

**DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
October 30, 2015**

The Executive Formulary Committee convened on Friday, October 30, 2015 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Messer, Acting Chair at 10:05 a.m.

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

Guests Present: Lisa Mican, Pharm.D., Austin State Hospital; Steven Braun, Pharmacy Student, ASH; Heather Rozea, Pharmacy Volunteer ASH; Michelle Ding, Pharm.D., Resident ASH; Marshall George, Pharmacy Student SASH; Isaac Pan, Pharm.D., Resident SASH

Introduction and Other Information

With Dr. Ward's departure from North Texas State Hospital, Dr. Messer, Terrell State Hospital was appointed as the newest member of the Committee. Dr. Wright and Dr. Hall are participating by phone due to the inclement weather. Since Dr. Wright was participating by phone, Dr. Messer volunteered to serve as Chair.

Approval of Minutes of July 24, 2015

On a motion of Ms. Millhollon, seconded by Dr. Matthews, the minutes of the July 24th meeting were approved as previously distributed.

Conflict of Interest

Dr. Messer completed his disclosure statement and did not report any conflict of interest. None of the Committee members present reported any conflicts of interest.

Issues from the Medical Executive Committee

The Medical Executive Committee did not submit any issues to the Committee.

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed several adverse drug reaction reports that were received from the field.

On 5/5/15, a 53 year old male was admitted from a local hospital. On June 4th, he was started on capreomycin for rifampin-resistant tuberculosis. Capreomycin 1 gram IM was administered on June 4th and 5th. His other medications at that time were moxifloxacin (Avelox®) 800 mg daily, pyrazinamide 2,000 mg daily, ethambutol (Myambutol®) 2,000 mg daily, isoniazid 600 mg daily, linezolid (Zyvox®) 600 mg rally daily (discontinued 6/26/15), metformin (Glucophage®) 1,000 mg twice a day, glipizide (Glucotrol®) 10 mg daily (only one dose administered), aspirin enteric coated 81 mg daily, ondansetron (Zofran®) 4 mg daily, pyridoxine, 50 mg daily, pantoprazole (Protonix®) 20 mg daily, pravastatin (Pravachol®) 40 mg bedtime, ramipril (Altace®) 2.5 mg daily, and gabapentin (Neurontin®) 300 mg twice a day (discontinued July 13th). On June 8th, he was converted to capreomycin 1 gram IV daily Monday through Friday and he received this until June 29th. On June 29th, capreomycin was changed back to IM and he received 1 gram IM daily Monday through Friday until July 16th when serum creatinine was 4.0 mg/dL (normal 0.44-1.27 mg/dL). He had been experiencing nausea and anorexia for about three days prior to the lab draw. On July 16th, all medications are discontinued except for aspirin enteric coated 81 mg daily and ondansetron 4 mg daily.

A 32 year old male had an ophthalmology appointment on 9/24/2015 for a follow-up on macular pigment hyperplasia and optic nerve hypoplasia, both eyes. At this office visit, mild nuclear sclerotic (senile) cataracts, bilateral were discovered. The ophthalmologist did not recommend any intervention since the individual already has significant visual impairment. The previous eye exam performed 9/12/2012 found no cataracts. Routine eye exams were performed by the Primary Care Practitioner in the intervening years and no red reflex was seen. He was started on quetiapine (Seroquel®) for excessive movement disorder while in the hospital in December 2014 and has taken it continually since then. At this time, quetiapine therapy will be continued.

A 35 year old male was admitted to the psychiatric hospital diagnosed with Intermittent Explosive Disorder, Impulse Control Disorder and Severe Intellectual Disability as well as medical conditions including neurogenic bladder, frequent UTIs and macrocytic anemia. Baseline labs were within normal limits except glucose 50 mg/dl, AST 53 U/L, and ALT 82 U/L. The CBC showed RBC 3.92 M/mm³, hemoglobin 13.9 g/dl, hematocrit 40.7%, MCV 103.9 fL and MCH 35.4 pg/cell with 1+ macrocytes on RBC morphology. TSH, B12, and RBC folate were within normal limits. A follow up CMP obtained 2 weeks later showed normal glucose and LFTs. Medications on admission were divalproex (Depakote®) DR 500 mg twice daily, lorazepam (Ativan®) 1 mg three times daily, quetiapine (Seroquel®) 200 mg three times daily and trazodone (Desyrel®) 50 mg at bedtime prn insomnia. An EKG obtained 3 days after admission at 8:57 am showed QTc prolongation with QTc 512 msec, heart rate was 129 bpm with sinus tachycardia. The patient had received a prn dose of trazodone the night before the EKG along with the other scheduled medications. Quetiapine was tapered and discontinued over the next 5 days. Lorazepam was also tapered to a dose of 0.5 mg in the morning, 0.5 mg at noon and 1 mg at bedtime. Divalproex and trazodone were continued at the same doses. A follow-up EKG 10 days after the initial EKG was within normal limit with QTc 400 msec and heart rate 83 bpm. Trazodone had not been administered the night preceding the EKG.

A 33 year old male was admitted to the psychiatric hospital a little over 3 months prior to the event. He is diagnosed with bipolar disorder and seasonal allergies. All admission labs including CMP, CBC, TSH, and lipids were within normal limits. Admission EKG was within normal limits with QTc 389 msec and heart rate 79 bpm. Initially the patient was treated with olanzapine (Zyprexa®) with some infrequent prn administrations of trazodone (Desyrel®) 50 mg and 100 mg during the first month of hospitalization, but he was subsequently switched to haloperidol (Haldol®) and lithium with diphenhydramine (Benadryl®) also being added to the regimen. Blood pressure and pulse generally were low normal during the hospitalization without symptomatic bradycardia or hypotension noted prior to event. On the day of the adverse event, the patient received his usual scheduled medications of lithium 900 mg at bedtime and diphenhydramine 25 mg twice daily. He was also receiving haloperidol decanoate 200 mg IM

injections with the last injection administered the day prior to the event. He had been on lithium, haloperidol and diphenhydramine for approximately 2 months. Recent lithium levels and CMPs were normal and a haloperidol level approximately one month prior to the event was low at 3.0 ng/mL. Trazodone 100 mg dose was administered on the night of the event at 8:19 pm and at 8:44 pm the patient had a syncopal episode after standing from a sitting position and fell to the ground on his back. He noted feeling dizzy and sleepy just prior to the event. The patient was noted by nursing staff to appear pale and when his blood pressure was taken by automatic cuff it was 66/33 mmHg with pulse of 50 bpm, a repeat blood pressure was also low at 84/52 mmHg with pulse of 60 bpm. After a bottle of water (approximately 1 hour after administration of trazodone) the blood pressure was 94/60 mmHg with a pulse of 60 bpm and normal color returned to his face and the patient reported feeling better. Trazodone was discontinued and no further events have been reported. Syncope with fall, severe hypotension and bradycardia was thought to be due to the administration of trazodone 100 mg just prior to the event.

A 53 year old male has taken osteoporosis medications over the past 10 years. Beginning with alendronate (Fosamax®) in September 2005 – October 2005, switching to ibandronate (Boniva®) from October 2005 – July 2011 and finally initiating denosumab (Prolia®) in August, 2013, receiving his last dose in February, 2015 for his severe osteoporosis. On August 21, 2015, the nurse noticed swelling of the right thigh as well as bruising below the right knee and bilateral swelling of the feet. An x-ray was ordered and a spiral fracture of the right femur was detected. No break in the skin was present. Earlier in the day, the patient had been moved via a sling and lift for a bath, but no trauma or falls occurred. After the x-ray was performed, the patient was sent to local medical hospital and an ORIF was conducted on August 22nd. The scheduled DEXA scan has been delayed and further doses of denosumab held pending healing of the fracture

New Drug Application

(Please refer to Attachment A for the monograph and application that were considered when determining action by the committee.)

Insulin detemir (Levemir®) - presented by Heather Rozea, Pharmacy Volunteer

Insulin detemir is a long acting recombinant human insulin analog. It acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs include the liver, skeletal muscle, and adipose tissue. The onset of action is 3-4 hours and Cmax is reached 6-8 hours post-dose. Insulin detemir is indicated for the treatment of type 1 diabetes mellitus and type 2 diabetes mellitus to improve glycemic control in adults and children (over the age of 2). Dose is dependent on type of diabetes and concomitant medications. The following shows the purchases of insulin detemir as compared to insulin glargine for FY15:

<u>Drug</u>	<u>Hospital</u>	<u>Living Center</u>
Insulin detemir (Levemir®)	\$24,026.45	\$14,604.84
Insulin glargine (Lantus®)	\$194,404.29	\$116,416.18

Following discussion, on motion of Dr. Matthews, seconded by Dr. Balfanz, the request to add insulin detemir (Levemir®) to the formulary as a reserve drug was approved. The reserve criteria shall be for those that are unable to tolerate insulin glargine.

Moxifloxacin (Moxeza®, Vigamox®) Ophthalmic

Moxifloxacin ophthalmic was added to the Formulary at the previous meeting. At that time, it was added to the Formulary without restrictions. The question arose as to whether or not moxifloxacin ophthalmic should be a reserve drug due to costs. **After reviewing the information, on a motion of Dr. Heidel, seconded by Dr. Pittman, it was recommend to change moxifloxacin ophthalmic to a reserve drug with the reserve criteria being: for bacterial conjunctivitis where MRSA or gram negative microorganisms is identified or suspected.**

Drug Deletions

At the July meeting, all recommendations for drug deletions were due to lack of commercial availability, so the field was not asked for their input.

New Dosage Strengths

It was requested to add mesalamine, delayed release: 800 mg tablet to the Formulary. Currently, there are several other mesalamine products on the Formulary. On a motion of Ms. Millhollon, seconded by Dr. Matthews, the recommendation to add mesalamine 800 mg delayed release tablet to Formulary was approved.

Dexmethylphenidate (Focalin®, Focalin® XR) Purchases

The following is a summary of dexmethylphenidate purchases for the State Hospitals and State Supported Living Centers for the past quarter:

Facility Type	Item Quantity	Total
State Hospitals	8	\$4,887.49
State Supported Living Centers	10	\$1,441.02
Grand Total	18	\$6,328.51

The Committee recommended monitoring dexmethylphenidate purchases for at least another quarter.

Psychotropic Audit Criteria & Guidelines - Antipsychotics

At the last meeting, it was recommended that waist circumference be added to the BMI criteria for the antipsychotic audit criteria and guidelines. The antipsychotic audit criteria and guidelines have been modified to include this recommendation. See Attachment B. On a motion of Ms. Millhollon, seconded by Dr. Heidel, the revised antipsychotic audit criteria and guidelines were approved. The antipsychotic audit criteria and guidelines will be distributed to the field.

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.

Drug Formulary Sectional Review-

**Infectious Disease Agents
Antineoplastic Agents**

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

Based on their review, the following recommendations were made to the Antibiotic Section:

- Delete the following antibiotic products from the Formulary due to lack of availability:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Amoxicillin	Amoxil®, Polymox®	Powder for oral suspension: 50 mg/ml	Capsule: 250 mg, 500 mg Powder for oral suspension: 125 mg/5 ml, 250 mg/5 ml Tablet: 500 mg, 875 mg Tablet, chewable: 125 mg, 250 mg
Amoxicillin-Clavulanate	Augmentin®	Tablet: 200 mg (contains clavulanate 28.5 mg), 400 mg (contains clavulanate 57 mg)	Suspension, oral: 400 mg (contains clavulanate 57 mg) per 5 ml, 600 mg (contains clavulanate 42.9 mg) per 5 ml Tablet: 250 mg (contains clavulanate 125 mg), 500 mg (contains clavulanate 125 mg), 875 mg (contains clavulanate 125 mg) Tablet, chewable: 125 mg (contains clavulanate 31.25 mg), 250 mg (contains clavulanate 62.5 mg) Tablet, extended release: 1,000 mg (contains clavulanate 62.5 mg)
Nafcillin	Unipen®	Capsule: 250 mg Powder for injection: 4 g Solution: 250 mg/5 ml tablet 500 mg	Powder for injection: 500 mg, 1 g, 2 g, 10 g
Penicillin G Benzathine	Bicillin L-A®	Injection: 300,000 units/ml	Injection: 600,000 units/ml
Penicillin G Benzathine – Penicillin G Procaine	Bicillin C-R®	Penicillin G Benzathine 150,000 units – Penicillin G Procaine 150,000 units	Penicillin G Benzathine 900,000 units – Penicillin G Procaine 300,000 units
Penicillin G Procaine	Wycillin®	Injection (suspension): 300,000 units/ml, 500,000 units/ml	Injection (suspension): 600,000 units/ml
Penicillin V Potassium	Pen-Vee K®, V-Cillin K®	Tablet: 125 mg	Powder for oral solution: 125 mg/5 ml, 250 mg/5 ml Tablet: 250 mg, 500 mg
Cefazolin	Kefzol®, Acef®	Powder for injection: 250 mg	Injection: 500 mg, 1 g Powder for injection: 500 mg, 1 g, 5 g, 10 g, 20 g

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Cephalexin	Keflex	Powder for oral suspension: 100 mg/ml Tablet: 1 g	Capsule: 250 mg, 500 mg Powder for oral suspension: 125 mg/5 ml, 250 mg/5 ml Tablet: 250 mg, 500 mg
Azithromycin	Zithromax®	Powder for oral solution: 400 mg/5 ml	Powder for oral solution: 200 mg/5 ml Tablet: 250 mg, 500 mg, 600 mg
Tetracycline		Capsule: 100 mg Suspension, oral 125 mg/5 ml Tablet: 250 mg, 500 mg	Capsule: 250 mg, 500 mg
Gentamicin		Infusion, premixed in D5W: 60 mg, 80 mg, 100 mg	Infusion, premixed in NS: 40 mg, 60 mg, 80 mg, 90 mg, 100 mg, 120 mg Injection: 10 mg/ml, 40 mg/ml Injection, intrathecal (preservative free): 2 mg/ml
Vancomycin	Vancocin®	Powder for oral solution: 1 g, 10 g Powder for injection: 2 g	Capsule: 125 mg, 250 mg Powder for injection: 500 mg, 1 g, 5 g, 10 g

- Delete the following trade names from the generic listings:
 - Unipen® from nafcillin
 - Ancef® from cefazolin
 - Achromycin® and Panmycin® from tetracycline
 - Amikin® from amikacin
 - Garamycin® from gentamicin
 - Mycifradin® from neomycin
 - Nebcin® from tobramycin
 - Seromyacin® from cycloserine
 - Co-Trimoxazole® and Septra® from sulfamethoxazole-trimethoprim

- Add the following to the Formulary

Generic Name	Brand Name	Dosage forms to be added
Penicillin G Benzathine – Penicillin G Procaine	Bicillin C-R®	Penicillin G Benzathine 600,000 units– Penicillin G Procaine 600,000 units/2 ml

In discussing the erythromycin products it was noted that there are safer and more effective alternative antibiotic therapies available, therefore, the Committee considered deleting these products from Formulary. It was noted that the State Supported Living Centers use erythromycin not for an antibiotic but for gastroparesis. Based on this, it was recommended that the following products be removed from the Infectious Disease Agents and moved to the gastrointestinal section:

- Erythromycin base:
 - Capsule, delayed release: 250 mg
 - Tablet, film coated: 250 mg, 500 mg
- Erythromycin ethylsuccinate:
 - Granules/powder for oral suspension: 200 mg/5 ml, 400 mg/5 ml
 - Suspension, oral: 200 mg/5 ml, 400 mg/5 ml
 - Tablet: 400 mg

For the erythromycin products it was recommended that the following products be deleted:

Generic Name	Brand Name	Dosage forms to be deleted	*Dosage forms still available
Erythromycin base	Eryc®, E-Mycin®, Ery-Tab®, E-Base®, PCE®	Tablet, enteric coated: 250 mg, 333 mg, 500 mg Tablet, polymer coated particles: 333 mg, 500 mg	Capsule, delayed release: 250 mg Tablet, film coated: 250 mg, 500 mg
Erythromycin ethylsuccinate	EryPed®, EES®	Suspension, oral (drops): 100 mg/2.5 ml Tablet, chewable: 200 mg	Granules/Powder for oral suspension: 200 mg/5 ml, 400 mg/5 ml Suspension, oral: 200 mg/5 ml, 400 mg/5 ml Tablet: 400 mg

* Moved to gastrointestinal section

Based on their review, the following recommendations were made to the Antifungal Section:

- Delete the following antifungal products from the Formulary due to lack of availability:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Griseofulvin	Fulvicin®	Microsize: Capsule: 125 mg, 500 mg Tablet: 250 mg Ultramicrosize: Tablet: 165 mg, 330 mg	Microsize Suspension, oral: 125 mg/5 ml with 0.2% alcohol Tablet: 500 mg Ultramicrosize: Tablet: 125 mg, 250 mg
Nystatin	Mycostatin®	Powder for oral suspension: 50 million units, 1 billion units, 2 billion units, 5 billion units Troche: 200,000 units	Suspension, oral: 100,000 units/ml Tablet, oral: 500,000 units

- Add trades Grifulvin V® and Gris-Peg® to griseofulvin

Based on their review, the following recommendations were made to the Antitubercal Section:

- Delete the following antitubercular products from the Formulary due to lack of availability:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Isoniazid		Tablet: 50 mg	Injection: 100 mg/ml Syrup: 50 mg/5 ml Tablet: 100 mg, 300 mg

- Add the following trade name:
 - Trecator® to ethionamide

For the antiviral section, it was recommended that amantadine (Symmetrel®) be removed from the section but remain in the Antiparkinson Agents section.

Based on their review, the following recommendations were made to the Antihelminthics Section:

- Delete the following anthelmintic products from the Formulary due to lack of availability:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Thiabendazole	Mintezol	Suspension, oral: 500 mg/5 ml Tablet, chewable: 500 mg	None

Based on their review, the following recommendations were made to the Urinary Anti-Infectives Section:

- Delete the following urinary anti-infective products from the Formulary due to lack of availability:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Nitrofurantoin	Macrochantin®	Capsule: 50 mg, 100 mg Capsule, extended release: 100 mg	Capsule, macrocrystal: 25 mg, 50 mg 100 mg Capsule, macrocrystal/ monohydrate: 100 mg Suspension, oral: 25 mg/5 ml

There were no recommended changes for the Miscellaneous Anti-Infectives section.

Dr. Hall presented the review of the Antineoplastic Agents section. Currently, the Antineoplastic Agents section includes tamoxifen (Nolvadex®) 10 mg and 20 mg, and the following statement: “All commercially available oncologic agents used in the treatment of cancer are considered to be formulary agents, if prescribed by an oncologist for the active treatment of cancer.” It was noted that some antineoplastic agents are used as immune modifying agents. The Committee recommended adding the following statement to this section: “All commercially available oncologic agents prescribed by a field specialists are considered to be on formulary.”

It was recommended to remove the trade name Nolvadex® from the listing as the trade name product is no longer available.

On a motion by Dr. Matthews, seconded by Dr. Smith, all recommended changes to the Infectious Disease and Antineoplastic sections were approved.

Hydroxyzine – QTc Interval Follow Up & Audit

The facilities had until September 30th to complete their hydroxyzine audit. There are a few facilities that have not turned in audits. The data analysis has not been completed. Hopefully, it will be available for the next meeting.

Drug Formulary Table Review

The address and fax number for the Executive Formulary Committee is being added to the “Procedure for Addition of Drugs to the Formulary” section.

Dr. Richards provided a summary of the changes recommended for the Drug Formulary tables. The review/revision date was updated for all tables.

- Children and Adolescent Treatment of Behavioral Emergencies Intramuscular Short-Acting Agents
 - Changed cited date to 10-27-15 for Lexicomp® Online
- Adult Treatment of Behavioral Emergencies Intramuscular Short-Acting Agents
 - Changed reference #3 to show cited date 10-27-15
 - Changed reference #4 to Micromedex® 2.0 (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA (Cited: 10-27-15)
 - Updated reference #7 to 7-23-15
 - Updated reference #8 to 8-20-15
- Antipsychotics
 - Add the following antipsychotic entries
 - Aripiprazole lauroxil (Aristada®) – Non-Formulary; Adult dose 882 mg q 28 days
 - Brexpiprazole (Rexulti®) – Non-Formulary, Adult dose 4 mg
 - Cariprazine (Vraylar®) – Non-Formulary, Adult dose 6 mg
 - Paliperidone palmitate (Invega® Trinza™) – Non-Formulary; 819 mg q 3 month
 - Add the antipsychotic plasma concentration table from the July 2015 meeting minutes for those antipsychotics that are available in the U.S. Remove any reference to plasma levels currently listed in table.

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

- Antidepressants
 - No changes
- Mood Stabilizers
 - No changes
- Stimulants
 - Add lisdexamfetamine (Vyvanse); Adult, child (6 < 12 years old), Adolescent – 70 mg
- Miscellaneous Drugs Used for Psychotropic Purposes
 - No changes
- Anxiolytics
 - No changes
- Sedatives and Hypnotics
 - Change the “ND” footnote listing to “ID – insufficient data to suggest support regarding its efficacy or to provide maximum dose guidelines in this patient population”
- Therapeutic Serum Concentration of Some Anticonvulsants
 - Changed Lexicomp® Online cited date to 10-29-15

On a motion of Dr. Matthews, seconded by Dr. Heidel, the recommended changes were approved.

Drug Formulary Reserve Drug Review

Dr. Richards presented the reserve drugs. The following listing will be added to the Reserve Drug list based on action taken earlier in the meeting:

- Insulin detemir (Levemir®) with the criteria “for those that are unable to tolerate insulin glargine”.
- Moxifloxacin (Moxeza®, Vigamox®) ophthalmic with the criteria “for bacterial conjunctivitis where MRSA or gram negative microorganisms is identified or suspected. “

On a motion of Ms. Millhollon, seconded by Dr. Matthews, the recommended changes to the Reserve Drug List were approved.

DSHS/DADS 2016 Drug Formulary

The 2016 Drug Formulary was presented to the Committee. It was recommended that the changes made in the meeting be included in the 2016 version. On a motion of Dr. Heidel, seconded by Dr. Pittman, the 2016 Drug Formulary was approved.

Dr. Richards will facilitate the updating of the Formulary and will arrange for posting on our website.

FDA Drug Safety Communications

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

The FDA is warning health care professionals and patients that reports of confusion between the antidepressant Brintellix® (vortioxetine) and anti-blood clotting medication Brilinta® (ticagrelor) have resulted in the wrong medication being prescribed or dispensed. The FDA determined that the main reason for the confusion between these two medications is the similarity of their brand (proprietary) names. None of the reports indicates that a patient ingested the wrong medication; however, reports of prescribing and dispensing errors continue.

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), and alogliptin (Nesina®) may cause joint pain that can be severe and disabling. The FDA has added a new Warning and Precaution about this risk to the labels of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors.

The FDA is making changes to the requirements for monitoring, prescribing, dispensing, and receiving the schizophrenia medicine clozapine, to address continuing safety concerns and current knowledge about a serious blood condition called severe neutropenia. Severe neutropenia is a dangerously low number of neutrophils, white blood cells that help fight infections. Severe neutropenia can be life-threatening. There are two parts to the changes in the requirements for treating patients with clozapine. First, the FDA clarified and enhanced the prescribing information for clozapine that explains how to monitor patients for neutropenia and manage clozapine treatment. Second, the FDA approved a new, shared risk evaluation and mitigation strategy (REMS) called the Clozapine REMS Program. The revised prescribing information and the Clozapine REMS Program will improve monitoring and management of patients with severe neutropenia. The shared REMS is also expected to reduce the burden and possible confusion related to having separate registries for individual clozapine medicines. The requirements to monitor, prescribe, dispense, and receive all clozapine medicines are now incorporated into the Clozapine REMS Program.

The FDA is requiring the Kayexalate® (sodium polystyrene sulfonate) manufacturer to conduct studies to investigate Kayexalate®'s potential to bind to other medications administered by mouth – drug interactions that could affect how well the other medications work. The approved labeling for Kayexalate® describes its potential to decrease absorption of lithium and thyroxine; however, extensive drug-drug interaction studies with Kayexalate have not been performed. During FDA's review of another potassium-lowering drug, Veltassa® (patiromer), it was

found that Veltassa® bound to about half of the medications tested, some of which are commonly used in patients who require potassium-lowering drugs. Such binding could decrease the effects of these medications. The label for Veltassa® contains a warning not to take other orally administered medications within 6 hours of taking Veltassa®. Similar to Veltassa®, Kayexalate® may also bind to other medications administered by mouth. To reduce this potential risk, prescribers and patients should consider separating Kayexalate® dosing from other medications taken by mouth by at least 6 hours. This includes both prescription medications, such as antibiotics, blood pressure lowering agents and blood thinners, and those purchased over-the-counter without a prescription, such as antacids and laxatives. Health care professionals should monitor blood levels or clinical response to the other medications when appropriate. If the studies conducted by the Kayexalate® manufacturer, Concordia Pharmaceuticals, confirm significant interactions with other medications, the FDA will require all manufacturers of sodium polystyrene sulfonate products to update the drug labels to include information about these drug interactions.

An FDA safety review has found no clear evidence of an increased risk of heart attacks, stroke, or other cardiovascular events associated with the use of entacapone for the treatment of Parkinson's disease. As a result, recommendations for using Comtan® (entacapone) and Stalevo® (a combination of entacapone, carbidopa, and levodopa) will remain the same in the drug labels. The FDA alerted patients and health care professionals about a possible increased risk for cardiovascular events and death with Stalevo® in August 2010. This possible safety issue was observed in a clinical trial called the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) and in a meta-analysis that combined the cardiovascular-related findings from 15 clinical trials comparing Stalevo® to carbidopa/levodopa. Carbidopa and levodopa have been used extensively and have not been shown to have an increased cardiovascular risk. The FDA was concerned that the entacapone in Stalevo® was responsible for these cardiovascular risks because the comparison drugs do not contain this ingredient. To better understand the significance of these findings, the FDA required the Stalevo® manufacturer, Novartis, to study the potential for cardiovascular risk with the entacapone component of the drug. The FDA examined the results from this required study and from one additional study and concluded they do not show an increased risk of cardiovascular adverse events with entacapone. The results observed in the original meta-analysis were driven by results of a single study (STRIDE-PD), which was not designed to assess cardiovascular risks. The FDA believes that the meta-analysis and STRIDE-PD results are chance findings and do not represent a true increase in risk due to entacapone.

Medical Director for Behavioral Health

Dr. Muse was unable to attend the meeting.

Quarterly Non-Formulary Drug Justification Report

For the fourth quarter of fiscal year 2015, all facilities reported use of non-formulary agents. The DADS facilities submitted 986 non-formulary requests and the DSHS facilities had 403 requests. The following were the top non-formulary agents that were prescribed:

- Saccharomyces boulardii capsule (Florastor®)
- Levalbuterol (Xopenex®)
- Omega-3 product
- Guanfacine ER (Intuniv®)
- Meningococcal conjugate vaccine (Menactra®)
- Fiber-Stat Natural solution packets
- Losartan (Cozaar®)

Sectional Review for Next Meeting

The following section will be reviewed at the next meeting:

- Nutritional/Nutritional Supplements
- Dementia/Miscellaneous CNS

Migraine

Other Issues

The following information was shared with the Committee members:

Bloomberg News reports that “Pfizer Inc. won’t bring an over-the-counter version of its cholesterol [drug] Lipitor [atorvastatin] to the U.S. market, after a trial found that patients couldn’t take the drug correctly without a doctor’s help.” The company conducted a trial of 1,300 patients who were recruited “with a toll-free number, then directed to a pharmacy where they could get a 10 milligram dose of the drug.” The trial “looked at whether they would check their cholesterol after starting the drug, and take the right medical action after getting the results” and ultimately found that they couldn’t.

The AP reports that the Food and Drug Administration “has approved the first prescription drug made through 3-D printing: a dissolvable tablet that treats seizures.” Aprecia Pharmaceuticals announced on Monday that the FDA approved Spritam (levetiracetam), a tablet “manufactured through a layered process via 3-D printing” which “dissolves when taken with liquid.” The FDA had previously approved several medical devices made with 3-D printing, but the agency confirmed “the new drug is the first prescription tablet approved that uses the process.”

Reuters reports that CVS Health Corp. announced that it will exclude 31 additional prescription drugs from insurance coverage, including Viagra (sildenafil citrate) and several commonly used medicines for diabetes and multiple sclerosis. The ability to exclude certain drugs from the formulary can give pharmacy benefit managers leverage to obtain favorable pricing

Bloomberg News reports that Teva Pharmaceutical Industries Ltd.’s acquisition of Allergan Plc’s generic business “creates far and away the biggest generic drugmaker” and may encourage other generic drugmakers to consolidate in order to compete. According to the article, “more mergers could lead to higher generic-drug prices, a trend that’s already getting attention in Washington and among consumer groups.”

The Telegraph (UK) reports that researchers from Oxford University and Harvard Medical School examined 24 studies and concluded that the narcolepsy treatment modafinil “really does improve thinking skills, particularly in long complex tasks,” and also helped with “planning, decision making, flexibility, learning and memory, and creativity.” The results were published in *European Neuropsychopharmacology*.

Reuters reports that a 150,000-participant study published in *The Lancet Respiratory Medicine* found that the smoking cessation medication Chantix (varenicline) does not raise the risk of heart attack or depression, despite prior reports to the contrary.

The Los Angeles Times reports in “Science Now” that selective serotonin reuptake inhibitors, “a widely prescribed class of antidepressants,” may “make some patients more likely to commit violent crimes.” The study linked SSRIs to “a 40% increased risk of being convicted of a violent crime” in men between the ages of 15 and 24. Among women in this age group, “the risk increased by 75%.” The findings of the study, which encompassed data on “nearly eight million Swedes,” were published Sept. 15 in *PLOS Medicine*.

Reuters reports that UK-based GW Pharmaceuticals Plc’s experimental cannabis treatment, cannabidiol, was superior to a placebo in a mid-stage trial to treat schizophrenia. The trial included 88 patients with schizophrenia who had not responded to antipsychotic medication.

From CredibleMeds®:

We have evaluated the available evidence for two drugs used to treat psychosis, quetiapine (Seroquel®) and ziprasidone (Geodon® and Zeldox®) that we have had on our list of drugs with **Possible Risk of TdP** and found substantial evidence that they are associated with reports of TdP but, in almost all cases, only under certain conditions (e.g. overdose, concomitant drug with TdP risk, hypokalemia, etc.). Therefore, we have moved these two drugs from the list of drugs with **Possible Risk of TdP** to the list of drugs with **Conditional Risk of TdP**.

We have also reviewed the available evidence for the antibiotic gatifloxacin (Tequin®) that is now on our list of drugs with **Possible Risk of TdP**. Gatifloxacin has a strong signal for TdP in the FDA's adverse event database and has been withdrawn from the US market due to reports of TdP. Because it is currently being tested as an investigational drug for tuberculosis, we believe it should remain on our lists but be moved to the list of drugs with **Known Risk of TdP**.

Reuters reports that a late-stage clinical trial of Intra-Cellular Therapies Inc.'s experimental schizophrenia treatment, ITI-007, showed that it was effective in reducing the intensity of schizophrenia symptoms when compared to a placebo. The company also reported that a separate trial showed that patients taking the medication did not gain significant weight and also had reduced risks of other side effects.

The New York Times reports that in 2001, GlaxoSmithKline "published a study showing that the antidepressant Paxil [paroxetine] was safe and effective for teenagers." Yesterday, however, the British Medical "posted a new analysis of the same data concluding that the opposite is true."

The U.S. Food and Drug Administration today approved Vraylar (cariprazine) capsules to treat schizophrenia and bipolar disorder in adults.

Bloomberg News (9/18, Koons) reports that the Food and Drug Administration requested Pfizer Inc. in August to "alter Zoloft's warnings to show some researchers have found an "increased risk of congenital cardiac defects" in babies whose mothers took the drug," according to court papers filed earlier this month. Legal experts believe that the label change could help "bolster claims by those who have already sued over Zoloft," but could also "help the company fend off future lawsuits." According to a statement by Pfizer, the new label language, although still being drafted, "reflects the extensive science supporting the safety and efficacy of Zoloft, stating a complete review of the scientific evidence finds that there is no difference in birth defect risks between pregnant women who took Zoloft and those who did not."

The Wall Street Journal reports that the Food and Drug Administration approved Aristada (aripiprazole lauroxil), Alkermes PLC's drug to treat schizophrenia.

US News & World Report reports that the Food and Drug Administration is currently considering a medication by Otsuka Pharmaceutical and Proteus Digital Health that combines the antipsychotic Abilify (aripiprazole) with "a digital sensor the size of a pencil tip in each [tablet] that would allow doctors or caregivers to see whether patients are taking their medication." According to US News & World Report, the treatment "could offer a solution to one of the largest barriers to treating people with a serious mental illness" by increasing "adherence to medication."

HealthDay reports that according to a study funded by the National Institutes of Mental Health and published Oct. 21 in the Journal of Clinical Psychiatry, the use of antipsychotic medications in US "seniors increases with age." The study revealed that "the percentage of people aged 80 to 84 who received a prescription for an antipsychotic...was twice that of people aged 65 to 69." The increased use of such medications among seniors "is occurring despite the known risks of serious side effects such as stroke, kidney damage, and death, they added." Medical Daily points out that in arriving at the study's findings, researchers "analyzed de-identified prescription data from nearly 33,000 retail pharmacies," looking "for prescriptions of haloperidol, pimozide, aripiprazole, and olanzapine." In total, the data they gathered "captured 63 percent of all retail prescriptions in the US, a nationally representative sample with respect to age, sex, and health insurance."

Next Meeting Date

The next meeting was scheduled for January 29, 2016.

Adjourn

There being no further business, the meeting was adjourned at 1:23 p.m.

Approved: *Mark Messer, D.O.*
Mark Messer, D.O., Acting Chairman

Attachments

Attachment A – New Drug Applications

Attachment B – Antipsychotics Audit Criteria and Guidelines

Minutes Prepared by:

Ann L. Richards, Pharm.D., BCPP

APPENDIX 1: NEW DRUG APPLICATION FORM

415 — C
EXHIBIT A

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION
(for inclusion in the TDMHMR Drug Formulary)

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

Date: 7/10/2015

Name of practitioner submitting the application: Nicolas Baida, M.D.

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)):

Information regarding new drug:

Therapeutic Classification	<i>Antidiabetic Agent</i>
Generic Name	<i>Insulin Detemir</i>
Trade Name(s)	<i>Levemir</i>
Manufacturer(s)	<i>Novo Nordisk</i>
Dosage Form(s)	<i>10 ml vial</i>

Explain the pharmacological action or use of this drug: *Therapeutic equivalent to Lantus.*

Explain the advantages of this drug over those listed in the formulary: *Cost. Morris Dickson
Levemir \$102.698 vs. Lantus \$248.509*

State which drugs this new drug would replace or supplement:
Lantus

- application is approved
- OR
- application is appropriate and complete

signature of chairman of facility pharmacy and therapeutics committee

Nicolas Baida

signature of clinical/medical director or designee

Insulin detemir Levemir®

Classification: Recombinant human insulin analog, long-acting

Description:

- Levemir® 10 mL vial, 100 Units/mL
- Levemir® FlexPen® 3mL, 100 Units/mL - discontinued September 2014
- Levemir® FlexTouch® 3mL, 100 Units/mL

Pharmacology: Acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs include the liver, skeletal muscle, and adipose tissue.

Pharmacokinetics:¹

Onset of action: 3-4 hours, Cmax 6-8 hours post-dose

Systemic bioavailability: 60%

Distribution: Vd: 0.1 L/kg

Protein binding: >98% (albumin)

Half-life elimination: 5-7 hours (dose dependent)

Excretion: Urine

Indications: For the treatment of type 1 diabetes mellitus and type 2 diabetes mellitus to improve glycemic control in adults and children (over the age of 2).

Dosage:

Initiation, Type I Diabetes

Approximately 1/3 of the total daily insulin requirement administered in 1-2 divided doses, a rapid or short acting pre-meal insulin should be used to complete the balance of the total daily insulin requirement. When administering once daily, the dose should be administered with the evening meal or at bedtime.

Initiation, Type II Diabetes, inadequately controlled on oral antidiabetic mediations

10 Units (or 0.1-0.2 Units/kg) administered once daily in the evening or at bedtime or divided into a twice daily regimen, separated by 12 hours.

Initiation, Type II Diabetes, inadequately controlled on a GLP-1 agonist

10 Units administered once daily in the evening.

Converting from other insulin therapies:

If changing from Lantus® (insulin glargine) to Levemir® (insulin detemir) the change can be done on a unit-to-unit basis.

If changing from NPH to insulin detemir, the change can be done on a unit-to-unit basis, but those with type 2 diabetes may require more Insulin detemir than NPH as observed in one trial.

Administration:

Subcutaneous route of administration. Do not administer intravenously or intramuscularly due to the risk of severe hypoglycemia. Inject into the thigh, abdominal wall, or upper arm; rotate injection sites

within the same region to reduce the risk of lipodystrophy. Don't dilute or mix with other insulin or solution. Not for use in insulin pumps.

Storage:

Vial:

Unopened (unused) vial: Refrigerate [2-8°C (36-46°F)]. May be stored until expiration date on the container. If refrigeration is not possible, store at room temperature[<30°C (86°F)] and keep as cool as possible, for 42 days. Do not freeze. Protect from direct heat and light.

Opened vial: Refrigerate [2-8°C (36-46°F)] or store at room temperature [<30°C (86°F)]. Discard after 42 days. Do not freeze. Protect from direct heat and light.

Vial after initial use: Vials should be discarded 42 days after initial use whether refrigerated or unrefrigerated even if it still contains insulin.

FlexTouch®:

Unopened Flex Pens may be refrigerated and stored until expiration date on container.

After initial use, store at room temperature [<30°C (86°F)] NOT the refrigerator, for 42 days. Do not refrigerate or store with the needle in place after initial use. Protect from direct heat and light.

Contraindications:

Known hypersensitivity to insulin detemir or any of its excipients.

Precautions:

- Never share a FlexTouch® pen between patients.
- Hypoglycemia is the most common adverse reaction and when a GLP1 receptor agonist is use in combination, the dose of insulin detemir may need to be lowered or more carefully titrated to minimize this risk.
- Renal impairment: There were no differences in the pharmacokinetics of insulin detemir between those patients without diabetes and renal impairment and healthy volunteers. Although, some studies have shown increased circulating insulin concentrations in patients with renal impairment so careful monitoring of blood glucose and dose adjustment may be needed in renal impairment.
- Hepatic impairment: In those patients with severe hepatic dysfunction and without diabetes, lower systemic exposures to insulin detemir were observed compared to healthy volunteers. However, some studies with human insulin have shown an increase in circulating insulin concentrations in patients with hepatic dysfunction so careful monitoring of blood glucose and dose adjustment may be needed in hepatic impairment.
- Pregnancy: category B
- Nursing Mothers: it is unknown if insulin detemir is excreted in human milk but because many drugs are, including human insulin, use caution when administering insulin detemir to a nursing woman.
- Thiazolidinediones (TZDs), peroxisome proliferator-activated receptor (PPAR)-gamma agonists, when used in combination with insulin detemir can cause dose-dependent fluid retention, which may exacerbate or lead to heart failure.

Interactions:

Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia and may require close monitoring or insulin dose adjustment.

Hypoglycemia

Fibrates

Disopyramide

Pentoxifylline

Salicylates

Hyperglycemia

Corticosteroids

Diuretics

Sympathomimetic agents

Thyroid hormones

ACE-inhibitors	Progestogens, estrogens (OCs)
MAO inhibitors	Atypical antipsychotic medications
Sulfonamide antibiotics	Protease inhibitors
Fluoxetine	Danazol
Oral antidiabetic agents	Phenothiazine derivatives
Somatostatin analogs	Isoniazid
Pramlintide acetate	Niacin
Glucagon	Somatropin

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose lowering effect of insulin.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Adverse Reactions:

Adverse reactions reported with an incidence >5% in clinical trials included: hypoglycemia, upper respiratory tract infection, headache, pharyngitis, influenza-like illness, abdominal pain, back pain, gastroenteritis, bronchitis, pyrexia, cough, viral infection, nausea, rhinitis, and vomiting.

Other potential adverse reactions include: lipodystrophy (can decrease risk by alternating injection sites), weight gain, peripheral edema, antibody production, and local and systemic allergic reactions.

Hospital costs:

Levemir 10mL vial \$127.65, 3mL FlexTouch pen \$190.95

Lantus 10mL vial \$92.81, 3mL Solostar pen \$139.22

NPH 10mL Novolin N \$18.12, Humulin N \$11.83, Humulin N 3mL pen \$10.57

Levemir/Lantus Hospital Purchases (FY2015):

Levemir 10mL vial: Item Qty 163, Item Total \$24,026.45

Lantus 10mL vial: Item Qty 1370, Item Total \$189,830.73

Lantus 3mL Solostar pen: Item Qty 21, Item Total \$4,573.56

Levemir/Lantus Living Centers Purchases (FY2015):

Levemir 10 mL vial: Item Qty 62, Item Total \$12,600.06

Levemir 3mL FlexTouch pen: Item Qty 6, Item Total \$2,004.78

Lantus 10 mL vial: Item Qty 769, Item Total \$115,111.35

Lantus 3 mL Solostar pen: Item Qty 7, Item Total \$1,304.83

Monitoring:

Glucose monitoring is essential for all patients. Make sure patients also know how to recognize signs and symptoms of hypoglycemia and hyperglycemia.

Changes in insulin strength, manufacturer, type of insulin product, or method of administration may result in the need for a change in the insulin dose or adjustment of concomitant anti-diabetic treatment.

The time course of action for insulin detemir may vary in different individuals or at different times in the same individual and is dependent on many conditions including local blood supply, local temperature and physical activity.

Efficacy:

Insulin detemir vs. NPH

A study by Hermansen and colleagues compared the efficacy and safety of insulin detemir to NPH insulin dosed twice daily in those with type 2 diabetes on oral medication and A1c 7.5-10% (n=476). Over 24 weeks insulin doses were titrated starting at 10 units per injection to a goal prebreakfast and predinner blood glucose of 108 mg/dL or less. This was an open-label protocol because insulin detemir is a clear solution and NPH is a cloudy suspension. At 24 weeks there was no significant difference in A1c reduction between products (-1.8% insulin detemir and -1.9% NPH) and both groups had a similar percentage of participants achieving a goal of A1c 7% or less (70%). There did appear to be less hypoglycemia and less weight gain with insulin detemir than NPH. Subjects achieving A1c goal without hypoglycemia 26% with insulin detemir and 16% with NPH (p=0.008). Nocturnal hypoglycemia was reduced by 55% with insulin detemir (p=<0.001). Weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH (p< 0.001).²

In a randomized, open-label, active-control, 26 week study, the efficacy and safety of a basal-bolus insulin regimen with either insulin detemir or NPH insulin along with mealtime insulin aspart was evaluated in those with type 2 diabetes (n=505). Those receiving more than one basal insulin injection per day pretrial continued on twice-daily injections, all others received once daily injections. Significant reductions were seen in A1c and FPG for both types of insulin and were similar between groups. There was no difference in adverse events including risk of hypoglycemia or nocturnal hypoglycemia between the groups. There was less within-subject day-to-day variation in FBG with insulin detemir (p=0.021). There was also less weight gain with insulin detemir, 1kg, than with NPH, 1.8 kg (p=0.017).³

A 16 week, randomized, open-label, active control study compared the safety and efficacy of twice daily insulin detemir (either before breakfast and bedtime or at a 12 hour interval) compared to twice daily NPH in type 1 diabetes (n=408). Insulin aspart was administered before each meal. Fasting plasma blood glucose was lower with insulin detemir than NPH using both insulin detemir dosing intervals (detemir 12h vs. NPH, mean difference -1.5 mmol/l, p=0.004; detemir morning+bedtime vs. NPH, mean difference -2.3 mmol/l, p<0.001). A1c was lower in the pooled insulin detemir groups (mean difference -0.18% [-0.34 to -0.02], p=0.027). The risk of minor hypoglycemia was also lower in both insulin detemir groups compared to NPH (25% lower for 12 hour interval and 32% lower for morning+bedtime regimen); most of the difference was noted to be attributable to a much lower risk of nocturnal hypoglycemia. Within person between-day variation in self measured fasting blood glucose levels were lower in the insulin detemir groups (both p<0.001). There was more weight gain associated with the NPH group (0.86 kg) than the insulin detemir groups (0.02 kg 12 hour interval and 0.24 kg morning+bedtime regimen).⁴

Insulin detemir vs. Insulin glargine

A randomized 52 week, randomized, open-label, treat-to-target trial compared once or twice daily insulin detemir (a second insulin detemir morning dose was given if pre-dinner plasma glucose was >126 mg/dL after titrated on insulin detemir) with once daily insulin glargine when given as an add-on to glucose reducing drugs in insulin naïve type 2 diabetes (n=582). The percentage of patients who met their A1c goal of <7% in absence of symptomatic hypoglycemia was similar (33% insulin detemir, 35% insulin glargine). The rate of hypoglycemic events was comparable, 5.8 insulin detemir vs 6.2 insulin glargine. Weight gain was lower in the insulin detemir group (3 kg vs. 3.9 kg, p=0.01). Insulin detemir had a higher rate of injection site reactions (4.5% vs 1.4%). Mean daily insulin detemir dose was higher (0.78 U/kg) compared to insulin glargine (0.44 U/kg).⁵

In a 26 week, open-label, parallel-group trial, 320 adults with type 1 diabetes were randomized to either twice-daily insulin detemir (given in the morning and at bedtime) or once-daily insulin glargine (given at bedtime). Insulin aspart was given prior to each meal. The objective of this study was to compare the risk of hypoglycemia and glycemic control of these two treatments. There was no significant difference

in A1c between treatment groups (both 8.2%) at the study endpoint. Insulin detemir has a slightly higher fasting plasma glucose (7.7 mmol/L) than insulin glargine (7.0 mmol/L) at endpoint ($p<0.001$). Predinner plasma glucose was less with insulin detemir (2.6 mmol/L) compared to insulin glargine (2.9 mmol/L), $p=0.049$; however, there was no significant difference in prebreakfast, prelunch, or overall values. The overall risk of hypoglycemia was similar between the groups; however, the risk of severe hypoglycemia was 72% lower and the risk of nocturnal hypoglycemia was 32% lower with insulin detemir compared with insulin glargine ($p<0.05$). Weight gain between the groups was not significant (0.52 kg insulin detemir vs. 0.96 kg insulin glargine, $p=0.193$).⁶

A Cochrane review was conducted comparing insulin detemir with insulin glargine in patients with type 2 diabetes mellitus and examined four trials lasting 24 to 52 weeks ($n=2250$). All four studies dosed insulin glargine once-daily in the evening. Three studies dosed insulin detemir once-daily in the evening with the option of an additional morning dose whereas the last study initiated twice-daily dosing. At the end of the trial for the three aforementioned studies, 13.6% to 57.2% of the randomized patients were injecting insulin detemir twice-daily. There was no significant difference between treatment groups for glycemic control, which was measured by A1C equal to or less than 7%, with or without hypoglycemia. There were no significant differences on occurrence of nocturnal and severe hypoglycemia between treatment groups. Although, there was a lower daily basal insulin dose necessary with insulin glargine. In addition, in 24-hour profiles of the two insulin analogs, there was no significant difference in the variability of glucose or FPG values. Less weight gain was seen with insulin detemir (one study showed a 0.9 kg difference) whereas a lower amount of injection site reactions were seen with insulin glargine (1.8% patients treated with insulin detemir versus 0.4% treated with insulin glargine). Lastly, one of the studies reported no significant differences on quality of life between the two randomized groups.⁷

Conclusions:

Current studies show insulin detemir to be effective in managing type 1 and 2 diabetes. Most studies evaluating insulin detemir compared to NPH or insulin glargine show similar reductions in A1c and fasting plasma glucose values; however, in order to achieve these similar rates, some studies have indicated a higher total daily insulin dose/kg was necessary for insulin detemir than the other insulins. The Rosenstock study reported a mean daily insulin detemir dose was higher (0.78 U/kg) compared to insulin glargine (0.44 U/kg). That means in a 70 kg person, the cost per day (using the DSHS prices of \$127.65 per 10 mL vial of detemir and \$92.81 per 10 mL vial of glargine) of detemir comes out to be roughly \$6.97 per day versus \$2.86 for glargine. Compared to insulin glargine and NPH, most comparator trials indicate insulin detemir causes slightly less weight gain. Insulin detemir can be dosed once or twice daily. Some studies have shown lower rates of hypoglycemia and nocturnal hypoglycemia with insulin detemir than NPH or insulin glargine; however, most of the information on lower risk of hypoglycemia comes from twice daily insulin detemir dosing vs. once daily insulin detemir dosing. Insulin detemir was also found to have a higher rate of injection site reactions compared to insulin glargine. Insulin detemir does not appear to have a significant advantage over other currently available formulary options aside from a slight decrease in potential weight gain as well as possible lower risk of hypoglycemia and nocturnal hypoglycemia when dosed twice daily. Although, when taking into account the 2015 fiscal year hospital and living centers purchases, insulin detemir is being currently being purchased by state hospitals, albeit the item quantity for detemir was 1207 less than glargine. Therefore, insulin detemir should be added to the formulary but it would not be the preferred product due to higher cost.

Formulary Recommendation:

Recommended for addition to the formulary as a reserve use drug for those unable to tolerate insulin glargine.

References:

1. Levemir® Package Insert. Plainsboro, NJ. Novo Nordisk. 2015.
2. Hermansen K, Davies M, Derezinski T, et al. A 26-Week, Randomized, Parallel, Treat-to Target Trial Comparing Insulin detemir with NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin Naïve People With Type 2 Diabetes. *Diabetes Care* 2006; 29:1269-1274.
3. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 2005; 56-64.
4. Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH in people with type 1 diabetes. *Diabetes Care* 2004; 27(5):1081-1087.
5. Rosenstock J, Davies M, Home PD, et al. A randomized, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin naïve people with type 2 diabetes. *Diabetologia* 2008; 51:408-416.
6. Pieber TR, Treichel H, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. *Diabetic Medicine* 2007; 24:635-642.
7. Swinnen Sg, Simon AC, Holleman F, et al. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database syst Rev.* 2011 Jul 6;(7):CD006383.

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ANTIPSYCHOTICS

chlorpromazine (Thorazine®), fluphenazine (Prolixin®), haloperidol (Haldol®), loxapine (Loxitane®), perphenazine (Trilafon®), thiothixene (Navane®), trifluoperazine (Stelazine®)

INDICATIONS

- 1) Disorders with psychotic symptoms (schizophrenia, schizoaffective disorder, manic disorders, depression with psychotic features, drug-induced psychosis, psychosis associated with other organic conditions)
- 2) Tourette's disorder (haloperidol only)
- 3) Personality disorders – schizotypal, paranoid and borderline
- 4) Acute and/or short term use for management of aggressive or violent behavior
- 5) Stereotypies

PRECAUTIONS TO CONSIDER

Contraindications

Absolute:

- 1) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed or structurally related medication
- 2) Severe CNS depression

Relative:

- 1) Pregnancy/nursing mothers
- 2) History of drug-induced agranulocytosis or leukopenia
- 3) Breast cancer
- 4) History of neuroleptic malignant syndrome
- 5) Narrow angle glaucoma (for chlorpromazine)
- 6) Impaired hepatic function
- 7) Prostatic hypertrophy (for chlorpromazine)
- 8) Parkinson's disease
- 9) Severe cardiovascular diseases, including certain conduction disturbances

Precautions

Alcoholism (active), recent or current blood dyscrasias, angina, hypotension, congestive heart failure, arrhythmias, glaucoma, poorly controlled seizure disorder, urinary retention, patients at risk for paralytic ileus, severe tardive dyskinesia, dementia-related psychosis.

Pregnancy and Breast-Feeding

See relative contraindications. Most antipsychotics are FDA Pregnancy Category C.

ANTIPSYCHOTICS - (continued)

chlorpromazine (Thorazine®), fluphenazine (Prolixin®), haloperidol (Haldol®), loxapine (Loxitane®), perphenazine (Trilafon®), thiothixene (Navane®), trifluoperazine (Stelazine®)

PRECAUTIONS TO CONSIDER (continued)

Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Antithyroid agents
- 3) Concomitant use of agents that cause EPS (including droperidol, prochlorperazine, promethazine, metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 4) Concomitant use of hypotension producing agents
- 5) Levodopa
- 6) Concomitant anticholinergic drugs (for chlorpromazine)
- 7) Strong inhibitors or inducers of Cytochrome P450
- 8) The following are the major metabolic pathways for the typical antipsychotics:
Chlorpromazine: major substrate CYP 2D6, major inhibitor CYP 2D6
Fluphenazine: major substrate CYP 2D6
Haloperidol: major substrate CYP 2D6 and 3A4, moderate inhibitor CYP2D6 and 3A4
Loxapine: unknown
Perphenazine: major substrate CYP 2D6
Thiothixene: major substrate CYP 1A2
Trifluoperazine: major substrate CYP 1A2

SEE TABLE A: **Cytochrome P450 Drug Metabolism/Inhibition**

Age-Specific Considerations

- 1) Conservative dosing and careful monitoring are advised in children and the elderly

Side Effects Which Require Medical Attention

- 1) Anticholinergic effects
- 2) Visual changes
- 3) Extrapyramidal side effects (dystonia, pseudo-Parkinsonism)
- 4) Akathisia
- 5) Tardive dyskinesia
- 6) Hypotension
- 7) Rashes, photosensitivity and altered pigmentation
- 8) Early symptoms of agranulocytosis effects (fever, sore throat, weakness)
- 9) Galactorrhea
- 10) Amenorrhea
- 11) Gynecomastia
- 12) Poikilothermia
- 13) Fluctuating vital signs
- 14) Altered consciousness
- 15) Signs and symptoms of neuroleptic malignant syndrome

ANTIPSYCHOTICS - (continued)

chlorpromazine (Thorazine®), fluphenazine (Prolixin®), haloperidol (Haldol®), loxapine (Loxitane®), perphenazine (Trilafon®), thiothixene (Navane®), trifluoperazine (Stelazine®)

PATIENT MONITORING

Patient Monitoring Parameters

- 1) Pregnancy test – as clinically indicated
- 2) BMI and waist circumference measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.
- 3) Fasting plasma glucose level or hemoglobin A_{1c} – before initiating a new antipsychotic, then yearly.

If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.

- 4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl

If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.

- 5) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly.

If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.

- 6) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.
- 7) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase
- 8) Tardive dyskinesia evaluation – every 3 months and as clinically indicated
- 9) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly
- 10) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients.

Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

Exceptions to maximum dosage must be justified as per medication rule.

Medication Audit Criteria and Guidelines
Drug Audit Checklist 19

Reviewer:		Date:	
Class:			
<i>Drug: ANTIPSYCHOTICS</i>			
chlorpromazine (Thorazine®), fluphenazine (Prolixin®), haloperidol (Haldol®), loxapine (Loxitane®), perphenazine (Trilafon®), thiothixene (Navane®), trifluoperazine (Stelazine®)			
Audit#	Comments	Requires Phys.Review	
Patient#		Yes	No
Ordering Physician			

INDICATIONS	1. Disorders with psychotic symptoms (schizophrenia, schizoaffective disorder, manic disorders, depression with psychotic features, drug-induced psychosis, psychosis associated with other organic conditions)			
	2. Tourette's disorder (haloperidol only)			
	3. Personality disorders – schizotypal, paranoid and borderline			
	4. Acute and/or short term use for management of aggressive or violent behavior			
	5. Stereotypies			
	1. History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed or structurally related medication			
	2. Severe CNS depression			
	1. Pregnancy/nursing mothers			
	2. History of drug-induced agranulocytosis or leukopenia			
	3. Breast Cancer			
	4. History of neuroleptic malignant syndrome			
	5. Narrow angle glaucoma (for chlorpromazine)			
	6. Impaired hepatic function			
	7. Prostatic hypertrophy (for chlorpromazine)			
	8. Parkinson's disease			
	9. Severe cardiovascular diseases, including certain conduction disturbances			

Drug Audit Checklist 19

Page 2.

Drug: ANTIPSYCHOTICS Continued

chlorpromazine (Thorazine®), fluphenazine (Prolixin®), haloperidol (Haldol®), loxapine (Loxitane®), perphenazine (Trilafon®), thiothixene (Navane®), trifluoperazine (Stelazine®)

Patient #		Comments		Requires Phys.Review	
				Yes	No
Ordering Physician					
PATIENT MONITORING	Patient Monitoring Parameters	1. Pregnancy test – as clinically indicated.			
		2. BMI and waist circumference measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.			
		3. Fasting plasma glucose level or hemoglobin A _{1c} – before initiating a new antipsychotic, then yearly. If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.			
		4. Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.			
		5. Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly. If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.			

Drug Audit Checklist 19

Page 3.

Drug: ANTIPSYCHOTICS

chlorpromazine (Thorazine®), fluphenazine (Prolixin®), haloperidol (Haldol®), loxapine (Loxitane®), perphenazine (Trilafon®), thiothixene (Navane®), trifluoperazine (Stelazine®)

Patient#	Comments	Requires Phys.Review	
		Yes	No
Ordering Physician			

PATIENT MONITORING Continued	Patient Monitoring Parameters	6. Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.			
		7. EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase			
		8. Tardive dyskinesia evaluation – every 3 months and as clinically indicated			
		9. Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly			
		10. Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients.			

Dosing	See DSHS/DADS Drug Formulary for dosage guidelines.			
	Exceptions to maximum dosage must be justified as per medication rule.			

Date Referred	Date Reviewed	Comments	Physician's Signature

Additional Comments:

ANTIPSYCHOTICS

thioridazine (Mellaril®)

INDICATIONS

- 1) Schizophrenia, refractory (failed other classes of antipsychotics)

PRECAUTIONS TO CONSIDER

Contraindications

Absolute:

- 1) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed or structurally related medication
- 2) Severe CNS depression
- 3) QTc > 450 msec
- 4) Concomitant use of other drugs known to prolong QTc interval
- 5) Congenital long QT syndrome
- 6) Personal history of syncope
- 7) Family history of sudden death at an early age (under age of 40 years)
- 8) Known heart disease
- 9) Hypomagnesemia
- 10) Hypokalemia
- 11) Retinitis Pigmentosa
- 12) Known poor CYP2D6 metabolizer
- 13) Concomitant use with drugs that inhibit thioridazine metabolism (fluvoxamine, propranolol, pindolol)
- 14) Concomitant use with drugs that inhibit CYP2D6 (fluoxetine, paroxetine)

Relative:

- 1) Pregnancy/nursing mothers
- 2) History of drug induced agranulocytosis or leukopenia
- 3) Breast cancer
- 4) History of neuroleptic malignant syndrome
- 5) Narrow angle glaucoma
- 6) Impaired hepatic function
- 7) Prostatic hypertrophy
- 8) Parkinson's disease

Precautions

Alcoholism (active), recent or current blood dyscrasias, angina, hypotension, congestive heart failure, arrhythmias, glaucoma, poorly controlled seizure disorder, urinary retention, patients at risk for paralytic ileus, severe tardive dyskinesia, dementia-related psychosis.

Pregnancy and Breast-Feeding

See relative contraindications. Most antipsychotics are FDA Pregnancy Category C.

ANTIPSYCHOTICS - continued

thioridazine (Mellaril®)

PRECAUTIONS TO CONSIDER (continued)

Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Antithyroid agents
- 3) Concomitant use of agents that cause EPS (including droperidol metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 4) Concomitant use of hypotension producing agents
- 5) Levodopa
- 6) Concomitant anticholinergic drugs
- 7) Concomitant use with drugs that inhibit thioridazine metabolism (fluvoxamine, propranolol, pindolol)
- 8) Concomitant use with drugs that inhibit CYP2D6 (fluoxetine, paroxetine)
- 9) Concomitant use of CYP2D6 inducers

SEE TABLE A: Cytochrome P450 Drug Metabolism/Inhibition

Age-Specific Considerations

- 1) Conservative dosing and careful monitoring are advised in children and the elderly

Side Effects Which Require Medical Attention

- 1) Anticholinergic effects
- 2) Visual changes
- 3) Extrapyrimal side effects (akathisia, dystonia, pseudo-Parkinsonism)
- 4) Tardive dyskinesia
- 5) Hypotension
- 6) Rashes, photosensitivity and altered pigmentation
- 7) Early symptoms of agranulocytosis (fever, sore throat, weakness)
- 8) Galactorrhea
- 9) Amenorrhea
- 10) Gynecomastia
- 11) Fluctuating vital signs
- 12) Altered consciousness

PATIENT MONITORING

Patient Monitoring Parameters

- 1) Pregnancy test – as clinically indicated
- 2) BMI and waist circumference measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated and quarterly when the antipsychotic dose is stable.

ANTIPSYCHOTICS - continued

thioridazine (Mellaril®)

PATIENT MONITORING (continued)

- 3) Fasting plasma glucose level or hemoglobin A_{1c} – before initiating a new antipsychotic, then yearly.

If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.

- 4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl

If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.

- 5) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly.

If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly

- 6) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.
- 7) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase
- 8) Tardive dyskinesia evaluation – every 3 months and as clinically indicated.
- 9) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly
- 10) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients
- 11) Serum potassium level – baseline, every six months and as clinically indicated
- 12) Serum magnesium level – baseline and as clinically indicated (especially if potassium level is low)
- 13) EKG prior to initiating therapy; 7-14 days after dose change; 7-14 days after other medication changes that could significantly alter the cardiac effects of thioridazine; every six months; and as clinically indicated.

Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

Exceptions to maximum dosage must be justified as per medication rule.

Medication Audit Criteria and Guidelines
Drug Audit Checklist 20

Reviewer:	Date:
Class:	
Drug: ANTIPSYCHOTICS	
thioridazine (Mellaril®)	

Audit#	Comments	Requires Phys.Review	
Patient#		Yes	No
Ordering Physician			

INDICATIONS	1. Schizophrenia, refractory (failed other classes of antipsychotics)			

Contraindications	Absolute	1) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed or structurally related medication			
		2) Severe CNS depression			
		3) QTc > 450 msec			
		4) Concomitant use of drugs known to prolong QTc interval			
		5) Cogential long QT syndrome			
		6) Personal history of syncope			
		7) Family history of sudden death at an early age (under age of 40 years)			
		8) Known heart disease			
		9) Hypomagnesemia			
		10) Hypokalemia			
		11) Retinitis Pigmentosa			
		12) Known poor CYP2D6 metabolizer			
		13) Concomitant use with drugs that inhibit thioridazine metabolism (fluvoxamine, propranolol, pindolol)			

	14) Concomitant use with drugs that inhibit CYP2D6 (fluoxetine, paroxetine)		
Drug Audit Checklist 20			
<i>Drug: ANTIPSYCHOTICS</i> thioridazine (Mellaril®)			Page 2
Patient#	Comments	Requires Phys.Review	
		Yes	No
Ordering Physician			

Contraindications -	<small>continued</small> Relative	1) Pregnancy/Nursing Mothers		
		2) History of drug induced agranulocytosis or leukopenia		
		3) Breast Cancer		
		4) History of neuroleptic malignant syndrome		
		5) Narrow angle glaucoma		
		6) Impaired hepatic function		
		7) Prostatic hypertrophy		
		8) Parkinson's disease		

PATIENT MONITORING	Patient Monitoring Parameters	1) Pregnancy test – as clinically indicated		
		2) BMI <u>and waist circumference</u> measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated and quarterly when the antipsychotic dose is stable.		
		3) Fasting plasma glucose level or hemoglobin A _{1c} – before initiating a new antipsychotic, then yearly. If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.		
		4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.		

Drug: ANTIPSYCHOTICS

thioridazine (Mellaril®)

Patient#	Comments	Requires Phys.Review	
		Yes	No
Ordering Physician			

PATIENT MONITORING Continued	patient Monitoring Parameters	<p>5) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly.</p> <p>If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly</p>			
		6) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.			
		7) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase.			
		8) Tardive dyskinesia evaluation – every 3 months and as clinically indicated.			
		9) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly			
		10) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients			
		11) Serum potassium level – baseline, every six months and as clinically indicated			
		12) Serum magnesium level – baseline and as clinically indicated (especially if potassium level is low)			
		13) EKG prior to initiating therapy; 7-14 days after dose change; 7-14 days after other medication changes that could significantly alter the cardiac effects of thioridazine; every six months; and as clinically indicated.			

Drug Audit Checklist 20				
Drug: ANTIPSYCHOTICS thioridazine (Mellaril®)			Page 4	
Patient#		Comments		Requires Phys.Revie w
				Yes No
Ordering Physician				

	Dosing	See DSHS/DADS Drug Formulary for dosage guidelines. Exceptions to maximum dosage must be justified as per medication rule.			
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Date Referred	Date Reviewed	Comments	Physician's Signature

Additional Comments:

CLOZAPINE (CLOZARIL®, FAZACLO®)

INDICATIONS

- 1) For use in patients with refractory schizophrenia or schizoaffective disorder, defined as failure on two antipsychotics from two different chemical families given for sufficient time (6-12 weeks) at a sufficient dose (1000 mg/day of chlorpromazine equivalents).
- 2) For use in schizophrenic or schizoaffective patients who cannot tolerate other antipsychotics.
- 3) Psychosis associated with other organic conditions, (who have failed two antipsychotics, or who cannot tolerate other antipsychotics)
- 4) Manic disorders with psychosis (in patients who have failed two antipsychotics)
- 5) Reduction in the risk of aggression or recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder

PRECAUTIONS TO CONSIDER

Contraindications

Absolute:

- 1) History of anaphylactic reaction or similarly severe significant hypersensitivity to the medication prescribed
- 2) Myeloproliferative disorders
- 3) History of clozapine-induced agranulocytosis or severe granulocytopenia
- 4) Concomitant use of agents that may cause bone marrow suppression, including carbamazepine (Tegretol®, Carbatrol®, Equetro®)
- 5) Uncontrolled epilepsy
- 6) Severe CNS depression
- 7) Paralytic ileus

Relative:

- 1) History of drug induced agranulocytosis or leukopenia
- 2) Breast cancer
- 3) History of neuroleptic malignant syndrome
- 4) Narrow angle glaucoma
- 5) Impaired hepatic function
- 6) Prostatic hypertrophy
- 7) Parkinson's disease
- 8) Severe cardiovascular diseases
- 9) History of seizure
- 10) Diabetes Mellitus

PRECAUTIONS TO CONSIDER (continued)

Precautions

Alcoholism (active), recent or current blood dyscrasias, angina, hypotension, congestive heart failure, arrhythmias, glaucoma, obesity, urinary retention, patients at risk for paralytic ileus, pregnancy/nursing mothers, dementia-related psychosis, phenylketonurics (Fazaclo®)

Pregnancy and Breast-Feeding

See precautions. FDA Pregnancy Category B.

Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Antithyroid agents
- 3) Concomitant use of agents that cause EPS (including droperidol, prochlorperazine, promethazine, metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 4) Concomitant use of hypotension producing agents
- 5) Levodopa
- 6) Concomitant use of agents that cause bone marrow suppression
- 7) Clozapine is a major substrate of CYP 1A2 and a moderate inhibitor of CYP 2D6.
- 8) Strong inhibitors or inducers of Cytochrome P450 (1A2)

SEE TABLE A: **Cytochrome P450 Drug Metabolism/Inhibition**

Age-Specific Considerations

Safety and efficacy have not been established in children under the age of 16. Geriatric patients may be more susceptible to orthostatic and anticholinergic effects.

Side Effects Which Require Medical Attention

- 1) Anticholinergic effects
- 2) Visual changes
- 3) Tardive dyskinesia or other late-onset EPS
- 4) Hypotension
- 5) Rashes, photosensitivity and altered pigmentation
- 6) Early symptoms of agranulocytosis (fever, sore throat, weakness)
- 7) Fluctuating vital signs
- 8) Altered consciousness
- 9) Drooling
- 10) Hepatitis
- 11) Seizure
- 12) Fever

PRECAUTIONS TO CONSIDER (continued)

Side Effects Which Require Medical Attention (continued)

- 13) Cardiomyopathy/myocarditis - Symptoms of myocarditis including unexplained fatigue, dyspnea, tachypnea, fever, etc.
- 14) Pulmonary embolism or DVT
- 15) Hyperglycemia
- 16) Clinically significant weight gain
- 17) Hypercholesterolemia or hypertriglyceridemia

PATIENT MONITORING

Patient Monitoring Parameters

- 1) CBC as indicated by guidelines established by the manufacturer
- 2) Pregnancy test – as clinically indicated
- 3) BMI and measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.
- 4) Fasting plasma glucose level or hemoglobin A_{1c} – before initiating a new antipsychotic, then yearly.

If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.

- 5) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl

If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.

- 6) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly

If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.

- 7) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.
- 8) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase.
- 9) Tardive dyskinesia evaluation – every 3 months and as clinically indicated.
- 10) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly

CLOZAPINE (CLOZARIL®, FAZACLO®) - continued

PATIENT MONITORING (continued)

Patient Monitoring Parameters (continued)

- 11) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients
- 12) EKG – baseline, annually and as clinically indicated (e.g., myocarditis, unexplained fatigue, tachypnea, etc.)
- 13) Troponin and C-reactive protein as clinically indicated for suspected myocarditis

Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

Exceptions to maximum dosage must be justified as per medication rule.

Medication Audit Criteria and Guidelines
Drug Audit Checklist 21

Reviewer:	Date:
Class:	
Drug: clozapine (Clozaril®, Fazaclo®)	

Audit#	Comments	Requires Phys.Review	
Patient#		Yes	No
Ordering Physician			

INDICATIONS	Description			
	1) For use in patients with refractory schizophrenia or schizoaffective disorder, defined as failure on two antipsychotics from two different chemical families given for sufficient time (6-12 weeks) at a sufficient dose (1000 mg/day of chlorpromazine equivalents).			
	2) For use in schizophrenic or schizoaffective patients who cannot tolerate other antipsychotics.			
	3) Psychosis associated with other organic conditions, (who have failed two antipsychotics, or who cannot tolerate other antipsychotics)			
	4) Manic disorders with psychosis (in patients who have failed two antipsychotics)			
	5) Reduction in the risk of aggression or recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder			

Contraindications	Absolute	Description			
		1) History of anaphylactic reaction or similarly severe significant hypersensitivity to the medication prescribed			
		2) Myeloproliferative disorders			
		3) History of clozapine-induced agranulocytosis or severe granulocytopenia			

Drug: clozapine (Clozaril®, Fazacllo®) (continued)		Drug Audit Checklist 21		Page 2.	
Patient#		Comments		Requires Phys.Review	
Ordering Physician				Yes	No
		4) Concomitant use of agents that may cause bone marrow suppression, including carbamazepine (Tegretol®, Carbatrol®, Equetro®)			
		5) Uncontrolled epilepsy			
		6) Severe CNS depression			
		7) Paralytic ileus			
	<i>Relative</i>	1. History of drug induced agranulocytosis or leucopenia			
		2. Breast cancer			
		3. History of neuroleptic malignant syndrome			
		4. Narrow angle glaucoma			
		5. Impaired hepatic function			
		6. Prostatic hypertrophy			
		7. Parkinson's disease			
		8. Severe cardiovascular diseases			
		9. History of seizure			
		10. Diabetes Mellitus			

Drug: clozapine (Clozaril®, Fazaclo®) (continued)		Drug Audit Checklist 21		Page 3.	
Patient#	Comments	Requires Phys.Revie w			
		Yes	No		
Ordering Physician					

PATIENT MONITORING	Patient Monitoring Parameters	1. CBC as indicated by guidelines established by the manufacturer or as clinically indicated			
		2. Pregnancy Test – as clinically indicated			
		3. BMI and waist circumference measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.			
		4. Fasting plasma glucose level or hemoglobin A _{1c} – before initiating a new antipsychotic, then yearly. If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.			
		5. Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.			
		6. Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.			

Drug: clozapine (Clozaril®, Fazaclo®) (continued)		Drug Audit Checklist 21	Page 4.
Patient#	Comments		Requires Phys.Revie w

		Yes	No
Ordering Physician			

PATIENT MONITORING Continued	Patient Monitoring Parameters (continued)	7. Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.			
		8. EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase			
		9. Tardive dyskinesia evaluation – every 3 months and as clinically indicated.			
		10. Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly			
		11. Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients			
		12. EKG – baseline, annually and as clinically indicated (e.g., myocarditis, unexplained fatigue, tachypnea, etc.)			
		13. Troponin and C-reactive protein as clinically indicated for suspected myocarditis			
	Dosing	See DSHS/DADS Drug Formulary for dosage guidelines. Exceptions to maximum dosage must be justified as per medication rule.			

Drug: clozapine (Clozaril®, Fazaclo®) (continued)		Drug Audit Checklist 21		Page 5.	
Patient#		Comments		Requires Phys.Revie w	
Ordering Physician				Yes	No

Date Referred	Date Reviewed	Comments	Physician's Signature

Additional Comments:

DECANOATES

fluphenazine decanoate (Prolixin®, Decanoate), haloperidol decanoate (Haldol®, Decanoate)

INDICATIONS

- 1) Chronic psychotic disorder requiring prolonged parenteral treatment

PRECAUTIONS TO CONSIDER

Contraindications

Absolute:

- 1) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed or structurally related medication
- 2) Severe CNS depression

Relative:

- 1) Pregnancy/nursing mothers
- 2) History of drug induced agranulocytosis or leukopenia
- 3) Breast cancer
- 4) History of neuroleptic malignant syndrome
- 5) Impaired hepatic function
- 6) Parkinson's disease
- 7) Severe cardiovascular diseases

Precautions

Alcoholism (active), recent or current blood dyscrasias, angina, hypotension, congestive heart failure, arrhythmias, poorly controlled seizure disorder, severe tardive dyskinesia, dementia-related psychosis.

Pregnancy and Breast-Feeding

See relative contraindications. FDA Pregnancy Category C.

Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Antithyroid agents
- 3) Concomitant use of agents that cause EPS (including droperidol, prochlorperazine, promethazine, metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 4) Levodopa
- 5) Strong inhibitors or inducers of Cytochrome P450
- 6) The following are the major metabolic pathways:
Fluphenazine: major substrate CYP 2D6
Haloperidol: major substrate CYP 2D6 and 3A4, moderate inhibitor CYP2D6 and 3A4

DECANOATES - continued

fluphenazine decanoate (Prolixin®, Decanoate), haloperidol decanoate (Haldol®, Decanoate)

PRECAUTIONS TO CONSIDER (continued)

Age-Specific Considerations

Conservative dosing and careful monitoring are advised in children and the elderly

Side Effects Which Require Medical Attention

- 1) Extrapyramidal side effects
- 2) Akathisia
- 3) Tardive dyskinesia or other late-onset EPS
- 4) Rashes
- 5) Early symptoms of agranulocytosis (fever, sore throat, weakness)
- 6) Galactorrhea
- 7) Amenorrhea
- 8) Gynecomastia
- 9) Fluctuating vital signs
- 10) Altered consciousness
- 11) Signs and symptoms of neuroleptic malignant syndrome

PATIENT MONITORING

Patient Monitoring Parameters

- 1) Pregnancy test – as clinically indicated
- 2) BMI and waist measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.
- 3) Fasting plasma glucose level or hemoglobin A_{1c} – before initiating a new antipsychotic, then yearly.

If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.

- 4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl

If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.

- 5) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly.

If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.

- 6) Prolactin level if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.

DECANOATES - continued

fluphenazine decanoate (Prolixin®, Decanoate), haloperidol decanoate (Haldol®, Decanoate)

PATIENT MONITORING (continued)

- 1) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase
- 2) Tardive dyskinesia evaluation – every 3 months, and as clinically indicated.
- 3) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly
- 4) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients

Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

Exceptions to maximum dosage must be justified as per medication rule.

Medication Audit Criteria and Guidelines
Drug Audit Checklist 22

Reviewer:		Date:		
Class:				
Drug: DECANOATES fluphenazine decanoate (Prolixin®, Decanoate), haloperidol decanoate (Haldol®, Decanoate)				
Audit #		Comments		Requires Phys.Revie w
Patient #				Yes No
Ordering Physician				
INDIC	1. Chronic psychotic disorder requiring prolonged parenteral treatment			
Contraindications	<i>Absolute</i>	1) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed or structurally related medication		
		2) Severe CNS depression		
	<i>Relative</i>	1) Pregnancy/nursing mother		
		2) History of drug induced agranulocytosis or leukopenia		
		3) Breast cancer		
		4) History of neuroleptic malignant syndrome		
		5) Impaired hepatic function		
		6) Parkinson's disease		
	7) Severe cardiovascular diseases			
PATIENT MONITORING	Patient Monitoring Parameters	1) Pregnancy test – as clinically indicated.		
		2) BMI and waist circumference measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.		
		3) Fasting plasma glucose level or hemoglobin A _{1c} – before initiating a new antipsychotic, then yearly. If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.		

Reviewer:		Date:			
Class:					
Drug: DECANOATES Fluphenazine decanoate (Prolixin® Decanoate), haloperidol decanoate (Haldol® Decanoate)					
Audit #		Comments		Requires Phys.Review	
Patient #				Yes No	
Ordering Physician					
PATIENT MONITORING	continued	Patient Monitoring Parameters - continued	4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.		
			5) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly. If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.		
			6) Prolactin level if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.		
			7) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase		
			8) Tardive dyskinesia evaluation – every 3 months, and as clinically indicated.		

Reviewer:		Date:		
Class:				
Drug: DECANOATES				
Fluphenazine decanoate (Prolixin® Decanoate), haloperidol decanoate (Haldol® Decanoate)				
Audit #		Comments		Requires Phys.Review
Patient #				Yes No
Ordering Physician				
PATIENT MONITORING	continued	9) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly		
	Dosage	10) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients		
		See DSHS/DADS Drug Formulary for dosage guidelines. Exceptions to maximum dosage must be justified as per medication rule.		

Date Referred	Date Reviewed	Comments	Physician's Signature

Additional Comments:

ATYPICAL ANTIPSYCHOTICS

(Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa® Relprevv™), paliperidone (Invega®, Invega sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)

INDICATIONS

- 1) Disorders with psychotic symptoms (schizophrenia, schizoaffective disorder, manic disorders, depression with psychotic features, drug-induced psychosis, psychosis associated with other medical conditions)
- 2) Schizophrenia adolescents – risperidone (13 to 17 years old), olanzapine (13 to 17 years old), paliperidone (12 to 17 years old), quetiapine (13 to 17 years old), aripiprazole (13 to 17 years old)
- 3) Severe aggression secondary to a psychiatric disorder
- 4) Self Injurious Behavior secondary to a psychiatric disorder
- 5) Bipolar disorder (not paliperidone iloperidone, or lurasidone)
- 6) Bipolar disorder, adolescents – risperidone (10 to 17 years old, monotherapy), quetiapine (10 to 17 years old, adjunct & monotherapy), olanzapine (13 to 17 years old, acute & maintenance), aripiprazole (10 to 17 years old, adjunct & monotherapy)
- 7) Irritability associated with autistic disorders in children and adolescent – risperidone (5 to 16 years old) and aripiprazole (6 to 17 years old)
- 8) Adjunct for patients on antidepressants for major depressive disorder (aripiprazole, quetiapine)

PRECAUTIONS TO CONSIDER

Contraindications

Absolute:

- 1) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed
- 2) For ziprasidone - Recent myocardial infarction, uncompensated congestive heart failure or when other drugs are being used that also prolong the QT interval such as (not complete list) quinidine, dofetilide, pimozide, sotalol, thioridazine, moxifloxacin, and sparfloxacin
- 3) For lurasidone – use of ketoconazole (3A4 inhibitor) or rifampin (3A4 inducer)

Relative:

- 1) Pregnancy/nursing mothers
- 2) History of drug induced agranulocytosis or leukopenia
- 3) Breast cancer
- 4) History of neuroleptic malignant syndrome
- 5) Impaired hepatic function
- 6) Parkinson's disease
- 7) Severe cardiovascular diseases
- 8) Known clinically significant QTc prolongation

ATYPICAL ANTIPSYCHOTICS (continued)

(Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa® Relprevv™), paliperidone (Invega®, Invega sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)

PRECAUTIONS TO CONSIDER (continued)

Precautions

Alcoholism (active), cataracts (quetiapine), recent or current blood dyscrasias, diabetes mellitus, angina, hypotension, congestive heart failure, arrhythmias, obesity, poorly controlled seizure disorder, severe tardive dyskinesia, dementia-related psychosis, renal impairment (paliperidone and ziprasidone injection)

Pregnancy and Breast-Feeding

See relative contraindications. FDA Pregnancy Category C except for lurasidone is a Category B

Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Concomitant use of agents that cause EPS (including droperidol, metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 3) Concomitant use of hypotension producing agents
- 4) levodopa
- 5) Antithyroid agents
- 6) Drugs that prolong the QT interval
- 7) Strong inhibitors or inducers of Cytochrome 450
- 8) The following are the major metabolic pathways for the atypical antipsychotics:
 - Risperidone: CYP 2D6
 - Olanzapine: CYP 1A2
 - Quetiapine: CYP 3A4
 - Aripiprazole: CYP 2D6 and 3A4
 - Ziprasidone; aldehyde oxidase
 - Paliperidone (non-hepatic, primarily renal elimination)
 - Asenapine: CYP 1A2 and UGT1A4 (direct glucuronidation)
 - Iloperidone: CYP 3A4 and 2D6
 - Lurasidone: CYP 3A4

SEE TABLE A: Cytochrome P450 Drug Metabolism/Inhibition

Age-Specific Considerations

Aripiprazole, olanzapine, paliperidone, quetiapine and risperidone have approved specific indications for designated ages in children. The safety and efficacy have not been established in children under the age of 18 for the other medications. Conservative dosing is advised in the elderly.

ATYPICAL ANTIPSYCHOTICS (continued)

(Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa® Relprevv™), paliperidone (Invega®, Invega sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)

PRECAUTIONS TO CONSIDER (continued)

Side Effects Which Require Medical Attention

- 1) Anticholinergic effects
- 2) Visual changes
- 3) Extrapyramidal side effects (dystonia, pseudo-Parkinsonism)
- 4) Akathisia
- 5) Tardive dyskinesia
- 6) Hypotension
- 7) Rashes, photosensitivity and altered pigmentation
- 8) Early symptoms of agranulocytosis (fever, sore throat, weakness)
- 9) Galactorrhea (risperidone, paliperidone)
- 10) Amenorrhea (risperidone, paliperidone)
- 11) Gynecomastia (risperidone, paliperidone)
- 12) Fluctuating vital signs
- 13) Altered consciousness
- 14) Hyperglycemia
- 15) Clinically significant weight gain
- 16) Hypercholesterolemia or hyperlipidemia
- 17) QTc > 500 msec
- 18) Cataracts (quetiapine)

PATIENT MONITORING

Patient Monitoring Parameters

- 1) Pregnancy test – as clinically indicated
- 2) BMI and waist circumference measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.
- 3) Fasting plasma glucose level or hemoglobin A_{1c} – before initiating a new antipsychotic, then yearly.

If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.

- 4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl

If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.

ATYPICAL ANTIPSYCHOTICS (continued)

(Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa® Relprevv™), paliperidone (Invega®, Invega sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)

PATIENT MONITORING (continued)

- 5) EKG (for patients on ziprasidone)– For patients with known heart disease, a personal history of syncope, a family history of sudden death at an early age (under age 40 years, especially if both parents had sudden death), or congenital long QT syndrome, then a baseline EKG before treatment is initiated. A subsequent EKG is indicated if the patient presents with symptoms associated with a prolonged QT interval (e.g., syncope).
- 6) EKG (for patients on iloperidone) – at baseline
- 7) Serum potassium and magnesium level baseline and periodic for patients on iloperidone who are at risk for significant electrolyte disturbances
- 8) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly

If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.

- 9) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.
- 10) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase
- 11) Tardive dyskinesia evaluation – every 3 months and as clinically indicated.
- 12) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly
- 13) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients
- 14) After each olanzapine pamoate injection continuously observe patient for at least 3 hours for symptoms consistent with olanzapine overdose, including sedation (ranging from mild in severity to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment) (Post-Injection Delirium /Sedation Syndrome)

Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

Exceptions to maximum dosage must be justified as per medication rule.

Medication Audit Criteria and Guidelines
Drug Audit Checklist 23

Reviewer:		Date:	
Class:			
Drug: risperidone (Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa ®Relprevv™), paliperidone (Invega®, Invega sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)			
Audit#	Comments	Requires Phys. Review	
Patient#		Yes	No
Ordering Physician			

INDICATIONS	1) Disorders with psychotic symptoms (schizophrenia, schizoaffective disorder, manic disorders, depression with psychotic features, drug-induced psychosis, psychosis associated with other medical conditions)			
	2) Schizophrenia adolescents – risperidone (13 to 17 years old), olanzapine (13 to 17 years old), paliperidone (12 to 17 years old), quetiapine (13 to 17 years old), aripiprazole (13 to 17 years old)			
	3) Severe aggression secondary to a psychiatric disorder			
	4) Self Injurious Behavior secondary to a psychiatric disorder			
	5) Bipolar disorder (not paliperidone, iloperidone, or lurasidone)			
	6) Bipolar disorder, adolescents – risperidone (10 to 17 years old, monotherapy), quetiapine (10 to 17 years old, adjunct & monotherapy), olanzapine (13 to 17 years old, acute & maintenance), aripiprazole (10 to 17 years old, adjunct & monotherapy)			
	7) Irritability associated with autistic disorders in children and adolescent – risperidone (5 to 16 years old) and aripiprazole (6 to 17 years old)			
	8) Adjunct for patients on antidepressants for major depressive disorder (aripiprazole, quetiapine)			

Medication Audit Criteria and Guidelines
Drug Audit Checklist 23

Reviewer:		Date:				
Class:						
Drug: <i>risperidone (Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa ®Relprevv™), paliperidone (Invega®, Invega Sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)</i>						
Audit#		Comments			Requires Phys. Review	
Patient#					Yes	No
Ordering Physician						
Contraindications	Absolute	3) History of anaphylactic reaction and similarly severe significant hypersensitivity to medication prescribed				
		4) For ziprasidone - Recent myocardial infarction, uncompensated congestive heart failure or when other drugs are being used that also prolong the QT interval such as (not complete list) quinidine, dofetilide, pimozone, sotalol, thioridazine, moxifloxacin, and sparfloxacin				
		4) For lurasidone – use of ketoconazole (3A4 inhibitor) or rifampin (3A4 inducer)				
	Relative	1) Pregnancy/nursing mothers				
		2) History of drug induced agranulocytosis or leukopenia				
		3) Breast cancer				
		4) History of neuroleptic malignant syndrome				
		5) Impaired hepatic function				
		6) Parkinson’s disease				
		7) Severe cardiovascular diseases				
		8) Known clinically significant QTc prolongation				

Drug audit Checklist 23 (Continued)

Drug: risperidone (Risperdal®, Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa ®Relprevv™), paliperidone (Invega®, Invega Sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)

Page 3.

Patient#	Comments	Requires Phys. Review	
		Yes	No
Ordering Physician			

PATIENT MONITORING	Patient Monitoring Parameters	1) Pregnancy test – as clinically indicated		
		2) BMI and waist circumference measurements– when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable		
		3) Fasting plasma glucose level or hemoglobin A _{1c} – before initiating a new antipsychotic, then yearly. If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.		
		4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.		
		5) EKG (for patients on ziprasidone)– For patients with known heart disease, a personal history of syncope, a family history of sudden death at an early age (under age 40 years, especially if both parents had sudden death), or congenital long QT syndrome, then a baseline EKG before treatment is initiated. A subsequent EKG is indicated if the patient presents with symptoms associated with a prolonged QT interval (e.g., syncope).		
		6) EKG (for patients on iloperidone) – at baseline		

Drug audit Checklist 23 (Continued)

Drug: *risperidone (Risperdal®), Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa ®Relprevv™), paliperidone (Invega®, Invega Sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Mainena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)*

Page 4

Patient#	Comments	Requires Phys. Review	
		Yes	No

Ordering Physician

PATIENT MONITORING (continued)	Patient Monitoring Parameters (continued)	7) Serum potassium and magnesium level baseline and periodic for patients on iloperidone who are at risk for significant electrolyte disturbances		
		8) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.		
		9) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.		
		10) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase		
		11) Tardive dyskinesia evaluation – every 3 months and as clinically indicated.		
		12) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly		
		13) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients		

Drug audit Checklist 23 (Continued)

Drug: <i>risperidone (Risperdal®), Risperdal Consta®), olanzapine (Zyprexa®, Zyprexa ®Relprevv™), paliperidone (Invega®, Invega Sustenna®), quetiapine (Seroquel®) ziprasidone (Geodon®), aripiprazole (Abilify®, Abilify® Maintena™), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®)</i>	Page 5
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Patient#	Comments	Requires Phys. Review	
		Yes	No

Ordering Physician			
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		14) After each olanzapine pamoate injection continuously observe patient for at least 3 hours for symptoms consistent with olanzapine overdose, including sedation (ranging from mild in severity to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment) (Post-Injection Delirium /Sedation Syndrome)			
	Dosing	15) See DSHS/DADS Drug Formulary for dosage guidelines. Exceptions to maximum dosage must be justified as per medication rule.			

Date Referred	Date Reviewed	Comments	Physician's Signature

Additional Comments:

