BOX 1-2
***Marijuana and Medicine: Assessing the Science Base* (1999)**
Conclusions and Recommendations

Conclusions:

- At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:
  - Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
  - The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
  - The brain develops tolerance to cannabinoids.
  - Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
  - Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).
- The different cannabinoid receptor types found in the body appear to play different roles in normal human physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.
- Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily tetrahydrocannabinol (THC), for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.
- The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.
- Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease. A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea, and cramping.
- Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

Recommendations:

- Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.
- Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.
- Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.
- Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

- Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than 6 months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.
- Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:
  - failure of all approved medications to provide relief has been documented,
  - the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
  - such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness,
  - and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

SOURCE: IOM, 1999.

The scientific literature on cannabis use has grown substantially since the publication of *Marijuana and Medicine* in 1999. The current committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO and initially retrieved more than 24,000 abstracts for articles published since the 1999 report that could potentially be relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by "anonymous" authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report. (See Appendix B for details.)

The methodological approach taken by the committee to conduct this comprehensive literature review and meet the objectives outlined in the Statement of Task is detailed in Appendix B and briefly described here. Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research that studied one or more of eleven groups of health endpoints (see Figure 1-1 and Box 1-3). For each health endpoint, systematic reviews were identified and assessed for quality using methods adapted from published criteria (Whiting et al., 2016); only reviews that were assessed by the committee as being of good or fair quality were considered in this comprehensive review. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant primary literature that was determined to be fair- and good-quality that was published after the most recent systematic review. Where no systematic review existed, the committee reviewed all relevant primary research from January 1, 1999 through August 1, 2016. Primary research was evaluated using global assessments of the quality of available studies guided by standard approaches and methodologies (Cochrane Quality Assessment [Higgins et al., 2011], Newcastle-Ontario scale [Wells et al., 2014]). Any deviations from this approach are noted in the relevant chapters. For a comprehensive description of the committees approach to evaluating the available literature, please refer to Appendix B.