State Operated Facilities
Executive Formulary Committee Minutes

Date

The Executive Formulary Committee convened on October 5, 2018 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Messer, Chair at 9:34 a.m.

Jean Baemayr, PharmD- secretary	√	Ashton Wickramasinghe, MD	√
John Bennett, M.D.	√	Vacant- local authority practitioner	
Bonnie Burroughs, PharmD	√	Vacant- local authority practitioner	
Barbara Carroll, RN	√	Tim Bray (non-voting)	Absent
Cleveland "Chip" Dunlap, RN	√	Connie Horton, RNP (non-voting)	Absent
Catherine Hall, PharmD	√	Raul Luna, RN, MSN (non-voting)	Absent
Jeanna Heidel, PharmD	√	Mike Maples (non-voting)	Absent
N. Kubista, DO	√	Nina Muse, M.D. (non-voting)	Absent
Jeff Matthews, MD	√	Peggy Perry (non-voting)	Absent
Mark Messer, DO- Chair	√	Rachel Samsel, (non-voting)	Absent
Scott Murry, MD	Absent	E. Ross Taylor, MD (non-voting)	√
Kenda Pittman, PharmD	√	.	
Rishi Sawhney, MD	Absent	.	
Glenn Shipley, DO	√	.	

Guests Present: Lisa Mican, PharmD, Interim Pharmacy Director Austin State Hospital; Ann Richards, PharmD.

Introduction and Other Information

The committee members and guests attending the meeting introduced themselves.

Dr. Wickramasinghe was introduced as the new physician representative for the State Supported Living Centers (SSLCs). Dr. Sawhney was not present but has been appointed to the committee as the Behavioral Health Medical Director, per TAC 25 Chapter 415 Subchapter C.

Approval of Minutes of April 20, 2018

On a motion of Dr. Matthews, seconded by Dr. Pittman, the minutes of the April 20, 2018 meeting were approved as previously distributed.

Conflict of Interest

The committee members present did not reveal any issues with conflict of interest. The new committee members had previously submitted their conflict of interest forms and did not indicate any issues.

The committee reviewed the revised conflict of interest policy which now includes those individuals who are appointed to work groups that report to the EFC.

On a motion of Dr. Messer, seconded by Dr. Bennett, the revised policy and form were approved.

The revised form will be posted on the EFC home webpage under "Documents" and will also be included as an appendix in the 2019 Formulary.

Old Business

Clozapine myocarditis/myopathy monitoring protocol (April 2018)

The monitoring protocols as presented by Dr. Guidry at the April EFC meeting were approved at the System Medical Executive Committee (SMEC) meeting on May 17, 2018.

To be consistent with the protocols, the patient monitoring parameters section of the clozapine auditing criteria and guidelines would need to be revised to add "brain natriuretic peptide (BNP) every 3 months or as clinically indicated".

On a motion of Dr. Heidel seconded by Dr. Messer, the clozapine audit criteria and guidelines will be updated as described above.

The revised audit criteria and checklist will be available on the EFC "Medication Audit Criteria and Checklists" webpage.

Psychotropic medication utilization parameters for children & youth (April 2018)

Two additional physicians have been appointed to the workgroup at the request of Dr. Muse: Roberto Rodriguez, MD—pediatrician and Medical Director for CPS at DFPS, and Rishi Sawhney, MD—general psychiatrist, Medical Director of (Community) Behavioral Health, MSS Division HHSC. The workgroup has met and is making progress. The recommendations from the workgroup are scheduled to be presented at the January EFC meeting.

TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)

The work group appointed by the committee has not met. A new workgroup to review Chapter 415 in its entirety is currently being assigned by HHSC Medical and Social Services Division.

Audit criteria & guidelines development- chemical dependency adjunct (January 2012)

The Chemical Dependence Adjunct Audit Criteria and Guidelines for acamprosate, disulfiram, buprenorphine, and buprenorphine/naloxone not been developed. The criteria and guidelines for naltrexone and topiramate have been developed but were last reviewed in 2006 and 2015, respectively.

Dr. Matthews may have a clinical pharmacist that is interested in working on reviewing these documents.

Audit criteria & guidelines review-antidepressants (April 2012)

The Antidepressant Audit Criteria and Guidelines have not been reviewed. There are separate audit criteria and guidelines for the following categories:

amoxapine, bupropion, duloxetine, mirtazapine, MAOI's, trazodone, SSRI's, TCA's, and venlafaxine. These were all last updated in 2006.

Dr. Hall will review the audit criteria for antidepressants and provide recommendations for revisions and also for combining some of the categories where appropriate.

New Business

Audit criteria & guidelines update-atypicals

The FDA has approved a new indication for lurasidone: as monotherapy in the treatment of children and adolescents with major depressive episodes associated with bipolar I disorder. With this new lurasidone indication, the medication audit guidelines were updated to include: lurasidone (10 to 17 years old, monotherapy-major depressive episode with bipolar I disorder).

On a motion of Dr. Messer, seconded by Dr. Pittman, the atypical audit criteria and guidelines were approved as modified to include the new indication for lurasidone.

The revised audit criteria and checklist will be available on the EFC "Medication Audit Criteria and Checklists" webpage.

Adverse Drug Reaction Reports

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

> A 58-year-old female was admitted to the psychiatric hospital almost 2 years ago for treatment of schizophrenia. Other medical diagnoses include type 2 diabetes, obesity, hyperlipidemia, hypertension, urinary incontinence, constipation, sleep apnea and COPD. During the admission, she has been prescribed a relatively stable medication regimen which includes clozapine since admission and the addition of sertraline approximately 1 year ago. The only recent medication changes were an increase in sertraline from 50 mg

daily to 75 mg daily approximately 3 months prior to the adverse event due to dysphoria and a dose increase of clozapine from 375 mg daily to 400 mg daily 1 month prior to the adverse event due to continued delusions and response to internal stimuli. Other medications include: atorvastatin 20 mg daily for hyperlipidemia, vitamin D3 2,000 units daily, amlodipine 5 mg in the morning for hypertension, lisinopril 5 mg daily for hypertension and diabetes, metformin 1,000 mg twice daily for diabetes, docusate calcium 240 mg daily for constipation, oxybutynin 10 mg at bedtime for incontinence, aspirin 81 mg daily for heart health, calcium carbonate 500 mg three times a day as needed for indigestion, albuterol inhaler 2 puffs every 4 hours as needed for asthma. A previous EKG 6 months prior reported sinus tachycardia with a HR of 110 bpm and QTc 441 ms. A total clozapine level 2 months prior to the adverse event at a dose of 325 mg daily was 808 ng/mL. Approximately 1 month after the last dose increase in clozapine, the patient reported having a "seizure" and lied down on a chair with her eyes closed. She also reported chest pain and not being able to breathe well. She was administered a 1 mg dose of oral lorazepam and symptoms improved. No other prn or stat medications were administered around this time. The following morning, an EKG was obtained which revealed sinus tachycardia with HR 115 bpm and QTc 506 ms. Sertraline was discontinued and clozapine was continued at the 400 mg daily dose. Four days after the severe QTc prolongation, another EKG was obtained and showed sinus tachycardia with HR 107 bpm, left atrial abnormality and normal QTc of 446 ms. A CMP and serum Mg were obtained and were within normal limits. The severe QTc prolongation resolved off of sertraline with clozapine 400 mg daily continued.

This adverse event was reported to the FDA's MedWatch program.

Formulary status change

The committee discussed the FDA approved indication for clobazam, treatment of seizures, and determined that other uses, such as for the treatment of anxiety, were not appropriate at this time.

On a motion of Dr. Matthews, seconded by Dr. Messer, it was recommended that clobazam be added to the Formulary reserve drug list with the following guideline for use: To be used for the treatment of seizures.

New Drug Applications

1. Ketamine - presented by Dr. Hall

Please refer to Appendix A for the monograph and application that were considered when determining action by the committee

The committee discussed several factors regarding the treatment of drug resistant depression. These include: the lack of alternatives for patients with major depressive disorder who do not respond to available antidepressant medications and who do not want ECT, the lack of state hospitals that have facilities to

administer intravenous preparations, the greater possibility of patient acceptance of a nasal dosage form versus an intravenous dosage form, the need to have the nasal preparation compounded by an outside pharmacy, and the pending FDA approval for Janssen's esketamine nasal spray.

On a motion of Dr. Bennett, seconded by Dr. Messer, it was recommended to add ketamine, both nasal and IV administration dosage forms to the formulary as Reserve Use drugs, using the American Psychiatric Association (APA) consensus statement on the use of ketamine infusion, as detailed in the monograph and listed below, as the guidelines for use of both the intranasal and the intravenous formulations:

1. A comprehensive diagnostic assessment should be completed to establish current diagnosis and evaluate history of substance use and psychotic disorders.
2. Assessment of baseline symptom severity should be completed to allow later assessments of clinical change with treatment[a].
3. A thorough history of antidepressant treatment should be collected and documented to confirm previous adequate trials of antidepressant treatments.
4. A thorough review of systems should be performed to evaluate potential risk factors associated with ketamine treatment[b].
5. Decisions on the specific physical examination and laboratory screening assessments should be made according to established guidelines and advisories issued by the American College of Cardiology Foundation/American Heart Association and the American Society of Anesthesiologists and should be based on a patient's individual clinical characteristics[c].
6. A careful review of past medical and psychiatric records and/or corroboration of the past history by family members are strongly encouraged; all current medications and allergies should be reviewed, including histories of opiate and benzodiazepine use; the use of a baseline urine toxicology screen is strongly encouraged to ensure the accuracy of the reported substance use and medication record.
7. An informed consent process, including discussion of the risks associated with the treatment[d], the limits of the available information pertaining to the potential benefits of the treatment, the fact that this is an off-label use of ketamine, and a discussion of alternative treatment options should be completed; this discussion should be complemented with written materials, and the patient should provide written informed consent before initiating treatment.

[a] Self-report versions of the Inventory of Depressive Symptomatology and Quick Inventory of Depressive Symptomatology (http://counsellingresource.com/quizzes/depression-testing/qids-depression/) are examples of scales that are available at no cost to clinicians and researchers.

[b] This review should also include questions pertaining to functional exercise capacity, which has been demonstrated to provide a good screening tool for patients that are at increased risk for adverse events associated with anesthesia exposure and surgical procedures.
[c] American College of Cardiology Foundation and the American Heart Association guidelines for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery and practice advisory from the American Society of Anesthesiologists.
[d] The Ketalar package insert provides essential information related to risk of ketamine administration.

The Formulary Check List was completed and no issues were detected. System ketamine use will be evaluated in one year. The formulary status of the nasal dosage form of ketamine will be reevaluated when a commercially prepared esketamine nasal dosage form is available.

2. Dexmethylphenidate ER (Focalin XR®) - presented by Dr. Mican

Please refer to Appendix B for the monograph and application that were considered when determining action by the committee.

The committee discussed several factors, including sporadic shortages of stimulant medications, the ability to open the capsules and sprinkle the contents in food, and the relatively low cost of generic dexmethylphenidate. On a motion of Dr. Pittman, seconded by Dr. Matthews, it was recommended to add dexmethylphenidate ER to the Formulary.

The Formulary Check List was completed and no issues were detected.

3. Hepatitis B vaccine (Heplisav-B®)- presented by Dr. Heidel

Please refer to Appendix C for the monograph and application that were considered when determining action by the committee.

The committee discussed several factors, including the advantage of a two dose regimen versus the three doses required with Engerix-B® (currently on Formulary), the recommendation by ACIP to offer Heplisav-B® as an alternative option for hepatitis B vaccination, and also the lack of long term efficacy and safety data. On a motion of Dr. Messer, seconded by Dr. Matthews, it was recommended to add Heplisav-B® to the Formulary.

The Formulary Check List was completed and no issues were detected. As this is a new product on the market, system Heplisav-B® use will be evaluated in one year to determine if any adverse drug reactions or medication errors have occurred.

Linaclotide (Linzess®)

The request to consider the addition of linaclotide (Linzess®) to the formulary is being tabled pending monograph development.

Dr. Burroughs will present a monograph at a future date.

Outsourcing sterile compounding-assessing a vendor

The FDA publishes a list of facilities that are registered as Human Drug Compounding Outsourcing Facilities:

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm

Registered facilities are subject to FDA inspection and must be in compliance with current good manufacturing practice (CGMP) requirements as well as other conditions and requirements stipulated under section 503B of the Federal Food, Drug, and Cosmetic Act.

Since there are very limited number of facilities that are FDA approved compounders, the committee discussed options as to limiting the liability of outsourcing compounding needs. Besides the FDA registration, The Joint Commission offers accreditation for those entities that seek it. For those compounding facilities that do not seek outside registration or accreditation, facilities can use a standard process to evaluate the facilities on their policies and procedures for compounding. The American Society for Health-System Pharmacists (ASHP) produces an assessment tool to evaluate such facilities.

On a motion of Dr. Bennett, seconded by Dr. Matthews, the committee recommended that a pharmacy using any outsourced sterile compounding facility insure that this outsourced facility has either an FDA registration or Joint Commission accreditation as a compounding facility. If a registered or accredited facility cannot be used, then the chosen facility should be assessed using an assessment tool similar to the one published by ASHP, available at: http://www.outsourcingassessment.org/blank-vendor-assessment.pdf

Hepatitis C Drug Purchases

For the second and third quarters of 2018 (April-June and July-September, respectively), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: 2nd quarter: $105,753.93 3rd quarter: $42,352.64

SLCs: none in 2nd or 3rd quarters

It was noted that individuals in the SSLCs that have Medicare Part D have their drug treatment for hepatitis C obtained from an outside pharmacy. Otherwise, the facility will purchase the drug. The committee will continue to monitor these purchases.

Quarterly Non-Formulary Drug Justification Report

For the 3rd and 4th quarters of fiscal year 2018, only the State Hospitals reported use of non-formulary agents. There has been an increase every quarter throughout the fiscal year, from 358 orders in 1st quarter to 703 orders in 4th quarter. The SSLC facilities still do not have the reporting capabilities to obtain the non-formulary drugs from their computer system. The following were the top non-formulary agents that were prescribed in the State Hospitals:

losartan
dexmethylphenidate ER

clotrimazole/betamethasone cream
acetaminophen/caffeine/pyrilamine (Midol Menstrual Complete®)
apixiban (Eliquis®)

Dr. Heidel recommended adding losartan to the formulary. She will prepare a monograph for the committee.

The committee will review the Reserve Drug List at the next meeting to determine if other ARBs on the formulary (valsartan and olmesartan) should be moved to regular formulary status.

Drug Deletion

The committee did not consider deleting any additional products not already specified in the sectional review.

New Dosage Strengths

The committee received a request to add oseltamivir (Tamiflu®) 30 mg capsules. Currently only 75 mg capsules have formulary status. In addition to the 30 mg capsules, 45 mg capsules and oral suspension are also non-formulary.

The committee discussed adopting the policy that all strengths of approved dosage forms of approved medications already on the formulary would be considered formulary items. Specific doses could be listed as excluded if necessary.

On a motion of Dr. Messer, seconded by Dr. Heidel, with subsequent formulary sectional reviews and new drug additions, the formulary will no longer list each strength of formulary medications. All oral capsule and suspension dosage forms of oseltamivir are to be considered formulary products.

Drug Formulary Sectional Review:

1. Gastrointestinal agents
    i. Antacids
        i. Aluminum hydroxide: delete "Amphogel" tradename
        ii. Aluminum hydroxide-magnesium trisilicate: Add "Suspension-oral". Delete "each tablet contains Aluminum hydroxide-magnesium trisilicate"
        iii. Aluminum hydroxide-magnesium hydroxide: delete "containing Aluminum hydroxide-magnesium hydroxide"
        iv. Aluminum hydroxide-magnesium hydroxide-simethicone: Delete "Aludrox" tradename. Delete "containing Aluminum hydroxide-magnesium hydroxide". Change "Liquid" to "Suspension".
        v. Calcium carbonate: Delete "Titralac" trade name. Add "TUMS" tradename. Change "Liquid" to "Suspension".
    ii. Antispasmotic/Anticholinergic Agents

i. Propantheline: Delete

iii. Histamine (H_2) Antagonists
   i. Ranitidine: delete tablet, effervescent

iv. Proton Pump Inhibitors
   i. Pantoprazole: add injection
   ii. omeprazole: add suspension
   iii. esomeprazole: remove from reserved status

v. Antiflatuants
   i. Simethicone: add "Gas-X", "Phazyme" trade names. Delete "Mylicon" trade name

vi. Laxatives
   i. Magnesium hydroxide: Change "liquid" to "Suspension"
   ii. Epsom salts- delete from laxative section

vii. Bulk Laxtives
   i. Methylcellulose: change "with sucrose" to "with sucrose and maltodextrin". Change "with phylalanine" to "with phenylalanine"
   ii. Retitle Magnesium citrate and magnesium hydroxide to "Saline Osmotic Laxatives"

viii. Antidiarrheals
   i. Lactobacillus acidophilus: Add "Florajen" trade name

ix. Rectal Agents
   i. Combine the rows with single ingredient hydrocortisone products into one row "hydrocortisone" with the following dosage forms- rectal foam cream, ointment, suppository
   ii. Pramoxine (Tronothane): delete row
   iii. Rectal hemorrhoidal ointment (Anusol): delete row
   iv. Rectal hemorrhoidal suppositories: delete row
   v. Create new row: phenylephrine (Preparation H) with the following dosage forms- cream, ointment, suppository
   vi. Create new row: pramoxine (Anusol) with the following dosage forms- ointment, suppository

x. Miscellaneous Gastrointestinal Agents
   i. Activated charcoal: delete from formulary (including antidote table)
   ii. Create new category for lubiprostone under laxatives: chloride channel activator

iii. Mesalamine: add "Canasa" to trade names. Add "enema" to rectal suspension line. Change "capsule, extended release" to capsule controlled release"

iv. Pancrelipase: delete tablet. Change "Pancrease" to "Pancreaze"

2. Muscle relaxants

i. Antispasticity Agents

i. Baclofen: delete "Lioresal" tradename

ii. Muscle relaxant agents

i. Cyclobenzaprine: delete "Flexeril" tradename

On a motion of Dr. Messer, seconded by Dr. Heidel, the changes recommended above were approved and the formulary will be updated.

Antipsychotic Tier Schedule- annual review

The committee reviewed the antipsychotic tier schedule. The title will be changed to "Texas HHS Health and Specialty Care System Antipsychotic Tier Schedule"

Cariprazine will be moved to Tier 2.

On a motion of Dr. Messer, seconded by Dr. Heidel, the antipsychotic tier schedule was approved with the changes above.

The revised TX Health and Specialty Care System Antipsychotic Tier Schedule will be posted on the EFC home webpage under "Documents".

Formulary Reserve drug table- annual review

The committee will review the Formulary reserve drug table at the next meeting.

Formulary Psychotropic dosing tables- annual review

The following revision was approved: Add 60 mg [Ritalin SR, Metadate CD] to the Methylphenidate, sustained release row for adults and adolescents in the Stimulants suggested maximum dose (mg/day) table.

The committee will review the Formulary Psychotropic dosing tables in detail at the next meeting.

On a motion of Dr. Messer, seconded by Dr. Baemayr, the change to the Formulary psychotropic dosing tables was approved.

Texas HHS State Operated Facilities 2019 Drug Formulary- annual review

The HHSC State Operated Facilities 2019 Drug Formulary will be reviewed at the next committee meeting.

Policy review: OP 3-7 Anticoagulation Therapy Management

The committee reviewed the recommendations made by the work group assigned to review the anticoagulation management policy. The revised policy is based on the

proposed new The Joint Commission's National Patient Safety Goals (NPSG) and includes the management of direct oral anticoagulant (DOAC) agents.

On a motion of Dr. Bennett, seconded by Dr. Heidel, the policy was approved and will forwarded to SMEC for final approval.

Dr. Hall shared documents she prepared that compare the different properties of oral anticoagulants. Please see Appendix D "Oral anticoagulants_2018"

Policy review: OP 3-16 Pain Management

The committee reviewed the new policy which went into effect June 22, 2018.

Issues from the Medical Director, State Hospital System

Dr. Muse was not present and did not provide any information to report.

Issues from the Medical Director, State Supported Living Centers

Dr. Taylor noted that the Department of Justice monitors were paying close attention to polypharmacy in the SSLC's. For the SSLC's, the definition for polypharmacy is the use of two medications for the same indication or three different psychotropics. Minimizing polypharmacy is challenging, especially when anticonvulsants are being used to treat seizure disorders. In addition, the monitors are looking for documentation of side effects or adverse effects.

FDA Drug Safety Communications

The FDA has issued the following safety communication that may impact our facilities.

Lamictal (lamotrigine)

The FDA is warning that the medicine Lamictal (lamotrigine) for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. As a result, we are requiring a new warning about this risk be added to the prescribing information in the lamotrigine drug labels. The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent fever, usually greater than 101°F, and it can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs. Healthcare professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. Advise patients to seek immediate medical

attention if they experience symptoms of HLH during lamotrigine treatment. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms:

- fever and rash
- enlarged spleen
- cytopenias
- elevated levels of triglycerides or low blood levels of fibrinogen
- high levels of blood ferritin
- hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
- decreased or absent Natural Killer (NK) Cell activity
- elevated blood levels of CD25 showing prolonged immune cell activation

HLH can occur within days to weeks after starting treatment. A physical examination and specific laboratory blood tests and other evaluations are used to diagnose HLH. Signs and symptoms of HLH include but are not limited to:

- fever
- enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly
- swollen lymph nodes
- skin rashes
- yellow skin or eyes
- unusual bleeding
- nervous system problems, including seizures, trouble walking, difficulty seeing, or other visual disturbances

Juluca, Tivicay, Triumeq (dolutegravir)
Serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects. To date, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy. We are investigating this new safety issue and will update the public when we have more information. Healthcare professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. In addition:

- Healthcare professionals should weigh the benefits and the risks of dolutegravir when prescribing antiretroviral medicines to women of childbearing age. Alternative antiretroviral medicines should be considered. Discuss the relative risks and benefits of appropriate alternative antiretroviral therapies.
- If the decision is made to use dolutegravir in women of childbearing age, health care professionals should reinforce the consistent use of effective birth control.
- Perform pregnancy testing before initiating a dolutegravir-containing regimen in women of childbearing age to exclude pregnancy.

Fluoroquinolone Antibiotics:
The FDA is strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. Most fluoroquinolone antibiotic drug labels include a warning that blood sugar disturbances, including high blood sugar and low blood sugar and depending on the fluoroquinolone antibiotic class, a range of mental health side effects are already described under Central Nervous System Effects in the Warnings and Precautions section of the drug label, which differed by individual drug. The new label changes will add that low blood sugar levels, also called hypoglycemia, can lead to coma and the new label will also make the mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:

- disturbances in attention
- disorientation
- agitation
- nervousness
- memory impairment
- serious disturbances in mental abilities called delirium.

SGLT2(sodium-glucose cotransporter-2) Inhibitors for Diabetes:
The FDA is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide. SGLT2 inhibitors are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. First approved in 2013, medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (see FDA-Approved SGLT2 Inhibitors). In addition, empagliflozin is approved to lower the risk of death from heart attack and stroke in adults with type 2 diabetes and heart disease. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

Tramadol (Ultram ®):
Summary of changes for all opiate labeling:

1. REMS name changed to Opioid Analgesic REMS. REMS modified to:
2. Include immediate-release (IR) opioid analgesics intended for use in an outpatient setting
3. Ensure that training is made available to healthcare providers involved in the treatment and monitoring of patients with pain (including nurses and pharmacists)

4. Implement an updated FDA Blueprint for Healthcare Provider (HCP) Education which requires the education to cover broader information about appropriate pain management.

Tramadol Boxed Warning (Additions and/or revisions are underlined)
WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE -THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
ADDICTION, ABUSE AND MISUSE
ULTRAM exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTRAM, and monitor all patients regularly for the development of these behaviors and conditions.
5 Warnings and Precautions
WARNINGS
Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS- compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

FDA Drug Recalls

The FDA has issued the following recall communications that may impact our facilities.

Fluticasone

May 31, 2018

Apotex Corp. is voluntarily recalling one (1) lot of Fluticasone Propionate Nasal Spray, USP, 50 mcg per spray, 120 Metered Sprays, to the consumer level. The spray was found to contain small glass particles. The glass particles could block the actuator and impact the functionality of the pump. The issue was discovered through a customer complaint. There is a potential for patients to be exposed to the glass particles and mechanical irritation cannot be ruled out. Local trauma to the nasal mucosa might occur with use of the defective product. To date, Apotex Corp. has not received any reports of adverse events related to recall.

Valsartan-Containing Products**:**

July 2018-ongoing

Voluntary recalls due to the presence of an impurity, N-nitrosodimethylamine (NDMA), in the valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals, China. NDMA is a substance that occurs naturally in certain foods, drinking water, air pollution, and industrial processes, and has been classified as a probable human carcinogen as per International Agency for Research on Cancer (IARC) classification. The presence of the potentially cancer-causing NDMA was unexpected, and the agency believes the NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.

- Teva Pharmaceuticals USA labeled as Major Pharmaceuticals — recall is at the retail level because these products are only used in facilities where they are directly administered to patients by health care professionals.
- Prinston Pharmaceuticals Inc. labeled as Solco Healthcare LLC — recall is at the consumer/user level.
- Teva Pharmaceuticals labeled as Actavis LLC — recall is at the consumer/user level.
- Camber Pharmaceuticals, Inc. – recall is to the hospital, retail and consumer level. (API manufactured by Hetero Labs Limited, Unit I).
- Torrent Pharmaceuticals Limited - recall is to the consumer level.

Hydrochlorothiazide

August 27, 2018

Accord Healthcare Inc. is voluntarily recalling one lot (Lot PW05264 – 46632 Bottles, NDC 16729-182-01) of Hydrochlorothiazide Tablets USP, 12.5 mg, to the consumer level. A 100 count bottle of Hydrochlorothiazide Tablets USP 12.5 mg has been found to contain 100 Spironolactone Tablets USP 25 mg. Since the individual lot of the product is involved in a potential mix-up of labeling, Accord is recalling this individual lot from the market. Based on findings of both preliminary and interim investigations carried out at the manufacturing site, Accord believes that no other lots of hydrochlorothiazide tablets are involved in this mix-up. Accord became

aware of this finding through a product complaint reported from a pharmacy. Use of spironolactone tablets instead of hydrochlorothiazide tablets, poses the risk of contracting hyperkalemia (increase potassium levels) in certain individuals resulting in adverse events that range from limited health consequences to life-threatening situations in certain individuals. To date, Accord has not received any reports of adverse events related to this recall.

Montelukast

August 31, 2018

The U.S. Food and Drug Administration is warning consumers and health care professionals about a voluntary recall of one lot of Montelukast Sodium Tablets – lot number MON17384, expiration 12/31/2019, NDC: 31722-726-30 by Camber Pharmaceuticals, Inc., Piscataway, N.J. Sealed bottles labeled as montelukast sodium tablets, 10 milligram, 30-count bottle from Camber were found to instead contain 90 tablets of Losartan Potassium Tablets, 50 mg. Montelukast is used to prevent wheezing, difficulty breathing, chest tightness and coughing caused by asthma. It is also used to prevent bronchospasm (breathing difficulties) during exercise and to treat the symptoms of seasonal and perennial allergic rhinitis. Montelukast is in a class of medications called leukotriene receptor antagonists (LTRAs) which work by blocking the action of substances in the body that cause the symptoms of asthma and allergic rhinitis.

News Briefs

The following information was shared with the committee members:

The AP (7/12, Johnson) reports the Food and Drug Administration "said Thursday that it's forming a task force to find ways to improve the supply of crucial drugs." The article points out that recent shortages "have led to rationing of some drugs and disrupted hospital operations."

Healio Cardiology Today (7/24, Dobkowski) reports, "Patients with depression and recent" acute coronary syndrome (ACS) "who were treated with escitalopram had lower risk for major adverse cardiac events compared with those given placebo," researchers concluded after analyzing "data from 300 patients with depression and recent ACS." The findings were published in the July 24/31 issue of the Journal of the American Medical Association.

MedPage Today (7/24, Susman) reports that "a real-world study that included more than 100,000 people living with HIV infection appears to confirm that a treatment regimen based on the integrase inhibitor dolutegravir (Tivicay) suppresses the virus to undetectable levels better than therapy based on the non-nucleoside reverse transcriptase inhibitor efavirenz (Sustiva), researchers said" at the International AIDS Conference. Approximately "82.5% of patients on dolutegravir were able to achieve undetectable viral loads using a stringent 50 copies/ml assay compared with 78% of patients on efavirenz ($P<0.001$), said Mariana Veloso Meireles, MSc."

Medscape (8/1, Frellick, Subscription Publication) reports researchers found in two phase 3 trials that four months of rifampin may be as safe and effective

as nine months of isoniazid at preventing active tuberculosis in patients with latent tuberculosis. The two trials compared the shorter-course of rifampin and the longer-course of isoniazid in children and adults. The findings of both clinical trials were published in the New England Journal of Medicine

STAT (8/2, Thielking) reports that hundreds of people have filed lawsuits against Bristol-Myers Squibb and Otsuka, claiming that their antipsychotic medication Abilify (aripiprazole) caused them to compulsively "gamble, eat, or have sex." The lawsuits have been consolidated and are now presided over by Judge M. Casey Rodgers in the North District Court of Florida who has ordered the plaintiffs and the companies "to work out a framework for a global settlement by Sept. 1." In 2016, the Food and Drug Administration issued a safety warning, "saying that uncontrollable urges to gamble, binge eat, shop, and have sex had been reported with use of the antipsychotic." The article outlines the history of the medication, including the Food and Drug Administration's 2016 safety warning advising people of reports that the drug can cause compulsive behaviors.

The Wall Street Journal (9/9, Evans, Subscription Publication) reports the FDA has recently increased scrutiny of the compounding pharmacy industry, saying that high costs of brand name drugs are not one of the acceptable reasons to compound a medicine – compounding is allowed to address a shortage or to modify a drug to account for an allergy. FDA Commissioner Scott Gottlieb took the step of removing some drug ingredients from a list that can be used for bulk compounding.

Pulmonary Hypertension News (9/10, Pena) reports researchers found in a review that the "use of antidepressants during pregnancy doubles the risk for persistent pulmonary hypertension in the newborn." The findings were published in the American Journal of Obstetrics & Gynecology

The Drug Enforcement Administration (DEA) (August 16) published a proposed rule to slash the annual production quotas (APQs) for certain opioids, including fentanyl, hydromorphone, hydrocodone, morphine, oxycodone, and oxymorphone. DEA notes that these are the six "most frequently misused opioids," but it does not distinguish among dosage forms when setting APQs (i.e., there are not separate quotas for oral solids versus injectables that have the same active ingredient). The proposed cuts range from 7-15% of the 2018 APQs, with an average 44% decrease from the 2016 APQs, consistent with the administration's "Safe Prescribing Plan" to reduce U.S. production of opioid medications.

Open Forum

No items.

Next Meeting Date

The next meeting was scheduled for January 11, 2019.

Adjourn

There being no further business, the meeting was adjourned at 1:40 p.m.

Approved: *Mark Messer, D.O.*

Mark Messer, D.O., Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

Appendix A – Ketamine New Drug Application and monograph
Appendix B – Dexmethylphenidate XR New Drug Application and monograph
Appendix C – Hepatitis B vaccine (Heplisav-B®) New Drug Application and monograph
Appendix D - Oral anticoagulants_2018

APPENDIX 1: NEW DRUG APPLICATION FORM

State Operated Facilities

(Formerly: Texas Department of Mental Health and Mental Retardation)

NEW DRUG APPLICATION

(for inclusion in the *State Operated Facilities Drug Formulary*)

Date: 4/3/18

Name of practitioner submitting the application: Mark Messer D.O.

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):

Information regarding new drug:

Therapeutic Classification	
Generic Name	Ketamine
Trade Name(s)	
Manufacturer(s)	
Dosage Form(s)	IV + intra-nasal

Explain the pharmacological action or use of this drug

Explain the advantages of this drug over those listed in the formulary:

State which drugs this new drug would replace or supplement:

****

☐application is approved

OR

☐application is appropriate and complete

signature of chairman of facility pharmacy and therapeutics committee

signature of clinical/medical director or designee

Ketamine

Approximately one-third of individuals with major depressive disorder (MDD) do not respond to available antidepressant medications and are considered to have treatment-resistant depression (TRD). Current therapies mainly target monoaminergic systems and have a delayed onset of effect.

Several studies have shown rapid antidepressant efficacy with IV ketamine. Proposed mechanisms of ketamine's antidepressant action include *N*-methyl-*D*-aspartate receptor (NMDAR) modulation, GABAergic interneuron disinhibition, direct effects of its hydroxyl-norketamine (HNK) metabolites, and numerous downstream actions. These proposed mechanisms of action may complement each other to improve symptoms of depression by increasing activity at excitatory synapses in affective-regulating brain circuits.

Currently, the Food and Drug Administration (FDA) has only approved ketamine hydrochloride injection (Ketalar) for the induction and maintenance of general anesthesia. Because of increased interest in the off-label use of ketamine infusions for the treatment of mood disorders, the American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments recently published a consensus statement, the intent of which is to provide guidance on issues and considerations associated with this relatively new therapy. The consensus statement is not meant to serve as an absolute standard or guideline because the APA does not believe that there is enough high-quality evidence to support such a policy. **The following is a summary of the issues discussed in the consensus statement and its supplement.**

Patient selection

There are no formal indications for the use of ketamine in the treatment of psychiatric disorders but the strongest data are in its use in patients with MDD without psychotic features. Most of these studies only measure antidepressant efficacy during the first week following a single infusion of ketamine but some investigations assess the efficacy of repeated dosing over longer time periods. The consensus statement recommends that the following measures be taken.

1. A comprehensive diagnostic assessment should be completed to establish current diagnosis and evaluate history of substance use and psychotic disorders.
2. Assessment of baseline symptom severity should be completed to allow later assessments of clinical change with treatment[a]
3. A thorough history of antidepressant treatment should be collected and documented to confirm previous adequate trials of antidepressant treatments
4. A thorough review of systems should be performed to evaluate potential risk factors associated with ketamine treatment[b]
5. Decisions on the specific physical examination and laboratory screening assessments should be made according to established guidelines and advisories issued by the American College of Cardiology Foundation/American Heart Association and the American Society of Anesthesiologists and should be based on a patient's individual clinical characteristics[c]
6. A careful review of past medical and psychiatric records and/or corroboration of the past history by family members are strongly encouraged; all current medications and allergies should be reviewed,

including histories of opiate and benzodiazepine use; the use of a baseline urine toxicology screen is strongly encouraged to ensure the accuracy of the reported substance use and medication record

7 An informed consent process, including discussion of the risks associated with the treatment,[d] the limits of the available information pertaining to the potential benefits of the treatment, the fact that this is an off-label use of ketamine, and a discussion of alternative treatment options should be completed; this discussion should be complemented with written materials, and the patient should provide written informed consent before initiating treatment.

[a] Self-report versions of the Inventory of Depressive Symptomatology and Quick Inventory of Depressive Symptomatology (http://counsellingresource.com/quizzes/depression-testing/qids-depression/) are examples of scales that are available at no cost to clinicians and researchers.

[b] This review should also include questions pertaining to functional exercise capacity, which has been demonstrated to provide a good screening tool for patients that are at increased risk for adverse events associated with anesthesia exposure and surgical procedures.

[c] American College of Cardiology Foundation and the American Heart Association guidelines for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery and practice advisory from the American Society of Anesthesiologists.

[d] The Ketalar package insert provides essential information related to risk of ketamine administration.

Clinician experience and training

Currently, there are no pre-defined training requirements that clinicians must meet before administering sub-anesthetic doses of ketamine.

When used to treat depression, intravenous (IV) ketamine is usually dosed 0.5 mg/kg and given over 40 minutes, resulting in peak plasma concentrations between 70 to 200 ng/ml. These plasma concentrations are not high enough to produce general anesthesia, which requires peak plasma concentrations between 2000-3000 ng/ml and are lower than those associated with waking up from ketamine anesthesia (500-1000 ng/ml).

When administered to patients with depression who are in other ways generally healthy, a 40-minute infusion of IV ketamine 0.5 mg/kg does not appear to significantly affect respiratory status. However, the therapy could impact blood pressure and heart rate. Wan and colleagues (2015) studied 84 otherwise healthy patients with depression who received a total of 205 infusions of ketamine hydrochloride 0.5 mg/kg per 40 minutes IV. No significant changes in oxygen saturation were observed but transient mean (SD) peak increases in systolic (19.6 [12.8] mm Hg) and diastolic (13.4 [9.8] mm Hg) were reported during the infusions. Approximately 30% of patients experienced blood pressures $\geq$ 180/100 mm Hg or pulses $\geq$ 110 beats per minute. **Because of these potential cardiovascular complications, the APA consensus statement recommends that clinicians who provide 40-minute IV infusions of ketamine hydrochloride 0.5 mg/kg be licensed to administer a Drug Enforcement Administration (DEA) Schedule III medication and possess Advanced Cardiac Life Support certification.**

During ketamine treatment, some patients experience prominent transient dissociative or psychotomimetic effects. Clinicians must be proficient in the behavioral management of patients with marked mental status changes and the treatment of emergency behavioral situations. Before discharge, an on-site clinician needs to evaluate the patient for psychiatric risks, including suicidal

ideation. Treating clinicians also need to ensure that swift psychiatric follow-up is available after discharge should the need arise.
Clinicians also need to acquire experience with the method of ketamine administration. Local community standards of practice and/or clinical practice committees should determine the substance of this experience. One resource for the development of these standards is the American Society of Anesthesiologists' *Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners Who Are Not Anesthesia Professionals.*

Treatment Setting

There is little evidence to support the use of any specific monitoring methods for mitigating the risks associated with sub-anesthetic doses of ketamine. Treatment facilities should be prepared to monitor basic cardiovascular (electrocardiogram, blood pressure) and respiratory (oxygen saturation or end-tidal CO_2) status. They should also be able to administer oxygen to patients with reduced respiratory function and restrain patients whose behavior endangers themselves or others. Treatment facilities need a plan for how to manage sustained alterations in cardiovascular function, such as the provision of advanced cardiac life support or transfer to an inpatient setting that deals with acute cardiovascular events. When pretreatment evaluation identifies higher risk patients, these should undergo treatment at a facility appropriately equipped and staffed to manage any cardiovascular or respiratory events that may occur.

Medication Delivery

Dose

Most clinical trials and case reports have used the 0.5 mg/kg per 40 minutes IV dose of ketamine hydrochloride. Although other doses and infusion rates have been studied, the authors of the Consensus Statement do not believe that there is sufficient information to "allow any meaningful analysis of any specific dose or route of treatment compared with the standard dose of 0.5 mg/kg per 40 minutes IV." However, they state that "the use of alternative doses and routes of administration could be appropriate for individual patients under specific conditions".
One such circumstance is patients whose BMI is 30 or greater. In the Wan study (which utilized the 0.5 mg/kg per 40 minutes IV regimen), greater hemodynamic changes were seen in patients whose BMI was 30 or higher. Calculating a patient's ideal body weight (IBW) and basing the ketamine dose on that IBW may be safer in this patient population but this has not been well studied.

Delivery Procedure

The Consensus authors strongly recommend the development of site-specific standard operating procedures (SOP). The SOP **before the infusion** should include

(1) Confirmation of pre-procedural evaluation and informed consent
(2) Assessment of baseline vital signs, including blood pressure, heart rate, and oxygen saturation or end-tidal CO_2
(3) Criteria for acceptable baseline vital signs before initiation of medication delivery

a. If SBP ≥150 mmHg or DBP ≥95 mmHg at baseline, treatment of hypertension should be considered
b. If HR < 60 bpm or > 100 bpm, relative risks of treatment should be considered
c. Baseline SpO2 should be > 94

(4) Incorporation of a "time-out" procedure in which the name of the patient and correct dosing parameters are confirmed

SOPs must also describe how patients' physiological and mental status will be monitored **during the infusion**. This includes

(1) Assessment of respiratory status (ie, oxygen saturation or end tidal CO_2)
(2) Assessment of cardiovascular function (blood pressure and heart rate, reported on a regular basis)
    a. Goal SBP < 180 mmHg, DBP < 110 mmHg at all times during the infusion
    b. Age adjusted maximum heart rates
        i. 20 yo < 140 bpm, 30 yo < 133, 40 yo < 126, 50 yo < 119, 60 yo < 112
(3) Assessment of level of consciousness
    - Modified Observer's Assessment of Alertness/Sedation Scale
(4) Delineation of criteria for stopping the infusion and a plan for handling cardiovascular or behavioral events during treatment
    a. Pallor, cyanosis, or any symptoms suggesting poor perfusion
    b. Shortness of breath, wheezing
    c. Chest, jaw or arm pain
    d. Patient's desire to stop

After the infusion, clinicians must ensure that patients' physiological and mental status has returned to baseline. Outpatients treated with ketamine will need a responsible adult to drive them home. Follow-up procedures should be reviewed with an emphasis on how a patient will quickly contact an appropriately trained clinician should the need arise.

Follow-up and Assessments

Efficacy Measures of Short-term Repeated Administration

Most of the ketamine literature is comprised of studies that last less than one month.

In a two week, randomized, placebo-controlled trial conducted in 68 patients with treatment-resistant major depressive disorder, Singh and colleagues evaluated the efficacy of twice versus thrice weekly ketamine administration (0.5 mg/kg per 40 minutes IV). There was little difference in efficacy between the two treatment regimens. After two weeks of twice-weekly treatment, 69% of individuals responded (versus 15% of placebo patients) and 37.5% of patients remitted (versus 7.7% of placebo patients). After two weeks of thrice-weekly treatment, 53.8% of patients responded (versus 6% of placebo patients) and 23.1% of patients remitted (versus 0% of placebo patients).

Some patients entered an open-label phase that lasted an additional two weeks. These individuals continued their original ketamine schedule (either twice or thrice weekly). The average reduction in MADRS score was 27 points for the 13 individuals who received four weeks of ketamine twice- weekly versus 23 points for

the 13 patients who received four weeks of ketamine thrice-weekly. **The results of this trial suggest that twice-weekly administration is as efficacious as thrice-weekly for a period of up to four weeks.**
There are a few reports of patients not responding until the fourth ketamine infusion but the question of when to declare a patient "ketamine resistant" remains unanswered. Cusin and colleagues studied the efficacy of increased doses in patients who had failed to respond to standard IV ketamine dosing (0.5 mg/kg per 40 minutes). See below.

Efficacy of Longer-term Repeated Administration
A significant downside to the use of ketamine to treat mood disorders is the lack of data on its long-term effectiveness and safety. This must be discussed with patients during the preprocedural informed consent process. Some clinics are providing a two or three-week course of ketamine given two or three times per week, followed by a taper period and/or additional treatments based on observed duration of response. However, other than a few case series, there are no published data that support sustained efficacy with ongoing treatment. Because of the potential risks associated with long-term exposure to ketamine, clinicians must consider the relative benefit of each ketamine infusion.

Safety Measures and Continuation of Treatment
Chronic high-frequency ketamine use has been associated with cognitive impairment but **studies that have examined the cognitive effects of sub-anesthetic doses of ketamine have not demonstrated adverse cognitive effects.** Individuals receiving ongoing ketamine for the treatment of mood disorders should undergo periodic cognitive testing; however, there is no agreed upon type or frequency of evaluation. **Cystitis** has also been reported with chronic high-frequency ketamine use. Clinicians should ask individuals receiving ongoing ketamine infusions about urinary symptoms and pelvic pain.
The development of **ketamine use disorder** in patients receiving ongoing treatment is a serious concern and clinicians should use the fewest number of treatments necessary to bring about the desired response. If abuse is suspected, providers should test patients' urine and ask if the individual has sought additional treatments at other facilities.
By the second month of treatment, if once weekly dosing does not produce the desired clinical response, the consensus authors recommend stopping ketamine.
The studies described below evaluate **maintenance therapy with iv ketamine.**
Wilkinson et al., 2018

Wilkinson and colleagues report on the outcomes of 54 patients with severe and treatment-resistant mood disorders who received multiple ketamine infusions at the ECT suite of the Yale Psychiatric Hospital. From October 2014 to February 2017, clinicians at this facility provided off-label ketamine on a case-by-case basis to individuals who did not qualify for research protocols. The main reasons for their failure to qualify were as follows: disallowed comorbid conditions (general medical and/or psychiatric), evidence of ultra-refractoriness (failing numerous previous treatment trials or ECT), current hospitalization, inability to delay treatment long enough to complete required study procedures (medication washout, observation periods), presence of significant suicidal ideation or behavior, age outside of protocol limits.

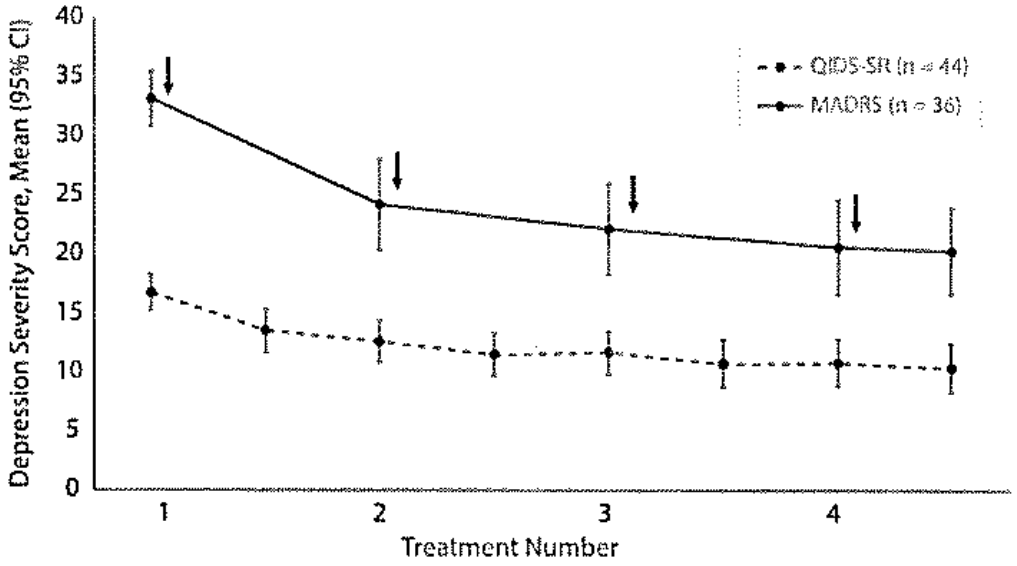
Ketamine 0.5 mg/kg was mixed in 500 ml of 0.9% normal saline and infused over 40 minutes. Ideal body weight was used for patients whose BMI $\geq$ 30 kg/m2. Patients remained on their psychotropic medications but took them after ketamine on the days of treatment; clinicians tried to avoid benzodiazepines in the 8 hour period before the infusion. Both inpatients and outpatients were treated. Outpatients were not allowed to drive on the day of treatment and had to meet the following criteria: (1) return to predose hemodynamic parameters, (2) Clinician-Administered Dissociative State Scale (CADSS) score of 0 (or $\leq$ pretreatment score), (3) at least 30 minutes of observation after the end of the infusion. For patients whose response was not sustained, the clinicians attempted to develop an individualized, symptom-triggered tapering regimen, the goal of which was to maintain response while giving ketamine every three or four weeks. The CogState battery (www.cogstate.com) was performed at baseline and every 6-12 treatments.

During the 29-month study period, 54 patients (16-87 yo, mean age = 46.7) were treated with at least one ketamine infusion and a total of 518 infusions were given. Approximately 80% of the patients had major depressive disorder and the average baseline QIDS-SR score was 19.8 (6.0). Half had been treated with ECT and 65% had a history of hospitalization for suicidal ideation or attempt.

Acute Phase

Forty-four (44) of the 54 total patients suffered from a primary mood disorder and completed an acute treatment period, which consisted of four infusions over two weeks. Response was defined as 50% or greater improvement in QIDS-SR and remission was defined as QIDS-SR score $\leq$ 5. After the first infusion, 31.8% (n = 14) of patients responded and 11.4% (n = 5) remitted. By the fourth infusion, 45.5% (n = 20) responded and 27.3% (n = 12) remitted. **The majority of the improvement occurred between the first and second infusions.** Five patients dropped out of the acute phase—four because of lack of efficacy and one because of inability to tolerate the infusions.

Figure 1. Depression Severity Over Time in a 4-Infusion Ketamine Protocol[a]



[a]Last observation carried forward was used for missing data. A mixed-effects, general linear model showed a main effect of time using the QIDS-SR (main effect of time: $t = -7.72$, $P < .001$) as well as the MADRS ($t = -8.48$, $P < .001$). Treatments were given twice weekly. Time points between treatments were 2–4 days; the QIDS-SR was administered 24 hours following each treatment. Arrows indicate ketamine infusions.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

With regard to dissociative effects in the acute phase, the mean (SD) CADSS score was 6.79 (8.51) at 40 minutes and nearly zero at 70-80 minutes (mean [SD] score = 0.12 [0.32]). Following the second, third, and fourth infusion, mean (SD) CADSS scores at 40 minutes were 5.86 (6.25), 4.52 (5.03) and 4.53 (7.16), respectively. At 70-80 minutes, mean CADSS scores were 0.07 (0.26), 0.04 (0.19), and 0.00 (0.00), respectively.

Continuation/maintenance phase

Fourteen (14) patients received continuation/maintenance ketamine treatment that lasted at least 14 weeks (range 14-126 weeks). Overall, 351 treatments were administered. The average number of treatments per patient was 25.1 (10.5) and the mean length of course of treatment was 75.7 (39.2) weeks. **Not including the acute phase of four treatments given twice per week, the mean (SD) time between treatments was 22.3 days (22.7).** One (1) patient experienced tachyphylaxis, remitting after the acute phase but relapsing when the infusions were tapered to every two weeks. No clinical improvement was seen even after twice weekly therapy was restarted. Two (2) patients relapsed and required hospitalization after attempting suicide. After ketamine twice weekly was restarted, both recovered response status. Seven (7) patients relapsed (depression score < 25% improvement from baseline) but were able to recover response status. One (1) patient moved to another state for six months but responded partially after a second acute series of ketamine treatment. Three (3) individuals did not relapse during longer-term follow-up. **Qualitatively, 7 of these 14 patients said that ketamine's antidepressant effect started to fade approximately 3 weeks after an infusion**.

The CogState battery was performed at baseline and every 6-12 treatments thereafter. There was no correlation between number of infusions and change in cognition. Neither cystitis nor increased psychosis were observed. Other than one of the 14 patients who was dismissed from the program because of cannabis abuse, there was no indication of increased drug-seeking behavior.

Archer and colleagues (2018) performed a retrospective case series of patients with TRD who received acute and maintenance IV ketamine infusions at a hospital in Canada. The investigators defined TRD as a depressive disorder diagnosis (unipolar or bipolar), failure of at least five antidepressants, refractory to psychotherapy, and refractory to or unable to undergo ECT. Exclusion criteria included psychosis, primary personality disorder, substance use disorder, or uncontrolled medical condition. Ketamine was given at a dose of 0.5 mg/kg, infused for 40 minutes. The institution's ketamine protocol required the following baseline labs: CBC, creatinine, electrolytes, TSH, liver enzymes, 12-lead electrocardiogram.

During the one-year review period (January 1, 2016-December 31, 2016), 30 patients underwent an acute course of IV ketamine. The acute phase consisted of twice weekly infusions for either six or eight treatments. Based on response in the acute phase, the treating psychiatrist decided which patients would benefit from maintenance therapy; **the treating psychiatrist determined the frequency and number of treatments during the maintenance phase on a case by case basis.** Most patients continued their existing medication regimens during both phases of the study. Patients completed the Beck Depression Inventory II (BDI-II) before each infusion. No specific BDI-II cutoffs were used in determining eligibility for maintenance therapy—rating scale scores were just one part of the overall evaluation of response.

Of the 30 patients who received acute treatment, 11 (10 females) entered the maintenance phase. The patients ranged in age from 31 to 69 years, eight had unipolar depression (three had bipolar depression), and all had received at least one course of ECT. The total number of treatments ranged from 10 to 51; total length of treatment ranged from 6 to 49 weeks.

All patients who entered the maintenance phase experienced a decrease in BDI-II scores during the acute phase. In all patients, the median maintenance and final BDI-II score were lower than the baseline BDI-II score. **However, only 4 of the 11 patients demonstrated median maintenance and final BDI-II scores $\leq$ the post-acute BDI-II score.** At the end of the one-year period, only 4 of the 11 patients were continuing maintenance ketamine infusions.

Nursing staff used a tracking sheet to monitor vital signs and side effects. All patients experienced transient side effects during the infusions. These included heart rate and blood pressure elevations, feeling faint, drowsiness, blurred vision, headache, dry mouth, restlessness, feelings of dissociation, changes in perception of stimuli, difficulty concentrating. One patient discontinued maintenance treatment because of dissociative symptoms and irritability which subsided a couple of days after the infusions. There were no reported lab abnormalities or cognitive or urinary side effects.

The authors concluded that maintenance ketamine treatments may be appropriate for a select subset of patients.

The studies summarized below evaluate the effects of **iv ketamine's effects in patients with suicidal ideation** and **escalating iv ketamine doses.**

Wilkinson et al., 2017

Wilkinson and colleagues examined the effects of a single dose of intravenous ketamine on suicidal ideation (si) in patients with major depression, PTSD, and bipolar disorder. Researchers extracted individual patient data from studies published between January 1, 2000 and November 15, 2016; included studies were required to have used either saline or midazolam as a control. Inclusion criteria included active or passive suicidal ideation, which was defined as a score $\geq$ 2 on MADRS item 10 ("weary of life/fleeting suicidal ideation") or a score $\geq$ 1 on the HAM-D suicidal ideation item ("feels life is not worth living"). For self-report scales, si was defined as a score of $\geq$ 1 on QIDS-SR item 12 ("I feel that life is empty or wonder if it's worth living") or a score $\geq$ 1 on the Beck Depression Inventory (BDI) item 9 ("I have thoughts of killing myself, but I would not carry them out").

Ten trials were included in the meta-analysis. One hundred sixty-seven patients (167) from these trials met the criteria for baseline si. Average baseline rating scale scores were as follows: MADRS score = 33.4, HAM-D = 20.5, QIDS-SR = 17.7, BDI = 29.2. About 48% of patients were receiving psychotropic medications. The primary outcome measures were the suicide items from the above listed rating scales, obtained for up to one week after ketamine administration.

In depressed patients with si, iv ketamine reduced si within one day and the effect lasted up to a week. Compared with control treatments, ketamine had significant benefits on the individual suicide items of the MADRS, HAM-D, and the QIDS-SR but not the BDI. Ketamine's effects on si were partially independent of its effect on mood.

Cusin et al., 2017

In an open-label study, Cusin and colleagues attempted to assess (1) the clinical antidepressant safety and efficacy of two-step repeated intravenous dose ketamine augmentation in outpatients with TRD and (2) the duration of ketamine's antidepressant efficacy as augmentation to ongoing antidepressants for three months after the final infusion.

Patient were required to stay on their current antidepressant medication regimen for 4 weeks prior to the start of the study and the duration of the trial period. Inclusion criteria were (1) age 18-65 years; (2) primary diagnosis of MDD; (3) HAM-D_{28} score $\geq$ 20 at screening; (4) history of three or more failed antidepressant treatment trials of adequate dose/duration during the current episode (including current regimen); (5) SI for more than 3 months, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS), without the requirement for immediate hospitalization; (6) score on HAM-D_{28} suicide item $\geq$ 2 (current SI, thoughts of own death). Exclusion criteria were (1) pregnancy; (2) unstable medical illness; (3) bipolar disorder; (4) past multiple adverse drug reactions; (5) psychotic illness; (6) substance use disorder within 1 year; (7) positive urine toxicology; (8) past history of ketamine abuse and (9) SI requiring immediate hospitalization or immediate risk.

Study participants received the infusions at Massachusetts General Hospital's Clinical Research Center (CRC) where an anesthesiologist and a psychiatrist were

present during all infusions. Side effects and vital signs were monitored 30 minutes prior to the infusion, every 5 minutes during the infusion, and for 2 hours afterwards by the nursing staff. Before being discharged home under the care of a responsible adult, patients were taken from the CRC to the outpatient psychiatry clinic for further evaluation by a psychiatrist or psychologist. For three weeks, patients received twice weekly infusions for a total of six treatments. The initial dose was 0.5 mg/kg administered over 45 minutes. **After Infusion 3, if a participant's HAM-D_{28} score did not improve by at least 30%, the dose was increased to 0.75 mg/kg for Infusions 4,5, and 6.**
Fourteen individuals (14) met inclusion criteria and 12 completed all six infusions. The mean baseline HAM-D_{28} score was 28.6 $\pm$ 4.8. Participants were taking an average of 1.9 $\pm$ 1.0 antidepressants, 1.9 $\pm$ 1.7 other psychotropic medications (mood stabilizers, atypical antipsychotics, benzodiazepines) and, in the current episode, had failed 8.3 $\pm$ 5.7 previous antidepressant trials. Six of the 14 (42.9%) had failed an adequate course of ECT either in the current episode or lifetime.
After the completion of three ketamine infusions, 7.1% (1/14) of patients responded. Of patients who completed all six infusions, 5/12 (41.7%) met criteria for response and 2/12 (16.7%) met criteria for remission. **The authors concluded that there was more pronounced improvement during the higher dose phase.** See Figure 1.
During the three-month follow-up, patients were seen every two weeks. **One of the five responders maintained response for six weeks after the final infusion but the other four responders relapsed within two weeks.**
No serious adverse events were reported and both doses were well tolerated. The most common side effects were mild in nature and included the following: visual and auditory disturbances (buzzing sounds), dissociative symptoms, drowsiness, sedation, headache, and nausea. Most of these resolved within one to two hours after the end of the infusion. All patients experienced at least a 10 mmHg elevation in systolic blood pressure during the infusion but there were no significant changes in pulse or oxygen saturations.

Ionescu et al., 2018

In a double-blind, randomized, placebo-controlled study, Ionescu and colleagues studied medicated outpatients with severe MDD with chronic SI. Twenty-six (26) outpatients were randomized to six ketamine infusions (0.5 mg/kg over 45 minutes) or saline placebo over three weeks. Researchers assessed depression and SI at baseline, 240 minutes' post-infusion, and during a three-month follow-up phase.

During the three-week infusion phase, there were no differences in depression severity or SI between ketamine and placebo. At the end of the three weeks, two ketamine patients and one placebo patient met remission criteria. At three-month follow-up, two patients in each group met remission criteria. The authors concluded that outpatients with severe TRD and chronic SI may require more than 0.5 mg/kg of intravenous ketamine.

Given that intravenous ketamine administration may not be feasible in outpatient settings, researchers have begun exploring the **intranasal route**.

Lapidus et al., 2014

In a randomized, double-blind, cross-over, proof of concept trial, Lapidus et al. studied intranasal ketamine in adults (age 21-65) with depression. Participants had to have failed at least one prior antidepressant (AD) trial in the current episode and were allowed to continue stable doses of psychotropics (including AD) throughout the study. Inclusion criteria included a diagnosis of Major Depressive Disorder (MDD), chronic or recurrent, without psychotic features and a baseline score $\geq$ 30 on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C) Exclusion criteria included the following: unstable medical/neurological condition, axis I disorder other than MDD, high risk of suicide, substance abuse/dependence in past 6 months, psychotic disorder, bipolar disorder, developmental disorder, lifetime abuse/dependence on ketamine/phencyclidine.
The study consisted of two seven-day treatment periods; treatment periods were at least seven days apart. To progress from the first to the second treatment period, participants had to have an IDS-C score ≥ 24. **An anesthesiologist in a clinical research unit provided the 20-minute administration of either 50 mg of racemic ketamine hydrochloride or placebo (0.9% saline solution).** Study drug or placebo was provided in identical syringes, containing clear solutions of either 100 mg/ml ketamine in 0.9% saline or saline alone. An LMA MADgic mucosal atomization device (LMA North America, Inc., San Diego, CA) was used to provide 5 intranasal applications of solution (volume 100 µl), separated by five minutes. Each of five ketamine applications provided 10 mg of study drug.
Vital signs (heart rate, blood pressure, respiration, and pulse oximetry) were continuously monitored for at least four hours in the research unit following treatment. In the original protocol, participants remained in the research unit overnight but after safety was shown, the protocol was changed to allow for discharge four hours after treatment with outpatient follow-up.
The primary outcome was change in the Montgomery-Asberg Depression Rating Scale (MADRS) at 24 hours following intervention. In each treatment period, assessments occurred at +40 min, +120 min, +240 min, +24 h, + 48 h, +72 h, and +7 days following treatment administration. Secondary outcomes included change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) and Hamilton Anxiety Rating Scale (HAM-A) and the proportion of participants meeting response (≥ 50% decrease in MADRS from baseline) or remission (MADRS ≤ 9) criteria.
Safety and tolerability were evaluated using the following instruments: Brief Psychiatric Rating Scale-Positive sub-scale (BPRS+), Clinician-Administered Dissociative States Scale (CADSS), mood item of the Young Mania Rating Scale (YMRS), Systematic Assessment for Treatment Emergent Effects (SAFTEE). Clinically significant changes were defined as systolic or diastolic blood pressure > 180/100 mmHg or heart rate > 110 beats/minute. Management of adverse effects was provided per protocol or as believed necessary by the treating anesthesiologist.
Twenty individuals qualified for the study and were randomized to one of two treatment orders: ketamine-placebo or placebo-ketamine. Two participants withdrew consent and did not participate in both treatment periods. Thus, 18 patients completed both treatment periods and were included in the modified intent to treat (mITT) sample.
Table One summarizes demographic and clinical characteristics of the study participants.

Characteristic	Value
Participants treated, n (%)	20 (100)
Gender (M/F)	10/10
Age at enrollment (yrs)	**48.0 ±12.8**
Race (%)	
Caucasian	**18/20 (90)**
Asian	1/20 (5)
Black	0/20 (0)
Other	1/20 (5)
Hispanic (%)	3/20 (15)
Married (%)	6/20 (30)
Employed (%)	10/20 (50)
Age of Onset	21.4 ±12.0
Illness Duration in Years	**27.4 ± 13.7**
Length of Current Episode in Years	**15.2 ±17.4**
Failed Antidepressant Medications	4.1 ± 3.9
History of ECT (%)	4/20 (20)
History of Psychotherapy (%)	17/19 (89)
History of Suicide Attempts (%)	2/20 (10)
Past Substance Use Disorder (%)	3/20 (15)
Current Anxiety Disorder (%)	4/20 (20)
Melancholic (%)	9/20 (45)
Atypical (%)	2/20 (10)
Baseline IDS-C (Screen)	**42.7 ± 8.5**

Results

Compared to placebo, ketamine administration was associated with significant improvement of depressive symptoms at the 24 hour post-intervention time point. The estimated mean difference in MADRS score was 7.6 ± 3.7 (95% CI: 3.9-11.3). Response was defined as a 50% drop in MADRS score. **Twenty-four hours after ketamine administration, 8/18 (44%) of participants responded; 24 hours after placebo administration, 1/18 (6%) responded. Improvement in depressive symptoms was not sustained and there was no significant difference at 72 hours or seven days.** With regard to secondary outcomes, ketamine administration was associated with significant improvement on the QIDS-SR and HAM-A at the 24-hour time point. Mean difference in QIDS-SR was 3.0 ± 2.4 (95% CI: 1.1-4.9). Mean difference in HAM-A was 4.5 ± 3.2 (95% CI: 1.4-7.6).

Intranasal ketamine was associated with small increases on measures of psychosis (BPRS+) and dissociation (CADSS). No relationship was found between antidepressant response and ketamine associated changes in dissociative or psychotomimetic symptoms. Four participants experienced treatment-emergent increases in systolic blood-pressure > 130 mm Hg following ketamine compared to three following placebo. No patients had a diastolic blood pressure > 100 mm Hg. All hemodynamic changes resolved four hours post infusion and there was no association between antidepressant response and hemodynamic changes. The most common adverse events related to ketamine administration were feeling strange/unreal, poor memory, weakness/fatigue. **There were no serious adverse events and most resolved within four hours.**

Daly et al., 2018

Daly and colleagues conducted a phase 2, double-blind, doubly randomized, delayed-start, placebo-controlled study of intranasal esketamine adjunctive to oral antidepressant therapy—the first clinical study to date of intranasal esketamine for TRD. Esketamine, the *S*-enantiomer of ketamine, has a higher affinity for the NMDA receptor than the *R*-enantiomer and rapid antidepressant efficacy has been shown with its intravenous administration.
Participants were medically stable adults (20-64 years) with a diagnosis of MDD (DSM-IV-TR). All had TRD, defined as inadequate response to 2 or more antidepressants (with at least 1 inadequate response in the current episode). Inclusion criteria included a score of ≥ 34 on the 30-item, clinician-rated Inventory of Depressive Symptomatology, which corresponds to moderate to severe depression. Exclusion criteria included the following: recent or current suicidal ideation with intent to act, suicidal behavior, or homicidal ideation or intent, diagnosis of bipolar or related disorders, intellectual disability, psychotic disorder, MDD with psychosis, PTSD, OCD, substance/alcohol use disorders in the past year, recent use of cannabis.
Study participants continued on established oral antidepressant therapy. A disposable nasal spray device contained 200 µL of solution (ie, 2 sprays). Each device provided either esketamine hydrochloride, 16.14 (14 mg of esketamine base) per 100 µL spray or placebo. On each dosing day during phase 2, participants self-administered 1 spray of study drug into each nostril at 3 points, each separated by 5 minutes. During phase 3, participants self-administered 1 spray of esketamine into each nostril at 1,2, or 3 points (28, 56, or 84 mg), each separated by 5 minutes.
The study was conducted in multiple outpatient referral centers and included **four phases**:

- (1) screening (n=126)
- (2) double-blind treatment (days 1-15), **made up of two 1-week periods**
- (3) optional open-label treatment (days 15-74)
- (4) post-treatment follow-up (8 weeks).

See Figure 1. At the beginning of double-blind treatment, 67 patients were randomized (3:1:1:1) to intranasal placebo or esketamine 28, 56, or 84 mg, twice weekly (days 1 and 4). Thirty-eight of these 67 patients were women, mean [SD] age = 44.7 [10.0] years.

At the end of period 1, 28 of 33 placebo patients (85%) continued to have moderate to severe symptoms (QIDS-SR_{16} total score $\geq$ 11). These 28 patients were re-randomized (1:1:1:1) to intranasal esketamine 28 mg, 56 mg, or 84 mg or placebo twice weekly (days 8 and 11). Placebo patients who had mild or no symptoms at the end of period 1 continued placebo (n=4).
Regardless of response in the double-blind phase (phase 2), all study participants had the option of entering the open-label phase (phase 3), the purpose of which was to evaluate the efficacy of less-frequent intranasal esketamine dosing. Sixty of 67 patients (90%) completed periods 1 and 2 and 57 patients entered the open-label phase (phase 3). Esketamine 56 mg was administered on day 15 and investigators adjusted subsequent doses (range, 28-84 mg) based on their clinical judgment. **Administration was twice weekly for the first 2 weeks, weekly for the next 3 weeks, then every 2 weeks thereafter.**
The primary efficacy end point was change from baseline (pre-dose, day 1 in each period) to end point (day 8 in each period) in MADRS total score.
The MADRS was performed on days 1 (predose and 2 hours postdose), 2, 8 (predose), 9 and 15.
Before ketamine administration and at 40 minutes and two hours' post-dose, researchers assessed the following safety measures: vital signs, the Clinician Administered Dissociative States Scale (CADSS), 4 item positive symptom subscale from the Brief Psychiatric Rating Scale (BPRS).
Results
In all 3 esketamine groups, change (least squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) was superior to placebo (esketamine 28 mg: -4.2 [2.09], p = 0.02; 56 mg: -6.3 [2.07], p = 0.001; 84 mg: -9.0 [2.13], p < 0.001. In the open label phase, improvement was sustained (-7.2 [1.84]) even though intranasal ketamine was dosed less frequently. **At the end of the open-label phase (74 days), approximately 65% of remaining patients were classified as responders (decrease in MADRS total score $\geq$50%) and 32.4% met remission criteria (MADRS total score $\leq$ 10).** See Figures 2 and 3. During the double-blind phase, three individuals who received nasal esketamine left the study because of adverse events (versus none receiving placebo). These events included syncope, headache and dissociative syndrome. During the open-label phase, one individual left the study because of an adverse event (ectopic pregnancy).

Canuso et al., 2018

In a double-blind, randomized, multicenter, proof-of-concept study, Canuso and colleagues evaluated the efficacy of standard-of-care (SOC) treatment plus intranasal esketamine or placebo in patients with MDD at imminent suicide risk. Sixty-eight (68) individuals were randomly assigned to receive esketamine 84 mg or placebo twice weekly (in addition to standard care) for four weeks. Participants were individuals aged 19-64 years who had presented to an emergency department or inpatient psychiatric unit. Inclusion criteria included: diagnosis of MDD without psychotic features according to DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI); affirmative response to MINI question B5 ("Think about suicide [killing yourself]?") in the present and B9 ("Intend to act on thoughts of killing yourself?") in the past 24 hours; score $\geq$ 22 on the MADRS on day 1 before dosing; voluntary agreement to SOC treatment, including hospitalization (5 days after randomization unless treating physician

determined that longer/shorter period was warranted) and initiation or optimization of one or more non-investigational antidepressants. Exclusion criteria included a current diagnosis of bipolar disorder, moderate to severe substance use disorder, intellectual disability, antisocial personality disorder, borderline personality disorder, current/past diagnosis of a psychotic disorder.

The study consisted of four weeks of db treatment (days 1 to 25) followed by eight weeks of posttreatment follow-up (days 26 to 81). During the four week db phase, participants were randomized to receive either twice-weekly intranasal esketamine 84 mg or matching placebo in addition to SOC. Randomization was stratified by study center and type of SOC antidepressant (monotherapy or AD plus augmentation therapy). Under the supervision of a health care provider, participants self-administered the study drug via a nasal spray device. Each device held 200 uL of solution (i.e., two sprays, each 100 uL spray delivering 14 mg of esketamine or placebo). Three nasal sprays were required to deliver 84 mg of esketamine; a bittering agent was added to the placebo to help mask treatment assignment. **The primary efficacy endpoint was change in MADRS score from baseline to four hours after initial dose. Clinicians' global judgment of suicide risk was also assessed using the Suicide Ideation and Behavior Assessment Tool.** After hospital discharge, outpatient appointments occurred twice weekly through day 25 of db treatment. During posttreatment follow-up (days 26 to 81), study participants only received SOC antidepressant treatment. Appointments were weekly through day 52 and biweekly through day 81.

Most randomized participants (49/68) completed the db treatment phase and entered post-treatment follow-up, which 44 individuals completed.

Baseline MADRS score was 38.5 (6.17) and 38.8 (7.02) in the esketamine and placebo groups, respectively. At 4 and 24 hours, a significantly greater improvement in MADRS score was observed in the esketamine group compared to the placebo group (least-square mean difference = - 5.3, SE = 2.10, effect size = 0.61; least-square mean difference = -7.2, SE = 2.85, effect size = 0.65). At day 25, the difference in improvement between the two groups was not significant (least-square mean difference = - 4.5, SE = 3.14, effect size = 0.35. See Figure 2.

Patients who received esketamine experienced significantly greater improvement on the MADRS suicidal thoughts item score at 4 hours (effect size = 0.67) but not at 24 hours (effect size = 0.35) or at day 25 (effect size = 0.29). See Figure 3.

A clinician global judgment of suicide risk score of 0-1 was thought to indicate a resolution of suicide risk. In a post-hoc analysis, a greater number of participants in the esketamine group (compared to the placebo group) achieved resolution of suicide risk at 4 hours (21.2% vs 9.7%) and 24 hours (40.0% vs 6.5%) after the first dose. See Figure 4.

Nasal esketamine was generally well tolerated. The most common adverse events in patients who received esketamine were nausea, dizziness, dissociation, unpleasant taste, and headache. Five patients in the esketamine group dropped out of the db phase because of adverse events. These were agitation, aggression, unpleasant taste, and ventricular extrasystoles in one participant each and dizziness/dyspnea/nausea in one participant. Transient elevations in blood pressure were observed the esketamine group across all dosing days (maximum mean increase from predose measurement: systolic, 16.7 mmHg (SD= 10.46), compared with 8.7 mm Hg (SD = 7.48) for the placebo; diastolic, 11.9 mm Hg (SD = 8.88) compared with 7.6 mm Hg (SD = 9.35) for the placebo group. Blood pressure elevations peaked at 40 minutes after dosing and returned to pretreatment levels within 2 hours after dosing. Dissociative symptoms (CADSS)

peaked at 40 minutes after dosing, resolved by 2 hours, and lessened with repeated dosing.

Conclusions and Recommendations

Ketamine provides rapid relief for many patients with TRD and when given under appropriate supervision, both the intravenous and intranasal routes of administration seem generally well tolerated. For patients who do respond well to standard antidepressants, ketamine could provide fast relief while the medication is reaching its full effect. Significant downsides to ketamine's use include its abuse potential and lack of information about long-term efficacy and optimal dosing strategies. More studies are clearly needed and Johnson & Johnson is currently seeking FDA approval for the use of intranasal esketamine in patients with major depression who are treatment resistant and/or acutely suicidal. If ketamine is used in HHSC state operated facilities, I would suggest adherence to the recommendations of the 2017 APA Consensus Statement.

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Catherine Hall, PharmD, BCPP, BCACPClinical Pharmacist, San Antonio State Hospital, October 5, 2018

415 – C
EXHIBIT A

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION

(for inclusion in the *DSHS/DADS Drug Formulary*)

** (THE NEW DRUG APPLICATION PROCESS IS DESCRIBED ON THE BACK OF THIS FORM.) **

Date: 05-10-18

Name of practitioner submitting the application: Cecilia De Varona

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state school, state center, or local authority (state-operated community services (SOCS) or community MHMR center)): El Paso Psychiatric Center

Information regarding new drug:

Therapeutic Classification	Stimulant
Generic Name	Dexmethylphenidate Hydrochloride
Trade Name(s)	Focalin XR
Manufacturer(s)	Novartis
Dosage Form(s)	capsules – 5, 10, 15, 20 mg

Explain the pharmacological action or use of this drug: ADHD symptoms

Explain the advantages of this drug over those listed in the formulary: less intensive side effects

State which drugs this new drug would replace or supplement:

****

☑ application is approved

OR

☐ application is appropriate and complete

signature of chairman of facility pharmacy and therapeutics committee

signature of clinical/medical director or designee

Dexmethylphenidate Hydrochloride Extended-Release (Focalin XR®)

Classification:

Central Nervous System (CNS) Stimulant – Schedule CII

Pharmacology:

Mechanism of Action: Dexmethylphenidate hcl is the pharmacologically active *d-threo* enantiomer of racemic methylphenidate hcl (Ritalin®). Dexmethylphenidate hcl is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase release of these monoamines into the extraneuronal space.

Pharmacokinetics:

Absorption: Dexmethylphenidate produces a bi-modal plasma concentration-time profile that displays the first peak at approximately 1.5 hours (range 1-4 hours) and the second peak at approximately 6.5 hours (range 4.5-7 hours) after oral administration. The initial rate of absorption for dexmethylphenidate XR is similar to that of dexmethylphenidate IR tablets given in two doses 4 hours apart. Ranges vary more with dexmethylphenidate XR although the AUC after daily administration is equivalent to the same total dose of dexmethylphenidate IR. Due to first-pass metabolism, mean absolute bioavailability of dexmethylphenidate when administered in various formulations was 22-25%. No food effect study performed with dexmethylphenidate XR. However, food effect findings with racemic methylphenidate are applicable to dexmethylphenidate XR; after high fat breakfast, there was longer lag time until methylphenidate absorption began and variable delays in peak concentrations.

Distribution: Dexmethylphenidate has a volume of distribution of 2.65 ± 1.11 L/kg. The plasma protein binding of dexmethylphenidate is unknown. Although racemic methylphenidate is bound to plasma proteins by 12-15%. Plasma dexmethylphenidate concentrations decline monophasically following oral administration of dexmethylphenidate XR.

Metabolism: Dexmethylphenidate is metabolized primarily to *d-a*-phenyl-piperidine acetic acid (*d*-ritalinic acid) by de-esterification. This metabolite has little to no pharmacological activity.

Elimination: The elimination half-life of dexmethylphenidate is variable with a mean of 3 hours (ranges 2-4.5 hours) with occasional elimination half-lives between 5-7 hours. Children have shorter elimination half-lives ranging from 2-3 hours.

Indications:

CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

Dosage:

Intended for oral administration once daily in the morning. Dexmethylphenidate XR may be given with or without food. For patients unable to swallow capsule, contents may be sprinkled on applesauce. Extended-release capsules should not be crushed, chewed, or divided.

Recommended starting dose for patients new to dexmethylphenidate XR is 5 mg once daily for pediatric population and 10 mg once daily for adults. The dose may be titrated up in 5mg increments for pediatric population and 10 mg increments for adults. Doses above 30 mg/day in children and 40 mg/day in adults have not been studied.

For patients currently using methylphenidate, initiate dexmethylphenidate XR with half the current daily dose of methylphenidate. For patients using dexmethylphenidate immediate release, switch to same daily dose of dexmethylphenidate XR.

Contraindications:

- Known hypersensitivity to methylphenidate, dexmethylphenidate or other product components
- Marked anxiety, tension, and/or agitation
- Glaucoma
- History of motor tics or a family history or diagnosis of Tourette's syndrome
- Structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, or other serious cardiovascular problem
- During or within 14 days following discontinuation of a monoamine oxidase inhibitor (MAOI)

Warnings/Precautions:

- History of drug dependence or alcoholism – [Boxed Warning] may lead to tolerance and psychological dependence
- Pregnancy Category C – no adequately controlled studies in pregnant women
- Nursing Mothers – unknown if dexmethylphenidate is excreted in human milk
- Children under 6 years old – safety and efficacy of dexmethylphenidate XR not established
- Geriatric population – dexmethylphenidate XR has not been studied
- New onset or preexisting psychosis – stimulants may exacerbate symptoms
- New onset or preexisting bipolar disorder – possible induction of mixed/manic episode
- Seizure disorder – stimulants may lower seizure threshold
- Cardiac conditions (hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia) – stimulants increase blood pressure and heart rate
- Visual disturbance – accommodation difficulty and blurry vision reported with stimulants
- Long-term suppression of growth in children
- Peripheral vasculopathy (including Raynaud's phenomenon)
- Priapism

Interactions:

- MAO inhibitors (concurrently or within previous 2 weeks)
- Use cautiously with pressor agents due to effects on blood pressure
- May decrease effectiveness of anti-hypertensives

- Antacids or acid suppressants could alter the release of dexmethylphenidate XR: can increase initial absorption but decrease delayed absorption since modified release is pH dependent
- Racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g. imipramine, clomipramine, desipramine); downward dose adjustments or therapeutic monitoring may be necessary.

Adverse Reactions:

The most common reasons for dexmethylphenidate XR discontinuation were motor and vocal tics, anorexia, insomnia and tachycardia in the pediatric population, and insomnia, anorexia, anxiety and feeling jittery in the adult population.

The most common side effects for pediatric patients were dyspepsia, decreased appetite, headache, and anxiety. Whereas the most common side effects for the adult population were dry mouth, dyspepsia, headache, and anxiety.

HHSC Cost: (daily dosing)

Dexmethylphenidate XR 5 mg: $3.95
Dexmethylphenidate XR 10 mg: $3.95
Dexmethylphenidate XR 15 mg: $2.97
Dexmethylphenidate XR 20 mg: $3.96
Dexmethylphenidate XR 25 mg: $3.26
Dexmethylphenidate XR 30 mg: $3.79
Dexmethylphenidate XR 35 mg: $3.26
Dexmethylphenidate XR 40 mg: $5.73
Price Comparison:
Dexmethylphenidate IR (BID dosing): 5 mg ($0.55), 10 mg ($0.70)
Concerta® (daily dosing): 18mg ($4.96), 27mg ($3.31), 36 mg ($5.48), 54 mg ($3.63)
Metadate CD® (daily dosing): 10mg ($2.56), 20 mg ($2.56), 30 mg ($2.56), 40 mg ($3.51), 50mg ($4.32), 60 mg ($4.32)

Monitoring:

HHSC monitoring: weight and height is all that is currently required
Drug labeling monitoring:

- Hematological monitoring: periodic CBC, differential, and platelet counts advised during prolonged therapy as there have been rare cases of leukopenia, anemia, and thrombocytopenic purpura.
- Blood pressure and heart rate: recommended for all patients due to risk for increase in blood pressure (2-4 mmHg) and heart rate (3-6 bpm).
- EKG: American Academy of Pediatrics does not recommend unless clinically indicated.

Product Identification:

Extended-Release Capsules:
5 mg (NDC 0078-0430-05) light-blue (imprinted NVR D5)
10 mg (NDC 0078-0431-05) light caramel (imprinted NVR D10)
15 mg (NDC 0078-0493-05) green (imprinted NVR D15)
20 mg (NDC 0078-0432-05) white (imprinted NVR D20)
25 mg (NDC 0078-0608-05) light-blue and white (imprinted NVR D25)

30 mg (NDC 0078-0433-05) light caramel and white (imprinted NVR D30)
35 mg (NDC 0078-0609-05) light-blue and light caramel (imprinted NVR D35)
40 mg (NDC 0078-0434-05) green and white (imprinted NVR D40)
Store Focalin XR® at 25°C (77°F), excursions permitted 15°–30°C (59°–86°F).
Dispense in tight container (USP).

Efficacy:

The effectiveness of dexmethylphenidate XR in the treatment of ADHD was established in multiple randomized, double-blinded, placebo-controlled studies in children, adolescents and adults who met DSM-IV criteria for ADHD.[1]

Children/Adolescents**:**

A double-blind, placebo-controlled study randomized 97 pediatric patients (ages 6-17) to receive dexmethylphenidate XR 5-30mg/day or placebo once daily for 7 weeks.[2] ADHD signs and symptoms were evaluated using teacher-rated Conners ADHD/DSM-IV Scales (CADS-T). The study compared mean change from baseline scores to endpoint scores using intent-to-treat analysis. Results showed statistically significant treatment effect in favor of dexmethylphenidate XR. Two additional cross-over studies in pediatric patients aged 6-12 years old compared dexmethylphenidate XR 20 mg to placebo. Dexmethylphenidate XR showed a statistically significant treatment effect vs. placebo on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale combined score.[1]
An additional double blind, crossover study randomized 56 children and adolescents with ADHD to receive dexmethylphenidate XR (10, 20, 25-30 mg) or ER mixed amphetamine salts (10, 20, 25-30 mg).[3] Participants were enrolled in both trials with a week of placebo in between each drug period. Efficacy was assessed using ADHD Rating Scale-IV; adverse events measured with parent-completed Stimulant Side Effects Rating Scale. In the primary efficacy measure, results showed dexmethylphenidate ER and amphetamine ER were both associated with dose-dependent medication response in reductions in ADHD symptoms regardless of stimulant class ($p<0.001$). Although side effect profile was similar in both stimulants and showed increase rates of insomnia and decreased appetite at higher doses, results were statistically insignificant. Furthermore, two head-to-head, double-blind, crossover studies compared Focalin XR® to Concerta® (20 mg vs. 36 mg; 30 mg vs. 54 mg) in children aged 6-12 years.[4-5] Results demonstrated Focalin XR® had earlier onset of efficacy with greater improvements from baseline in SKAMP scores earlier in the day at 2 hours post dose, whereas Concerta® showed greater improvement and retained greater effect at 12 hours post dose. Differences in onset of action is likely attributed to different drug-release technology as d-MPH mimics twice-daily IR dosing and d,l-MPH ER formulation immediately releases 22% of drug, then gradually increases, peaking later in the day.

Adults:

The efficacy of Focalin XR® for the treatment of ADHD in adults (18-60 years old) was established in a 5-week multicenter, randomized, fixed-dose, double-blind, placebo-controlled study.[6] 221 adults were randomized to receive either 20 mg, 30 mg, or 40 mg of Focalin XR® or placebo once daily. Study drug participants were initiated on 10 mg/day and titrated by increments of 10 mg/day to randomly assigned fixed dose. ADHD signs and symptoms were evaluated by comparing mean change from baseline to endpoint using intention-

to-treat analysis using DSM-IV ADHD Rating Scale. All three dexmethylphenidate XR groups had statistically significant improvements in mean ADHD RS-IV scores versus placebo with no definite increase in efficacy with increasing dose. A 6-month study follow up noted no clinically significant changes in vital signs, cardiac events, or any remarkable changes in laboratory data.[7]

Another study compared pharmacokinetics of dexmethylphenidate XR 20 mg given once daily, dexmethylphenidate IR 10 mg given 4 hours apart, and Ritalin LA 40 mg given once daily.[8] The primary pharmacokinetic endpoints (C_{max}, AUC) showed bioequivalence between all three formulations. Each formulation may offer advantages depending on time of day when ADHD symptoms occur. A systematic review evaluating long-acting methylphenidate formulations in the treatment of ADHD concluded past comparative data shows there is no formulation superior to another. Specific patient factors and subtle differences between formulations should be considered for treatment optimization.[9]

Conclusions:

The American Academy of Pediatrics recommends a stimulant, either a methylphenidate or amphetamine derivative, as first line therapy for ADHD.[10] MPH and AMP formulations have equal efficacy and similar side effect profiles according to several review, practice guidelines, and algorithms.[3] The choice of formulation depends on patient-specific factors such as patient age, preferred length of coverage time, ability to swallow tablets/capsules, expense of medication, time of day when ADHD symptoms occur, and abuse potential. If a trial with one group of stimulants is unsuccessful, a trial from the second group should be attempted. Although more expensive, extended-release formulations are generally preferred over immediate-release formulations due to their longer duration of action and dosing convenience. Unlike immediate-release formulations, they preclude the need for school-based administration. Some adolescents may need coverage for more than 12 hours, requiring the need for an immediate-release formulation in addition to an extended-release formulation. For patients unable to swallow tablets/capsules, long-acting capsules containing microbeads may be opened and sprinkled on food. Other formulation alternatives include a chewable tablet, long-acting suspension, long-acting orally disintegrating tablet, or transdermal patch. If time of ADHD symptoms occur later in the day, patients may benefit from long acting coverage such as Concerta® that peaks less in the morning with an increased effect later in the day. Dexmethylphenidate XR has biphasic peaks and a duration of 8-12 hours, which may benefit patients who have ADHD symptoms throughout the entire school day. In regards to efficacy of stimulants, dexmethylphenidate has similar efficacy compared to other methylphenidate and amphetamine formulations. In conclusion, it would be beneficial to add dexmethylphenidate XR to our formulary. It is the only other stimulant that is not on our formulary and would benefit patients that come into our facility already on dexmethylphenidate XR. It is now available in generic and comparable in price to other stimulants. In addition, it would be advantageous to have in our formulary should a drug-shortage on other stimulants arise.

Recommendation:

Recommended for addition to the formulary

References:

1. Product Information: FOCALIN XR(TM) extended-release oral capsules, dexmethylphenidate hydrochloride extended-release oral capsules. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2015. –revised 1/2017
2. Greenhill L, Muniz R, Ball R, Leving A, Pestreich L, and Jiang H. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(7):817-823.
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5. Silva R, Muniz R, McCague K, Childress A, Brams M, and Mao A. Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexmethylphenidate and D,L-methylphenidate and placebo in a laboratory classroom setting. *Psychopharmacology Bull.* 2008; 41(1), 19-33.
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7. Adler L A, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. *J Atten Disord. 2009; 12(5):449-59.*
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10. American Academy of Pediatrics. Implementing the Key Action Statements: An Algorithm and Explanation for Process of Care for the Evaluation, Diagnosis, Treatment, and Monitoring of ADHD in Children and Adolescents. *American Academy of Pediatrics*. 2011; 128(5): SI1-121.

Prepared by:

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September 2018

APPENDIX 1: NEW DRUG APPLICATION FORM
State Operated Facilities

(Formerly: Texas Department of Mental Health and Mental Retardation)

NEW DRUG APPLICATION
(for inclusion in the *State Operated Facilities Drug Formulary*)

Date: 09-17/2018

Name of practitioner submitting the application: Jeanna Heidel,

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)): Rusk State Hospital, EFC member.

Information regarding new drug:

Therapeutic Classification	Vaccine
Generic Name	HepB-CpG vaccine
Trade Name(s)	Heplisav-B
Manufacturer(s)	Dynavax Technologies Corporation.
Dosage Form(s)	IM

Explain the pharmacological action or use of this drug: HepB-CpG contain recombinant yeast-derived hepatitis B surface antigen (HBsAg), with a synthetic adjuvant, CpG. This adjuvant is thought to lead to the production of cytokines such as interleukin-12 and interferon-alpha.

Explain the advantages of this drug over those listed in the formulary: HepB-CpG vaccine is the only hepatitis B vaccine that can be given over two doses, one month apart. This would be more convenient for patients and possibly increasing the likelihood that patients will complete the series.

State which drugs this new drug would replace or supplement: Engerix-B and /or Recombivax HB

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☒ application is approved

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of clinical/medical director or designee

JON GUIDRY, MD

Hepatitis B Vaccine Recombinant, Adjuvant (HEPLISAV-B)

Classification: Vaccines

Description:

Hepatitis B is a liver infection caused by the Hepatitis B virus (HBV). HBV is transmitted when blood, semen, or another body fluid from a person infected with the Hepatitis B virus enters the body of someone who is not infected. This can happen through sexual contact; sharing needles, syringes, or other drug-injection equipment; or from mother to baby at birth. For some people, hepatitis B is an acute, or short-term, illness but for others, it can become a long-term, chronic infection. Risk for chronic infection is related to age at infection: approximately 90% of infected infants become chronically infected, compared with 2%–6% of adults. Chronic HBV can lead to serious health issues, like cirrhosis or liver cancer. [1] In 2016, a total of 3,218 cases of acute hepatitis B were reported to CDC. [2] The rate of new HBV infections has declined from 1990–2014. The decline has been greatest among children born since 1991, when routine vaccination of children was first recommended. Since 2014, there has been an increase in the rate of new HBV infections, which is likely due to increasing injection drug use.[3]

Pharmacology:

All HBV vaccines in the US available in the US contain recombinant yeast–derived hepatitis B surface antigen (HBsAg), with an immunostimulatory adjuvant. While all other available hepatitis B vaccines use aluminum hydroxide as an adjuvant, Heplisav-B uses CpG as the adjuvant. This is thought to lead to the production of cytokines such as interleukin-12 and interferon–alpha. [5, 7]

Indication:

Heplisav-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. It is approved for use in adults 18 years or of age or older.[6]

Dosage and administration:

Two doses, 0.5 ml each, one month (at least 4 weeks) apart.[6,7]

Administer HEPLISAV-B by intramuscular injection in the deltoid region.

Heplisav-B is a clear to slightly opalescent, colorless to slightly yellow solution; do not administer if particulate matter or discoloration is present.

2-dose Heplisav-B vaccine series only applies when both doses consist of HepB-CpG, administered at least 4 weeks apart.

A series consisting of a combination of one dose of HepB-CpG and a vaccination from a different manufacture (HepB-aluminum) should adhere to the following:

- Adhere to the 3 dose schedule with minimum intervals of 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3. However, if HepB-CpG is substituted for dose 2 of Hep-B Alum, a provider has the option of administering the next dose

of HepB-CpB a minimum of 4 weeks from the previous dose for a complete series.[7]

Contraindications:

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast.[6,7]

Precautions:

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B. [6.]
Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B. [6]
Hepatitis B has a long incubation period. HEPLISAV-B may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration. [6]

Interactions:

Use with immune globulins. There are no data to assess the commodities use of Heplisav-B with immune globulin. When concomitant administration of Heplisav-B and immune globulin are required, they should be given with different syringes at different injection sites.[6]
Interference with laboratory values: Serum HBsAg may not have diagnostic value within 28 days after receipt of Heplisav-B.[6]

Use in special Populations:

Pregnancy: There is a pregnancy exposer registry that monitors pregnancy outcome in women exposed to Heplisav-B. There are no clinical studies of Heplisav-B in pregnant women.[6] Until safety data is available for Heplisav-B, providers should continue to vaccinate pregnant women needing Hepatitis B Vaccine with Hep-B-Alum (ENGERIX-B® or RECOMBIVAX HB®) [7].
Lactation: It is not known whether Heplisav-B is excreted in human milk. Data are not available to assess the effects of Heplisav-B on the breast feeding infant or on milk production/excretion. [6]

Safety and efficacy of Heplisav-B have not been established in adults on hemodialysis. [6]

Adverse Effects:

The most common adverse effects of Heplisav-B in clinical trials were:
Injection site pain (23% to 39%)
Fatigue (11%-17%), and headaches (8%-17%). [5]

Cost:

Heplisav-B AWP cost per vial $138.00
AWP Cost per series $276.00
Sold as box of 5 doses.
Engerix-B AWP Cost per vial $68.70
AWP Cost per series $206.10
Sold as box of 10 doses.

Efficacy:

The immunogenicity of the new vaccine was evaluated in three randomized, observer-blind, studies that compared the rates of seroprotection after two doses of Heplisav-B at one and 4 weeks, to the other after 3 doses of Engerix-B given at 0, 2, and 6 months. Separation rates were significantly higher with Heplisav-B than with Engerix-B.

Conclusion:

The Advisory Committee on Immunization Practices (ACIP) has approved the recommendation for Heplisav-B vaccine to be an option for previously unvaccinated or incompletely vaccinated persons, including adults 18 years and older who have specific risk, or lack a risk factor but want protection.[7] In clinical trials, two doses of Heplisav-B were more immunogenic than three doses of an older hepatitis B vaccine (Engerix-B), but Heplisav-B caused more injection site reactions. The rate of serious adverse effects with the two vaccines were similar, but long term safety of Heplisav-B remains to be established. [5]

Recommendation: Add to Formulary.

References:

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2. CDC. Viral Hepatitis Surveillance–United States, 2016. 2018.
3. Harris AM, Iqbal K, Schillie S, Britton J, Kainer MA, Tressler S, et al. Increases in Acute Hepatitis B Virus Infections – Kentucky, Tennessee, and West Virginia, 2006-2013. MMWR Morb Mortal Wkly Rep. 2016;65(3):47-50.
4. CDC, Hepatitis B questions and answers for healthcare professionals. What are the hepatitis B vaccines licensed for use in the United States?
5. From the Medical letter on drugs and therapeutics. A Two Dose Hepatitis B Vaccine for Adults, (Heplisav-B) JAMMA, February 17, 2018. Volume 319, numbers 8.
6. Heplisav-B Package insert, Dynavax.
7. Advisory Committee on Immunization Practices (ACIP) recommendations. Heplisav-B (HepB-Cp-GpG) Vaccine.

Prepared by Dr. Jeanna Heidel, PharmD

Appendix D

Oral Anticoagulants

No required lab monitoring with direct oral anticoagulants (DOACs) because compared to the vitamin K antagonists (VKA), there is less variability in drug effect for a given dose. Before starting,

- CBC with differential; renal function (at least annually per AHA/ACC/HRS, 2014), hepatic function

Single missed dose of DOAC more likely to lead to inadequate anticoagulation than a single missed dose of warfarin

- for patients who tend to miss doses, consider warfarin

DOACs not appropriate in

- Severe renal insufficiency
- Pregnancy
    - Lack of clinical experience (use LMW heparin)
- Prosthetic heart valves
    - Greater risk of valve thrombosis compared to VKA
- BMI > 40 kg/m^2, weight > 120 kg
    - Rivaroxaban (Xarelto) product label, "extremes of body weight (< 50 kg or > 120 kg) do not significantly influence rivaroxaban exposure"

Helpful references

- Kearon C, Akl E, Ornelas J, et al. Antithrombotic Therapy for VTE Disease. CHEST Guideline and Expert Panel Report. CHEST 2016; 149 (2): 315-352
- Guyatt GH, Akl E, Crowther M, et al. Executive Summary. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141 (2) (Suppl) 7S-47S
- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1-76.

	Apixaban (Eliquis) (direct factor Xa inhibitor)
Approved Indications and Usual Dose (U.S)	Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (5 mg BID; 2.5 mg BID for patients with two or more of the following: age 80 years and older, weight 60 kg or less, serum creatinine 1.5 mg/dL or greater) VTE prevention post-hip or knee replacement (2.5 mg twice daily for 35 days [hip] or 12 days [knee] starting 12 to 24 hours post-op) DVT/PE treatment (10 mg BID for seven days, then 5 mg BID) DVT/PE prevention of recurrence (2.5 mg BID after at least six months of treatment)
Renal dosing	A fib indication, see above. Based on limited data, a dose of apixaban 2.5 mg BID instead of 5 mg BID might be considered in hemodialysis patients.
Antidote/pre-op, pre-procedure washout (if indicated)	Reversal agent: *Andexxa* (coagulation factor Xa). ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.
Therapeutic Considerations	BID dosing Not recommended in patients with prosthetic heart valves Severe liver impairment: not recommended Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement For VTE treatment, continue for at least three months. Benefit of extended use may not outweigh risk in patients with high bleeding risk[18]
Switching To/From Other Anticoagulants	To switch from warfarin, stop warfarin, then start apixaban when INR < 2 To switch to warfarin: apixaban increases INR, thus confounding initial warfarin dosing. U.S.: Consider starting a parenteral anticoagulant plus warfarin when the next dose of apixaban would have been due, then discontinuing the parenteral agent when the INR reaches the desired range. See product labeling for instructions for switching to/from other anticoagulants.
Select Drug Interactions (U.S)	Reduce dose by 50% with strong inhibitors of BOTH CYP3A4 and P-gp (e.g., itraconazole, ketoconazole, ritonavir). Avoid in patients already taking 2.5 mg BID. Avoid strong inducers of BOTH CYP3A4 and P-gp (e.g., carbamazepine, phenytoin, phenobarbital, St. John's wort, rifampin). Caution with antiplatelets and anticoagulants Dual antiplatelet therapy about doubles bleeding risk

	Betrixaban (Bevyxxa [U.S.]) (direct factor Xa inhibitor)
Approved Indications and Usual Dose	VTE prevention in acutely ill medical, non-surgical patients with moderate or severely limited mobility plus other VTE risk factors (160 mg x 1, then 80 mg once daily **with food**, for 35 to 42 days)
Renal dosing	For CrCl 15 to < 30 mL/min (calculated using actual body weight): 80 mg x 1, then 40 mg once daily **with food** for 35 to 42 days Patients with CrCl < 15 mL/min, dialysis patients, and patients likely to need dialysis within three months were excluded from the clinical trial used for FDA approval
Antidote/pre-op, pre-procedure washout (if indicated)	No specific antidote Half-life 19 to 27 hours. Expect betrixaban's effect to last for at least 72 hours after the last dose.
Switching To/From Other Anticoagulants	No data
Select Drug Interactions	Reduce dose to 40 mg qd (after 80 mg loading dose) with strong P-gp inhibitors (e.g., amiodarone, azithromycin, clarithromycin, ketoconazole, verapamil). Patients with CrCl 15 to < 30 mL/min requiring a strong P-gp inhibitor were excluded from the clinical trial used for FDA approval. Avoid in such patients. Caution with antiplatelets and anticoagulants. Not studied in patients requiring dual antiplatelet therapy.

	Dabigatran (Pradaxa) (direct thrombin inhibitor)
Approved Indications and Usual Dose (U.S.)	Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (150 mg BID) DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant)/prevention of recurrence (150 mg BID). VTE prevention post-hip replacement (220 mg once daily x 28 to 35 days.)
Renal Dosing	Check renal function at baseline and when clinically indicated. See drug interactions section, below. A fib (U.S.): use 75 mg BID if CrCl 15 to 30 mL/min. No dosing information for CrCl < 15 mL/min or dialysis. DVT/PE treatment/prevention and VTE prevention post-hip replacement (U.S.): no dosing information for CrCl ≤30 mL/min or dialysis.
Antidote/pre-op, pre-procedure washout (if ind.)	If possible, discontinue 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. If surgery cannot be delayed, there is an increased risk of bleeding *[see Warnings and Precautions (5.2)]*. This risk of bleeding should be weighed against the urgency of intervention *[see Warnings and Precautions (5.1, 5.3)]*. Use a specific reversal agent (idarucizumab, *Praxbind*) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed. Refer to the idarucizumab prescribing information for additional information. Restart PRADAXA as soon as medically appropriate

	Dabigatran (Pradaxa) (direct thrombin inhibitor)
Therapeutic Considerations	Requires BID dosing for A fib and DVT/PE treatment/prevention indications Causes gastrointestinal symptoms in over 10% of patients Caution if 75 years or older, poor renal function, or underweight Contraindicated with mechanical heart valve, and not recommended with bioprosthetic valves Dispense/store in original package. Once bottle opened, use within 4 months. For VTE treatment, continue for at least three months. Benefit of extended use may not outweigh risk in patients with high bleeding risk Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement
Switching To/From Other Anticoagulants	To switch from warfarin, stop warfarin, then start dabigatran when INR < 2 To switch to warfarin, start warfarin three days (if CrCl ≥50 mL/min), two days (if CrCl 30 to 50 mL/min), or one day (if CrCl 15 to 30 mL/min) before discontinuing dabigatran. See product labeling for instructions for switching to/from other anticoagulants
Select Drug Interactions	P-gp inhibitors may increase dabigatran levels A fib indication: avoid P-gp inhibitors if CrCl < 30 mL/min. Reduce dose to 75 mg BID with ketoconazole or dronedarone if CrCl 30 to 50 mL/min VTE/PE treatment/prevention (including post-hip replacement): avoid use of P-gp inhibitors if CrCl < 50 mL/min. Consider separating by several hours if CrCl ≥ 50 mL/min (hip replacement indication). P-gp inducers could decrease dabigatran efficacy. Avoid P-gp inducers per U.S. labeling Caution with antiplatelets.

	Edoxaban (Savaysa [U.S.]) (direct factor Xa inhibitor)
Approved Indications and Usual Dose (U.S.)	Thromboembolism (e.g., stroke) prevention in nonvalvular A fib in patients with **CrCl > 50 to ≤ 95 mL/min** (60 mg once daily). DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant (60 mg once daily; 30 mg once daily if body weight ≤60 kg).
Renal Dosing (U.S.)	A fib: 60 mg once daily for CrCl > 50 to ≤ 95 mL/min, or 30 mg once daily for CrCl 15 to 50 mL/min. Not for use in patients with CrCl > 95 mL/min DVT/PE treatment: 30 mg once daily for CrCl 15 to 50 mL/min Not recommended if CrCl < 15 mL/min
Antidote/pre-op, pre-procedure washout (if indicated)	No specific antidote. Discontinue at least 24 hours before invasive procedures/surgery.
Therapeutic Considerations	For A fib, concerns that efficacy may be less than warfarin at higher CrCl is reflected in the U.S. prescribing information, but Canadian labeling does not reflect these concerns. Numerical differences are small and not statistically significant. Not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis For VTE treatment, continue for at least three months. Benefit of extended use may not outweigh risk in patients with high bleeding risk. Not recommended in moderate or severe hepatic impairment.

	Edoxaban (Savaysa [U.S.]) (direct factor Xa inhibitor)
Switching To/From Other Anticoagulants	To switch from warfarin, stop warfarin, then start edoxaban when INR ≤ 2.5. To switch to warfarin, reduce edoxaban dose by half and start warfarin. Check INR at least weekly, just prior to edoxaban dose. Stop edoxaban once INR ≥ 2 and is stable. Alternatively, stop edoxaban and "bridge" with a parenteral anticoagulant until INR is ≥2 and is stable. See product labeling for instructions for switching to/from other anticoagulants.
Select Drug Interactions	Use with anticoagulants not recommended. Caution with antiplatelets. Avoid rifampin (P-gp inducer). U.S. Reduce dose to 30 mg once daily for DVT/PE indication in patients taking certain P-gp inhibitors (e.g., azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole, quinidine, or verapamil)

	Rivaroxaban (Xarelto) (direct factor Xa inhibitor)
Approved Indications and Usual Dose (U.S.)	VTE prevention post-hip or knee replacement (10 mg once daily for 35 days [hip] or 12 days [knee] starting 6 to 10 hrs post-op, assuming hemostasis achieved) Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (20 mg once daily with evening meal to improve absorption) DVT/PE treatment/prevention of recurrence (15 mg twice daily x 3 weeks, then 20 mg once daily (**with food** to improve absorption) for six months, then 10 mg once daily)
Renal Dosing	Check renal function at baseline, yearly (Canada) and when clinically indicated. A fib indication requires renal dosing (U.S.: 15 mg with evening meal for CrCl 15 to 50 mL/min DVT/PE prevention and treatment and VTE prevention post-hip/knee replacement, avoid if CrCl < 30 mL/min
Antidote/pre-op, pre-procedure washout (if indicated)	Reversal agent: *Andexxa* (coagulation factor Xa). If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, XARELTO should be stopped at least 24 hours before the procedure to reduce the risk of bleeding. In deciding whether a procedure should be delayed until 24 hours after the last dose of XARELTO, the increased risk of bleeding should be weighed against the urgency of intervention. XARELTO should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short. If oral medication cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant.
Therapeutic Considerations	For A fib, some data suggest once-daily dosing insufficient, but BID dosing untested Not recommended in patients with prosthetic heart valves Avoid in patients with moderate or severe liver impairment or liver disease with coagulopathy. For VTE treatment, continue for at least three months. Benefit of extended use may not outweigh risk in patients with high bleeding risk. Caution in elderly. Underweight patients have slightly increased levels/response. Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.

	Rivaroxaban (Xarelto) (direct factor Xa inhibitor)
Switching To/From Other Anticoagulants	To switch from warfarin, stop warfarin, then start rivaroxaban when INR < 3 To switch to warfarin: rivaroxaban increases INR, thus confounding initial warfarin dosing. U.S.: consider starting a parenteral anticoagulant plus warfarin when the next dose of rivaroxaban would have been due. Canada: continue rivaroxaban with warfarin until the INR > 2. Use the "usual" initial warfarin dose for the first two days. Thereafter, check INR just prior to the next dose of rivaroxaban to minimize rivaroxaban interference with the INR. See product labeling for guidance on switching to/from other anticoagulants.
Select drug interactions	Avoid use with drugs that are BOTH P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, ritonavir) In patients with CrCl 15 to < 80 mL/min., the decision to use a combined P-gp/moderate CYP3A4 inhibitor (e.g., erythromycin) is a risk/benefit determination Drugs that are P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) may decrease efficacy. Avoid. Avoid use with other anticoagulants. Antiplatelets increase bleeding risk; co-administer with caution.

	Warfarin (Coumadin) inhibits formation of vitamin-K dependent clotting factors
Approved Indications **(warfarin dosing variable and patient specific)**	U.S.: Prevention/treatment of venous thrombosis/PE Prevention/treatment of thromboembolism due to A fib or prosthetic heart valve Secondary prevention post-MI
Renal Dosing	Adjust per INR testing. Renal function minor determinant of warfarin response. Preferred anticoagulant for A fib with CrCl < 15 mL/min
Antidote/pre-op, pre-procedure washout (if indicated)	Vitamin K (usually only given when INR > 10) Some dental or surgical procedures may necessitate the interruption or change in the dose of warfarin sodium tablets therapy. **See Guyatt 2012, p. 14S** Consider the benefits and risks when discontinuing warfarin sodium tablets even for a short period of time. Determine the INR immediately prior to any dental or surgical procedure. In patients undergoing minimally invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of warfarin sodium tablets to maintain the INR at the low end of the therapeutic range may safely allow for continued anticoagulation.
Therapeutic Considerations	INR monitoring required at least every four weeks. Per Guyatt 2012 p. 9S, "For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B)" Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement. Not more effective than aspirin for noncardioembolic stroke Preferred anticoagulant for A fib with CAD For VTE treatment, continue for at least three months. Benefit of extended use may not outweigh risk in patients with high bleeding risk.

	Warfarin (Coumadin) inhibits formation of vitamin-K dependent clotting factors
Select drug interactions	Many drug and food interactions Potential for significant interactions with inducers/inhibitors of CYP2C9, 2C19, 1A2, and 3A4 Use with antiplatelets increases bleeding risk. Benefit of combo (most data with aspirin or clopidogrel) may outweigh risk in certain patients, such as mechanical heart valve patients, or in A fib plus recent stent or recent CABG

Adapted from Comparison of Oral Anticoagulants, Pharmacist's Letter/Prescriber's Letter, May 2016. Detail Document #320506 and package inserts of the listed products
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