The Pharmacist Activist

Volume 14, No. 10 • October 2019

"For the Lord gives wisdom, and from His mouth come knowledge and understanding." Proverbs 2:6

Editorial

CANNABIS CHAOS

I have always been an advocate for the scientific and evidence-based processes through which drugs are developed, evaluated, approved, and used in the United States, as well as the authority and regulatory roles of the Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA). However, in the case of cannabis, this system has failed us. The Congress, FDA, and DEA have failed to enable/encourage research and appropriate policy initiatives at the national level, and I am not optimistic they will do so any time soon. In many states, citizens and legislators have decided they will no longer wait for research and evidence, or laws and policies from Congress and federal agencies. The result is that 30 states have now legalized cannabis for medicinal use, and 11 states have legalized it for recreational use. The pertinent laws and policies vary widely from state to state, and all are in conflict with federal law. The consequence is chaos!

I had been opposed to the legalization of cannabis by individual states. However, I believe that cannabis and/or individual cannabinoids may be of clinical benefit in the treatment of numerous medical problems, for which there is no or very limited study or documentation because of bureaucratic paralysis in removing barriers and making decisions that will enable progress. Accordingly, I no longer oppose the approval of cannabis for medicinal use by individual states, although I continue to strongly oppose legalization for recreational use. Our society is not even close to effectively dealing with the problems of excessive alcohol and tobacco use, and these challenges would only be exacerbated by another potentially-addictive substance that would be available with few restrictions.

Cannabis facts

Through history, research, and experiences, there is information that qualifies as "facts" with respect to cannabis and related materials. Examples include:

- Cannabis has been used medicinally for thousands of years.
- Cannabis is widely used for both medicinal and recreational purposes in the U.S.
- There is an endocannabinoid system in our bodies and specific cannabinoid receptors have been identified.
- Tetrahydrocannabinol (THC) is the major psychoactive component of cannabis and has a potential for intoxication and addiction.

Contents

- Many cannabis products now contain a much higher percentage of THC than the cannabis products used in the 1970s.
- Dronabinol (Marinol, Syndros) is a synthetic THC that is approved for the treatment of nausea and vomiting associated with cancer chemotherapy, and for the treatment of anorexia associated with weight loss in patients with AIDS. It is classified in Schedule III.
- Nabilone is a synthetic cannabinoid with activity similar to that of THC and is approved for the treatment of nausea and vomiting associated with cancer chemotherapy. It is classified in Schedule II.
- Cannabidiol (CBD) is a component of cannabis that is not psychoactive and does not cause euphoria or intoxication.
- Cannabidiol (Epidiolex) has been demonstrated to be effective for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome, and is the first natural product derived from cannabis to be approved by the FDA. It is classified in Schedule V.
- Adverse events and other risks are associated with the use of CBD (please see the new drug review in this issue).
- In addition to being derived from the Cannabis sativa plant, CBD can also be derived from hemp, a plant in the cannabis family that contains very little THC. Products derived from hemp have variable CBD content, and their effectiveness and safety have not been demonstrated in controlled clinical studies.
- CBD-containing products are widely available as dietary supplements and added to foods, but are not regulated and therapeutic claims can't be made for their use.
- Nabiximols (Sativex) is a standardized cannabis extract that contains a mixture of THC and CBD, but is not approved for use in the U.S.
- Many individuals and organizations support greater availability of cannabis products for reasons motivated by concerns for patients with unmet medical needs.
- Many individuals and organizations support greater availability of cannabis products for reasons motivated by economic and profit opportunities.
- There is an underground market for cannabis products of unknown composition.

Unknowns and uncertainties

Much remains to be learned about the composition of cannabis plants, and the properties, potential uses, benefits, and risks of plant extracts and individual components, as well as the quality and safety of cannabis products. Examples include:

- In addition to THC and CBD, cannabis contains hundreds of other cannabinoids, terpenes, and other components. The activity of these other components is essentially unknown.
- It is not known whether the suggested benefits of cannabis plant products are included within the activity of THC or CBD when used as single cannabinoids. Might a product containing all of the constituents of cannabis have greater benefits than THC or CBD alone or in combination?
- The ratio in which THC and CBD are present in cannabis products influences the resultant activity. Some have suggested that, with certain ratios, CBD may reduce some of the unwanted effects of THC.
- Different parts of the cannabis plant have different components and different activity.
- Growing conditions are a factor with respect to the activity of cannabis products.
- Cannabis plants may have been exposed to pesticides, heavy metals, microorganisms, and other potential contaminants.
- Cannabis products are not regulated, with the one exception of Epidiolex.
- Seemingly similar cannabis products often vary in their composition.
- Standardization of cannabis products is variable.
- The amount of cannabis products that will result in psychoactive effects and impairment has not been determined.

Recommendations

The following recommendations are provided primarily for consideration and implementation at the national level and in states that have not legalized the availability of cannabis for medicinal or recreational use. They may also be of value for states that have legalized cannabis and encountered implementation problems, and wish to voluntarily make changes in their programs. The experiences of

(Continued on Page 4)

New Drug Review

Cannabidiol
(Epidiolex – Greenwich)

Antiepileptic Drug

New Drug Comparison Rating (NDCR) = 5
(important advance)
in a scale of 1 to 5 with 5 being the highest rating

Indications:
Treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome in patients 2 years of age and older.

Comparable drugs:
None.

Advantages:
- Is the first drug to be approved for the treatment of patients with Dravet syndrome;
- Is the first natural product to be derived from marijuana to be approved;
- Is not likely to be associated with dependence and addiction (is classified in Schedule V).

Limitations:
- Causes central nervous system depressant effects in many patients;
- May interact with numerous other medications.

Most important risks/adverse events:
Central nervous system depressant effects (e.g., sedation); suicidal behavior and ideation; hypersensitivity reactions; hepatic adverse events (may cause elevations of liver transaminases [ALT, AST]; serum transaminases and total bilirubin concentrations should be determined prior to starting treatment, at 1, 3, and 6 months after initiation of treatment, and periodically thereafter); pregnancy (studies in animals suggest a risk of adverse developmental effects; patients who are pregnant should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry); dosage should be reduced in patients with moderate or severe hepatic impairment; activity may be increased by the concurrent use of moderate or strong CYP3A4 and/or CYP2C19 inhibitors, and decreased by strong CYP3A4 and/or CYP2C19 inducers (adjustment of dosage should be considered); concurrent use with clobazam (Onfi) may increase activity of both drugs; may increase the activity of phenytoin and diazepam; product labeling should be consulted for additional information regarding interactions.

Most common adverse events:
Somnolence (25%), fatigue/asthenia (12%), lethargy (8%), sedation (6%), decreased appetite (22%), diarrhea (20%), rash (13%), infections (40%), liver transaminase elevations (16%).

Usual dosage:
Exposure is increased 4-fold when it is administered with a high fat/high calorie meal; initially, 2.5 mg/kg twice a day; after one week, dosage can be increased to a maintenance dosage of 5 mg/kg twice a day; may be further increased to a maximum maintenance dosage of 10 mg/kg twice a day, in weekly increments of 2.5 mg/kg twice a day; dosage should be decreased in patients with moderate or severe hepatic impairment; when treatment is to be discontinued, dosage should be reduced gradually to reduce risk of increased seizure frequency.

Products:
Oral solution – 100 mg/mL in bottles containing 100 mL; inactive ingredients include sesame seed oil; any solution remaining 12 weeks after first opening the bottle should be discarded.

Comments:
Dravet syndrome is a rare genetic epileptic disease that appears during the first year of life and is associated with frequent seizures. Lennox-Gastaut syndrome is a rare epileptic disease in which children usually begin having frequent seizures between ages 3 and 5. Cannabidiol (CBD) is a natural component of the Cannabis sativa plant (marijuana) that exhibits anticonvulsant activity. However, unlike tetrahydrocannabinol (THC), the major psychoactive component of marijuana, CBD does not cause euphoria or intoxication. CBD is the first drug to be approved for the treatment of patients with Dravet syndrome, and joins 6 other antiepileptic drugs (clobazam, valproate, lamotrigine, rufinamide, topiramate, felbamate) that have been approved for the treatment of Lennox-Gastaut syndrome. The mechanism through which CBD exerts its anticonvulsant action is not known, but it does not appear to be related to interaction with cannabinoid receptors. Its effectiveness was demonstrated in 14-week placebo-controlled trials in which either CBD or placebo was added to existing treatment (most often clobazam). In patients with Dravet syndrome, the median percent reduction in the frequency of convulsive seizures (39%) was significantly greater than in those receiving placebo (13%). In patients with Lennox-Gastaut syndrome, the median percent reduction in the frequency of drop seizures (43%) was significantly greater than in those receiving placebo (20%). CBD was reclassified by the Drug Enforcement Administration from Schedule I to Schedule V.

Daniel A. Hussar

the states that have legalized cannabis should be reviewed to identify strategies/polices that work well, and also the ones that should be improved or abandoned.

1. Cannabis should be switched from Schedule I (not legally available) to Schedule II. This action will enable much greater availability for use in clinical research studies.

2. Research studies should be conducted to evaluate the benefits and risks of cannabis in the treatment of medical problems for which they have been suggested to be of benefit. Priority should be given to research studies in patients with conditions for which effective treatment options are not available (e.g., autism, chronic fatigue syndrome) and cannabis has been suggested to be of benefit. If pharmaceutical companies do not consider the humanitarian reasons and/or profit incentive to be sufficient to conduct this research, the federal government should conduct the research itself (e.g., National Institutes of Health) or provide funding to appropriate healthcare institutions/universities/organizations to conduct the research. The clinical research program that resulted in the FDA approval of cannabidiol (Epidiolex) can be used as a model.

3. Cannabis products, including hemp-derived CBD products available as dietary supplements, should only be available in pharmacies that have been certified as meeting criteria that will assure the appropriate security, distribution, counseling, and monitoring for these products. As an existing, regulated drug distribution system that is staffed by licensed pharmacists, the use of pharmacies avoids the need for dispensaries and other facilities and an additional regulatory program.

4. The inclusion of cannabis components in food products and cosmetics should be prohibited.

5. The FDA should regulate cannabis-containing dietary supplements to increase the assurance of use of good manufacturing practices and avoidance of therapeutic claims.

6. The health professionals who prescribe and the pharmacists who dispense cannabis products should participate in an educational program regarding the appropriate use of cannabis products as a condition for certification. Almost all currently licensed health professionals have had no, or very little, training regarding cannabis products in their professional degree programs.

7. Instruction regarding cannabis should be included in a required course in the curricula of health professional schools.

8. Criteria should be developed that will assure standardization among similar cannabis products and among batches of a particular product.

9. The minimal concentration of THC in the blood that will result in impairment (e.g., while driving) should be determined, and tests for accurately and quickly analyzing blood THC concentrations should be developed.

10. Penalties for possession of cannabis in an amount consistent with personal use should be reduced or rescinded. Penalties for illegal distribution and use in an amount that results in harm to others, or places others at risk of harm, should be retained but reevaluated.

Could it be that peoples of ancient civilizations better understood how to appropriately use cannabis than we do? We must bring order out of chaos!

Daniel A. Hussar
danandsue3@verizon.net

Author/Editor – Daniel A. Hussar, Ph.D.
Dean Emeritus and Remington Professor Emeritus at
Philadelphia College of Pharmacy, University of the Sciences
Assistant Editor – Suzanne F. Hussar, B.Sc. (Pharmacy)
Publisher - G. Patrick Polli II **Publications Director** - Jeff Zajac

The opinions and recommendations are those of the author and do not necessarily represent those of his former employer or the publisher.

The Pharmacist Activist, 620 Allendale Rd #60884, King of Prussia, PA 19406
610-337-1050 • Fax: 610-337-1049
E-mail: pharmacistactivist@news-line.com

NEWS-Line PUBLISHING