

DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
January 31, 2014

The Executive Formulary Committee convened on Friday, January 31, 2014 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Matthews, Acting Chair at 9:40 a.m.

Phillip Balfanz, M.D.	√	Jennifer Wright, M.D.	Absent
James Baker, M.D.	√	Valerie Kipfer, MSN, RN (non-voting)	Absent
Mary Bowers RN, BSN	√	Lilani Muthali, M.D. (non-voting)	√
Catherine Hall, Pharm.D.	√	Nina Muse, M.D. (non-voting)	Absent
Jeanna Heidel, Pharm.D.	√	Jay Norwood, MSN, RN (non-voting)	Absent
Marla Knight, Pharm.D., CGP, FASCP	√	Peggy Perry (non-voting)	Absent
Jeff Matthews, M.D.	√	Scott Schalchlin (non-voting)	Absent
Connie Millhollon, RN	√	Mike Maples (non-voting)	Absent
Victoria Morgan, M.D.	√	Kerry Raymond (non-voting)	Absent
Kenda Pittman, Pharm.D.	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant DADS Physician	
Robert L. Ward, D.O.	√		

Guests Present: Thongsamuth Noymany, Pharm.D., Student, ASH; Lisa Mican, Pharm.D., ASH; Debra Stewart, Pharm.D. Student, SASH; Karen Hardwick, PhD

Introduction and Other Information

Since Dr. Wright is not available for the meeting, Dr. Matthews will serve as Acting Chair.

Dr. Morgan reported that she has resigned her position at Brenham State Supported Living Center effective mid-February. Therefore, she will be leaving the Committee. DADS will appoint another physician to the Committee.

Approval of Minutes of October 18, 2013

On a motion of Dr. Morgan, seconded by Dr. Heidel, the minutes of the October 18th meeting were approved as previously distributed.

Issues from the Clinical Directors' Meeting

Dr. Baker presented two issues that are being addressed. The first issue is the management of withdrawal from the use of substances (e.g., marijuana, stimulants, nicotine, etc.) that do not have a physiologic withdrawal process. His concern is the influence of withdrawing from these substances on violence. As a result of this concern, Dr. Baker is asking each facility to review these factors.

The other area Dr. Baker expressed concern was the multiple drug formularies that our patients have to use as they move between systems (inpatient to outpatient and then if under a managed care organization, pharmacy benefit management, Medicaid or another system). Committee members noted that often the outpatient clinic will share their Formularies with the hospital so that the outpatient formulary can be considered when prescribing medications. Ideally, it would be optimal to have one Formulary that flows from inpatient to the outpatient arena and vice versa. Initially, Dr. Baker wanted to have all involved parties work together to develop a synced formulary. However, in discussing the EFC's process for adding drugs to the Formulary, it was recommended that our Formulary be used by all parties. Dr. Ward reported that Hill Country has already adopted our Formulary.

Conflict of Interest Disclosure Forms

All Committee members completed their annual conflict of interest forms. Only Dr. Morgan reported any potential issues. In her case, she reported attending a luncheon provided by a manufacturer.

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed several adverse drug reaction reports.

In the first case, a 25 year old white male admitted to the psychiatric hospital from jail where he had been residing the previous 4 months and treated with citalopram (Celexa®), trazodone (Desyrel®) and hydroxyzine (Atarax®). Primary psychiatric diagnosis is bipolar disorder. He also has a history of substance dependence including marijuana, ecstasy, alcohol, hydrocodone, and amphetamines. Medical conditions are dental carries, joint pain and obesity (BMI 35). Admission labs included: CMP – within normal limits except glucose 65 mg/dl, globulin 1.9 g/dl, A:G ratio 2.3, ALK Phos 33 U/L; lipids within normal limits; ferritin within normal limits; CBC within normal limits except hematocrit 41.6%; RPR nonreactive; UA within normal limits; Hepatitis ABC negative; and HIV negative. On August 23rd, the TSH was 2.53 MU/L. One month after admission, an EKG was obtained with automated reading noting consider WPW type b, QRS (T) Contour abnormality, consider inferior myocardial damage, QTc 510 msec, heart rate 96 bpm. He denied episodes of palpitations, syncope, or arrhythmias. He reported one episode of increased heart rate during this admission due to anxiety in which lorazepam was helpful. Scheduled medications at the time of abnormal EKG included lithium carbonate ER 300 mg in the morning and 600 mg at bedtime (lithium level 0.82 mmol/L), aripiprazole (Abilify®) 20 mg daily, paliperidone (Invega®) 9 mg daily, mirtazapine (Remeron®) 15 mg at bedtime, and citalopram 30 mg daily. The day of the abnormal EKG, aripiprazole was discontinued due to akathisia. The attending psychiatrist saw the abnormal EKG two days later and discontinued citalopram, and prescribed bupropion (Wellbutrin®) XL 150 mg in the morning. In addition, a repeat EKG was ordered for the following day. The repeat EKG was much improved with the automated reading noting incomplete RBBB, QTc 430 msec, heart rate 76 bpm. Based on available clinical studies evaluating QTc, citalopram would have greater QT prolongation potential (8.5-12.6 msec for 20 - 30 mg daily dose- FDA data) than aripiprazole (mean 7.6 msec, Pharmacoepidemiol Drug Saf. 2013 Jul 16) however, either alone or in combination may have potentially contributed with citalopram being most likely of the two. Paliperidone and lithium may also prolong QTc; however, QTc improved despite continuation of these medications. In addition, clinically significant QTc prolongation is not typically seen unless the lithium levels are above 1.2 mmol/liter. Steady state level obtained in this case was only 0.82 mmol/L. The other issue addressed by this facility was the fact that the attending physician read the report two days later. The hospital is looking into a process that will identify triggers that would require immediate notification of the physician.

The next case involves a 34 year old black male with a diagnosis of schizoaffective disorder, bipolar type. He had been non-compliant with medication and abusing methamphetamine and marijuana for approximately 6 months prior to being admitted to a short term psychiatric facility. On January 19, 2013, he was transferred to a State psychiatric facility. At admission, he was taking divalproex (Depakote®) ER 1,000 mg BID, fluphenazine (Prolixin®) 15 mg BID, hydrocodone/acetaminophen (Norco®) 10 mg TID, hydrocortisone 1% cream, and quetiapine (Seroquel®) 300 mg at bedtime. On January 22, 2013, he complained that divalproex is “making me pass out in bed.” He appears over sedated and has a difficult time staying awake during his interview. An ammonia level was 60 mcg/dl. The divalproex was discontinued on January 22, 2013 and lactulose was ordered. The follow up ammonia levels were: January 25, 2013 - 55 mcg/dl; February 6, 2013 – 43 mcg/dl; February 20, 2013 – 33 mcg/dl. The patient was discharged.

A 17 year-old white male was admitted to an acute psychiatric hospital on October 1, 2013 for the treatment of Bipolar Disorder, mixed episode, and ADHD. His medications prior to admission included: divalproex (Depakote®) ER 1,000 mg at bedtime for mood stabilization, risperidone (Risperdal®) 1 mg in the morning and afternoon plus 2 mg at bedtime

for mood stabilization, quetiapine (Seroquel®) 200 mg four times daily for mood stabilization, and lisdexamfetamine (Vyvanse®) 30 mg daily for ADHD. He was transferred to the facility from another hospital. Labs from this outside facility were drawn on both August 24, 2013 and September 28, 2013. Labs drawn August 24th were notable for: moderate leukopenia WBC 2.9 K/mm³, severe neutropenia ANC 0.7 K/mm³, low neutrophils 24%, elevated lymphocytes 61%, and elevated monocytes 11%. Valproic acid level was within normal limits for mood stabilization at 111 mcg/mL. Labs drawn September 28, 2013 were almost identical and were notable for: moderate leukopenia WBC 2.9 K/mm³, severe neutropenia ANC 0.7 K/mm³, low neutrophils 24%, elevated lymphocytes 61%, and elevated monocytes 12%. Valproic acid level was within normal limits for mood stabilization at 103 mcg/mL. Basic metabolic panel was within normal limits. Urinalysis showed 1+ protein and trace ketones, but was otherwise normal. Upon admission to the state facility, baseline labs drawn October 2, 2013 showed: mild leukopenia WBC 3.3 K/mm³, severe neutropenia ANC 0.8 K/mm³, low neutrophils 23%, elevated lymphocytes 64%, and elevated eosinophils 6%. Comprehensive metabolic panel, lipid panel, and TSH were within normal limits. HIV antigen/antibody combination assay was non-reactive. Upon admission, the following medication changes were made: quetiapine was reduced to 600 mg at bedtime and risperidone was decreased to 3 mg at bedtime. The divalproex was reduced to 500 mg daily for two days, then 250 mg daily for two days and then discontinued. The lisdexamfetamine was discontinued. On October 3, 2013, the risperidone was increased to 4 mg at bedtime. The quetiapine was tapered over 16 days and discontinued on October 16, 2013. Follow-up labs drawn on October 4, 2013 showed low WBC 3.6 K/mm³, moderate neutropenia ANC 1.2 K/mm³, low neutrophils 33%, and elevated monocytes (16%). Lymphocytes were within normal limits at 51%. HIV antigen/antibody combination assay was again non-reactive. Follow-up labs drawn October 7, 2013 showed low-normal WBC 4.5 K/mm³, moderate neutropenia ANC 1.2 K/mm³, low neutrophils 27%, elevated lymphocytes 54.5%, elevated monocytes 14.2% and elevated eosinophils 3.7%. Follow-up labs drawn October 14, 2013 showed low-normal WBC 4.5 K/mm³, mild neutropenia ANC 1.6 K/mm³, low neutrophils 35.7%, normal lymphocytes 50.2%, normal monocytes 9.3%, and elevated eosinophils 3.8%. On October 14, 2013, the lisdexamfetamine was restarted at 30 mg daily and was continued through discharge. The final labs drawn at the state facility on October 21, 2013 showed low WBC 4.3 K/mm³, mild neutropenia ANC 1.6 K/mm³, low neutrophils 36.5%, normal lymphocytes 51%, normal monocytes 7.6%, and elevated eosinophils 3.9%. The patient was discharged on October 27, 2013 on risperidone 4 mg bedtime and lisdexamfetamine 30 mg daily. The CBC values improved upon taper and discontinuation of quetiapine and divalproex; however, they were still in the low-normal range upon discharge. The patient was afebrile throughout his admission at the state facility and had no signs or symptoms of possible infection. No hematology consult was obtained while he was hospitalized in the state facility.

In the next case, a 63 year old Caucasian male with a long history of schizophrenia and current diagnosis of dementia, hypertension, hyperlipidemia, EPS and history of myocardial infarction, A-Fib, and embolic stroke was admitted to a psychiatric facility on November 5, 2012. At the time of admission, he was on aripiprazole (Abilify®) 10 mg daily, benzotropine (Cogentin®) 1 mg BID, donepezil (Aricept®) 10 mg daily, simvastatin (Zocor®) 80 mg daily, potassium, and warfarin (Coumadin®). Due to history of embolic stroke and other cardiovascular disease, he receives on-going warfarin therapy with INR goal of 2.0 – 3.0. Patient had stable INRs within goal range for an extended period of time with a dose of 5 mg alternating with 6 mg. On May 28, 2013 his INR dropped to 1.4. The INR was re-evaluated 2 days later and had dropped further to 1.0. Unable to determine the cause of the drop in INR, the warfarin dose was increased to 7 mg and enoxaparin (Lovenox®) was ordered due to patient's high risk of embolic stroke. The INR frequency increased to twice weekly. On June 3, 2013, the INR increased to 1.8, so no dose changes were made and the enoxaparin continued. The next INR was scheduled for June 6, 2013. On June 5, 2013, the patient was noted to have sudden onset of symptoms including left hemiplegia and aphasia, significantly worse than baseline, and the patient was anxious and appeared dazed. He was promptly transported to emergency care where acute right posterior frontal parietal intracerebral hematomas were noted with peri-hematoma edema. The INR on admission to the ER was 3.2 and patient was given 2 units of FFP as well as vitamin K 10 mg IV. The patient was admitted to the ICU. The patient continued to decline and expired on June 28, 2013.

A 45 year old Hispanic female was admitted to the psychiatric hospital on December 6, 2013 from prison. Little is known about her past treatment history, although she does report using crack cocaine daily outside of incarceration since her early 30's. The psychiatric diagnosis includes schizoaffective disorder, bipolar type, history of cocaine dependence (daily use prior to incarceration), nicotine dependence, and rule out PTSD. Other diagnosis include history of borderline personality disorder, hypertension, mild asthma, abnormal PAP on October 15, 2013, amenorrhea, history of vaginitis and UTI, peptic ulcer, H. pylori, "electrolyte caloric and water balancing agents causing adverse effects in her therapy" noted to be first observed April 24, 2013. No known drug allergies were reported. Medications prescribed after admission and at the time of the adverse drug reaction include divalproex (Depakote®) ER 1,000 mg at bedtime for mood stabilization, fluphenazine (Prolixin®) decanoate 12.5 mg IM every 14 days for psychosis (last injection administered on December 7th), fluoxetine (Prozac®) 20 mg in the morning for depression, diphenhydramine (Benadryl®) 25 mg at bedtime for insomnia, hydrochlorothiazide 25 mg in the morning for hypertension, potassium chloride SR capsule 20 mEq in the morning, nicotine 14 mg patch daily for smoking cessation, nicotine gum 2 mg every hour as needed for nicotine withdrawal, fluphenazine 10 mg orally every 6 hours as needed for psychosis or agitation. Admission labs were mostly

within normal limits except for mild anemia, H. pylori positive, low vitamin D level, dilute urine, as well as low sodium and chloride. On December 9, 2013, the CBC was within normal limits except RBC 4.19 M/mm³, hemoglobin 11.9 g/dl, hematocrit 35%. The UA was within normal limits except a specific gravity of 1.000. The urine drug screen was negative. The CMP was within normal limits except BUN 4 mg/dl, serum creatinine 0.41 mg/dl, sodium 123 mEq/L, chloride 86 mEq/L (potassium normal at 3.8 mEq/L) and the lipids were within normal limits. The valproic acid plasma level was 74.6 mcg/ml. The RPR was nonreactive and the serum pregnancy negative. The TSH was 2.52 MU/L, G6PD 13.6 U/g Hb, Hepatitis ABC negative, HIV nonreactive, H. pylori positive, and Vitamin D 10 ng/ml. Vital signs were within normal limits except for periodic elevated heart rate. An EKG obtained on December 19, 2013 showed sinus tachycardia with HR 111 beats per minute, left atrial abnormality, and QTc 504 msec. A repeat EKG obtained on December 12, 2013 showed only minimal improvement with tachycardia with a HR 101 beats per minute, left atrial abnormality, and QTc 496 msec. Fluoxetine was discontinued December 12, 2013 as it was no longer needed for depressive symptoms (non-reported) in addition the fluphenazine prn was discontinued due to prolonged QTc interval. Fluid restriction was implemented due to low sodium and chloride and suspected psychogenic polydipsia. Magnesium level on December 13, 2013 was within normal limits and a follow up CMP on December 16 showed improvement with sodium 133 mEq/L and chloride 100 mEq/L (potassium continued to be within normal limits). A repeat EKG obtained December 20th significantly improved with normal sinus rhythm and QTc 443 msec. At this time, the patient was on fluphenazine decanoate, divalproex, hydrochlorothiazide and potassium chloride.

A 63 year old Hispanic male on an extended commitment at an inpatient psychiatric hospital, was admitted to a local medical hospital on December 14, 2013 for swelling and blistering rash on his left arm/wrist/hand and hypotension. Prior to his transfer on December 14th, he had a temperature of 101.7 degrees, blood pressure 90/56 mm Hg, and O₂Sat 91-95%. He had blisters of various sizes filled with clear liquid extending down his left arm and he felt weak. At the time of his reaction, he was on lamotrigine (Lamictal®) 25 mg once daily in the morning for 2 doses, haloperidol (Haldol®) 10 mg TID, haloperidol decanoate 200 mg every 4 weeks, ibuprofen (Motrin®) 800 mg BID prn, lacosamide (Vimpat®) 200 mg BID, lisinopril (Zestril®) 2.5 mg daily, loratadine (Claritin®) 10 mg daily, lorazepam (Ativan®) 2 mg TID, metoprolol (Toprol®) 12.5 mg daily, risperidone (Risperdal®) 2 mg BID, tamsulosin (Flomax®) 0.4 mg daily, trospium (Sanctura®) 20 mg TID, temazepam (Restoril®) 30 mg HS, and vitamin D3 10,000 units orally every Monday – Friday. Of note, the only new medication was the lamotrigine, as he has been on the other medications for at least one year. After admission to the medical hospital, his lamotrigine was continued for 2 additional doses when the doctor discontinued the medication after suspecting Stevens-Johnson Syndrome (SJS). He had a fasciotomy performed on December 17th and a skin biopsy resulted in “sub-acute spongiotic dermatitis with eosinophils.” An additional large healing lesion was also later discovered on the left side of his foot and a small lesion was found between his toes which could have possibly been deep blisters discovered in the healing stage.

A 57 year old African American male diagnosed with schizoaffective disorder, bipolar type was receiving lithium. He presented with altered gate, tremor, and mild confusion. A stat lithium level was ordered and a level of 1.66 mEq/l was reported. He was sent out to the local emergency room for possible dehydration and lithium toxicity. At the ER, the patient was given IV fluids, his creatinine was mildly elevated at 1.4 mg/dl, BUN normal at 15 mg/dl, electrolytes all within normal limits. The lithium was discontinued and replaced with oxcarbazepine (Trileptal®).

A 59 year old female complained of right upper arm pain on October 9, 2013 at 1330 after receiving a Pneumovax® injection. She was given ibuprofen (Motrin®) for pain at 1330 and a cool pack. The patient reported much relief after the cool pack. She was evaluated by a physician. She was given diphenhydramine (Benadryl®) 50 mg at 1430 for arm discomfort. On the night shift on October 10th, the patient had redness and induration on her arm. She complained of pain to her right upper arm and a headache. On October 10th, she reported to the day shift that she couldn't sleep last night due to pain in her right arm from the “pneumonia shot.” Early on October 11th, it was noted that her right arm (place injection was administered) was now slightly swollen with redness throughout her inner bicep and now spreading to her lower arm. The physician was notified and ordered ibuprofen 400 mg for one dose to be administered now as the ibuprofen prn was administered about 4 hours earlier. In addition, diphenhydramine 50 mg orally was administered. The day shift on October 11th, reported that the patient showed signs of cellulitis on her right upper arm as she had some redness, warmth and tenderness. At this time the patient denied pain.

In the last reported case, a patient was started on pyrazinamide 1,500 mg daily, isoniazid 300 mg daily, rifabutin 300 mg daily, phenytoin (Dilantin®) 100 mg at bedtime, ethambutol 1,200 mg daily, and pyridoxine 50 mg on November 4, 2013. The patient's serum creatinine on November 25th was 1.79 mg/dl (a previous serum creatinine on November 4th was 0.47 mg/dl) with positive eosinophils in his urine. It was determined that the patient developed acute interstitial nephritis by a

nephrologist. All tuberculosis medications were discontinued on November 25th. Prednisone 40 mg was administered once on December 2nd. The patient is currently still receiving prednisone. Isoniazid was restarted on December 6th; rifabutin was restarted on December 10th. The pyrazinamide was not re-challenged. As of December 12th, the patient's serum creatinine has declined to 0.79 mg/dl.

After reviewing the adverse drug reactions, Dr. Mican noted that Austin State Hospital had detected several cases of neutropenia and leukopenia in children and adolescents who were treated with the combination of valproate and quetiapine. In fact, ASH completed a retrospective review of children and adolescents who received valproate, quetiapine or a combination and found that children and adolescents on the combination of valproate and quetiapine and those that were on valproate had a higher incidence of leukopenia and neutropenia. This retrospective review was published in *The Annals of Pharmacotherapy* in May, 2009. The Committee recommended that this information be shared with the field.

Quetiapine (Seroquel®, Seroquel® XR) Purchases

Dr. Richards reviewed the State Hospital purchases and returns of Seroquel® and Seroquel® XR from October through December. The State Supported Living Centers' purchases were not reviewed since these facilities receive Medicare Part D funding for the majority of their residents. The following is a summary of the State Hospitals' Seroquel® and Seroquel® XR purchases:

Facility	October	November	December	Total	# Patients for Quarter
Kerrville	0	0	0	0	1
Rio Grande	\$4,755.39	0	\$4,588.44	\$9,343.83	7
Terrell	(\$8,779.19)	0	0	(\$8,779.19)	2
Vernon	\$1,674.36	\$3,348.72	\$1,674.36	\$6,697.44	2
Total	(\$2,349.44)	\$3,348.72	\$6,262.80	\$7,262.08	12

The facilities that did not purchase or return Seroquel® or Seroquel® XR are not included in the table. Dr. Richards noted that Kerrville State Hospital had one patient with an order for Seroquel® XR for less than 24 hours. Currently, there are only two patients on Seroquel® XR and both are at the Vernon campus of North Texas State Hospital. Both of these patients have been in a state hospital continuously since 2007. Since the last report, the number of patients on Seroquel® XR has declined.

The Committee recommended to continue to monitor this information.

Drug Deletions

Dr. Richards suggested that pergolide (Permax®) be removed from the Formulary as it is no longer on the market. On a motion of Dr. Ward, seconded by Ms. Millhollon, it was recommended that pergolide be removed from the Formulary. Since this drug is no longer available, feedback from the field will not be obtained.

New Dosage Strengths

The Committee did not review any new dosage strengths for addition to the Formulary.

Psychotropic Consent List

Dr. Richards presented the revised psychotropic consent list. The following changes were made:

- Added the trade name Khedezla® to desvenlafaxine
- Removed "Nonformulary" status from:
 - Acamprosate (Campral®)
 - Aripiprazole (Abilify® Maintena™)
 - Lisdexamfetamine (Vyvanse®)

- Added “Nonformulary” to isocarboxazid (Marplan®)

On motion by Dr. Heidel, seconded by Dr. Morgan, the revised psychotropic consent list was approved. The Committee recommended that the updated psychotropic consent list be posted on the website. See Appendix A.

Psychotropic Audit Criteria & Guidelines - Antidepressants

The Antidepressant Audit Criteria and Guidelines have not been reviewed.

Psychotropic Audit Criteria & Guidelines – Chemical Dependence Adjunct

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

Loxapine inhalation powder (Adasuve®) – presented by Debra Stewart, Pharm.D. student

Loxapine inhalation powder is a unique dosage formulation indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. It was approved by the FDA in December 2012. Inhaled loxapine has a very rapid absorption. This dosage formulation is contraindicated in individuals with:

- Current diagnosis or history of asthma, COPD, or other lung disease with bronchospasm
- Acute respiratory signs/symptoms
- Current use of medications to treat airway disease
- History of bronchospasm following loxapine inhalation powder treatment
- Known hypersensitivity to loxapine or amoxapine

The dose is 10 mg by oral inhalation as a single dose within a 24-hour period. The drug is only to be administered by a healthcare professional, in an enrolled healthcare facility. The inhalation powder has a unique packaging that requires specific steps to be completed in order to insure that all of the medication is administered to the patient. Prior to administration, all patients need to be screened for:

- Current use of medications to treat asthma or COPD
- History of asthma, COPD, or other pulmonary disease
- Examine patients (including chest auscultation) for respiratory abnormalities, like wheezing

Once administered, the patient has to be monitored every 15 minutes for at least 1 hour for signs and symptoms of bronchospasm. Monitoring includes performing a physical examination, including chest auscultation and vital signs. In addition, the patient needs to be asked every 15 minutes if they are having any difficulty breathing.

Loxapine inhalation powder is unique in that it has a REMS program that has the following requirements:

- Can only be administered at an enrolled healthcare facility
- Each facility has to re-enroll every 3 years
- Each facility will elect a representative to maintain records and ensure proper training to all personnel; all records are subject to audit
- Qualifications for healthcare facility enrollment:
 - Immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
 - Immediate access on-site to a metered-dose inhaler and nebulized form of a short-acting beta-agonist bronchodilator (i.e. albuterol)
 - Procedures, protocols, and/or order sets to ensure the following:
 - Patient screening, prior to treatment, for a history of pulmonary disease and for acute pulmonary signs and symptoms by physical exam, including taking vital signs and chest auscultation, and inquiring if patient is taking medication to treat asthma or COPD
 - Patients are monitored at least every 15 minutes for a minimum of 1 hour following treatment for signs and symptoms of bronchospasm, including taking vital signs and chest auscultation
 - Administration of loxapine inhalation powder is limited to 1 dose per patient within 24 hours

- Healthcare providers within the facility (prescribers, nurses, monitoring staff, or pharmacists) are trained on safe use of loxapine inhalation powder using the Adasuve REMS Education Program

After reviewing this information, the Committee recommended that this product is not suitable in our facilities due to the REMS facility requirements. See Appendix B.

New Drug Applications

The Committee did not receive any new drug requests.

Drug Formulary Sectional Review-

Blood Modifying Agents Antidotes/Deterrents/Poison Control Agents Antidiabetic Agents Intravenous Solutions & Additives

Dr. Hall provided the review on the agents in the Blood Modifying sections. See Attachment C. Dr. Hall provided a review of the novel oral anticoagulants as compared to warfarin. The following is a summary of findings found in the Pharmacist's Letter® that compared the novel oral anticoagulants to warfarin for preventing strokes in atrial fib.

- Apixaban (Eliquis®) prevents about 3 more strokes per 1000 patients per year than warfarin. Has 10 fewer bleeds and 4 fewer deaths.
- Dabigatran (Pradaxa®) prevents about 5 more strokes per 1000 patients per year than warfarin. Has similar overall bleeding risk as warfarin. Dabigatran is the only new agent that reduces ischemic strokes compared to warfarin; in addition to hemorrhagic strokes.
- Rivaroxaban (Xarelto®) doesn't prevent more strokes than warfarin. Has a similar risk of major bleeding. Given once a day.
- Warfarin is the only one with an antidote, INR monitoring may improve adherence and it costs less

After reviewing this section, Dr. Hall did not make any recommended changes.

Dr. Hall provided the review on the agents in the Antidotes/Deterrents/Poison Control section. See Attachment D. Dr. Hall did not make any recommended changes.

Dr. Hall provided the review on the agents in the Antidiabetic section. See Attachment E. Dr. Hall provided a brief overview of Type 2 diabetes, treatment guidelines for type 2 diabetes and a summary of medications used. Dr. Hall recommended that the following drugs be deleted from the Formulary:

- Tolbutamide (Orinase®)
- Insulin, Lente
- Insulin, Ultralente

On a motion of Dr. Ward, seconded by Dr. Knight, the recommendation to delete these agents was approved. Feedback will be obtained from the field regarding this recommendation.

Dr. Hall provided the review on the agents in the Intravenous Solutions and Additives section. See Attachment F. Dr. Hall did not make any recommended changes.

Proposed Formulary Review Schedule

Dr. Richards presented the proposed Drug Formulary review schedule. This schedule continues the current review schedule in the same pattern as it had been reviewed. On a motion of Dr. Ward, seconded by Dr. Pittman, the updated schedule was approved. See attachment G for the approved Formulary Review Schedule.

DSHS/DADS 2014 Drug Formulary

Dr. Richards reported that the 2014 Drug Formulary is available on the following website:

<http://www.dshs.state.tx.us/mhprograms/Formulary.shtm>

FDA Drug Safety Communications

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

The FDA has determined that recent data for rosiglitazone-containing drugs, such as Avandia®, Avandamet®, Avandaryl®, and generics, do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin (Glucophage®) and sulfonylurea. As a result, the FDA is requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on FDA review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI). Previous data from a large, combined analysis of mostly short-term, randomized clinical trials of rosiglitazone had suggested an elevated risk of heart attack, so the FDA required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The Rosiglitazone REMS program restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks. Although some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains, in light of the new re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, the FDA's concern is substantially reduced and the rosiglitazone REMS program requirements will be modified. The FDA is also requiring revisions to the rosiglitazone prescribing information and the patient Medication Guide to include this new information.

The FDA is warning the public that the anti-seizure drug clobazam (Onfi®) can cause rare but serious skin reactions that can result in permanent harm and death. The FDA approved changes to the clobazam drug label and the patient Medication Guide to describe the risk of these serious skin reactions. These skin reactions, called Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur at any time during clobazam treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when clobazam is stopped and then re-started. All cases of SJS and TEN in the FDA case series have resulted in hospitalization, one case resulted in blindness, and one case resulted in death. Clobazam is a benzodiazepine medication used in combination with other medicines to treat seizures associated with a severe form of epilepsy called Lennox-Gastaut Syndrome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment or when re-introducing therapy. Healthcare professionals should discontinue use of clobazam and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related. Patients taking clobazam should seek immediate medical treatment if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Stopping clobazam suddenly can cause serious withdrawal problem.

The FDA is warning that methylphenidate products, one type of stimulant drug used to treat attention deficit hyperactivity disorder (ADHD), may in rare instances cause prolonged and sometimes painful erections known as priapism. Based on a recent review of methylphenidate products, the FDA updated drug labels and patient Medication Guides to include information about the rare but serious risk of priapism. If not treated right away, priapism can lead to permanent damage to the penis. Priapism can occur in males of any age and happens when blood in the penis becomes trapped, leading to an abnormally long-lasting and sometimes painful erection. Another ADHD drug, atomoxetine (Strattera®), has also been associated with priapism in children, teens, and adults. Priapism appears to be more common in patients taking atomoxetine than in those taking methylphenidate products; however, because of limitations in available information, the FDA does not know how often priapism occurs in patients taking either type of product. Healthcare professionals should talk to male patients and their caregivers to make sure they know the signs and symptoms of priapism and stress the need for immediate medical treatment should it occur. Younger males, especially those who have not yet reached puberty, may not recognize the problem or may be embarrassed to tell anyone if it occurs.

The FDA is recommending health care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 mg of acetaminophen per tablet, capsule or other dosage unit. There are no available data to show that taking more than 325 mg of acetaminophen per dosage unit provides additional benefit that outweighs the added risks for liver injury. Further, limiting the amount of acetaminophen per dosage unit will reduce the risk of severe liver injury from inadvertent acetaminophen overdose, which can lead to liver failure, liver transplant, and death. Cases of severe liver injury with acetaminophen have occurred in patients who:

- took more than the prescribed dose of an acetaminophen-containing product in a 24-hour period;
- took more than one acetaminophen-containing product at the same time; or
- drank alcohol while taking acetaminophen products.

The FDA recommends that health care providers consider prescribing combination drug products that contain 325 mg or less of acetaminophen. The FDA also recommends that when a pharmacist receives a prescription for a combination product with more than 325 mg of acetaminophen per dosage unit that they contact the prescriber to discuss a product with a lower dose of acetaminophen. A two tablet or two capsule dose may still be prescribed, if appropriate. In that case, the total dose of acetaminophen would be 650 mg (the amount in two 325 mg dosage units). When making individual dosing determinations, health care providers should always consider the amounts of both the acetaminophen and the opioid components in the prescription combination drug product.

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2014, all facilities reported use of non-formulary agents. The DADS facilities submitted 640 non-formulary requests and the DSHS facilities had 475 requests. The following were the top non-formulary agents that were prescribed:

Saliva substitute/dry mouth solution
UTI-Stat Liquid
Quetiapine extended release (Seroquel® XR)
Moxifloxacin (Avelox®) ophthalmic drops
Guanfacine ER (Intuniv® ER)

Sectional Review for Next Meeting

The following sections will be reviewed at the next meeting:

Endocrine Agents
Osteoporosis Agents
Genitourinary Agents

Other Issues

The following information was shared with the Committee members:

It was announced that GlaxoSmithKline anti-seizure treatment ezogabine (Potiga®) now displays a boxed warning in the US on risks including potential vision loss. The new warning “underscores risks of abnormalities in the eye, vision loss and skin discoloration, all of which may become permanent,” the FDA said in a statement. The manufacturer stated: “In light of these reported adverse events, we have worked closely with regulators to update the medicine’s labeling to restrict its use to those patients where other appropriate medicine combinations have proved inadequate or have not been tolerated.”

Acadia Pharmaceuticals experimental medication pimavanserin may alleviate hallucinations and delusions in patients with Parkinson’s disease. The results of the study published online in *The Lancet*, also found that the medication provided “some relief without debilitating side effects.”

Major newspapers, wire sources, and business journals report that Johnson & Johnson will pay more than \$2.2 billion to settle US civil and criminal cases alleging false marketing practices for the antipsychotics risperidone (Risperdal®) and paliperidone (Invega®), as well as for the heart medicine nesiritide (Natrecor®), in what is the third largest healthcare fraud settlement the US has seen to date. The civil settlement will resolve lawsuits filed under the False Claims Act.

Researchers “examined 150 men and women older than 18 trying to quit alcohol dependence.” Study “participants were either given a placebo or gabapentin, in daily doses of 900 or 1,800 milligrams, over a” period of about three months. The data indicated that “patients receiving the highest dose of gabapentin were found most likely to avoid heavy drinking, or to quit completely.”

A study published Nov. 1 in the American Journal of Psychiatry, showed that lamotrigine, a medication “used to treat bipolar disorder [BD], becomes less effective during pregnancy, meaning that expectant mothers may require higher doses of the medication.” Some women in the eight-patient “study had worsening symptoms of depression as the levels of lamotrigine in their blood fell.”

A spokeswoman for Bristol Meyers said the drug maker will be laying off around 70 to 75 researchers currently working on developing treatments for hepatitis C, neurological disorders, and diabetes. The drug maker will be abandoning drug discovery for those diseases so it can focus on different areas that have shown promise. Chief scientific officer at Bristol, Francis Cuss, said in a statement, “We are focusing our R&D organization on delivering the opportunities where the value is greatest.”

According to Forest Laboratories Inc., the FDA is seeking more information on its “potential schizophrenia treatment cariprazine before” it decides whether to approve the drug. The FDA “indicated that additional clinical trial data” would be required. Forest said “it believes this request was made to better define the best dosing regimen to maintain the drug’s effectiveness while minimizing side effects.” Forest and Hungarian firm Gedeon Richter PLC are partnering on the drug and plan to confer with FDA officials over future action. Richter developed cariprazine but licensed it to Forest in the US and Canada.

According to a study published online Dec. 18 in the New England Journal of Medicine, women taking selective serotonin reuptake inhibitor (SSRI) antidepressants while pregnant appear not to have an increased chance of having a child with autism.

It is reported that one new “nonhormonal option to treat hot flashes during menopause” is “an old medication dressed up in a new feminine name and packaging,” the antidepressant paroxetine. Paroxetine is also known under the trade name of Paxil®. Despite the fact that a Food and Drug Administration advisory panel voted last March not to approve Noven Therapeutics’ Brisdelle®, the FDA approved it this past June, “potentially because it saw a dearth of options for hot flash treatment.”

According to research presented Dec. 7 at the American Academy of Addiction Psychiatry’s annual meeting, atypical antipsychotic medications “are now being used to enhance the effects of other drugs or as a way to counter the adverse effects of illicit substances.” Researchers from the Columbia University College of Physicians and Surgeons in New York discovered that “of 429 patients from the detox and rehab units of the Addiction Institute of New York who were screened, 73 (17%) reported illegal or ‘nonmedical’ use of prescribed atypical antipsychotics in combination with alcohol, opioids, cocaine/crack, methamphetamine, and/or

cannabis.” Of all the antipsychotics, quetiapine appeared to be the most abused at 84.9%. The study also found that the majority of the antipsychotics abused were coming from family or friends.

The New York Times (12/22) reported on its front page on the damage done to Americans by taking dietary supplements, which now “account for nearly 20 percent of drug-related liver injuries that turn up in hospitals, up from 7 percent a decade ago.” The Times says supplements remain “largely unregulated,” with the FDA locked out of overseeing them due to a 1994 law, yet many Americans are “attracted by unproven claims that various pills and powders will help them lose weight, build muscle and fight off everything from colds to chronic illnesses.” Remarkably, “about half of Americans use dietary supplements, and most of them take more than one product at a time,” spending some \$32 billion a year on them.

According to a review published online Dec. 20 in the American Journal of Psychiatry, all antidepressant medications “may potentially cause liver injury, even at recommended doses, and some groups are more vulnerable than others.” Researchers arrived at this conclusion after reviewing “clinical data on antidepressant-induced liver injury from 158 reports, including 88 case reports, 38 original articles, and 32 reviews.” Notably, antidepressants tied to the “highest risk for hepatotoxicity are monoamine oxidase (MAO) inhibitors, tricyclic/tetracyclic antidepressants, nefazodone, bupropion, duloxetine, and agomelatine.”

Research suggesting Vitamin E may be beneficial for individuals with Alzheimer’s disease was reported by a couple of national news broadcasts, in the print editions or on the websites of several major papers, and by several other major websites and wires. This was based on a study published in The Journal of American Medical Association. The Los Angeles Times “Science Blog” reported “Compared with subjects who took placebo pills, those who took daily supplements of the antioxidant vitamin E and were followed for an average of two years and three months delayed their loss of function by a little over six months on average, a 19% improvement.” Investigators found that “the vitamin E group’s increased need for caregiver help was the lowest of several groups, including those taking the Alzheimer’s drug memantine, those taking memantine and vitamin E, and those taking a placebo.” The new findings “also cast doubt on earlier findings suggesting that vitamin E supplements hastened death in” patients with Alzheimer’s disease.

Neurocrine Biosciences disclosed that its experimental medication, NBI-98854, “helped reduce the symptoms of tardive dyskinesia” in a mid-stage clinical trial. The company said the medication “worked better than a placebo in the six-week study.”

The MedPage Today “Striking a Nerve” blog reports that certain anti-seizure medications are safer for the developing fetus during pregnancy than others, “with valproate probably the biggest no-no,” as evidenced by a study published online in the journal Neurology that compared language and cognitive development of youngsters born to mothers with epilepsy who took valproate, levetiracetam, or no anti-seizure medication at all during pregnancy. Kids whose moms took valproate during pregnancy had an increased risk for such problems, compared to kids whose moms took levetiracetam or no medication at all. Currently, because there is no set “algorithm for deciding which [medication] is best for a given patient,” the “decision still comes down to the individual clinician’s judgment and the patient’s tolerance for risk to herself and her unborn child.”

Medscape reports, “A genetic test in development promises to help doctors identify patients at increased risk for suicide after starting antidepressant therapy.” The new “test for treatment-emergent suicidal ideation is based on research carried out at the Max Planck Institute of Psychiatry in Munich, Germany, and published in 2011 in the journal Neuropsychopharmacology.” However, “Christine Moutier, MD, chief medical officer of the American Foundation for Suicide Prevention and member of the American Psychiatric Association, told Medscape Medical

News: ‘With regard to this genetic test, we feel it is premature to comment on its clinical utility, both because the state of clinical application of the science around this specific area is very early and also because there are specific unknowns about any linkage between medications and suicidal thinking or behaviors.’”

Research published online in BMJ suggests that “maternal antidepressant use has been linked to a low but statistically significant increased risk for persistent pulmonary hypertension (PPH) in newborns exposed to the drugs in late pregnancy.” In “a meta-analysis of 7 studies,” investigators found “a significant association between PPH and infants of expectant mothers who used selective serotonin reuptake inhibitors (SSRIs) during their last trimester, even after several moderator variables were examined.”

The Committee discussed the recent published articles regarding the use of memantine (Namenda®) as a cognitive enhancer. On a motion of Dr. Ward, seconded by Dr. Heidel, it was recommended that a further in-depth review of the use of memantine as a cognitive enhancer be completed in the future.

Next Meeting Date

The next meeting was scheduled for April 11, 2014.

Adjourn

There being no further business, the meeting was adjourned at 1:20 p.m.

Approved: *Jeff R. Matthews*
Jeff R. Matthews, M.D., Acting Chairman

Attachments

- Attachment A – Psychotropic Consent List
- Attachment B – Adasuve™ (loxapine inhalation powder)
- Attachment C – Blood Modifying Agents Sectional Review
- Attachment D – Antidotes/Deterrents/Poison Control Agents Sectional Review
- Attachment E – Antidiabetic Agents Sectional Review
- Attachment F – Intravenous Solutions & Additives Sectional Review
- Attachment G –Formulary Review Schedule

Minutes Prepared by:
Ann L. Richards, Pharm.D., BCPP

Classes of Medications Frequently Used for Psychiatric Indications

Consent is required for any medication that is used in the treatment of a psychiatric diagnosis or symptom, whether or not the medication is included in this list. Refer to physician order for determination of indication for use.

The classification of psychotropic medication is fairly standard but medications can be used for treatment of illnesses that would be considered listed under a different classification. For example, some medications listed under antipsychotics may be used as a mood stabilizer.

The Executive Formulary Committee does not endorse the use of nonformulary drugs

Antidepressants

amitriptyline (Elavil)
 amoxapine (Asendin)
 bupropion (Wellbutrin, Wellbutrin SR)
 bupropion (Wellbutrin XL)
 citalopram (Celexa)
 desipramine (Norpramin)
 desvenlafaxine (Pristiq, Khedezla)
nonformulary
 doxepin (Sinequan)
 duloxetine (Cymbalta)
 escitalopram (Lexapro)
 fluoxetine (Prozac)
 imipramine (Tofranil)
 maprotiline (Ludiumil)
 mirtazapine (Remeron, Remeron SolTab)
 nefazodone (Serzone) *nonformulary*
 nortriptyline (Pamelor, Aventyl)
 paroxetine (Paxil, Paxil CR)
 protriptyline (Vivactil)
 sertraline (Zoloft)
 trazodone (Desyrel)
 trimipramine (Surmontil)
 venlafaxine (Effexor, Effexor XR)
 vilazodone (Viibryd) *nonformulary*

Anxiolytics/Sedatives/Hypnotics

alprazolam (Xanax, Xanax XR)
 buspirone (BuSpar)
 chloral hydrate (Noctec)
 chlordiazepoxide (Librium)
 clonazepam (Klonopin)
 clorazepate (Tranxene)

 diazepam (Valium)
 diphenhydramine (Benadryl)
 eszopiclone (Lunesta) *nonformulary*
 flurazepam (Dalmane) *nonformulary*
 hydroxyzine (Atarax, Vistaril)
 lorazepam (Ativan)
 oxazepam (Serax)
 pentobarbital (Nembutal) *nonformulary*
 ramelteon (Rozerem) *nonformulary*
 temazepam (Restoril)
 triazolam (Halcion)
 zaleplon (Sonata)
 zolpidem (Ambien)

Antipsychotics

aripiprazole (Abilify)
 Aripiprazole (Abilify Maintena)
 asenapine (Saphris)
 chlorpromazine (Thorazine)
 clozapine (Clozaril, Fazaclo) Reserve
 droperidol (Inapsine) *nonformulary*
 fluphenazine (Prolixin)

 fluphenazine decanoate (Prolixin D)
 haloperidol (Haldol)
 haloperidol decanoate (Haldol D)
 iloperidone (Fanapt) Reserve
 loxapine (Loxitane)
 loxapine inhalant (Adasuve) *nonformulary*
 lurasidone (Latuda)
 olanzapine (Zyprexa, Zyprexa Zydis)
 olanzapine pamoate (Zyprexa Relprevv) Reserve
 paliperidone (Invega)
 paliperidone palmitate (Invega Sustenna)
 perphenazine (Trilafon)
 pimozide (Orap) *nonformulary*
 quetiapine (Seroquel)
 quetiapine (Seroquel XR) *nonformulary*
 risperidone (Risperdal, Risperdal M-Tab)
 risperidone (Risperdal Consta)
 thioridazine (Mellaril)
 thiothixene (Navane)
 trifluoperazine (Stelazine)
 ziprasidone (Geodon)

Mood Stabilizers

carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro)
 divalproex sodium (Depakote, Depakote ER)
 lithium (Eskalith, Eskalith CR, Lithobid)
 valproic acid (Depakene)
 oxcarbazepine (Trileptal)
 lamotrigine (Lamictal)

Stimulants

amphetamine/dextroamphetamine
 mixture (Adderall, Adderall XR)
 dexamethylphenidate (Focalin) *nonformulary*
 dextroamphetamine (Dexedrine)
 lisdexamfetamine (Vyvanse)
 methamphetamine (Desoxyn) *nonformulary*
 methylphenidate (Ritalin, Ritalin SR, Concerta, Metadate,

Chemical Dependency Adjuncts

acamprosate (Campral)
disulfiram (Antabuse)
naltrexone (ReVia, Vivitrol)
topiramate (Topamax)

Monoamine Oxidase Inhibitors

isocarboxazid (Marplan) *nonformulary*
phenelzine (Nardil)
selegiline (Emsam) *nonformulary*
tranylcypromine (Parnate)

Other

This category must be approved
prior to inclusion in this
instrument

Metadate CD)

methylphenidate patch (Daytrana) *nonformulary*

Miscellaneous Drugs

atomoxetine (Strattera)
atenolol (Tenormin)
clomipramine (Anafranil)
clonidine (Catapres)
clonidine ER (Kapvay) *nonformulary*
fluvoxamine (Luvox)
gabapentin (Neurontin)
guanfacine (Tenex)
guanfacine ER (Intuniv) *nonformulary*
metoprolol (Lopressor)
nadolol (Corgard)
propranolol (Inderal)
reserpine (Serpasil) *nonformulary*
naltrexone (ReVia)
olanzapine/fluoxetine (Symbyax) *nonformulary*
pindolol (Visken) *nonformulary*

ADASUVE™ (Loxapine inhalation powder)**Classification:**

Antipsychotic

Introduction**Pharmacology^{1, 2}**

Loxapine inhalation powder is tricyclic dibenzoxazepine approved by the FDA in December 2012. Loxapine shows high affinity for dopamine D₁, D₂, D₃ and D₄ receptors and serotonin 5-HT_{2A} receptors. The actual mechanism of action is unknown but is likely mediated by antagonism of dopamine and serotonin receptors.

Pharmacokinetics^{1, 2}

- Absorption: very rapid absorption; C_{max} and AUC increases linearly in a dose-dependent manner
- Distribution: 96.6% Plasma protein bound
- Metabolism: extensively metabolized in the liver via hydroxylation, N-oxidation, and demethylation; active metabolites: amoxapine, 8-hydroxyloxapine
- Excretion: 30% to 40% conjugated metabolites via the kidneys in urine; unconjugated metabolites in feces
- T_{1/2} life: 7.6 hours

Indications^{1, 2}

- Acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

Contraindications³

- Current diagnosis or history of asthma, COPD, or other lung disease with bronchospasm
- Acute respiratory signs/symptoms
- Current use of medications to treat airway disease
- History of bronchospasm following loxapine inhalation powder treatment
- Known hypersensitivity to loxapine or amoxapine
- Pediatrics – safety and efficacy has not been established in this population

Warnings and Precautions³

- Neuroleptic Malignant Syndrome: discontinue use
- Seizures: use with caution in patients with a history of seizures or if using other medications that can lower the seizure threshold
- Elderly patients treated with antipsychotics are at an increased risk of death and cerebrovascular adverse reactions; ADASUVE is NOT approved for use in elderly patients with dementia-related psychosis
- Hypotension and syncope: use with caution in patients with known cardio- and cerebrovascular disease
- May exacerbate glaucoma or cause urinary retention

- Potential cognitive and motor impairment when used with other CNS depressants
- Pregnancy category C. Should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus

Dosage and Administration^{1, 2}

- 10 mg by oral inhalation as a single dose within a 24-hr period
- Only to be administered by a healthcare professional, in an enrolled healthcare facility
- **PRIOR** to administration, screen **ALL** patients for:
 - Current use of medications to treat asthma or COPD
 - History of asthma, COPD, or other pulmonary disease
 - Examine patients (including chest auscultation) for respiratory abnormalities, like wheezing
- Healthcare provider should become familiar with ADASUVE® (see attached handout)
 - Has an indicator light that is off when removed from pouch
 - Indicator light turns green when tab is pulled out and ready for administration
 - Indicator light turns off after the dose is inhaled—meaning the dose has been delivered
 - If the light is still green, the dose has not been delivered, have patient repeat inhalation.
- 6 steps to proper administration:
 - 1) Open the pouch
 - 2) Pull tab – must use inhaler within 15 minutes after removing tab to prevent automatic deactivation of the product
 - 3) Explain procedures to the patient – the inhaler may produce a flash of light and a clicking sound, and may become warm during use. All are normal.
 - 4) Instruct the patient to exhale - holding the inhaler away from the mouth.
 - 5) Instruct patient to inhale – holding the inhaler between closed lips, inhale through the mouthpiece with a steady deep breath.
 - 6) Instruct patient to hold breath – for at least 10 seconds.
 - 7) If the green light did not turn off, have patient repeat steps 4-6³

Monitoring

- Monitor patient every 15 minutes for at least 1 hour for signs and symptoms of bronchospasm
 - Perform a physical examination, including chest auscultation and vital signs
- Ask patient every 15 minutes if there is any difficulty breathing

Drug Interactions

- CNS Depressants – increase the risk of respiratory depression, hypotension, syncope, profound sedation; consider reducing the dose of CNS depressants if used concomitantly
- Anticholinergic Drugs – Loxapine has anticholinergic activity; therefore, risk of anticholinergic adverse reactions are increased

Efficacy

See following clinic trial summary

Citation	Rapid acute treatment of agitation in individuals with schizophrenia: multicenter, randomized, placebo-controlled study of inhaled loxapine. BJP 2011; 198:51-58. Lesem M.D., Tran-Johnson T.K., et al.
Study Goals	To evaluate the efficacy and safety of inhaled loxapine 5 mg and 10 mg doses for acute treatment of agitation in schizophrenia
Methods	
Inclusion criteria	<ul style="list-style-type: none"> • Patients with schizophrenia and agitation – using the DSM-IV criteria • Total score ≥ 14 (out of 35) and a score of ≥ 4 (out of 7) on at least 5 items on the PANSS-EC evaluation • Male and Female (non-pregnant, non-lactating) • Age 18-65 years • Good general health (established by medical history, physical exam, 12-lead ECG, and standard serum chemistry, hematology and urinalysis tests)
Exclusion criteria	<ul style="list-style-type: none"> • Agitation primarily due to acute intoxication • A urine drug screen positive for psychostimulants • A history of drug or alcohol dependence in the previous 2 months • Serious risk of suicide • Use of benzodiazepines or other hypnotics or (oral or short-acting IM) antipsychotic drugs within 4 hours before the study treatment • Use of injectable depot antipsychotics within a one-dose interval before study treatment • Use of an investigational drug within 30 days prior to screening • Clinically significant acute or chronic pulmonary disease
Study design	Randomized, double-blind trial, multi-center, placebo-controlled, parallel-group conducted at 24 psychiatric facilities in the USA between February and June 2008.
Intervention	Randomization to a group (computer generated): <ul style="list-style-type: none"> • Loxapine 5 mg inhaled • Loxapine 10 mg inhaled • Placebo inhaled
Outcomes	<p>Primary efficacy outcome:</p> <ul style="list-style-type: none"> • Change from baseline in the PANSS-EC 2 hours after initial dose given compared to placebo <p>Secondary efficacy outcomes:</p> <ul style="list-style-type: none"> • Absolute CGI-I score 2 hours after initial dose given compared to placebo
Statistics	<ul style="list-style-type: none"> • Sample size calculation – needed 4094 patients enrolled (for the study to have of 90% power at a one-sided α level of 0.025); sample was increased to 5400 patients by the steering committee • Farrington and Manning method (noninferiority), YTH (hypothesis test), Cochran-Mantel-Haenszel method (RR and 95% CI), inverse-variance method (difference in risk), Kaplan-Meier curves • Intention to treat principle • Time-to-event methods • non-inferiority margins for RR < 1.8 and risk difference < 3.5 percentage points • Statistical analyses: SAS
Results	
Baseline	No significant differences in baseline characteristics between the study groups

<p>Outcomes</p>	<p>Primary efficacy outcome:</p> <ul style="list-style-type: none"> • Change from baseline in the PANSS-EC score 2 hours after initial dose <ul style="list-style-type: none"> ○ 5 and 10 mg doses resulted in significantly larger decreases in the PANSS-EC score relative to placebo; P = 0.0004, P < 0.0001 respectively. <p>Secondary efficacy outcomes:</p> <ul style="list-style-type: none"> • Change from baseline in the PANSS-EC score at each assessment from 10 minutes through 24 hours • Improved CGI-I score at 2 hour after initial dose <ul style="list-style-type: none"> ○ 5 and 10 mg doses resulted in significantly larger decreases in agitation compared with inhaled placebo as assessed by the CGI-I score ○ Placebo group: 2.8; 5 mg group: 2.3; 10 mg group: 2.1 (where 2 is much improved and 3 is minimally improved) ○ Overall, P < 0.0001
<p>Critique</p>	<p>Strengths</p> <ul style="list-style-type: none"> • Assessment of endpoints at various times after initial administration of study drug • Similar baseline characteristics • No patient refused or was unable to take a dose of the study drug—indicating ease of use and patient acceptance <p>Limitations</p> <ul style="list-style-type: none"> • No comparison to standard therapy (IM antipsychotics) • Treatment received in a controlled environment • PANSS-EC is not typically used to assess agitation in real world settings • Informed consent may not always be possible to obtain in the real world like it was in the study
<p>Comments</p>	<p>Loxapine inhaled powder showed to be effective in acute treatment of agitation in patients with schizophrenia. It is also less invasive than traditional IM methods.</p>

Costs

None known as of January 2014; not yet available from wholesalers

REMS info

- ADASUVE can only be administered at an enrolled healthcare facility
- Each facility has to re-enroll every 3 years
- Each facility will elect a representative to maintain records and ensure proper training to all personnel; all records are subject to audit
- Qualifications for healthcare facility enrollment:
 - Immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
 - Immediate access on-site to a metered-dose inhaler and nebulized form of a short-acting beta-agonist bronchodilator (i.e. albuterol)
 - Procedures, protocols, and/or order sets to ensure the following:
 - Patient screening, prior to treatment, for a history of pulmonary disease and for acute pulmonary signs and symptoms by physical exam, including taking vital signs and chest auscultation, and inquiring if patient is taking medication to treat asthma or COPD
 - Patients are monitored at least every 15 minutes for a minimum of 1 hour following treatment for signs and symptoms of bronchospasm, including taking vital signs and chest auscultation

- Administration of ADASUVE is limited to 1 dose per patient within 24 hours
- Healthcare providers within the facility (prescribers, nurses, monitoring staff, or pharmacists) who are trained on safe use of ADASUVE using the ADASUVE REMS Education Program

Conclusions

Loxapine inhaled powder showed to be effective in acute treatment of agitation in patients with schizophrenia and bipolar I disorder. It is also less invasive than traditional IM methods. With that being said, there are a lot of initial roadblocks, such as many contraindications for use and proper training of all staff, before ADASUVE can even be safely used in a facility. Facility enrollment and proper personnel training require increased man hours and paperwork. Facility enrollment criteria along with a lack of clinical data showing an advantage in outcomes over current therapy for acute treatment of agitation should be reviewed prior to any formulary consideration.

References

1. Product Information Loxapine™ (loxapine) Alexza Pharmaceuticals, Inc. Mountain View, California, 2013
2. Micromedex, Loxapine drug monograph, accessed electronically on January 21, 2014 via Micromedex online
3. Center for Drug Evaluation and Research, Application Number 022549 Medical Review, 2012
4. Rapid acute treatment of agitation in individuals with schizophrenia: multicenter, randomized, placebo-controlled study of inhaled loxapine. BJP 2011; 198:51-58. Lesem M.D., Tran-Johnson T.K., et al.

Prepared by: Debra Stewart, PharmD candidate 2014

SUMMARY

Pros:

- Noninvasive route of administration (oral inhalation)
- Rapid onset of action (within 10 minutes; median time = 2 minutes)
- Reduces agitation in patients with bipolar I disorder or schizophrenia
- Generally well tolerated

Cons:

- Approval was based on 2 clinical trials: one with agitated patients with schizophrenia and one with agitated patients with bipolar I disorder
- Risk of bronchospasm that can lead to respiratory distress and/or respiratory arrest
- Contraindicated in patients with airways disease associated with bronchospasm or acute respiratory signs or symptoms
- Contraindicated in patients currently taking medications for asthma or COPD
- Facility has to become certified to dispense **ADASUVE®** and recertify every 3 years (documentation can be audited)
- Staff need to be properly trained on how to administer and monitor patients (every 15 minutes for 1 hour after administering a dose)
- Must screen patients **PRIOR** to dosing (not very helpful if patient is having a psychotic episode)

- Examine patients for respiratory abnormalities (wheezing, dyspnea)
- Can only administer 1 dose per 24 hours due to increased pulmonary adverse events after dose 2
 - A higher percentage of patients required albuterol treatment after dose 2 compared to placebo (41% vs 8%)³
 - FEV₁s did not return to baseline up to 24 hours after dose 2
- Need to treat bronchospasm with an inhaled short-acting beta-agonist bronchodilator (albuterol)
- Provide additional therapy for bronchospasm per asthma guidelines, including intubation and mechanical ventilation as needed (requires crash carts or ER boxes and properly trained staff)

MEMORANDUM

To: Executive Formulary Committee
From: Catherine S. Hall, Pharm.D., BCPP
Through: Ann L. Richards, Pharm.D., BCPP
Subject: Class Review – Blood Modifying Agents
Date: January 31, 2014

No recommended changes

Blood Modifying Agents

Antiplatelet

Aspirin	\$
Clopidogrel (Plavix) – RESERVE USE	\$\$\$

Anticoagulant

Fondaparinux (Arixtra)	\$\$\$\$\$\$
Heparin	\$\$
Enoxaparin (Lovenox)	\$\$\$\$\$\$
Warfarin (Coumadin)	\$

Anticoagulation Antagonist

Phytonadione (Vitamin K ₁ , Mephyton)	\$\$ - \$\$\$
Protamine	\$

Miscellaneous Blood Modifying Agents

Epoetin alfa (Epogen, Procrit) RESERVE USE	\$\$\$\$\$\$
Ferrous Fumarate/Docusate Sodium (Ferro-Sequels) [33% elemental iron]	\$\$
Ferrous Sulfate (Feosol, Fer-In-Sol) [20% elemental iron]	\$

Aspirin

Suppository, rectal: 300 mg, 600 mg
Tablet: 325 mg
Tablet, buffered: 325 mg with buffering agents
Tablet, chewable: 81 mg
Tablet, enteric coated: 81 mg, 162 mg, 325 mg, 500 mg, 650 mg

Clopidogrel (Plavix) - RESERVE USE

Tablet: 75 mg

Fondaparinux (Arixtra)

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg

Heparin

Injection: 10 units/mL, 100 units/mL, 1,000 units/mL, 5,000 units/mL, 10,000 units/mL, 20,000 units/mL

Enoxaparin (Lovenox)

Injection: 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 150 mg

Warfarin (Coumadin)

Tablet: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6mg, 7.5 mg, 10 mg

Phytonadione (Vitamin K₁, Mephyton, Konakion)

Injection, aqueous colloidal: 2 mg/mL, 10 mg/mL
Injection, aqueous (IM only): 2 mg/mL, 10 mg/mL
Tablet: 5 mg

Protamine

Injection: 10 mg/mL

Epoetin alfa (Epogen, Procrit)- RESERVE USE

Injection: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, 20,000 units/mL, 40,000 units/mL

Ferrous Fumarate/Docusate Sodium (Ferro-Sequels)[contains 33% elemental iron]

Tablet, timed released: Ferrous fumarate 150 mg [50 mg]/Docusate Sodium 100 mg

Ferrous Sulfate (Feosol, Fer-In-Sol) [contains 20% elemental iron]

Elixir with 5% alcohol: 220 mg/5 mL [18 mg/5 mL]
Tablet: 160 mg [32mg], 300 mg [60 mg], 325 mg [65 mg]

MEMORANDUM

To: Executive Formulary Committee

From: Catherine S. Hall, Pharm.D., BCPP

Through: Ann L. Richards, Pharm.D., BCPP

Subject: Class Review – Antidotes/Deterrents/Poison Control Agents

Date: January 31, 2014

No recommended changes

Antidotes/Deterrents/Poison Control Agents

Acetylcysteine (Mucomyst)	
Activated Charcoal	
Deferoxamine (Desferal)	
Dimercaprol (B.A.L.)	
Disulfiram (Antabuse)	
Glucagon	
Glucose, oral	
Leucovorin (Wellcovorin)	
Naloxone (Narcan)	\$\$ - \$\$
Naltrexone (Trexan, ReVia)	\$\$\$
Nicotine Polacrilex (Nicorette)	\$\$ - \$\$\$\$\$
Nicotine Transdermal Patch (Nicoderm, Habitrol, ProStep, Nicotrol)	\$\$\$
Penicillamine (Cuprimine)	
Physostigmine (Antilirium)	
Phytonadione (Vitamin K ₁ , Mephyton)	\$\$ - \$\$\$
Protamine	\$

Acetylcysteine (Mucomyst)

Solution, inhalation: 10% [100 mg/mL], 20% [200 mg/mL]

Activated Charcoal

Capsules: 200 mg, 260 mg

Liquid, oral, activated, with sorbitol: 25 g, 30 g, 50 g

Powder for oral suspension, activated: 15 g, 30 g, 40 g, 120 g, 240 g

Tablet: 260mg

Deferoxamine (Desferal)

Powder for injection: 500 mg

Dimercaprol (B.A.L.)

Injection: 100 mg/mL

Disulfiram (Antabuse)

Tablet: 250 mg, 500 mg

Glucagon

Powder for injection: 1 mg

Leucovorin (Wellcovorin)

Injection: 3 mg/mL

Powder for injection: 25 mg, 50 mg, 100 mg, 350 mg

Tablet: 5 mg, 10 mg, 15 mg, 25 mg

Naloxone (Narcan)

Injection: 0.4 mg/mL, 1 mg/mL

Naltrexone (Trexan, ReVia)

Tablet: 50 mg

Nicotine (Nicoderm, Habitrol, ProStep, Nicotrol, Nicorette)

Patch, transdermal:

Habitrol: 21 mg/day, 14 mg/day, 7 mg/day

Nicoderm: 21 mg/day, 14 mg/day, 7 mg/day

Nicotrol: 15 mg/day (gradual release over 16 hours)

Pieces, chewing gum, as polacrilex: 2 mg/square, 4 mg/square

Penicillamine (Cuprimine)

Capsule: 125 mg, 250 mg

Tablet: 250 mg

Physostigmine (Antilirium)

Injection: 1 mg/mL

Phytonadione (Vitamin K₁, Mephyton, Konakion)

Injection, aqueous colloidal: 2 mg/mL, 10 mg/mL

Injection, aqueous (IM only): 2 mg/mL, 10 mg/mL

Tablet: 5 mg

Protamine

Injection: 10 mg/mL

MEMORANDUM

To: Executive Formulary Committee

From: Catherine S. Hall, Pharm.D., BCPP

Through: Ann L. Richards, Pharm.D., BCPP

Subject: Class Review – Antidiabetic Agents

Date: January 31, 2014

Delete tolbutamide (Orinase); insulin, Lente; insulin, Ultralente

Antidiabetic Agents

Insulins, Human

Insulin, Aspart (NovoLog)	\$\$\$\$\$\$\$\$
Insulin, Combination (70/30)	\$\$\$\$
Insulin, Glargine (Lantus)	\$\$\$\$\$\$\$\$
Insulin, Lente	\$\$\$\$
Insulin, Lispro (Humalog)	\$\$\$\$\$\$\$\$
Insulin, Lispro/Insulin, Lispro Protamine (Humalog Mix 75/25)	\$\$\$\$\$\$\$\$
Insulin, NPH	\$\$\$\$
Insulin, Regular	\$\$\$\$
Insulin, Ultralente	\$\$\$\$

Sulfonylureas

glipiZIDE (Glucotrol)	\$
glyBURIDE (Micronase, DiaBeta)	\$\$
TOLBUTamide (Orinase)	\$\$

Miscellaneous Antidiabetics

Metformin (Glucophage, Glucophage XR)	\$
Pioglitazone (Actos)	\$\$-\$\$\$
Repaglinide (Prandin)	\$\$ - \$\$\$\$

Glucose Elevating Agents

Dextrose 50% in Water	\$\$
Glucagon	\$\$\$\$\$\$\$\$
Glucose	\$ - \$\$\$

Insulin, Aspart (NovoLog)

Injection: 100 units/mL

Insulin, Combination (70/30)

Injection: 100 units/mL

Insulin, Glargine (Lantus)

Injection: 100 units/mL

Insulin, Lente

Injection: 100 units/mL

Insulin, Lispro (humaLOG)

Injection: 100 units/mL

Insulin, Lispro/Insulin, Lispro Protamine (Humalog Mix 75/25)

Injection: 100 units/mL

Insulin, NPH

Injection: 100 units/mL

Insulin, Regular

Injection: 100 units/mL

Insulin, Ultralente

Injection: 100 units/mL

glipiZIDE (Glucotrol)

Tablet: 5 mg, 10 mg

Tablet, extended release: 2.5 mg, 5 mg, 10 mg

glyBURIDE (Micronase, DiaBeta)

Tablet: 1.25 mg, 2.5 mg, 5 mg

Tablet, micronized: 1.5 mg, 3 mg, 6 mg

TOLBUTamide (Orinase)

Tablet: 250 mg, 500 mg

metFORMIN (Glucophage, Glucophage XR)

Tablet: 500 mg, 850 mg, 1000 mg

Tablet, extended release: 500 mg, 750 mg

Pioglitazone (Actos)

Tablet: 15 mg, 30 mg, 45 mg

Repaglinide (Prandin)

Tablet: 0.5 mg, 1 mg, 2 mg

Dextrose 50% in Water

Infusion

Syringe

Vials

Glucagon

Powder for injection: 1 mg

Glucose
Gel, oral
Tablet

MEMORANDUM

To: Executive Formulary Committee

From: Catherine S. Hall, Pharm.D., BCPP

Through: Ann L. Richards, Pharm.D., BCPP

Subject: Class Review – Intravenous Solutions and Additives

Date: January 31, 2014

No recommended changes

Intravenous solutions and additives

Intravenous Solutions

Amino Acid Injection (Aminosyn)	\$\$\$\$ - \$\$\$\$\$\$
Amino Acid Injection/Dextrose/Electrolytes (Clinimix E)	\$\$\$\$\$\$
Dextrose/Sodium Chloride Intravenous Solution	\$\$\$\$
Dextrose 5% in 0.2% Sodium Chloride	
Dextrose 5% in 0.45% Sodium Chloride	
Dextrose 5% in 0.9% Sodium Chloride	
Dextrose 5% in Water	\$ - \$\$
Dextrose 5% in Ringer's Lactate	\$
Dextrose 5% with Multiple Electrolytes (D5 E75, Baxter)	\$\$\$
Dextrose 5%/Sodium Chloride/Potassium Chloride Intravenous Solution	\$\$\$\$\$\$ - \$\$\$\$\$\$
Dextrose 5%/Sodium Chloride 0.2%/Potassium Chloride	
Dextrose 5%/Sodium Chloride 0.45%/Potassium Chloride	
Dextrose 5%/Sodium Chloride 0.9%/Potassium Chloride	
Dextrose 50% in Water	\$\$\$\$ - \$\$\$\$\$
Ringer's Lactate Solution (Hartmann's Solution)	\$\$
Sodium Chloride Intravenous Solution	\$\$\$\$ - \$\$\$\$\$
Sodium Chloride 0.2%	\$ - \$\$\$
Sodium Chloride 0.45%	
Sodium Chloride 0.9%	
Water for Injection	\$\$ - \$\$\$\$

Electrolyte Replacement Additives

Calcium Gluconate	\$\$
Magnesium Sulfate	\$ - \$
Potassium Chloride	\$ - \$\$
Sodium Bicarbonate	\$ - \$\$
Sodium Chloride	\$ - \$\$
Sodium Lactate	\$\$\$\$
Zinc Sulfate	\$ - \$\$

Amino Acid Injection (Aminosyn)

Infusion: 3.5%, 5%, 7%, 8.5%, 10%, 15%

Amino Acid Injection/Dextrose/Electrolytes (Clinimix E)

Infusion: 2.75%, 4.25%, 5%

Dextrose/Sodium Chloride Intravenous Solution

Infusion: Dextrose 5% in 0.2% Sodium Chloride

Infusion: Dextrose 5% in 0.45% Sodium Chloride

Infusion: Dextrose 5% in 0.9% Sodium Chloride

Dextrose 5%/Sodium Chloride/Potassium Chloride Intravenous Solution

Infusion: Dextrose 5%/Sodium Chloride 0.2%/Potassium Chloride

with Potassium Chloride: 10 mEq, 20 mEq

Infusion: Dextrose 5%/Sodium Chloride 0.45%/Potassium Chloride

with Potassium Chloride: 10 mEq, 20 mEq, 40 mEq

Infusion: Dextrose 5%/Sodium Chloride 0.9%/Potassium Chloride

with Potassium Chloride: 20 mEq, 40 mEq

Dextrose 5% in Water

Infusion

Dextrose 5% in Ringer's Lactate

Infusion

Dextrose 5% with Multiple Electrolytes (D5 E75, Baxter)

Infusion

Dextrose 50% in Water

Infusion

Syringe

Vials

Ringer's Lactate Solution (Hartmann's Solution)

Infusion

Sodium Chloride Intravenous Solution

Infusion: 0.2%, 0.45%, 0.9%

Water for Injection

Infusion

Calcium Gluconate [9% elemental calcium]

Injection: 10% [100 mg/mL]

Magnesium Sulfate (Epsom Salt)

Injection: 100 mg/mL, 125 mg/mL, 250 mg/mL, 500 mg/mL

Potassium Chloride

Injection, concentrate: 2 mEq/mL

Sodium Bicarbonate

Injection: 4.2% [5 mEq/10 mL], 8.4% [10 mEq/10 mL]

Sodium Chloride

Infusion: 0.2%, 0.45%, 0.9%, 3%, 5%, 20%, 23.4%

Injection, bacteriostatic: 0.9%
Injection, for admixtures: 50 mEq, 100 mEq, 635 mEq

Sodium Lactate

Injection: Sodium 167 mEq/Lactate 168 mEq per liter

Zinc Sulfate

Injection: 1 mg/mL, 5 mg/mL

Formulary Review Schedule

1/31/14

Proposed:

2014	Winter	Blood Modifying - 11 Antidotes/Deterrents/Poison Control- 17 Antidiabetic - 18 Intravenous Solutions and Additives – 18
2014	Spring	Endocrine - 23 Osteoporosis - 6 Genitourinary -21
2014	Summer	Antiparkinson Agents - 9 Cardiovascular - 50
2014	Fall	Analgesics/Antipyretics - 14 Anticonvulsants - 22 Sedative and Hypnotics - 14 Table Review Reserve Drug Review
2015	Winter	Nasal/mouth/throat - 15 Otics - 9 Ophthalmics – 33
2015	Spring	Psychotropic – 70
2015	Summer	Gastrointestinal - 58 Muscle Relaxants -6
2015	Fall	Infectious Disease – 64 Antineoplastic - 1 Table Review Reserve Drug Review
2016	Winter	Nutritional/Nutritional Supplements - 31 Dementia/Miscellaneous CNS - 5 Migraine - 12
2016	Spring	Respiratory – 37 Antihistamine - 11 Antiemetics/Antivertigo - 7
2016	Summer	Dermatologicals, (Acne agents to Anti-Infectives Antiseptic & germicides) – 57
2016	Fall	Dermatologicals (Scabicides to Wound agents) - 47 Irrigation – 2 Immunological - 12 Table Review Reserve Drug Review