

DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
April 29, 2016

The Executive Formulary Committee convened on Friday, April 29, 2016 in Room 125 - ASH Canteen. The meeting was called to order by Dr. Wright, Chair at 9:44 a.m.

Phillip Balfanz, M.D.	√	Connie Horton, RNP (non-voting)q	Absent
Mary Bowers RN, BSN	Absent	Lilani Muthali, M.D. (non-voting)	√
Catherine Hall, Pharm.D.	√	Nina Muse, M.D. (Acting Medical Director)	√
Jeanna Heidel, Pharm.D.	√	Peggy Perry (non-voting)	Absent
Marla Knight, Pharm.D., CGP, FASCP	√	Scott Schalchlin (non-voting)	Absent
Jeff Matthews, M.D.	√	Lauren Lacefield Lewis (non-voting)	Absent
Mark Messer, D.O.	√	Kerry Raymond (non-voting)	Absent
Connie Millhollon, RN	√	Vacant Center Position	
Kenda Pittman, Pharm.D.	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant DADS Nursing Director (non-voting)	
Archie Smith, M.D.	√	Vacant DADS Physician	
Jennifer Wright, M.D.	√	Vacant DSHS Nursing Director (non-voting)	

Guests Present: Lisa Mican, Pharm.D., Austin State Hospital; Michelle Ding, Pharm.D., Resident ASH; Van Nguyen, Pharm.D., Resident SASH; Ilona Shisko, Pharm.D., Resident SASH

Introduction and Other Information

Ms. Connie Horton has been appointed as the new Nursing Services Coordinator for DADS. Her schedule did not allow her to attend the meeting.

Approval of Minutes of January 29, 2016

On a motion of Ms. Millhollon, seconded by Dr. Heidel, the minutes of the January 29th meeting were approved as previously distributed.

Conflict of Interest

Dr. Knight reported that she attended a luncheon provided by Sunovion. No other members or presenters reported a conflict of interest.

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed one adverse drug reaction report that was received from the field.

On February 1st, a 38 year old male started lamotrigine (Lamictal®) 50 mg BID for intractable seizures. On February 3rd, after 3 doses of lamotrigine, he was noted to have a macular, erythematous rash over his trunk and bilateral upper extremities. The lamotrigine was put on hold until the cause of the rash could be investigated. On February 4th, the rash was noted to be almost completely resolved. No other cause for the rash could be determined so the lamotrigine was discontinued. The Committee noted that the starting dose of lamotrigine was above the normal recommendation. Dr. Knight noted that this was the second person that developed a lamotrigine rash that was started on a high dose.

Dr. Mican noted that Austin State Hospital has developed a titration schedule for lamotrigine that takes into account lamotrigine's use with valproate, inducers and its regular titration. The Committee members expressed interest in reviewing the titration schedule. Dr. Mican will distribute this titration schedule to the Committee members.

Texas Foster Care Guidelines

Dr. Richards noted that the "Psychotropic Medication Utilization Parameters for Children and Youth in Foster Care," fifth version was released in March. In the past, the Committee utilized these guidelines to determine the psychotropic maximum doses for the child and adolescent population. The new guidelines have added more age specific dosing.

Based on these guidelines, it was recommended that the following dosing changes be made to the psychotropic tables in the Formulary

Antipsychotics

- Aripiprazole
 - Child: Add ages 4-11; (Lit)
- Asenapine
 - Child: Change ID to ages 10 to < 12; 20 mg; (Lit)
 - Adolescent: Change ID to 20 mg
- Brexpiprazole
 - Child: Add ID
 - Adolescent: Add ID
- Cariprazine
 - Child: Shade box
 - Adolescent: Shade box
- Clozapine
 - Child: Add ages 8-11
- Haloperidol
 - Child: Change listing to – ages 3-12; Lesser of 0.15 mg/kg or 6 mg; (Lit)

- Adolescent: Change listing to – ages > 12; acute agitation 10 mg; psychosis 15 mg; Tourette 15 mg; (Lit)
- Olanzapine
 - Child: Change listing to – Ages 4-6; 12.5 mg; Ages 6-12; 20 mg; (Lit)
 - Adolescent: Add ages 13-17; Delete (Lit)
- Paliperidone
 - Adolescent: Delete (Lit)
- Perphenazine
 - Adolescent: Add ages >12
- Quetiapine
 - Child: Change (≤ 9 y/o) to (5-9 y/o)
 - Adolescent: Delete (Lit)
- Risperidone
 - Child: Change listing to – 5 to < 12; 3 mg; Delete (Lit)
- Ziprasidone
 - Child: Change listing to – 10-11; 80³ (≤ 45 kg); 160³ (> 45 kg); 40⁴; (Lit)

Antidepressants

- Bupropion (immediate release)
 - Child: Add ages 6 to < 12)
- Citalopram
 - Child: Add ages 6 to < 12)
- Clomipramine
 - Child: Change listing to – 10-11; Lesser of 3 mg/kg or 200 mg (OCD)
 - Adolescent: Change listing to – Lesser of 3 mg/kg or 200 mg (OCD)
- Duloxetine
 - Child: Change listing to - 7 – 12; 120; (Lit)
 - Adolescent: Change listing of 60 to 120
- Escitalopram
 - Child: Add ages 6-11
 - Adolescent: Add ages ≥ 12
- Fluoxetine
 - Child: Add ages 6 to < 12
- Fluvoxamine
 - Child: Add ages 8-11; (OCD)
 - Adolescent: Add ages 12-17 (OCD)
- Imipramine
 - Child: Add ages 6 to < 12
- Mirtazapine
 - Child: Change listing to – 3 to < 12; 45 mg (Lit)
 - Adolescent: Change listing to – 45 mg (Lit)
- Nortriptyline
 - Child: Add ages ≥ 6
- Sertraline
 - Child: Delete (Lit)
- Venlafaxine
 - Child: Add ages 7-11
 - Adolescent: Add ages ≥ 12

Mood Stabilizers

- Carbamazepine
 - Child: Change listing to - < 6; 35 mg/kg; 6 to < 12; 1,000 mg (6-12 mcg/ml)
- Lamotrigine
 - Child: add ages 6 to < 12
- Lithium
 - Therapeutic Serum Concentration: Change Child and Adol listings to – Child & Adol – Max 1.2 mEq/L: (Lit)
 - Child: Change listing to - ≥ 6; #; 1800 mg or (1.2 mEq/L); (Lit)
 - Adolescent: Change listing to - #; 1800 mg or (1.2 mEq/L); (Lit)
- Oxcarbazepine
 - Child: Add ages 7-12
- Valproic acid, valproate, divalproex
 - Child: Change listing to – 6 to < 10; 60 mg/kg; (Lit); ≥ 10; 60 mg/kg; #

Stimulants

- Amphetamine Mixture
 - Child: for immediate release add ages ≥3; for XR add ages ≥ 6
- Dextroamphetamine
 - Child: Change listing to – 3-5; 30 mg; ≥ 6; > 50 kg; 60 mg; (Lit)
 - Adolescent: Change listing to - > 50 kg; 60 mg; (Lit)
- Methylphenidate
 - Child: Add ages ≥ 6 to the immediate release; for Concerta® add ages 6-12

Miscellaneous Drugs Used for Psychotropic Purposes

- Atomoxetine
 - Child: Change listing to - ≥ 6; whichever is less; 1.8 mg/kg or 100 mg; (Lit)
 - Adolescent: Change listing to - whichever is less; 1.8 mg/kg or 100 mg; (Lit)
- Clonidine immediate release
 - Child: Add ages ≥ 6
- Clonidine extended release
 - Child: Add ages ≥ 6
- Guanfacine immediate release
 - Child: Add ages ≥ 6
- Guanfacine extended release
 - Child: Add ages 6-12
 - Adolescent: Change listing to ≥ 13; 7 mg

Hypnotics

- Diphenhydramine
 - Add the following note to listing: “Evidence suggests that tolerance develops to the hypnotic effects within 5-7 nights of continuous use”
- Hydroxyzine
 - Child: Change ages from 3-6 to 3-5

On a motion of Dr. Balfanz, seconded by Dr. Matthews, the recommended changes to the psychotropic maximum dose tables (based on the Foster Care Guidelines) were approved. See Attachment A.

Drug Formulary Sectional Review-

Respiratory Agents

Antihistamine Agents

Antiemetics/Antivertigo Agents

Dr. Hall provided the sectional review on these agents. Ms. Debra Gregg, Assistant Director at San Antonio State Hospital assisted in the review of the drug products.

For the Respiratory section, the following changes were recommended:

Bronchodilators

- Albuterol
 - Add – Powder, inhalation: ProAir Respiclick® 117 mcg/actuation
 - Delete trade name Vospire ER®
 - Delete size: 17 gm
 - Change “chlorofluorocarbon free” to “HFA”
 - Change “Solution, inhalation” to “Nebulization Solution, inhalation”
- Aminophylline
 - Delete all aminophylline products as the rectal suppository and oral tablet have been discontinued and it is unlikely that the injection would be used
- Ipratropium
 - Delete “Inhaler” from trade name
 - Change “18 mcg/actuation” to “17 mcg/actuation”
 - Change “Solution, nebulizing” to “Nebulization Solution, Inhalation”
- Salmeterol
 - Delete Aerosol, inhalation: 25 mcg/dose – no longer available
- Terbutaline
 - Delete trade name “Brethine”
 - Delete Aerosol, oral: 0.2 mg/actuation – no longer available
 - Remove terbutaline from respiratory section
- Theophylline
 - Delete all theophylline products. Any current patients on theophylline can obtain medication via the non-formulary process
- Tiotropium
 - Add Inhaler, aerosol solution Respimat® 1.25 mcg/actuation, 2.5 mcg/actuation

Bronchodilators, Combination/Short Acting

- Albuterol-Ipratropium
 - Delete trade name “DuoNeb” as no longer available
 - Delete Inhaler, oral: Albuterol 103 mcg – Ipratropium 18 mcg
 - Add Combivent Respimat, albuterol 100 mcg – Ipratropium 20 mcg
 - Change “Solution, inhalation” to “Nebulization Solution, inhalation”

Bronchodilators, Combination Steroid + Long Acting Beta-2 Agonists

- Fluticasone – salmeterol
 - Add Aerosol, inhalation; fluticasone 45 mcg – salmeterol 21 mcg; fluticasone 115 mcg – salmeterol 21 mcg; fluticasone 230 mcg – salmeterol 21 mcg

Steroids

- General changes
 - Change this section name to “Inhaled Corticosteroids”
- Beclomethasone

- Delete trade name “Beconase” as no longer available
- Budesonide
 - Add Powder, inhalation Flexhaler: 90 mcg/actuation; 180 mcg/actuation
 - Change Solution, inhalation to Suspension, inhalation
- Fluticasone
 - Add Powder, inhalation Diskus: 50 mcg/actuation; 100 mcg/actuation; 250 mcg/actuation
- Fluticasone – salmeterol
 - Also listed in the Bronchodilators, Combination Steroid + Long Acting Beta-2 Agonists section
 - Add Aerosol, inhalation; fluticasone 45 mcg – salmeterol 21 mcg; fluticasone 115 mcg – salmeterol 21 mcg; fluticasone 230 mcg – salmeterol 21 mcg
- Mometasone
 - Move to nasal section
- Triamcinolone
 - Delete Aerosol, oral, inhalation: 100 mcg/metered spray as no longer available
 - Move to nasal section
 - Delete size

Miscellaneous Respiratory Drugs

- Acetylcysteine
 - Delete trade name “Mucomyst”
- Cromolyn
 - Delete trade name “Intal”
- Zafirlukast
 - Delete trade name “Accolate”

Cough, Cold and Decongestant Preparations

- Benzonatate
 - Delete trade name “Tessalon “Perle”
- Brompheniramine
 - Change trade name to “Dimetapp Children’s Cold and Allergy”
- Brompheniramine – pseudoephedrine
 - Delete trade name “Bromfed”
 - Delete Capsule; Brompheniramine 12 mg – pseudoephedrine 120 mg as no longer available
 - Delete Elixir; Brompheniramine 4 mg – pseudoephedrine 30 mg as no longer available
 - Delete Liquid; Brompheniramine 12 mg – pseudoephedrine 1 mg per 5 ml as no longer available
 - Delete Syrup; Brompheniramine 2 mg – pseudoephedrine 30 mg as no longer available
 - Delete Tablet, sustained release; Brompheniramine 8 mg – pseudoephedrine 120 mg as no longer available
- Cetirizine
 - Add to this section
- Chlorpheniramine
 - Delete trade names “Chlor-Trimeton” and “Teldrin”
 - Delete Capsule: 12 mg as no longer available
 - Delete Tablet: 8 mg; 12 mg as no longer available
 - Delete Tablet, chewable: 2 mg as no longer available
 - Delete Tablet, timed release: 8 mg as no longer available
- Dextromethorphan
 - List only dosage forms. Consider all strengths for dosage forms listed as being on Formulary

- Consider any combination of drugs with dextromethorphan as being on Formulary as long as the individual ingredients are on the Formulary and the dosage form is listed as being on Formulary
- Diphenhydramine
 - Delete Tablet: 50 mg as no longer available
- Fexofenadine/Pseudoephedrine
 - Add Tablet, extended release 24 hr: fexofenadine 180 mg – pseudoephedrine 240 mg
- Guaifenesin-Codeine
 - Delete trade name “Robitussin AC”
- Guaifenesin-Dextromethorphan
 - Delete trade name “Robitussin DM”
 - List only dosage forms. Consider all strengths for dosage forms listed as being on Formulary
 - Consider any combination of drugs with dextromethorphan as being on Formulary as long as the individual ingredients are on the Formulary and the dosage form is listed as being on Formulary
- Hydrocodone-Guaifenesin
 - Delete trade names “Hycotuss” and “Kwelcof”
 - Change dosage strength to hydrocodone 2.5 mg-guaifenesin 200 mg per 5 ml
- Phenylephrine
 - Move to nasal section
 - Delete Solution, nasal, drops: 0.25%; 0.5%
- Pseudoephedrine
 - Change Liquid, oral concentration to 15 mg/5 ml; 30 mg/5 ml
 - Delete tablet, timed release: 120 mg as not available
 - Delete tablet, extended release: 240 mg as not available
- Triprolidine-Pseudoephedrine
 - Change trade name to “Aprodine”
 - Delete capsule, extended release: triprolidine 5 mg – pseudoephedrine 120 mg as not available
 - Delete syrup: triprolidine 1.25 mg – pseudoephedrine 30 mg per 10 ml as not available

Expectorants

- Guaifenesin
 - Delete Caplet, sustained release: 600 mg as no longer available
 - Delete Liquid, oral: 200 mg/5 ml as no longer available
 - Delete Tablet: 100 mg as no longer available
- Potassium Iodide
 - Delete Solution, oral: 100 mg/ml as no longer available

Antihistamines

- Cetirizine
 - Delete Tablet, chew: 5 mg, 10 mg
- Chlorpheniramine
 - Delete trade names “Chlor-Trimeton” and “Teldrin”
 - Delete Capsule: 12 mg as no longer available
 - Delete Tablet: 8 mg; 12 mg as no longer available
 - Delete Tablet, chewable: 2 mg as no longer available
 - Delete Tablet, timed release: 8 mg as no longer available
- Diphenhydramine
 - Delete Tablet: 50 mg as no longer available
- Hydroxyzine

- Delete Suspension: 25 mg/5 ml as not available from wholesaler
- Delete Tablet: 100 mg

In reviewing this section, Dr. Hall recommended that levalbuterol (Xopenex®, Xopenex HFA®) be added to Formulary.

Levalbuterol is an inhaled beta₂-adrenergic agonist. Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic AMP. This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. Levalbuterol is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease. Levalbuterol continues to be a highly used nonformulary agent. See Attachment B.

On a motion of Dr. Pittman, seconded by Dr. Smith, the request to add levalbuterol (Xopenex®) to the Formulary was approved.

In reviewing the Respiratory Section, Dr. Hall suggested the following reorganization of this section:

- Delete all bronchodilators subsections
 - Create subsections based on mechanisms of action
- Create “Beta₂ Agonists” subsection
 - Create the following:
 - Short-acting: levalbuterol, albuterol
 - Long-acting: salmeterol
- Create “Anticholinergics” subsection
 - Create the following:
 - Short-acting: ipratropium
 - Long-acting: tiotropium
- Create “Combination Short-acting Beta₂ Agonist plus Anticholinergic” subsection
 - Add albuterol/ipratropium
- Create “Inhaled Corticosteroids” subsection
 - Add the following:
 - Beclomethasone
 - Budesonide
 - Fluticasone
- Create “Combination Long-acting Beta₂ Agonist plus Corticosteroid” subsection
 - Add the following
 - Budesonide-formoterol
 - Fluticasone-salmeterol
- “Miscellaneous Respiratory Drugs” subsection
 - No changes
- Change “Cough, Cold and Decongestant Preparations” to “Antihistamine, Cough and Decongestant Preparations”
- Delete the “Antihistamine” section
 - Move oral Antihistamine products to the “Antihistamine, Cough and Decongestant Preparations”

- “Expectorants”
 - No changes

During the review, all aminophylline and theophylline products were deleted from the Formulary.

On a motion by Dr. Heidel, seconded by Dr. Wright, the recommended changes to the Respiratory Agents sections were approved.

As part of the review for the Respiratory Agents, it was decided to move the oral antihistamines to the renamed section for “Antihistamine, Cough and Decongestant Preparations” and the nasal antihistamines to the Nasal section under Topical Agents.

Dr. Hall provided a review of the Antiemetics/Antivertigo Agents. The following recommendations were made based on this review:

- Diphenhydramine
 - Delete Tablet: 50 mg as no longer available
- Meclizine
 - Delete Tablet: 50 mg as no longer available
- Prochlorperazine
 - Delete Tablet: 25 mg as no longer available
- Trimethobenzamide
 - Delete Capsule: 250 mg as no longer available
 - Delete Suppository, rectal: 200 mg as no longer available

On a motion by Dr. Heidel, seconded by Dr. Wright, the recommended changes to the Antiemetics/Antivertigo Agents sections were approved.

Issues from the Medical Executive Committee

Dr. Muse attended the meeting briefly to indicate that the Medical Executive Committee did not have any issues for this Committee.

Medical Director for Behavioral Health

Dr. Muse briefly attended the meeting but did not have any issues to report.

Anti-Androgen Therapy for Aggression

Dr. Nguyen presented an overview on the use of anti-androgen therapy for aggression and the summary of evidence found in the literature regarding this treatment. Currently, the use of anti-androgens for the treatment of aggression, sexual or otherwise falls under the “Guidelines on Anti-Androgen Therapy for Aggression in State Mental Health Hospitals.” This therapy is considered a treatment of last resort and is restricted to those patients who have failed to respond to appropriate courses of pharmacological as well as non-pharmacological treatment of their aggression based upon the current scientific literature.

Several agents have been utilized to reduce testosterone and sexual drive in those with paraphilia or sexually abusive behaviors. These agents include, but are not limited to:

- Androgen receptor antagonists – block the effects of androgens at their receptor sites
 - Flutamide (Eulexin®)
 - Nilutamide (Nilandron®)
 - Bicalutamide (Casodex®)
 - Enzalutamide (Xtandi®)
 - Cyproterone (not available in the U.S.)
- Gonadotropin-releasing hormone analogues – causes GnRH release and a “hormonal surge” leading to feedback downregulation of androgens
 - Goserelin (Zoladex®)
 - Leuprolide (Lupron®)
- Progesterones – synthetic progesterone prevents the hypothalamus from releasing GnRh and the pituitary from releasing LH and FSH
 - Medroxyprogesterone (Provera®, Depo-Provera®)

Dr. Nguyen reported that a 2015 Cochrane Review evaluated the effects of pharmacological interventions of those who had been convicted or were at risk of a sexual offense.

- Seven studies were identified, totaling 138 patients. All male.
- All studies over 20 years old and authors deemed the overall quality of evidence as “poor.” Last completed study was reported in 1988.
- Majority of subjects had a previous sexual conviction, including exhibitionism, rape and child molestation
- Six studies examined the effectiveness of three testosterone-suppressing drugs: cyproterone acetate (not available in the U.S.), ethinyl estradiol, and medroxyprogesterone acetate, while the other studied antipsychotics (benperidol – not available in U.S. and chlorpromazine) as anti-libido treatments.
- A meta-analysis couldn’t be performed due to heterogeneity of interventions, comparators, study designs, and other issues
- Authors of the Cochrane review concluded that “while there are a number of serious ethical challenges in conducting trials in his area, the fact remains that the evidence in support of any pharmacological intervention for those who sexually offend is very limited.”

Dr. Nguyen noted that there have been a couple of pilot studies reported in the literature. Both studies were completed in patients with some form of dementia. Clinical cases have been reported in the literature. Five cases (three articles) involved patients with some form of dementia and four cases were reported for patients without dementia.

Based on this review, Dr. Muse noted that since there isn’t any current information in the literature regarding the use of anti-androgens that the concept of the “Guidelines on Anti-Androgen Therapy for Aggression in State Mental Health Hospitals” would probably remain unchanged. Other issues for consideration when reviewing and implementing this guideline are:

- Use of appropriate rating scales
- Checking bone density
- Time off medication
- Identification of lab parameters that should be monitored with use of these agents

The Committee discussed the possibility of identifying patients on these medications for the treatment of aggression.

Hepatitis C Treatment Costs

Dr. Richards presented a summary of drug costs for the treatment of Hepatitis C. Costs vary depending on genotype, illness characteristics, need for adjunct drug treatment and length of treatment. In addition, some of the drug manufacturers have special pricing through our group purchasing organization. Based on all of these factors, it appears that Harvoni® offers the facilities the best cost options. Gilead Sciences, Inc. (manufacturer of Harvoni® and Sovaldi®) offers special pricing. By signing Gilead's Declaration Form, the Pharmacy agrees to forgo all other discounts or reimbursement claims for the same products, including any third party public or private payer reimbursement other than inpatient mental health facilities that receive reimbursement from a third party public or private payer for Product based on a per-patient per diem payment rate. Facilities signing this Declaration Form, cannot bill Medicare Part D for reimbursement for this drug. With the loss of Medicare Part D coverage for the forensic patients, the number of patients at the State Hospitals qualifying for Medicare Part D coverage has declined. Since the majority of individuals at the State Supported Living Centers have Medicare Part D coverage, it was noted that their consumers could have their Hepatitis C Drug Treatment billed through Medicare Part D either through the facility's pharmacy or a local pharmacy.

On a motion of Dr. Matthews, seconded by Dr. Heidel, it was recommended that the State Hospitals sign Gilead's Declaration Form. Dr. Muse suggested that the submission of the Declaration Forms be monitored in order to insure compliance with the recommendation.

Dr. Muse stated that a request for additional funding to cover state hospital patients' drug treatment for Hepatitis C will be made to the legislature as an exceptional item.

Vitamin D Deficiency

The Regional Clinical Laboratory at the Austin State Hospital uses the following ranges for vitamin D in the adult population:

Deficient	< 20 ng/ml
Insufficient	20-29 ng/ml
Sufficient	30-100 ng/ml

There is no consensus on what defines an 'adequate' vitamin D levels or toxic vitamin D level. However, many different organizations support similar ranges.

Drug Deletion

The Committee did not receive any feedback from field regarding the deletion of the following:

- Phytonadione injection
- Vitamin A: 50,000 units (not available)
- Vitamin A injection
- Vitamin E tablets: 200 units, 400 units, 2,000 units (not available)
- Potassium phosphate powder for oral solution: 250 mg elemental phosphate/14.2 mEq potassium per packet (not available)

On a motion of Ms. Millhollon, seconded by Dr. Heidel, the products were deleted from the Formulary.

New Dosage Strengths

It was recommended to add the following dosage forms to the Formulary as other products of these drugs are on Formulary:

- Fluoxetine (Prozac®) 40 mg
- Humalog® Mix 50/50
- Hydrocodone/acetaminophen 7.5/325 mg tablet
- Ketoconazole shampoo 1%
- Pramoxine foam 1%
- Triamcinolone paste 1%
- Ciclopirox cream 0.77%

On a motion of Dr. Smith, seconded by Ms. Millhollon the recommendation to add these products was approved.

Psychotropic Audit Criteria & Guidelines - Antidepressants

The Antidepressant Audit Criteria and Guidelines have not been reviewed.

Psychotropic Audit Criteria & Guidelines – Chemical Dependence Adjunct

The Chemical Dependence Adjunct Audit Criteria and Guidelines have not been developed.

Cannabis Oil for Seizures

Dr. Ding presented a review of cannabidiol in the treatment of intractable epilepsy. The Texas Compassionate Use Act (Senate Bill 399) became effective on June 1, 2015. The Act requires the Texas Department of Public Safety (DPS) to regulate the medical use of low-THC cannabis. DPS is required to create a registry of physicians who treat epilepsy and of patients who have been diagnosed with intractable epilepsy. To prescribe low-THC cannabis, a physician must be certified by the American Board of Psychiatry and Neurology in epilepsy, neurology (or child neurology) or neurophysiology. The prescriber must dedicate a significant portion of clinical practice to the evaluation and treatment of epilepsy. DPS will license dispensing organizations, which will authorize the organizations to cultivate, process, and dispense low-THC cannabis to prescribed patients. DPS will begin licensing dispensing organizations starting June 2017 with the goal of licensing at least three organizations by September 1, 2017. See Attachment C.

The compassionate-use registry will record physician and patient information, dosage prescribed, means of administration, total amount of low-THC cannabis required to fill the prescription, and a record of each amount of low-THC cannabis dispensed by a dispensing organization to a patient under a prescription. The registry will be designed to prevent more than one physician from registering as the prescriber for a single patient, is accessible to law enforcement agencies and dispensing organizations for the purpose of verifying whether a patient was prescribed low-THC cannabis and whether the patient's prescription has been filled.

Currently, there is a lack of well-designed, prospective, randomized, placebo-controlled trials that evaluate the use of cannabinoids in patients with intractable epilepsy. Published literature mainly consists of case reports and surveys/questionnaires of parents whose children have intractable epilepsy. The

passing of this Act, will allow the legal use of medical low-THC cannabis for the treatment of intractable epilepsy as of September 1, 2017.

CDC Guideline for Prescribing Opioids for Chronic Pain

The “CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016” was published in March 2016. These recommendations are for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses:

- When to initiate or continue opioids for chronic pain
- Opioid selection, dosage, duration, follow-up, and discontinuation
- Assessing risk and addressing harms of opioid use

These recommendations are listed in the attached “Box 1. CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care.” See Attachment D. The sixth recommendation notes:

“Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.”

The Committee noted that clinicians starting patients on opioids for acute and chronic pain should consider these recommendations when doing so.

Metabolic Syndrome – Children/Adolescent+

At a previous meeting, the Committee recommended adding waist circumference to BMI monitoring requirement for antipsychotics. A question arose regarding metabolic syndrome in children and adolescents. Dr. Shishko provided a review of metabolic syndrome in children and adolescents.

Dr. Shishko noted that there is a greater incidence of metabolic syndrome with the second generation antipsychotics (SGA) than first generation antipsychotics (FGA). The following are characteristics associated with the use of antipsychotics:

- Weight gain
 - FGA: least common with haloperidol & loxapine
 - SGA: clozapine = olanzapine \geq quetiapine > risperidone = paliperidone > iloperidone > lurasidone = asenapine = ziprasidone = aripiprazole = cariprazine = brexpiprazole
- Hyperlipidemia
 - SGA: clozapine = olanzapine > quetiapine > iloperidone \geq asenapine \geq risperidone = paliperidone > ziprasidone = aripiprazole = lurasidone = cariprazine = brexpiprazole
- Hyperglycemia
 - FGA: most common: chlorpromazine
 - SGA: clozapine = olanzapine \geq quetiapine = risperidone = paliperidone > ziprasidone = aripiprazole = iloperidone = asenapine = lurasidone = cariprazine = brexpiprazole

Significant weight gain is defined differently by various organizations. The American Diabetes

Association (ADA) and American Psychiatric Association (APA) state that weight gain $\geq 5\%$ is significant. The Food and Drug Administration (FDA) defines significant weight gain as $\geq 7\%$.

Assessing metabolic syndrome in adolescents can be challenging. The adult definition of metabolic syndrome isn't applicable to children as blood pressure, lipid levels, and weight vary with age and puberty. Waist circumference is an independent predictor of all components of metabolic syndrome (insulin resistance, hyperlipidemia, and hypertension).

The ADA and APA recommend the following for metabolic monitoring:

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family History	X					X	
Weight/BMI	X	X	X	X	X		
Waist Circumference	X			X		X	
Blood Pressure	X			X		X	
A1c/Fasting Glucose	X			X		X	
Fasting Lipids	X			X			X

The 2007 International Diabetes Federation (IDF) recommends the following guidelines for diagnosing metabolic syndrome in children and adolescents:

Age Group (years old)	Diagnosis (dx)	Obesity (WC)	Triglycerides (TG)	Low high density lipoprotein (HDL-C)	Blood Pressure (BP)	Glucose
< 10	Unable to dx; but, strongly recommend weight reduction	$\geq 90^{\text{th}}$ percentile				
10-16	May diagnose with the following criteria 1) Abdominal obesity and 2) ≥ 2 other components (\uparrow TG, \downarrow HDL, \uparrow BP, \uparrow glucose)	$\geq 90^{\text{th}}$ percentile or adult cut-off if lower	≥ 150 mg/dl	< 40 mg/dl	≥ 130 mmHg systolic (SBP) or ≥ 85 mmHg diastolic (DBP)	≥ 100 mg/dl or known T2DM
≥ 16	Use adult criteria	Male: ≥ 94 cm Female: ≥ 80 cm	≥ 150 mg/dl	Male: < 40 mg/dl Female: < 50 mg/dl	≥ 130 mmHg SBP or ≥ 85 mmHg DBP	≥ 100 mg/dl or known T2DM

The following are recommendations regarding metabolic syndrome in children and adolescents:

- Monitor antipsychotics as recommended per ADA/APA guidelines plus height at each visit, may consider sooner follow up (every six months) on lipids/glucose/A1c if BMI > 85th percentile.
- ≥ 5% increase in body weight over a short period of time: consider alternative therapy and monitor more closely
- Assess obesity by:
 - Waist circumference: ≥ 90th percentile for age, sex, and race is significant
 - BMI: ≥85th percentile for age, sex, and height
- Diagnose hypertension: > 90th percentile for age
- Diagnose hyperlipidemia per National Heart, Lung, and Blood Institute and IDF guidelines:
 - LDL ≥ 130 mg/dl
 - TG ≥ 100 mg/dl (0-9 years old), ≥ 130 mg/dl (≥ 10 years old)
 - HDL < 40 mg/dl
- Diagnose DM per 2015 ADA guidelines

On a motion of Dr. Messer, seconded by Dr. Smith, the recommendations were approved.

New Drug Applications

The Committee did not receive any requests for addition of drugs to the Formulary.

FDA Drug Safety Communications

The FDA has issued the following safety communications that may have impact on our facilities.

The FDA is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. The FDA is requiring changes to the labels of all opioid drugs to warn about these risks.

The following are the risks that were identified:

- **Opioids can interact with antidepressants and migraine medicines** to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity. Cases of serotonin syndrome in the FDA Adverse Event Reporting System (FAERS) database were reported more frequently with the opioids fentanyl and methadone used at the recommended doses. Therefore, FDA is requiring a new statement in the Warnings and Precautions section to be added to these drug labels. Some opioids, including tramadol, tapentadol, and meperidine, already have warnings about serotonin syndrome. Cases were also reported with other opioids, so the labels of all these drugs will be updated to include information about serotonin syndrome in the Drug Interactions and Adverse Reactions sections. Patients taking an opioid along with a serotonergic medicine should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms generally start within several hours to a few days of taking an opioid with another medicine that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase. Health care professionals should discontinue opioid treatment and/or use of the other medicine if serotonin syndrome is suspected.

- **Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol.** Cortisol helps the body respond to stress. The FDA is requiring a new statement about adrenal insufficiency to be added to the Warnings and Precautions section of all opioid labels. Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Health care professionals should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.
- **Long-term use of opioids may be associated with decreased sex hormone levels** and symptoms such as reduced interest in sex, impotence, or infertility. The FDA reviewed published studies that assessed levels of sex hormones in patients taking opioids chronically; however, all had limitations that make it difficult to determine whether the symptoms were caused by the opioids or other factors. The labels of some opioids already describe this possible risk, and the FDA is now adding consistent information to the Adverse Reactions section of all opioid labels. Patients should inform their health care professionals if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility. Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.

The FDA is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. The FDA was asked to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function, and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. The FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function. The FDA is requiring changes to the metformin labeling to reflect this new information and provide specific recommendations on the drug's use in patients with mild to moderate kidney impairment. The FDA is also requiring manufacturers to revise the labeling to recommend that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of renal function (i.e., glomerular filtration rate estimating equation (eGFR)). This is because in addition to blood creatinine concentration, the glomerular filtration rate takes into account additional parameters that are important, such as the patient's age, gender, race and/or weight. The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information:

- Before starting metformin, obtain the patient's eGFR.
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².
- Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.

- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m².
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

The FDA is evaluating the results of a Danish study that conclude there is a possible increased risk of miscarriage with the use of oral fluconazole (Diflucan®) for yeast infections. The FDA is also reviewing additional data and will communicate final conclusions and recommendations when the review is complete. The current FDA drug label states that data available from studies in people do not suggest an increased risk of problems during pregnancy or abnormalities in developing babies when women are exposed to a single 150 mg dose of oral fluconazole to treat vaginal yeast infections. However, high doses of oral fluconazole (400-800 mg/day) taken by pregnant women for much longer than a single dose have resulted in reports of abnormalities at birth. In the Danish study, most of the oral fluconazole use appeared to be one or two doses of 150 mg. Until the FDA's review is complete and more is understood about this study and other available data, the FDA advises cautious prescribing of oral fluconazole in pregnancy. Health care professionals should be aware that the Centers for Disease Control and Prevention guidelines recommend only using topical antifungal products to treat pregnant women with vulvovaginal yeast infections, including for longer periods than usual if these infections persist or recur.

Quarterly Non-Formulary Drug Justification Report

For the second quarter of fiscal year 2016, all facilities reported use of non-formulary agents. The DADS facilities submitted 1,011 non-formulary requests and the DSHS facilities had 361 requests. The following were the top non-formulary agents that were prescribed:

Saccharomyces boulardii capsule (Florastor®)
 Levalbuterol (Xopenex®)
 Fiber-Stat Natural solution packets
 Omega 3 acid ethyl esters (Lovaza®)

Levalbuterol was added to the Formulary earlier in the meeting during the sectional review. The Committee recommended reviewing the newer oral anticoagulant drugs (direct Factor X_A inhibitors) at the next meeting. In addition, it was recommended to review Saccharomyces boulardii capsule (Florastor®) as it seems to be one of the leading non-formulary agents.

Sectional Review for Next Meeting

The following sections will be reviewed at the next meeting:

Dermatologicals (Acne agents to Anti-Infectives Antiseptic & germicides)

The Formulary Review Schedule starting next calendar year was reviewed. On a motion of Dr. Heidel, seconded by Dr. Pittman, the proposed schedule was approved. See Attachment E.

Other Issues

The following information was shared with the Committee members:

The New York Times reported that “since their introduction in 1990, the drugs collectively known as proton pump inhibitors (common brand names: Nexium [esomeprazole magnesium], Prevacid [lansoprazole], Prilosec [omeprazole]) have become among the most frequently prescribed in the country.” However, “they have also given users reason to be wary,” since “in recent years, scores of studies have reported associations between prescription P.P.I. use and an array of health problems, including bone fractures, low magnesium levels, kidney injuries and possibly cardiovascular drug interactions.” Notably, a recent study by John Hopkins researchers published in JAMA Internal Medicine found that those “who took prescription proton pump inhibitors were 20 percent to 50 percent more likely to develop chronic kidney disease than nonusers.”

Reuters reports that a Food and Drug Administration advisory committee on Wednesday recommended that the agency approve an expanded indication for Lundbeck’s antidepressant, Brintellix (vortioxetine), to cover cognitive dysfunction in major depression. If the FDA accepts the recommendation, the medicine would be the first indicated to treat depression-related cognitive dysfunction.

STAT reports that pharmaceutical “companies around the globe are spending big to push patients to take their” medications. Since pharmaceutical makers “loses tens of billions in worldwide sales each year when patients don’t fill, or refill, their prescriptions,” they are “pouring money into programs aimed at cajoling – or nagging – patients to take every last [drug] their [physicians] prescribe.”

The CBS News website reports on the growing misuse of the stimulant medication Adderall (amphetamine and dextroamphetamine), which is often prescribed for the treatment of attention-deficit/hyperactivity disorder (AD/HD). A study (2/17) published online Feb. 16 in the Journal of Clinical Psychiatry indicates that “incidences of misuse and emergency room visits related to Adderall increased dramatically for young adults between 2006 and 2011.” Researchers arrived at this conclusion after examining data from the “National Disease and Therapeutic Index, a survey of office-based practices; National Survey on Drug Use and Health, a population survey of substance use; and Drug Abuse Warning Network, a survey of hospital emergency department visits.”

The NBC News website reports that “more Americans than ever are overdosing on anxiety” medications. Researchers found that while the amount of filled prescriptions for anxiety medications has tripled from 1996 to 2013, the number of overdoses quadrupled over the same time period. The findings were published online in the American Journal of Public Health.

Medscape reports, “Increased dosing of selective serotonin reuptake inhibitors (SSRI) is associated with modest improvement of major depressive disorder (MDD),” the results of a 40-study meta-analysis suggest. But, “the benefits are offset at the highest doses by reduced tolerability.” The findings were published in the February issue of the American Journal of Psychiatry.

Reuters reported that the Food and Drug Administration has approved UCB SA's epilepsy-related seizure drug, Briviact (brivaracetam). The drug was approved for patients 16 years and older as an add-on therapy for the treatment of partial seizures due to epilepsy.

The Washington Post reports in "To Your Health" that "dozens of public health officials and academics across the country are pushing the Food and Drug Administration to warn people about the potential dangers of taking" opioid pain medications along with benzodiazepines. In a petition, officials from 41 state and municipal health departments, as well as some universities, "urged the agency" to add boxed warnings to both medications, "given evidence that using them together increases the chance of deadly overdoses."

STAT reports that a new analysis published in *Pharmacoepidemiology and Drug Safety* concludes that drug makers "generally fail to include key data that the FDA might use to assess future warnings" in their reports to the agency's Adverse Event Reporting System. According to the analysis, 40% of expedited reports and 51% of periodic reports filed by drug makers to the FDA were incomplete, with 38% lacking the patient's age and sex. Another 47% of reports did not include the date of the adverse event. According to STAT, "reports involving patient deaths offered the least amount of complete information for all of the key data points." A spokesperson for the FDA said the agency is "aware that the quality of adverse event reports may vary."

HealthDay reports that senior drivers who take the sleeping medication "zolpidem, sold widely as Ambien, may have a higher risk of motor vehicle crashes," research published online Dec. 28 in the journal *Sleep Medicine* suggests. After evaluating "the five-year driving records of 2,000 Alabama residents, aged 70 and older, comparing those who used the" sleeping medication "to those who did not," investigators found that women who used zolpidem "had a 61 percent higher probability of a crash over five years compared to nonusers." Drivers over the age of 80 had "twofold" higher risk.

The New York Times reports that the popular heartburn drugs known as proton pump inhibitors have been linked to a range of ills: bone fractures, kidney problems, infections and more. Now a large new study has found that they are associated with an increased risk for dementia as well. Proton pump inhibitors are widely available both by prescription and over-the-counter under various brand names, including Prevacid, Prilosec and Nexium.

HealthDay reports, "Children on medications for" attention-deficit/hyperactivity disorder (AD/HD) "may have lower bone density than their peers," research presented at the annual meeting of the American Academy of Orthopedic Surgeons indicates. After analyzing "data from a government health survey, researchers found that children taking AD/HD medications had, on average, lower bone density in the hip and lumbar spine" than youngsters who were not taking such medicines.

STAT reports that pharmaceutical advertisement spending "soared more than 60 percent in the last four years, hitting \$5.2 billion last year." According to an analysis by STAT, "one-quarter of the industry's \$5.2 billion in spending last year" was spent on just five drugs: Humira (adalimumab), Lyrica (pregabalin), Eliquis (apixaban), Cialis (tadalafil), and Xeljanz (tofacitinib).

Healio reports, “Pregabalin was effective in reducing pain and improving sleep quality among patients with fibromyalgia through 12 weeks, and adverse effects were consistent with the medication’s known safety profile,” researchers found after collecting data on 1,605 patients treated with pregabalin and “929 given a placebo.” The study’s findings were published in the March issue of the journal *Current Medical Research and Opinion*.

ProPublica reports, “A ProPublica analysis has found for the first time that” physicians “who receive payments from the medical industry do indeed tend to prescribe drugs differently than their colleagues who don’t.” The analysis indicated that “the more money they receive, on average, the more brand-name medications they prescribe.”

HealthDay reports that patients with Parkinson’s disease “who are given antipsychotics to treat dementia and psychosis may be more likely to die early,” the findings of a nearly 15,000-participant study published online March 21 in *JAMA Neurology* suggest. Researchers discovered that patients “who took antipsychotics were more than twice as likely to die over six months as those who didn’t.” Patients taking “the older typical antipsychotics...were at highest risk.”

HealthDay reports that selective serotonin reuptake inhibitor (SSRI) antidepressants appear not “to raise the risk for heart trouble among young and middle-age patients,” the findings of a 238,963-patient study published online March 22 in the *BMJ* suggest. After examining data on “different types of antidepressants, as well as dosage and duration,” researchers “concluded there was ‘no significant association’ between SSRIs and an increased risk for heart attack, stroke or an irregular heartbeat.”

Reuters reports that Food and Drug Administration scientists concluded that Acadia Pharmaceutical Inc.’s Nuplazid (pimavanserin) is an effective treatment for psychosis associated with Parkinson’s disease, according to a report released Friday. The report was released in anticipation of an FDA advisory panel scheduled to consider the drug on Tuesday.

STAT reports that there is “significant uncertainty surrounding” the cost and effectiveness of Acadia Pharmaceuticals’ Nuplazid (pimavanserin), which is designed to treat psychosis related to Parkinson’s disease. If approved by the Food and Drug Administration, Nuplazid “would undoubtedly cost far more than existing antipsychotics, which are...available as generics.” However, “in the pivotal trial behind Acadia’s marketing application, Nuplazid showed only modest improvements over placebo, and was tested in a way that makes it difficult to compare against other treatments.” Although a price has not been set, “analysts are expecting significant demand for the drug – to the point where some are projecting worldwide sales to top \$1 billion or more.”

STAT reports that the Food and Drug Administration has declined to expand approval for the antidepressant Brintellix (vortioxetine) to treat “foggy thinking and other cognitive problems that sometimes accompany depression.” According to STAT, the “rejection was unusual, given that an advisory panel to the FDA had voted 8-2 last month in favor of the drug makers’ application.”

TIME reports that a study published March 31 in the New England Journal of Medicine suggests that naltrexone “dramatically” improves a patient’s recovery from opiate dependence. In the study involving some 300 participants, researchers found 43% of patients taking naltrexone relapsed, “compared to 64% of those receiving standard treatment, and among those that relapsed, it took then twice as long until their first relapse as it did for people receiving counseling.” The effects, however, “last only as long as the people continue getting the injections.”

On the front of its Personal Journal section, the Wall Street Journal reports there appears to be an association between taking selective serotonin reuptake inhibitors during pregnancy and having children who may face a fourfold risk of depression by their fifteenth birthday. The findings of the study of some 65,000 women were published in the Journal of the American Academy of Child & Adolescent Psychiatry. Nada L. Stotland, MD, MPH, a past president of the American Psychiatric Association, emphasized that mothers who are depressed and need to take antidepressants during pregnancy should continue to do so.

HealthDay reports that use of the epilepsy medication lamotrigine “during pregnancy may not raise the risk for certain birth defects,” the findings of a study published online April 6 in Neurology suggest. After analyzing “data on more than 10 million births over 16 years, including almost 227,000 babies with birth defects,” researchers found that infants “born with cleft lip, cleft palate or clubfoot were not significantly more likely than those with other birth defects to have been born to mothers who took lamotrigine in the first trimester of pregnancy.”

Reuters reports that a Philadelphia Federal judge dismissed over 300 lawsuits against Pfizer, Inc. that claimed Zoloft (sertraline) had caused birth defects in children when taken by pregnant women. According to Judge Cynthia Rufe, the plaintiffs had failed to provide sufficient evidence of a scientific link between the defects and the medication.

The AP reported, “Seven years after US regulators slapped their strictest warning on two popular smoking-cessation medicines citing risks of suicidal behavior, a large international study found no such risk.”

Next Meeting Date

The next meeting was scheduled for July 29, 2016.

Adjourn

There being no further business, the meeting was adjourned at 2:05 p.m.

Approved: Jennifer Wright
Jennifer Wright, M.D., Chairman

Attachments

Attachment A – Psychotropic Dosage Tables

Attachment B – Levalbuterol (Xopenex®, Xopenex HFA®) Monograph

Attachment C – Texas Compassionate Use Act (Senate Bill 339)

Attachment D Box 1, CDC Guideline for Prescribing Opioids for Chronic Pain – United States,
2016

Attachment E – Formulary Review Schedule

Minutes Prepared by:

Ann L. Richards, Pharm.D., BCPP

Antipsychotics

Drug	Suggested Maximum Dose (mg/day)		
	Adult	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
ARIPiprazole (Abilify)	30	4-11 y/o 15 (Lit)	30
ARIPiprazole Extended Release (Abilify Maintena)	400 per 4 weeks		
ARIPiprazol lauroxil (Aristada) NON-FORMULARY	882 per 4 weeks		
Asenapine (Saphris)	20	10 to <12 y/o 20 (Lit)	20
Brexipiprazole (Rexulti)	4	ID	ID
Cariprazine (Vraylar) NON-FORMULARY	6		
chlorproMAZINE (Thorazine)	2,000	500 (\leq 45.5 kg)	800 (>45.5kg)
cloZAPine (Clozaril, Fazaclo, Versacloz) - RESERVE USE	900	8-11 y/o 300 (Lit)	600 (Lit)
fluPHENAZine(oral) (Prolixin)	60 400 per 4 weeks		
fluPHENAZine Decanoate (Prolixin Decanoate)			

Haloperidol (oral) (Haldol) Haloperidol Decanoate (Haldol Decanoate)	40 450 per month	3-12 y/o Lesser of 0.15 mg/kg or 6 (Lit)	> 12 y/o Acute agitation 10 Psychosis 15 Tourette 15 (Lit)
Iloperidone (Fanapt) RESERVE USE	24	ID	ID
Loxapine (Loxitane)	250		
Lurasidone (Latuda)	160	ID	ID
OLANZapine (ZyPREXA, ZyPREXA Zydys)	30	4-6 y/o 12.5 6-12 y/o 20 (Lit)	13-17 y/o 20
OLANZapine pamoate (ZyPREXA Relprevv) RESERVE USE	300 per 2 weeks 405 per 4 weeks		
Paliperidone (Invega) Paliperidone palmitate (Invega Sustenna) Paliperidone palmitate (Invega Trinza) NON-FORMULARY	12 234 per 4 weeks 819 per 3 months	ID	6 (<51kg) 12 (≥51kg)
Perphenazine (Trilafon)	64	ID	>12 y/o 64 (Lit)
QUetiapine (SEROquel)	800	5-9 y/o 400 10-12 y/o 800 (Lit)	800

Haloperidol (oral) (Haldol) Haloperidol Decanoate (Haldol Decanoate)	40 450 per month	3-12 y/o Lesser of 0.15 mg/kg or 6 (Lit)	> 12 y/o Acute agitation 10 Psychosis 15 Tourette 15 (Lit)
risperiDONE (RisperDAL, RisperDAL M-Tab) RisperDAL Consta	8 ² 50 per 2 weeks	5 to <12 y/o 3	6
Thioridazine (Mellaril) ¹ - RESERVE USE	(ABSOLUTE) 800		
Thiothixene (Navane)	60		
Trifluoperazine (Stelazine)	40		
Ziprasidone (Geodon)	240	10-11 y/o 80 ³ (≤45kg) 160 ³ (>45kg) 40 ⁴ (Lit)	160 ³ (>45kg) 40 ⁴ (Lit)

¹ A boxed warning has been added to advise clinicians of prolongation of the QTc interval

² Risperidone doses >6 mg/day have increased risk of EPS

³Bipolar Disorder

⁴Tourette's Disorder

ID – insufficient data

Lit – Literature Support

Drug	Therapeutic reference range/ Recommended drug concentration
Clozapine	350 – 600 ng/mL
Fluphenazine	1 – 10 ng/mL
Haloperidol	1 – 10 ng/mL
Olanzapine	20 – 80 ng/mL
Perphenazine	0.6 – 2.4 ng/mL
Thioridazine	100 – 200 ng/mL

Revised 30 Oct 2015

Antidepressants

Drug	Suggested Maximum Dose (mg/day)		
	Adult	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
Amitriptyline (Elavil)	300 ⁶		

	Suggested Maximum Dose (mg/day)		
buPROPion (Wellbutrin)	450 <i>(with no single dose > 150)</i>	6 to <12 Lesser of 6 mg/kg or 300 (Lit) ⁴	Lesser of 6 mg/kg or 300 (Lit) ⁴
buPROPion SR (Wellbutrin SR)	400 <i>(with no single dose > 200)</i>		400 (Lit) ⁴
buPROPion XL (Wellbutrin XL)	450		450 (Lit) ⁴
Citalopram** (celeXA)	40	6 to < 12 y/o 40 (Lit)	40 (Lit)
clomiPRAMINE (Anafranil)	250	10–11 y/o Lesser of 3 mg/kg or 200 mg (OCD)	Lesser of 3 mg/kg or 200 mg (OCD)
Desipramine (Norpramin)	300* ¹		
Doxepin (SINEquan)	300 ⁷		
DULoxetine (Cymbalta)	120	7-12 y/o 120 (Lit)	120 (Lit)
Escitalopram (Lexapro)	20	6-11 y/o 20 (Lit)	≥12y/o 30 (Lit)
FLUoxetine** (PROzac)	80	6 to < 12 y/o 60 (Lit)	60
fluvoxamine (Luvox)	300	8-11 y/o 200 (OCD)	12-17 y/o 300 (OCD)
Imipramine (Tofranil)	300* ²	6 to < 12 y/o Lesser of 4 mg/kg or 200 (Lit) ⁴	Lesser of 4 mg/kg or 200 (Lit) ⁴
Mirtazapine (Remeron)	45	3 to < 12 y/o	45 (Lit)

	Suggested Maximum Dose (mg/day)		
		45 (Lit)	
Nortriptyline (Pamelor, Aventyl)	150* ³	≥ 6 y/o Lesser of 2 mg/kg or 100 (Lit) ⁴	Lesser of 2 mg/kg or 100 (Lit) ⁴
PARoxetine (Paxil)	60	Not recommended	40 (Lit)
Phenelzine (Nardil)	90		
Protriptyline (Vivactil) - Non-formulary	60		
Sertraline** (Zoloft)	200	200	200
Tranlycypromine (Parnate)	60		
traZODone (Desyrel)	600	ID	100 (Lit) ⁵
Venlafaxine (Effexor) Venlafaxine XR (Effexor XR)	375 225 (XR)	7-11 y/o 150 (Lit)	≥12 y/o 375 (Lit)

*Plasma concentration monitoring is recommended if these doses are exceeded.

**Dose varies with diagnosis.

¹Desipramine Therapeutic = 100-300 ng/mL

²Imipramine Therapeutic Concentration = 150-250 ng/mL

³Nortriptyline Therapeutic Concentration = 50-150 ng/mL

⁴ For ADHD

⁵ For sedative hypnotic

⁶Amitriptyline Therapeutic Conc. = 120-250 ng/mL

⁷Doxepin Therapeutic Concentration = 150 ng/mL

Lit – Literature Support

ID = Insufficient data to suggest support regarding its efficacy or to provide maximum dose guidelines in this patient group.

Reviewed 30 October 2015

Mood Stabilizers

Drug	Therapeutic Serum Concentration	Suggested Maximum Dose (mg/day)*		
		Adult	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
carBAMazepine (TEGretol, TEGretol XR, Carbatrol)	4 - 12 mcg/mL Adol – Max 12 mcg/ml	1,600	<6 y/o 35 mg/kg 6 to < 12 y/o 1,000 (6-12 mcg/ml)	# 1,000 (12-15) 1,200 (>15)
lamoTRigine (LaMICtal)	nd	<ul style="list-style-type: none"> • With VPA 100 • Mono-therapy 200 • With EIAED 400 	6 to < 12 y/o <ul style="list-style-type: none"> • With VPA 1-3 mg/kg • With VPA & EIAED 1-5 mg/kg • Mono-therapy 4.5 – 7.5 mg/kg • With EIAED 5 – 15 mg/kg 	<ul style="list-style-type: none"> • With VPA 200 • With VPA & EIAED 400 • Monotherapy 375 • With EIAED 500
Lithium (Lithobid, Eskalith)	Adult – 0.6-1.5 mEq/L Elderly – 0.6-1.0 mEq/L Child & Adol – Max 1.2 mEq/L (Lit)	3,600 (<65 years old) 1,800 (≥65 years old)	≥6 y/o # 1,800 or 1.2 mEq/L (Lit)	# 1,800 or 1.2 mEq/L (Lit)
OXcarbazepine (Trileptal)	nd	2,400	7-12 y/o 60 mg/kg or 1,500 (Lit)	60 mg/kg or 2,100 (Lit)
Valproic Acid, Valproate, Divalproex (Depakene, Depakote, Depakote ER)	50 - 125 mcg/mL Adol – Max 125 mcg/ml (Lit) Divalproex ER 85-125	60 mg/kg	6 to < 10 y/o 60 mg/kg (Lit) ≥10 y/o 60mg/kg #	60mg/kg#

* Plasma concentration monitoring is recommended if these doses are exceeded

nd = not yet determined

- Maximum daily dose typically determined by drug serum concentration and individual patient tolerability.

Lit – Literature support

EIAED – Enzyme inducing anti-epileptic drugs (e.g., carbamazepine, phenobarbital, phenytoin, primidone)

VPA – valproic acid-valproate

Reviewed 30 October 2015

Stimulants

Drug	Suggested Maximum Dose (mg/day)		
	Adult	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
Amphetamine Mixture (Adderall, Adderall XR)	60	≥ 3 y/o 40 ≥ 6 y/o 30 (XR)	40 30 (XR)
Dextroamphetamine (Dexedrine, Dexedrine spansules)	60	3-5 y/o 30 mg ≥ 6 y/o >50 kg 60 (Lit)	>50 kg 60 (Lit)
Lisdexamfetamine (Vyvnase)	70	70 (6-12 years old)	70
Methylphenidate, immediate release (Ritalin, Methylin, Metadate) Methylphenidate, sustained release (Ritalin SR, Concerta, Metadate CD)	60 72 (Concerta)	≥ 6 y/o 60 6-12 y/o Concerta – 2 mg/kg (not to exceed 54 mg/day)	60 Concerta – 2 mg/kg (not to exceed 108 mg/day) (Lit)

Revised 30 October 2015

Miscellaneous Drugs Used for Psychotropic Purposes

Drug	Suggested Maximum Dose (mg/day)		
	Adult	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
atoMOXetine (Strattera)	100	≥6 y/o whichever is less 1.8mg/kg or 100 (Lit)	whichever is less 1.8mg/kg or 100 (Lit)
cloNIDine (Catapres)	0.4	≥6 y/o 0.2 (27-40.5kg) 0.3 (40.5-45kg) # (Lit)	0.4 (>45kg) # (Lit)
cloNIDine Extended Release (Kapvay) NON-FORMULARY	0.4	≥6 y/o 0.4*	0.4
guanFACINE (Tenex)	4	≥6 y/o 2 (27-40.5kg) 3 (40.5-45kg) # (Lit)	4 (>45kg) # (Lit)
guanFACINE Extended Release (Intuniv) NON-FORMULARY	4	6-12 y/o 4*	≥13 y/o 7
Naltrexone (ReVia)	200		
Propranolol (Inderal)	160 (anxiety)***		

*** Maximum dose has not been determined for aggression or self-injurious behavior (SIB).

For ADHD

* Not studied in children < 6 years old

Lit – Literature support

Reviewed 30 October 2015

Anxiolytics

Drug	Suggested Maximum Dose (mg/day)	
	Under 65 years (mg/day)	Over 65 years (mg/day)
ALPRAZolam (Xanax)	4	2
(exception: for panic disorder)	10	N/A
busPIRone (BuSpar)	60	60
chlordiazePOXIDE (Librium)	100*	40*
clonazePAM (KlonoPIN)	4^	4^
Clorazepate ¹ (Tranxene)	60	30
Diazepam ¹ (Valium)	60	20
LORazepam (Ativan)	10*	3*
Oxazepam (Serax)	90	60

*Larger doses may be necessary in some cases of alcohol-substance withdrawal.

¹ Long acting benzodiazepines are not recommended in the geriatric population.

^ doses up to 20 mg have been used to treat seizure disorders

Reviewed 30 October 2015

Hypnotics

Drug	Suggested Maximum Dose (mg/day)			
	Under 65 years (mg/day)	Over 65 years (mg/day)	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
*diphenhydrAMINE (Benadryl)	300	300	1 mg/kg up to max of 50	50 mg per dose up to a max 300 mg/day
hydrOXYzine (Atarax, Vistaril)	400	300	25 (3-5 y/o) 50 (6-12 y/o) (Lit)	100 (>12 y/o) (Lit)
Temazepam (Restoril)	30	15		
traZODone (Desyrel)	200	150	ID	100 (Lit)
Triazolam (Halcion) (Conscious sedation dosing)	0.25 (0.5)	0.125 (0.25)		
Zaleplon (Sonata)	10	5	NR	NR
Zolpidem (Ambien)	10 (Males) 5 (Females)	5	NR	NR

*Evidence suggests that tolerance develops to the hypnotic effects within 5-7 nights of continuous use.

NR – Not Recommended

ID – Insufficient data to suggest support regarding its efficacy or to provide maximum dose guidelines for this patient population.

Revised 30 October 2015

Levalbuterol

(Xopenex[®], Xopenex HFA[®])

Classification: Respiratory Agents; Bronchodilators

Description:

Levalbuterol hydrochloride inhalation solution is a sterile, clear, colorless, preservative-free solution of the (R)-enantiomer of (racemic) albuterol.

Levalbuterol tartrate aerosol for oral inhalation is a pressurized metered-dose aerosol inhaler (MDI) of the (R)-enantiomer of (racemic) albuterol. It contains a suspension of

micronized levalbuterol tartrate, propellant HFA-134a (1,1,1,2-tetrafluoroethane), Dehydrated Alcohol USP, and Oleic Acid NF

Vials of solution for inhalation must be stored in the protective foil pouch, protected from light and heat. Vials should be used within 2 weeks of opening pouch and 1 week if removed from pouch.

Inhalers should be protected from freezing temperatures and direct sunlight. Store inhaler with the actuator (or mouthpiece) down.

Pharmacology: Levalbuterol is an inhaled beta₂-adrenergic agonist. Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic AMP. This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta₂-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta₂-receptors in the human heart that comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established. However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Results from an *in vitro* study of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol.

Pharmacokinetics:

- Initial Response: 10 to 17 minutes with nebulization, 5.5 to 10.2 minutes with aerosol
- Duration: After 4 weeks of treatment, the duration of bronchodilatory effect (greater than a 15% increase in forced expiratory volume in 1 second (FEV-1) from baseline) is approximately 5 hours after a levalbuterol dose of 0.63 mg for nebulization and 6 hours after a 1.25-mg dose for nebulization. The duration of effect may be as long as 8 hours in some patients. After receiving a levalbuterol dose of 2 puffs per metered dose inhaler, the duration is 3 to 4 hours. The duration of effect with the inhaler may be as long as 6 hours in some patients.
- Absorption: A portion of inhaled dose is absorbed to systemic circulation
- Elimination: Half-life elimination: 3.3-4 hours. The primary route of elimination of albuterol enantiomers is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Indications: Xopenex is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

Dosage:

For bronchospasm: The recommended starting dose of Levalbuterol solution for

nebulization is 0.63 mg administered three times a day, every 6 to 8 hours. Patients with more severe asthma or patients who do not respond adequately with lower dose may benefit from a dosage of 1.25 mg three times a day. The recommended dose of Levalbuterol metered-dose inhaler is 2 puffs every 4-6 hours.

For exacerbation of asthma (acute, severe): The recommended dose of Levalbuterol metered-dose inhaler is 4-8 puffs every 20 minutes for up to 4 hours, then every 1-4 hours as needed. The recommended dose of Levalbuterol solution for nebulization is 1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed.

Contraindications and Precautions:

- Pregnancy category C
- Like other inhaled beta-adrenergic agonists, Levalbuterol can produce paradoxical bronchospasm, which may be life threatening
- Like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, ECG changes, and/or symptoms.
- Levalbuterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines.
- Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Interactions:

- Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with Levalbuterol to avoid deleterious cardiovascular effects.
- **Beta-blockers:** Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as Levalbuterol, but may also produce severe bronchospasm in asthmatic patients. If there is no acceptable alternative to the use of beta-adrenergic blocking agents in patients with asthma, cardio-selective beta-blockers could be considered.
- **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** Administer with extreme caution to patients being treated with MAOIs or TCAs, or within 2 weeks of discontinuation of such agents, because the action of Levalbuterol on the vascular system may be potentiated.
- **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics.

Adverse Reactions:

Immediate hypersensitivity reactions have occurred, including angioedema, oropharyngeal edema, urticaria, rash and anaphylaxis

The most frequent (>10%) adverse reactions include: hyperglycemia, hypokalemia, rhinitis, and respiratory infections. Less frequent (2% to 10%) adverse reactions include nervousness, tremor, anxiety, dizziness, migraine, tachycardia, dyspepsia, pharyngitis, cough, and sinusitis.

Costs and Monitoring:

Monitoring should include pulmonary function tests, assessment of symptoms. Consider periodic bp, pulse, serum potassium and glucose monitoring during chronic therapy.

Levalbuterol Costs:

Xopenex HFA Inhaler, 45 mcg/actuation, \$0.20 actuation

Levalbuterol Inhalation Solution, 0.63 mg/3mL: \$1.66/nebule

Levalbuterol Inhalation Solution, 1.25 mg/3mL: \$1.66/nebule

Albuterol Costs:

ProAir Respiclick, 117 mcg (90 mcg base)/actuation, \$0.25 actuation

Albuterol HFA, 90 mcg/actuation, \$0.23 actuation

Albuterol 2.5 mg/3 mL, \$0.15/nebule

Albuterol 5 mg/mL, \$0.33/nebule

Efficacy/Safety:

Solution for Inhalation

- During chronic therapy, nebulized Levalbuterol 0.625 mg three times daily was as effective as nebulized racemic Albuterol 2.5 mg three times daily, and had a similar duration of action. Levalbuterol 1.25 mg three times daily was more effective.
- One small study in patients with chronic obstructive pulmonary disease (COPD) failed to show clear clinical advantages in using Levalbuterol over conventional nebulized bronchodilators.
- Adverse Effects
 - In a small sample of intensive care (ICU) patients with and without baseline tachycardia, no statistically or clinically significant differences were observed between maximum heart rate increases induced by equipotent doses of Albuterol and Levalbuterol.
 - With single or multiple dosing, adverse effects of 0.625-mg doses of Levalbuterol were fewer than observed with 2.5-mg doses of racemic Albuterol, including tachycardia, nervousness, tremor, and changes in glucose and potassium levels. Adverse effects were similar with Levalbuterol 1.25 mg and racemic Albuterol 2.5 mg.

Inhalation Aerosol

- The efficacy and safety of XOPENEX HFA Inhalation Aerosol were established in two 8-week, multicenter, randomized, double-blind, active and placebo-controlled trials. In these two trials, XOPENEX HFA Inhalation Aerosol was compared to an HFA-134a placebo MDI, and the trials included a marketed albuterol HFA-134a MDI as an active control. Serial forced expiratory volume in 1 second (FEV1) measurements demonstrated that 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced significantly greater improvement in FEV1 over the pretreatment value than placebo.
 - 90 mcg (2 inhalations) of XOPENEX HFA Inhalation Aerosol produced similar results in improvement in FEV1 as the control group (racemic albuterol HFA 180 mcg).
- Adverse Effects
 - Adverse event information concerning XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol in adults and adolescents is derived from two 8-week, multicenter, randomized, double-blind, active- and placebo-controlled trials that compared XOPENEX HFA Inhalation Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler which found the incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) to be low and comparable across all treatment groups, including placebo.

Conclusions:

Levalbuterol is the (R)-enantiomer of (racemic) albuterol. Levalbuterol has been proven to be effective in moderate-to-severe asthma in children and adults.

Clinical studies suggest no overwhelming or consistent superiority of levalbuterol over racemic albuterol with regard to effectiveness or safety. GOLD 2016 states that “for single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional bronchodilators.” The NHLBI 2007 guidelines for the diagnosis and management of asthma conclude that “levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety.” Although there is no clear clinical advantage to using levalbuterol instead of albuterol, this is commonly done in our system and the two medications are now similarly priced.

Recommendation: Recommended for addition to the formulary at this time.

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Review of Cannabidiol in the Treatment of Intractable Epilepsy

Texas Executive Formulary Committee

Friday, April 29, 2016

Texas Compassionate Use Act (Senate Bill 339)¹:

The bill became effective on June 1, 2015, and requires the Texas Department of Public Safety (DPS) to regulate the medical use of low-THC cannabis. DPS is required to create a registry of physicians who treat epilepsy and of patients who have been diagnosed with intractable epilepsy. DPS will license dispensing organizations, which will authorize the organizations to cultivate, process, and dispense low-THC cannabis to prescribed patients. DPS will begin licensing dispensing organizations starting June 2017 with the goal of licensing at least three organizations by September 1, 2017.

The compassionate-use registry will record physician and patient information, dosage prescribed, means of administration, total amount of low-THC cannabis required to fill the prescription, and a record of each amount of low-THC cannabis dispensed by a dispensing organization to a patient under a prescription.

The registry will be designed to prevent more than one physician from registering as the prescriber for a single patient, is accessible to law enforcement agencies and dispensing organizations for the purpose of verifying whether a patient was prescribed low-THC cannabis and whether the patient's prescription has been filled.

- Definitions:
 - Intractable epilepsy: a seizure disorder in which the patient's seizures have been treated by 2 or more appropriately chosen and maximally titrated antiepileptic drugs that have failed to control the seizures
 - Low-THC cannabis: the plant *Cannabis sativa*, and any part of the plant or any compound, manufacture, salt, derivative, mixture, preparation, resin, or oil of that plant that contains:
 - Not more than 0.5% by weight of tetrahydrocannabinols (THC)
 - Not less than 10% by weight of cannabidiol (CBD)
 - Medical use: the ingestion by a means of administration other than by smoking of a prescribed amount of low-THC cannabis
 - Physician qualified to prescribe low-THC cannabis:
 - Licensed under this subtitle
 - Dedicates a significant portion of clinical practice to the evaluation and treatment of epilepsy and is certified by American Board of Psychiatry and Neurology in epilepsy, neurology (or child neurology), or neurophysiology
 - Prescription of low-THC cannabis: a physician may prescribe low-THC cannabis to alleviate a patient's seizures if:
 - The patient is a permanent resident of the state
 - The patient is diagnosed with intractable epilepsy
 - The physician determines the risk of the medical use of low-THC cannabis is reasonable due to the potential benefit for the patient
 - A second physician qualified to prescribe low-THC cannabis has concurred with the prescription and recorded in the patient's medical record
 - Patient treatment plan: the physician who prescribes low-THC cannabis must maintain a patient treatment plan that indicates:
 - The dosage, route of administration, and planned duration of treatment for low-THC cannabis
 - A plan for monitoring the patient's symptoms
 - A plan for monitoring indicators of tolerance or reaction to low-THC cannabis

An overview of cannabinoids²:

The Cannabis genus of flowering plants mainly comprises the *sativa* and *indica* species. The 2 major neuroactive components in cannabis are the psychoactive THC and the non-psychoactive CBD. Cannabis *sativa* has higher THC:CBD ratios than Cannabis *indica*. *Sativa* strains have more psychotropic effects and are more stimulating and *indica* strains are more sedating. The *sativa* strains are typically used by cannabis users. THC activates the endocannabinoid system via the G-protein coupled cannabinoid (CB) receptors. In the CNS, this system influences synaptic communication and modulates eating, anxiety, learning and memory, and growth and development.

Cannabinoid Pharmacology and Mechanism of Action^{2,3}:

C. sativa produces more than 80 different cannabinoid compounds. THC is one of the compounds that produce the psychotropic effects by binding to the CB1 and CB2 receptors to exert its effects. CBD does not activate CB1 and CB2 receptors (likely account for its lack of psychotropic activity) but likely interacts with many other non-endocannabinoid signaling systems, which includes enhancing the 5-HT_{1A} receptor. CBD is also a potent antioxidant. CBD may also potentiate some of THC's beneficial effects as it reduces the psychoactivity of THC to enhance its tolerability. People using products with high CBD:THC ratios are less likely to develop psychotic symptoms than products with low CBD:THC ratios. CB1 receptors are found primarily in the brain. CB2 receptors are mainly found in immune and hematopoietic cells.

The most common delivery form for CBD has been through inhaled route. The aerosolization or vaporization of CBD reaches peak plasma concentration in <10 minutes and has a bioavailability of about 31%. Oil-based capsule can also be used; however, due to low water solubility, the absorption from the GI system is erratic and leads to variable pharmacokinetics. The bioavailability of oral administration has been estimated to be around 6% due to extensive first-pass metabolism in the liver. Oral-mucosal/sublingual delivery through sprays/lozenges has similar bioavailability as oral route but with less variability (i.e. nabiximols oral spray: mixture of 1:1 THC and CBD of 10mg each). Distribution of CBD is influenced by its high lipophilicity with rapid distribution in the brain, adipose tissue, and other organs. It is also highly protein bound. CBD is extensively metabolized by the liver via CYP3A4, CYP2C9, and CYP2C19. It is a potent inhibitor of CYP3A and CYP2C family of enzymes. The half-life of CBD is around 18-32 hours. Short term side effects may include impairment in memory, judgment, and motor performance, high levels of THC are associated with psychosis and increased risk of motor vehicle accident. Longer term side effects may include risk of addiction, cognitive impairment, decreased motivation, and increased risk of psychotic disorders.

Cannabinoid Effects in Preclinical Models of Seizure and Epilepsy^{2,3}:

Early studies mainly evaluated effects of THC and synthetic CB1 agonists, and showed mixed efficacy in acute seizure models in various species. Some showed reduction in seizure frequency or severity and no effect or even potentiation of convulsive effects in others. These studies suggest that THC is not the only cannabinoid responsible for anti-seizure effects and the activation of CB1 receptors with THC is unlikely to yield therapeutic benefit. CBD has been shown to have anti-epileptiform and anticonvulsant effects in in-vitro and in-vivo models for active seizures. CBD modulates the intracellular Ca²⁺ concentration and inhibits T-type Ca²⁺ channels. It also has anti-apoptotic, neuroprotective, anti-inflammatory effects. Preliminary studies in humans have identified defects in the endocannabinoid system with epilepsy. The endocannabinoid system is strongly activated by seizures.

Evidence for the Use of Cannabinoids in Intractable Epilepsy:

Currently, there is a lack of well-designed, prospective, randomized, placebo-controlled trials that evaluates the use of cannabinoids in patients with intractable epilepsy. Published literature mainly consists of case reports and surveys/questionnaires of parents whose children who have intractable epilepsy.

Porter BE, et al⁴. reported results from a parent survey of CBD-enriched cannabis use in pediatric intractable epilepsy. The survey consisted of 24 questions that measured clinical factors including diagnosis, seizure types, parental reported effect of CBD enriched cannabis on child's seizure frequency and side effects. The survey was presented online to a Facebook group of parents supporting the use of CBD-enriched cannabis to treat seizures in their children with intractable epilepsy. The results consisted of 13 children with Dravet, Doose, and Lennox-Gastaut Syndrome (LGS) type seizures. On average, these children tried 12 other anti-epileptics (AEDs) before their parents began CBD-enriched cannabis. The dosage of CBD ranged from <0.5 mg/kg/day to 28.6 mg/kg/day. Dosages of THC contained in these products were 0 to 0.8 mg/kg/day. Seizure frequency prior to treatment ranged from 2 per week to 250 per day. The duration of CBD treatment ranged from 2 weeks to over 1 year.

- **Results:** 84% (16/19) of the parents reported a reduction in seizure frequency. Two parents reported their child became seizure free after >4 months of CBD use. Three reported >50% reduction in frequency, 3 reported >25% reduction, and 3 parents reported no change. Other beneficial effects observed: better mood (79%, 15/19), increased alertness (74%, 14/19), better sleep (68%, 13/19), and decreased self-stimulation (32%, 6/19). No side effect reported with the use of CBD.
- **Conclusions:** Parents report a high rate of success in using CBD-enriched cannabis to reduce seizure frequency. CBD appears to be well tolerated and may have beneficial effects on cognition and mood. The use of cannabis poses significant risks because of lack of standardization and regulation that affects quality and composition of the products, imprecise dosing, and possible medication interactions. Most parents reported using cannabis extracts from dispensaries or medical cannabis growers that often provide inaccurate labels, contain variable levels of CBD and THC, and can contain contaminants such as fungus and pesticides.
- **Limitation:** Positive selection bias because the parents who responded to the surveys were proponents of using CBD for their children.

One case report that was published in 2014 had garnered national attention after being featured on CNN⁵. The case was about a girl named Charlotte with a diagnosis of Dravet syndrome, which is a type of seizure that is often very difficult to treat. Charlotte's first seizure was prolonged status epilepticus at 3 months old with up to 50 generalized tonic-clonic seizures per day. By age 5, she had already failed many AED's including levetiracetam, oxcarbazepine, topiramate, zonisamide, valproate, clobazam, clonazepam, diazepam, and ketogenic diet. She also exhibits significant cognitive and motor delays and required feeding tubes and full assist with her activities of daily living (ADLs). After extensive research and assistance from a Colorado-based medical marijuana group, Charlotte's mother started her on adjunctive therapy with CBD-enriched cannabis, now known as Charlotte's Web. The formulation was started sublingually at low doses and titrated up slowly to a steady dose of 4 mg/lb/day. Her seizures eventually reduced from >300 per week to 2-3 nocturnal episodes per month (>90% reduction). In addition to successful reduction in seizure frequency, Charlotte also had improvements in her autistic behaviors, being able to feed and drink on her own, and able to sleep through the night.

Press, et al. published a retrospective chart review in 2015⁶ performed at the Children's Hospital of Colorado's neurology service. Children were included if they had epilepsy defined by the healthcare provider and had seizure frequency documented prior to starting oral cannabis extract treatment. Patients were on average at 7.33 years old. Main seizure types include Dravet, Doose, and LGS. 57% (43/75) reported at least some improvement in seizures. 33% reported to have >50% reduction in seizure frequency (treatment responders) and 0.3% were reported to be seizure free. If the family had moved to Colorado solely for seeking cannabis treatment (n = 34), responder rate increased to 47% (16/34) as compared to 22% (9/41) of the families already living in Colorado. There was no difference in responder rate based on specific seizure type. There was no control of the type of oral cannabis extracts. Of the family that reported benefits other than seizure frequency, patients exhibited improvements in behavior/alertness (33%), improved language (11%), and motor skills (11%). Common adverse drug reactions included: increased seizure/new onset (13%), somnolence/fatigue (12%), and GI symptoms (11%).

- Conclusion: Overall, there was 33% of patients reported to have a reduction in seizure frequency of >50% by parental report. Overall adverse events were reported in 44% of patients, and 78% of patients that experienced an adverse event had remained on oral cannabis extract.
- Limitation: Large placebo effect was seen amongst families who relocated to Colorado. The content of individual oral cannabis strains is largely unknown as there is a lack of regulation. No sufficient data to reliably determine if there was a dose dependency of response.

Devinsky et al.⁷ recently published an open-label interventional trial in 2016 that evaluated the safety and efficacy of CBD as add-on treatment to AED's in children/young adults with intractable epilepsy. This is a prospective, open-label, expanded-access trial at 11 independent epilepsy centers in the U.S. The study included patients age 1-30 years old, had intractable childhood onset epilepsy, had 4 or more countable seizures with a motor component per 4 week period, and had been receiving stable doses of AED for at least 4 weeks before enrollment. Patients received a 99% pure oil-based CBD extract of constant composition (Epidiolex) in a 100 mg/mL sesame oil-based solution administered orally or by gastric tube. CBD was initiated at a dose of 2-5 mg/kg/day divided in BID dosing and was added to baseline AED regimen. It was then titrated by 2-5 mg/kg once a week until intolerance or a max dose of 25 mg/kg/day was reached (some site allowed 50 mg/kg/day). Primary endpoint was to establish safety and tolerability of CBD and the primary efficacy outcome was median percent change in mean monthly frequency of motor seizures at 12 weeks (end of study period).

- Results: Most common seizure syndrome were Dravet and LGS.
 - Safety analysis (n = 162): 79% (128/162) experienced side effects. >5% had somnolence, decreased appetite, diarrhea, fatigue, convulsions, appetite changes, status epilepticus, lethargy, gait disturbance, sedation (most were mild/moderate or transient). Serious adverse events were reported in 30% of patients: status epilepticus, diarrhea, pneumonia, weight loss, and 1 death (unrelated to study drug).
 - Efficacy: Baseline median monthly frequency of motor seizures was 30 and was decreased to 15.8 over the 12-week study period (median change was -36.5%). Five (4%) were free of all motor seizures. Many patients get titrated to stable dose until half-way through the 12-week study period. Changes in seizures during the final 4 weeks of study showed 15 (11%) were free of motor seizures. 39% had a reduction of >50% in seizure frequency, 22% had >70% reduction, 8% had greater than 90% reduction.
- Conclusion: Add-on treatment with pure CBD led to clinically meaningful reduction in seizure frequency in many patients; however, the number of adverse events was higher than expected. Some side effects reported may be due to drug-drug interactions with baseline AED and CBD.
- Limitations: No placebo-controlled group to accurately assess for efficacy and side effects that are primarily exerted by add-on CBD. The effects of this highly purified form of CBD-enriched cannabis cannot be extrapolated to non-purified forms of medical marijuana currently available.

Conclusion:

Low-THC cannabis or CBD-enriched cannabis shows potential efficacy in the treatment of intractable epilepsy, especially in the child/adolescent population, without the psychoactive effects typically seen with high THC content. However, due to it being a federally classified Scheduled 1 substance, there is currently a lack of well-designed, prospective, randomized, placebo-controlled clinical trials (RCTs) to evaluate for efficacy and safety as well as dosing for the use of low-THC cannabis in intractable seizures. The lack of rules and regulations makes it difficult to control for the quality and consistency of these products. In response to this issue, the State of Texas currently passed a bill, Texas Compassionate Use Act, which allows the use of medical low-THC cannabis for the treatment of intractable epilepsy. This bill will provide standardized procedures on the prescribing and dispensing of low-THC cannabis. Current published literature primarily consists of case reports and surveys/questionnaires. The importance of conducting RCTs is currently being recognized, and there are currently 3 on-going RCTs registered on Clinicaltrials.gov (NCT02224703, NCT02224690, NCT02224560)

evaluating the effects of Epidiolex (pure oil-based CBD extract) for the treatment of Dravet syndrome and LGS in the child/adolescent population. Results of these studies will be available in the upcoming years. More data will be needed on efficacy and safety before low-THC cannabis can be recommended as an alternative option for intractable epilepsy.

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BOX 1. CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care**Determining When to Initiate or Continue Opioids for Chronic Pain**

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

* All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

Formulary Review Schedule
4/29/16

2017	Winter	Blood Modifying - 11 Antidotes/Deterrents/Poison Control- 15 Antidiabetic - 16 Intravenous Solutions and Additives - 18
2017	Spring	Endocrine - 22 Osteoporosis - 7 Genitourinary -22
2017	Summer	Antiparkinson Agents - 8 Cardiovascular - 46
2017	Fall	Analgesics/Antipyretics - 15 Anticonvulsants - 24 Table Review Reserve Drug Review
2018	Winter	Nasal/mouth/throat - 17 Otics - 9 Ophthalmics – 35
2018	Spring	Psychotropic – 68
2018	Summer	Gastrointestinal - 51 Muscle Relaxants -7
2018	Fall	Infectious Disease – 55 Antineoplastic - 1 Table Review Reserve Drug Review
2019	Winter	Nutritional/Nutritional Supplements - 34 Dementia/Miscellaneous CNS - 5 Migraine - 11
2019	Spring	Respiratory – 41 Antihistamine - 7 Antiemetics/Antivertigo - 8
2019	Summer	Dermatologicals, (Acne agents through Burns Agents) – 49

2017	Winter	Blood Modifying - 11 Antidotes/Deterrents/Poison Control- 15 Antidiabetic - 16 Intravenous Solutions and Additives - 18
2019	Fall	Dermatologicals (Corticosteroids through Miscellaneous Dermatologicals) - 44 Irrigation – 2 Immunological - 12 Table Review Reserve Drug Review