Chapter 15

Marijuana

1. Cannabis: Three Plants

a. Marijuana is a preparation of leafy material from the Cannabis plant that is smoked

i. Marijuana is classified separately because its effects are varied and complex;
   - Sedation, euphoria, altered consciousness
   - Pain relief, antiemetic (relieves nausea), appetite stimulant
   - Hallucinations, paranoia (in large doses)

ii. Effects it produces in most users are sufficiently different from the effects of other drugs such as depressants, narcotics, and hallucinogens to merit a separate classification.
1. Cannabis: Three Plants
   b. Three species
      i. Cannabis sativa
         • Origins in Asia but now grown worldwide
         • Grown primarily for fiber, from which many products, such as hemp rope and clothing are made.
         • Grows as a weed in the U.S. and Canada
           ▪ In nature, a lanky plant up to 18 feet high

   b. Cannabis: Three Species
      ii. Cannabis indica
         • Grown for its psychoactive resins
         • Cultivated in many areas of the world
         • A compact plant 2 to 3 feet high
         • Potency varies depending on plant genetics and environmental conditions
      iii. Cannabis ruderalis
         • Grown primarily in Russia
         • Lower THC content makes it less likely for recreational use

2. Active Ingredient of Cannabis
   a. Primary psychoactive agent in Cannabis is delta-9-tetrahydrocannabinol (THC)
   b. THC is concentrated in the resin, most of which is in the flowering tops (buds)
      ▪ Crystalline structure
      ▪ Less in the leaves
      ▪ Little in the fibrous stalks
   c. Psychoactive potency of Cannabis preparations depends on the amount of resin present.
3. Cannabis Preparations

Traditional preparations correspond roughly to the different parts of the Cannabis plant:

- **a. “Ganja” (Sinsemilla)**
  - From Spanish sin semilla, “without seeds”
  - Consists of dried flowering tops of plants with pistillate flowers (female plants)
  - Male plants are removed from the fields before the female plants are pollinated
    - Female plants don’t put their energy into seed production, thus increasing their potency
  - Average THC content of U.S. sinsemilla samples is about 7 to 12 percent

- **b. “Hashish” (Charas)**
  - Consists of pure resin (oil) that has been carefully removed from the surface of leaves and stems
    - May be less than pure depending on how carefully the resin has been separated from the plant material; one method of high potency is boiling the plant in alcohol and concentrating the oils through evaporation.
  - Rare in the U.S.
  - **Most potent:** Average THC content of U.S. hashish ranges from 3 to 8 percent
    - A few batches have tested as high as 20 percent THC
3. Cannabis Preparations

c. Bhang

i. Consists of the remainder of the Cannabis plant after the top has been picked;

ii. Plant material (mostly leaves) is dried, ground into a powder, and mixed into drinks or candies;

iii. Rare in the U.S., but about equivalent to low-grade marijuana consisting of leaves

iv. Average THC content of less than 1 percent

3. Cannabis Preparations

c. Bhang

d. Smokable marijuana available in the U.S.

i. Potency varies widely
   • Low-grade products (leaf) (less than 1 percent THC)
   • High-grade sinsemilla (bud) (9 percent or more THC)

ii. Typical potency is 2 to 8 percent THC

iii. Proportion of confiscated marijuana samples of higher-potency has increased since the 1980s but is still only about 15 percent
4. History of Marijuana

a. Early History

i. Earliest mention: Chinese pharmacy book (2737 BC)

ii. Social use of the plant had spread to the Muslim world and North Africa by AD 1000
   - "Hashishyya" religious cult carried out political murders
   - Story of cult spread in works by Marco Polo (1299) and Boccaccio (1350s)
     - Origin of the term assassin
   - Hashish use mentioned frequently in The Arabian Nights

b. Early 1900s U.S.: Little public interest or use

i. 1926: Series of newspaper articles linked marijuana and crime
   - Other reports by police and in popular literature followed
   - "Marijuana, Assassin of Youth"

ii. 1936: All states had laws regulating the use, sale, and/or possession of marijuana

iii. Most early regulation efforts non-scientific
   - Based on concerns about use and resultant behavior
   - Not based on direct evidence linking marijuana use with crime or violence

b. Early 1900s U.S., cont.

iv. Contributing factors to “pyramid of prejudice” against marijuana
   - Marijuana use associated with lower-class groups and recent immigrants
   - Regular references made in popular literature to the murdering cult of assassins as suggestive of the characteristics of the drug
     - Shaky factual ground of the stories
     - Individuals in the legends did NOT commit murder under the influence of hashish but rather received hashish as a reward for their actions
4. History of Marijuana

b. Early 1900s U.S., cont.

v. Marijuana Tax Act of 1937

• Act followed the regulation-by-taxation theme of the 1914 Harrison Act
  • Grower, distributor, seller, and buyer were taxed
  • Administratively almost impossible to deal in Cannabis
• Bureau of Narcotics uniform law specifically named *Cannabis sativa*
  • Current federal and uniform laws refer more generally to the genus Cannabis
• State laws made possession and use of *Cannabis* illegal per se
  • “Pot”: 1930s term comes from the Spanish “*potiguaya*”
• 1969: U.S. Supreme Court declared the Marijuana Tax Act unconstitutional

vi. After the Marijuana Tax Act

• Cost of marijuana increased significantly
• Reports continued to be published that marijuana use had less serious effects than commonly believed **BUT:**
  • Substantial disagreement over the interpretation of research findings

  • 1950s and ’60s
  • Little scientific research done on *Cannabis*
  • Use of *Cannabis* continued to increase
  • A common symbol of youthful rejection of authority
  • Identification with a new era of personal freedom

  • Usage rose around 1980, declined until the mid-1990s, and then peaked in the late 1990s, although never reaching the levels of the 1970s.

5: Pharmacology

a. Cannabinoid Chemicals

i. Chemistry of *Cannabis* is complex

• Active agent contains no nitrogen and thus is not an alkaloid like other psychoactive plant materials

ii. “Cannabinoids” are any of the 85 chemicals unique to the *Cannabis* plant

• Delta-9-tetrahydrocannabinol (THC)
  – Isolated and synthesized in 1964
  – The most pharmacologically active cannabinoid

• There may be several other active agents in *Cannabis*, including one shared by chocolate, “anandamide.”
5. Pharmacology:

a. Cannabinoid Chemicals

Delta-9 THC, the most active substance found in Cannabis (left), and anandamide, isolated from brain tissues (right)

b. Modes of Administration

i. Smoked marijuana
- THC is absorbed rapidly by the blood and travels to the brain and then the rest of the body
  - Within 30 minutes, most THC is gone from the brain
- Peak psychological and cardiovascular effects occur together within 5 to 10 minutes

ii. Oral THC
- THC is absorbed more slowly and the liver transforms it into 11-hydroxy-delta-9-THC
  - Less THC reaches the brain
- Peak effects occur about 90 minutes after ingestion

Time course for heart rate after smoking marijuana (left) and ingesting oral THC (right)
5. Pharmacology

c. The Science of Marijuana

i. Metabolites have different half-lives
   - After one week, 25 to 30 percent of the THC and its metabolites might remain in the body
   - Two or three weeks may be required to completely eliminate a large dose of THC and its metabolites

ii. High lipid solubility (think BBB) of THC and its metabolites
   - Selectively taken up and stored in fatty tissue, to be released slowly
   - No easy way to monitor THC and metabolite levels and relate them to effects (i.e. no good "breathalyzer" for pot)

5. Pharmacology

d. Mechanism of Action

i. Anandamide
   - Endogenous substance isolated from brain tissue with marijuana-like effects
   - From ananda, Sanskrit for "bliss"

ii. TH{C}C and other cannabinoids bind to two neurotransmission "Cannabinoid receptors"
   - CB1 receptor
   - CB2 receptor

5. Pharmacology

d. Mechanism of Action, cont.

- CB1 receptor found primarily in the brain but also unusually widespread throughout the body
  - Potential actions of cannabinoids are widespread
  - High density of CB1 receptors in specific brain regions
    - Basal ganglia (movement coordination) – sense of space
    - Cerebellum (fine body movement coordination) – video games?
    - Hippocampus (memory storage) – short-term memory loss
    - Cerebral cortex (higher cognitive functions) – profound revelations
    - Nucleus accumbens (reward) – euphoria

- CB2 receptor found mainly outside the brain in immune cells
  - Potential role of cannabinoids in the modulation of the immune system
5. Pharmacology
d. Mechanism of Action, cont.
  iii. Rimonabant, a selective CB1 receptor antagonist, is being tested
  - Shows promise in reducing food intake (the "anti-munchies") and helping people quit smoking
  - Concerns raised over use of the drug due to concerns about side effects such as depression and anxiety

6. Toxicity
a. Acute Physiological Toxicity
i. Pulmonary effects
  • Bronchodilation is seen following acute exposure to marijuana; no increased risk of lung cancer
ii. Reddening of the eyes
iii. Dryness of the mouth and throat
iv. No human overdose deaths have ever been reported.

v. Cardiovascular effects
  • Increased heart rate occurs after smoking marijuana and ingesting oral THC
    - Time course differs substantially following the two different methods of administration
  • Research findings on the effects of cannabinoids on blood pressure have been mixed
  • Cardiovascular risks of marijuana use haven’t been shown in young, healthy users
    - People with cardiovascular disease should probably avoid marijuana and oral THC due to effects on heart rate
6. Toxicity

b. Chronic Physiological Toxicity
   i. Reproductive effects
      • Reduced testosterone levels in men
      • Diminished sperm counts and abnormal sperm in men
      • A growing number of studies show that marijuana use by pregnant mothers does not appear to be associated with low birth weight or premature birth.
         • The amounts of marijuana used by the women in these studies were relatively low.
   ii. Immune system effects
      • Findings have been mixed
      • Some evidence that marijuana use reduces immunity to infection; others show enhancement of immune system
      • Mortality data do NOT show a relationship between marijuana use and overall death rate

6. Toxicity

c. Acute behavioral toxicity (subjective effects)
   i. Effects include euphoria, “high,” mellowness, hunger, and stimulation
      • Peak effects occur within 5 to 10 minutes and last for about two hours
      • Oral THC has similar effects but a different time course
      • Magnitude of effects is greater with increasing THC concentrations
   ii. Regular marijuana smokers can recognize the effects and distinguish between real and placebo marijuana cigarettes

6. Toxicity

c. Acute behavioral toxicity (subjective effects), cont.
   iii. Infrequent smokers
      • Experience similar but more intense effects compared with experienced smokers due to lower tolerance
      • At high THC concentrations, may report negative effects such as mild paranoia and hallucinations
6. Toxicity

c. Acute behavioral toxicity (subjective effects), cont.

iv. Food intake: Marijuana and oral THC significantly increase total daily calorie intake
   • Clinical use of cannabis-based drugs for appetite stimulation

v. Intensity of focus / short-term memory loss
   • Creative and passion drives are engaged, while ability to maintain focus is compromised

vi. Driving ability: Research findings mixed
   • Laboratory studies of computer-controlled driving simulations
     – Marijuana produces significant impairment
   • Epidemiological studies
     – No evidence of higher accident rates among drivers who use marijuana alone
   • Effects may be more severe in infrequent users

---

6. Toxicity

d. Chronic Behavioral Toxicity

i. Effects on long-term cognitive functioning are more difficult to predict
   • Studies have had divergent findings and interpretations
   • Current evidence suggests that after abstaining for more than a month, regular marijuana use produces few long-term effects on cognition
   • Additional (and better) research may change current thinking
6. Toxicity

d. Chronic Behavioral Toxicity, cont.

ii. Amotivational syndrome

• Concern has been expressed about the effect of regular marijuana use on behavior and motivation.
• Laboratory data do not support the hypothesis that frequent marijuana smokers exhibit diminished motivation.

6. Toxicity
e. Tolerance to many marijuana effects develops after regular use of high levels

• Tolerance may not develop uniformly to all effects
• Marijuana has abuse potential
• A significant minority of current marijuana users may be abusing or dependent on the drug; dependence is psychological only.

6. Toxicity

f. Abuse potential is negligible

i. Dependence is strictly psychological (no withdrawal effect – DSM-IV);

ii. Marijuana cigarettes with higher THC content are preferred;

iii. Oral THC does not have high abuse potential, likely due to its different time course.
• Less rapid onset of effects is usually associated with reduced risk of abuse
6. Toxicity

f. Abuse potential is negligible, cont.

iv. Some research suggests an abstinence syndrome does exist:

• Not very serious
• Symptoms
  • Negative mood states—anxiety, irritability
  • Decreased food intake
• Begins about 1 day after the last dose
• Lasts 4 to 12 days

6. Toxicity

g. Findings from Institute of Medicine report

• Marijuana is a relatively safe and effective medicine for patients suffering from certain chronic conditions
• More research is needed on marijuana and synthetic cannabinoids
• An effective inhaler should be developed to solve the problem of poor oral absorption of THC
• Compassionate use of smoked marijuana cigarettes should be allowed for no more than six months in certain patients with debilitating, intractable pain or vomiting under certain conditions

7. Medical Uses of Cannabis

a. U.S. medical use declined even before the 1937 Marijuana Tax Act

• New drugs were developed to treat most illnesses
• Variability of product (also a problem for research)
• Active ingredient insoluble in water (can’t be injected)
• Oral dose has delayed onset of action

b. 1941: Cannabis dropped from The National Formulary and The U.S. Pharmacopoeia
7. Medical Uses of Cannabis

c. Renewed interest in potential medical uses led to a review of older reports (1975)
   • May be effective as an anticonvulsant in some cases when preferred medication is ineffective
   • May relieve tension and migraine headaches

d. Reduces fluid pressure in the eyes
   • May be useful in glaucoma patients
   • Limited program in which NIDA supplied medical-grade marijuana cigarettes to certain patients on a "compassionate use" protocol

e. Reduces severe nausea (antiemetic) caused by certain drugs used to treat cancer
   • 1985: Oral THC (dronabinol; brand name Marinol) licensed for sale to cancer patients experiencing nausea from chemotherapy
   • 1993: Approved to stimulate appetite in AIDS patients

f. Legal Issues: state and federal action
   i. 1996: Arizona and California ballot initiatives pass
      • Physicians can recommend marijuana
      • Patients can use marijuana if recommended
   ii. Currently, 24 states have some form of similar legislation
7. Medical Uses of Cannabis

f. Legal Action, State and federal action, cont.
   ii. 1996: U.S. government announced plans to prevent medical marijuana use
      • Closure of Cannabis buyers' clubs
      • Revocation of the DEA registration of any physician who advised a patient to use marijuana
      • Prosecution of physicians and patients
   iii. 2005: U.S. Supreme Court ruled that patients could be prosecuted for possessing marijuana even if their physicians recommended its use for a serious illness.
   iv. In 2009, US Attorney General Eric Holder said that the federal government (DEA) would end its raids on state-approved marijuana dispensaries.

8. Marijuana and American Society

a. Marijuana has become the single most important drug issue in the United States.
   • Today 23 states have legalized medical marijuana and others considered this in the elections of 2012

b. In the 1960s and 1970s, there was a shift in attitude about marijuana
   • Marijuana was found to be pretty innocuous
   • Young people found out the government had been lying about drugs and it led to broad rejections of government information.
   • Seniors who smoked marijuana peaked at 60% in the 1970s.
   • Many famous people have “come out”

c. Changing attitudes toward decriminalization
   • 1972 report recommended decriminalizing possession of small amounts for personal use and casual distribution of small amounts without monetary profit
   • Beginning in 1973, several states altered laws
      • Possession of small amounts of marijuana became a civil offense rather than a criminal offense
      • Changing marijuana possession from a felony to a misdemeanor saved money on court costs, juries, and jails
      • Usage rates went up, but not substantially
   d. In 2009, the AMA called upon the Federal government to rethink its classification of marijuana as a Schedule I drug.
8. Marijuana and American Society

e. Changing attitudes toward decriminalization

- There are four factors toward the recent push:
  - Increasing amount of scientific evidence that marijuana is not as toxic as once thought.
  - While the economy in 2007 was crashing, billions of dollars were spent to stop illicit drug use.
  - A growing number of Americans believe the government could tax the growth, transportation and sale of marijuana if it were legal.
  - Reports of violence in Mexico due to the illicit drug trade.