I. Marijuana use in the USA
   A. Since 1996, voters have approved the medical use of marijuana
   B. These state ballot initiatives, and the wider discussion they spawned about appropriate national policies regulating marijuana, have been sharply divisive
   C. The director of the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to review the evidence for the potential benefits and risks associated with the use of marijuana in 1997
      1. The IOM is a non-governmental, apolitical, non-profit organization of scientists
   D. NIH held a scientific meeting in Feb 1997 to review the scientific data concerning the potential uses of marijuana and the need for and feasibility of additional research
      1. There is remarkable consensus on the potential of cannabinoid drugs for medical use
      2. There is far less convincing data about proven medical benefits
   E. Review of the science behind marijuana and cannabinoids suggests that the often emotional debate so far has been misunderstood

II. The History of marijuana use over time

![Timeline of marijuana use and regulations]
A. The earliest known descriptions of marijuana appear in the ancient writings and folklore of India and China
   a. It continues to be used in China as a folk remedy
B. Marijuana's double nature—"harmful" intoxicant versus beneficial medicine—was debated at least as early as the fifteenth century
C. The first American conference on the clinical use of marijuana physicians reported success in using marijuana to treat a variety of other conditions
D. Pharmaceutical firms attempted to produce consistently potent and reliable drugs from hemp
E. More effective synthetic drugs such as aspirin and barbiturates began replacing herbal remedies
F. Against the advice of the American Medical Association, the U.S. Congress passed the Marijuana Tax Act of 1937, which imposed tough restrictions on marijuana sales and prescription
G. In 1942, marijuana was removed from the United States Pharmacopoeia (USP) on the grounds that it was a harmful and addictive drug
H. Despite its illegality, millions of Americans use marijuana regularly
I. Clinical studies of marijuana are currently difficult to conduct

III. Cannabinoid Science
A. Cannabinoids are produced by resin glands on the female plant's leaves, stems, and calyces
B. More than 60 different but closely related cannabinoids have been isolated from marijuana
C. The chemical structure of most cannabinoids is similar to THC, the main psychoactive ingredient in marijuana
D. Recent studies indicate that cannabinoids produce most of their effects by binding to protein receptors on the surfaces of certain types of cells
E. To date, scientists have identified two main types of cannabinoid receptors (CB₁ & CB₂)
   1. CB₁ receptors are extraordinarily abundant in the brain
   2. CB₂ receptors are relatively scarce in the brain but plentiful in the immune system
F. THC binding to CB₁ & CB₂:
   1. When THC binds to CB₁ receptors in nerve cells, it triggers a cascade of reactions that ultimately slow down nerve impulses
   2. When THC binds CB₂ receptors on white blood cells, it may impede their natural response to infection
G. The largest populations of CB₁ receptors are found in parts of the brain that control movement, memory, response to stress, and complex thought
H. CB₁ receptors are moderately abundant in areas of the brain and spinal cord that control pain perception
I. Cannabinoids also appear to play a role in pain transmission along peripheral nerves, which detect sensations in all parts of the body and relay messages to the brain via the spinal cord
J. In addition to immune suppression caused by cannabinoids, marijuana use poses the additional—and probably greater—risk of immune damage due to smoking
IV. Cannabinoid Consequences:
   A. Although free of nicotine, marijuana smoke pollutes the lungs
      1. Preliminary research also suggests that marijuana smokers’ lung cells contain higher levels of an enzyme that converts PAHs into a cancer-causing form
      2. To date, only one large-scale study has sought to determine the frequency with which marijuana smokers develop cancer
   B. Exposure to cannabinoids can also affect the cardiovascular system
   C. A series of reports involving experimental animals injected with THC indicate that it inhibits several different reproductive functions, from hormone secretion to normal sperm development to embryo implantation
   D. Among the various cognitive domains studied, memory is one of the most frequently identified as being negatively affected by cannabis
   E. In summary, there are many reasons to worry that for people who might choose to use marijuana as medicine—and especially those who smoke it—the drug could actually add to their health problems

V. Use & Abuse:
   A. Even marijuana users who do not fit the DSM-IV criteria for abuse or substance dependence may experience symptoms of tolerance, physical dependence, and withdrawal
      1. Tolerance
      2. Withdrawal
      3. Dependence
         a. For certain patients (particularly adolescents, people with psychological or social problems and those with an inherited predisposition to substance abuse) marijuana-based medications may not be worth the risk
   B. Marijuana has also been shown to affect activities that require a fine balance of attention and muscular coordination, such as driving
   C. Clearly, the evidence that marijuana impairs cognitive and psychomotor performance indicates that medical users will need to limit their activities—much as after taking a strong painkiller or drinking alcohol
      1. No one under the influence of marijuana or THC should drive a vehicle or operate potentially dangerous equipment

VI. Gateway?
   A. Gateway drug
      1. Marijuana is a gateway drug in the sense that its use typically precedes rather than follows initiation into other illicit substances
   B. The “stepping stone” hypothesis
      1. The notion that marijuana possesses pharmacological properties that compel users to experiment with harder drugs

VII. MJ & Glaucoma:
   A. Glaucoma ranks among the most frequently cited reasons for using medical marijuana and is one of the indications for which the federal government once granted permission for compassionate marijuana use
      1. Research findings from as early as the 1970’s show that both marijuana and THC reduce IOP
a. The first such reports generated considerable interest because at the time conventional medications for glaucoma caused a variety of adverse side effects
b. Currently other treatments for the disorder have since eclipsed marijuana-based medicines
c. Several clinical studies have found that synthetic cannabinoids or marijuana reduce IOP as well as do most conventional glaucoma medications
d. In most trials a single dose of marijuana or cannabinoid maintained this effect for three to four hours
e. Researchers have yet to explain how marijuana and cannabinoids reduce IOP
f. The short duration of effect means that marijuana-based medicines must be taken up to eight times a day, which most patients are unlikely to do
g. **This is an important difference because patients need to control IOP continuously due to the progressive nature of glaucoma**
h. So for glaucoma…..
   1. There are far better management regimens now available
      - 3-4 hr efficacy ≠ good daily control
      - Constant intoxication ≠ good citizens
      - Health concerns ≠ good future safety profile
   2. Most states’ ODs can be certified for DEA Schedules 3 narcotic – 5
      - Marijuana is still Schedule 1
References:

5. Sidney S, Quesenberry CP Jr, Friedman GD, Tekawa IS. “Marijuana use and cancer incidence (California, United States).” *Cancer Cause and Control* 8:722-728, 1997