol. 109, no. 8, pp. 1306-1317, 2014, doi: 10.1111/add.12536.
13. S. E. Wakeman and J. D. Rich, “Addiction Treatment Within U.S. Correctional Facilities: Bridging the Gap between Current Practice and Evidence-Based Care,” J. Addict. Dis., vol. 34, no. 2-3, pp. 220-225, Jul. 2015, doi: 10.1080/10550887.2015.1059217.
14. K. A. Dolan, J. Shearer, M. MacDonald, R. P. Mattick, W. Hall, and A. D. Wodak, “A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system.,” Drug Alcohol Depend., vol. 72, no. 1, pp. 59-65, Oct. 2003, doi: 10.1016/s0376-8716(03)00187-x.
15. Sharma, K. E. O’Grady, S. M. Kelly, J. Gryczynski, S. G. Mitchell, and R. P. Schwartz, “Pharmacotherapy for opioid dependence in jails and prisons: research review update and future directions.,” Subst. Abuse Rehabil., vol. 7, pp. 27-40, 2016, doi: 10.2147/SAR.S81602.
16. M. and K. D. on behalf of the A. C. on A. P. Elie Aoun, MD; John Renner, “Position Statement on Treatment of Substance Use Disorders in the Criminal Justice System,” 2016.
17. American Correctional Association, “Joint Public Correctional Policy On The Treatment Of Opioid Use Disorders For Justice Involved Individuals 2018-2,” 2018.
18. S. Comer et al., “The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use ASAM National Practice Guideline for the Use of Medi-cations in the Treatment of Addiction Involving Opioid Use Guideline,” 2015.

RELEVANT AMA POLICY

Opiate Replacement Therapy Programs in Correctional Facilities H-430.987

1. Our AMA endorses: (a) the medical treatment model of employing opiate replacement therapy (ORT) as an effective therapy in treating opiate-addicted persons who are incarcerated; and (b) ORT for opiate-addicted persons who are incarcerated, in collaboration with the National Commission on Correctional Health Care and the American Society of Addiction Medicine.
2. Our AMA advocates for legislation, standards, policies and funding that encourage correctional facilities to increase access to evidence-based treatment of opioid use disorder, including initiation and continuation of opioid replacement therapy in conjunction with counseling, in correctional facilities within the United States and that this apply to all incarcerated individuals including pregnant women.
3. Our AMA supports legislation, standards, policies, and funding that encourage correctional facilities within the United States to work in ongoing collaboration with addiction treatment physician-led teams, case managers, social workers, and pharmacies in the communities where patients, including pregnant women, are released to offer post-incarceration treatment plans for opioid use disorder, including education, medication for addiction treatment and counseling, and medication for preventing overdose deaths and help ensure post-incarceration medical coverage and accessibility to medication assisted therapy.

Citation: Res. 443, A-05; Reaffirmed: CSAPH Rep. 1, A-15; Appended: Res. 223, I-17