

DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
October 19, 2012

The Executive Formulary Committee convened on Friday, October 19, 2012 in Room 124 - ASH Building 552. The meeting was called to order by Dr. Becker, Interim Chair at 9:45 a.m.

Emilie A. Becker, M.D.	√	Jennifer Wright, M.D.	√
Mary Bowers RN, BSN	Absent	Valerie Kipfer, MSN, RN (non-voting)	Absent
Catherine Hall, Pharm.D.	√	Lilani Muthali, M.D. (non-voting)	√
Jeanna Heidel, Pharm.D. (via phone)	√	Nina Muse, M.D. (non-voting)	Absent
Marla Knight, Pharm.D., CGP, FASCP	Absent	Jay Norwood, MSN, RN (non-voting)	Absent
Jeff Matthews, M.D.	√	Peggy Perry (non-voting)	Absent
Connie Millhollon, RN	√	Chris Adams (non-voting)	Absent
Victoria Morgan, M.D.	√	Mike Maples (non-voting)	Absent
Kenda Pittman, Pharm.D.	√	Kerry Raymond (non-voting)	Absent
Tran Quan, D.O.	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Robert L. Ward, D.O.	√		

Guests Present (for afternoon only): Lisa Mican, Pharm.D., Assistant Pharmacy Director –ASH, Saadia Ali, Pharm.D. Pharmacy Resident, Bryson Duhon, Pharm.D., Pharmacy Resident

Introduction and Other Information

Dr. Wright was introduced to the Committee as a new member. In the afternoon, the guests were introduced to the Committee members. Dr. Becker reported that she will be leaving the agency for a position with Texas Medicaid. Dr. Morgan volunteered to be the Interim Chair in January. Hopefully, a permanent chair will be appointed prior to the spring 2013 meeting.

Approval of Minutes of July 20, 2012

On a motion of Ms. Millhollon, seconded by Dr. Heidel, the minutes of the July 20th meeting were approved as previously distributed.

Conflict of Interest Disclosure Forms

Each Committee member, as well as the individuals submitting new drug applications and completing the monographs have submitted their disclosure forms. No conflicts were noted.

Adverse Drug Reaction Reports

The Executive Formulary Committee discussed several adverse drug reactions.

A 25 year old Hispanic male was admitted to a psychiatric hospital with major depressive disorder recurrent and panic disorder. Medical history includes hearing loss in left ear, past surgery in left ear, and tonsillectomy. The patient had been off medications for 3-4 months prior to admission secondary to financial issues. He denied allergies on admission, but records showed he is allergic to buspirone (BuSpar®) with a reaction of edema. His urine drug screen in the ER was positive for benzodiazepines and amphetamines; however he denied use of amphetamines. In addition, he had a blood alcohol concentration of 0.102%. His baseline LFTs are unknown. Collateral documents indicate that he is “addicted to Xanax.” On admission (7-3-12), he was started on clonazepam (Klonopin®) 0.5 mg BID, hydroxyzine (Atarax®) 50 mg BID, sertraline (Zoloft®) 50 mg in the morning, nicotine patch 21 mg in the morning, and trazodone (Desyrel®) 50 mg at bedtime. On July 5th, clonazepam was increased to 0.5 mg TID and ibuprofen (Motrin®) 400 mg q6 hours prn was initiated. On July 6th, trazodone was increased to 100 mg at bedtime. On July 9th, sertraline was increased to 100 mg in the morning. On July 11th, diphenhydramine (Benadryl®) 100 mg TID was initiated for sunburn-like rash. He had received olanzapine (Zyprexa®) ODT on July 3rd (5 mg), 4th (5 mg), and 15th (10 mg). On July 17th (2 weeks from the time of admission), the comprehensive metabolic panel was within normal limits except total bilirubin 1.4 mg/dl (high), direct bilirubin 0.5 mg/dl (high), AST 1,276 U/L (high), ALT 990 U/L (high), alk phos 130 U/L; CBC with differential was within normal limits except ANC 7.5 K/mm³, absolute monocytes 1.1 K/mm³, and lymphocyte 12.6% (low). Tramadol (Ultram®) 50 mg stat was administered on July 17th for abdominal pain. The patient was transferred to a local ER secondary to increased LFTs and right upper quadrant pain. At the ER, all tests performed were unremarkable including CT abdomen and ultrasound. The patient was transferred back to the psychiatric hospital because he tolerated food by mouth and did not appear to have jaundice. Per ER physician recommendations, sertraline was discontinued on July 18th. Clonazepam, hydroxyzine, trazodone, diphenhydramine, and ibuprofen were resumed without increase in LFTs. Follow-up labs on July 20th showed signs of improvement; total bilirubin decreased to 0.5 mg/dl, direct bilirubin decreased to 0.1 mg/dl, AST decreased to 65 U/L, ALT decreased to 379 U/L, alk phos remained 130 U/L. On July 24th, total and direct bilirubin remained within normal limits, AST decreased to 46 U/L, ALT decreased to 153 U/L, and alk phos decreased to 114 U/L. He was discharged on July 26th on clonazepam 0.5 mg TID, trazodone 100 mg at bedtime, and diphenhydramine 100 mg TID without further event.

On July 23, 2012, a 60 year old female was seen by the physician with symptoms of “leaning to the left” and some meal refusals. She is intellectually and developmentally disabled and is a poor historian. The physician found no evidence of neurological deficit and nothing remarkable on physical exam. On July 24th, she was again seen by the physician for “leaning to the right” and additional meal refusals. She was in no acute distress. The physician ordered UA, chest X-ray, abdominal x-ray, CBC, CMP, amylase and lipase, and trough level of phenytoin (Dilantin®) to look for underlying cause of meal refusals. X-rays were negative. Later on July 24th, direct care staff reported signs of pain/discomfort and continued meal and liquid refusals. Awaiting lab results, she was admitted to the infirmary for IV fluids and observation. On July 24th, lab results showed elevated amylase (217 U/L) and lipase (660 U/L) and she was diagnosed with acute pancreatitis possibly secondary to levetiracetam (Keppra®). Her evening dose of levetiracetam was held on July 24th. Follow-up amylase and lipase on July 25th were within normal limits. Her levetiracetam dose was decreased to 250 mg BID and her phenytoin dose was increased. She was kept in the infirmary through July 27th on the lower dose of levetiracetam and continued to improve with no other intervention. She was sent home on July 28th and continues to do well as of this reporting date of August 1st.

A 25 year old white male was admitted to the psychiatric hospital on July 10, 2012. Psychiatric diagnoses include major depressive disorder and alcohol abuse. Medical history includes right shoulder relocation x2. The patient had been drinking heavily prior to admission with last drink the day before admission (12 pack or more of beer daily and sometimes a half-box of wine). He only began drinking heavily this year but has had a longstanding problem with alcohol as well as a history of delirium tremens. He presented with tremors, diaphoresis, elevated blood pressure (155/95 mm Hg) and hematemesis. His only outpatient medication was sertraline (Zoloft®) 50 mg daily which he had been taking for seven months and ran out of three days prior to admission. On admission he was reinitiated on sertraline 50 mg daily. In addition, hydroxyzine 100 mg at bedtime, lorazepam for alcohol withdrawal, folic acid 1 mg daily, and thiamine 100 mg daily were also prescribed. On July 11th, he was started on omeprazole (Prilosec®) 20 mg daily and lorazepam 2 mg three times daily. Baseline CBC with differential on July 11th at 7:30 am was unremarkable except WBC 4.2 K/mm³ (low), absolute lymphocyte 0.8 K/mm³ (low), lymphocyte 20.3% (low), monocyte 12.3% (high), eosinophil 0.8% (high). Of note, platelets were 150 K/mm³ and ANC was 2.7 K/mm³. CMP was unremarkable except for total bilirubin 2.6 mg/dl (high), chloride 94 mEq/L (low); TSH

within normal limits; RPR nonreactive; lipid panel unremarkable except for cholesterol 212 mg/dl (high) and HDL 129 mg/dl (confirmed by repeat on dilution). Urine drug screen on July 12th at 6:30 am was unremarkable except positive for benzodiazepines (prescribed lorazepam). On July 13th, sertraline was switched to mirtazapine (Remeron®) 15 mg at bedtime due to inadequate response and the lorazepam dose was decreased to 1 mg four times daily. On July 16th at 7:26 am, CBC with differential (manual) was unremarkable except WBC 2.9 K/mm³ (low), RBC 4.44 K/mm³ (low), hematocrit 41.1% (low), platelets 75 K/mm³ (low), neutrophils 18% (low), monocytes 23% (high), and ANC 0.8 K/mm³ (low); RBC, platelet, WBC morphology were unremarkable; total bilirubin, direct bilirubin and indirect bilirubin were unremarkable. On July 16th, mirtazapine was switched to bupropion (Wellbutrin®) XL 150 mg daily due to potential side effects (neutropenia), zolpidem (Ambien®) 10 mg bedtime prn insomnia was initiated, and lorazepam was discontinued. No follow-up CBC was obtained prior to patient discharge on July 19th so it is unknown if leukopenia, neutropenia, or thrombocytopenia resolved after mirtazapine discontinuation.

A 21 year old white male was admitted to a psychiatric hospital on August 18, 2012. He had previously been hospitalized at a medical hospital since August 13th for acute psychosis after overdosing on Coricidin® Cold and Cough (dextromethorphan 30 mg and chlorpheniramine 4 mg) 8 tablets every 4 hours for 3-7 days. Psychiatric diagnoses were psychosis NOS, rule out drug-induced psychosis, cannabis (nightly for 1 week), cocaine (denies recent use), alcohol abuse (patient reports occasional social drinking). Bath salt abuse was suspected but patient denied use. His past medical history includes psoriasis. Urine drug screen in the ER was positive for benzodiazepines (received lorazepam at outside hospital). On August 18th, hydroxyzine 25 mg every 6 hours prn anxiety was initiated with a dose given on August 20th, 21st, 22nd, and 28th. Stat medications administered on August 18th were haloperidol 10 mg orally for 2 doses and lorazepam 2 mg orally for 2 doses. He was also started on hydrocortisone 1% topical cream for psoriasis. On August 20th, the CMP including LFTs was within normal limits except glucose 169 mg/dl; CBC with differential was within normal limits except ANC 6.9 K/mm³ (high), neutrophil 75.8% (high), lymphocyte 16.6% (low), eosinophil 0.3% (low); TSH 1.02 MU/L. On August 20th, olanzapine (Zyprexa®) ODT 5 mg BID was initiated. On August 22nd, hepatitis A/B/C and HIV were negative; RPR nonreactive; lipids within normal limits except HDL 37 mg/dl; Hgb Alc 4.8%. On August 28th, CMP was within normal limits except AST 134 U/L (high), ALT 276 U/L (high); CBC within normal limits except absolute monocyte count 0.9 K/mm³, neutrophil 41.3%, eosinophil 4.5%; TSH within normal limits. On August 28th, the olanzapine was discontinued due to concern for elevated liver enzymes and aripiprazole (Abilify®) 10 mg every morning was initiated. The patient was discharged August 29th prior to follow-up LFTs with recommendation to obtain follow-up in the community.

Quetiapine (Seroquel®, Seroquel® XR) Purchases

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

Facility	July	August	September	Total
Rio Grande	\$2,798.59	0	\$531.76	\$3,330.35
Rusk	\$1,497.28	\$1,497.28	\$1,063.51	\$4,058.07
North Texas – Vernon	\$2,883.66	0	\$2,994.56	\$5,878.22
North Texas – Wichita Falls	(\$1,690.79)	0	0	(\$1,690.79)
Total	\$5,488.74	\$1,497.28	\$4,589.83	\$11,575.85

The facilities that did not purchase or return Seroquel® XR are not included in the table. For April through June, the Seroquel® (both the immediate and extended release) net purchases were \$627.60. The Committee felt that the amount of product purchased during the July – September time period was high. As a result, it was recommended that the number of patients that are receiving this product be identified. The purchase of Seroquel® XR will continue to be monitored.

Drug Deletions

At the last meeting, the following products were recommended for deletion:

- tegaserod (Zelnorm®)
- psyllium granules
- attapulgate
- cascara sagrada
- docusate sodium with casanthranol
- ipecac

The field did not provide any feedback. On a motion of Dr. Ward, seconded by Dr. Morgan, these products were deleted.

New Dosage Strengths

At the last meeting, it was decided to expand the number of certifying bodies for supplements. As a result, more strengths of fish oil capsules can now be considered to be on formulary. The following are products that are listed as non-formulary in WORx:

Drug Name	Dosage Form
Fish Oil	Capsule: 225 mg; 500 mg, 1,000 mg, 1,400 mg

In CWS, most of the drugs are listed by name and the prescriber enters the dose. Fish oil is listed as Formulary; therefore, any strength is considered formulary in CWS. WORx can list different dosage strengths as being formulary or non-formulary. With the expansion of the certifying organizations, the dosage forms currently being used should be considered for Formulary status. On a motion of Dr. Matthews, seconded by Dr. Ward, it was recommended that these products be added to Formulary.

Drug Formulary Sectional Review-

Infectious Disease Antineoplastic

Dr. Hall provided the review on the agents in the infectious disease section. See Attachment A. Dr. Hall recommended that the following products be deleted from the Formulary:

- ticarcillin (Ticar®)
- ticarcillin/clavulanate (Timentin®)
- cefoperazone (Cefobid®)
- mebendazole (Vermox®)
- cloxacillin (Cloxapen®)
- oxacillin (Prostaphlin®)
- erythromycin ethylsuccinate/sulfisoxazole (Pediazole®)
- chloroquine (Aralen®)
- pyrantel (Antiminth®)

In addition, Dr. Hall recommended that the “Urinary Anti-Infectives” subsection be deleted and that nitrofurantoin be moved to the “Miscellaneous Antibiotics.” In addition, it was recommended that pentamidine be moved to the “Miscellaneous Antibiotics” section.

On a motion of Dr. Ward, seconded by Dr. Wright, the recommendations for the Infectious Disease section were approved.

For the Antineoplastic Section, it was recommended that a statement be added to this section that indicates any drug prescribed by an oncologist for the treatment of cancer be considered to be a formulary drug. This is similar to the statement for medications used to treat HIV.

Drug Formulary Table Review

The tables that are listed in the Formulary were reviewed for potential revisions. Dr. Richards recommended the following changes be made:

For the “Children and Adolescent Treatment of Behavioral Emergencies”

- In the introductory paragraph, add the following “unless otherwise indicated” to the last sentence so that it states: “These doses are not based on any literature support unless otherwise indicated and are to be used for general guidelines.”
- Update the “Drug Information Handbook” to the current edition

For the “Adult Treatment of Behavioral Emergencies Intramuscular Short-Acting Agents”

- Update the reference for the first and fifth reference

For the “Antipsychotics” table:

- Change the fluphenazine (Prolixin®) decanoate dosing from 100 (q 1 – 4 weeks) to 400 mg per 4 weeks. With the previous dose listing, it could be interpreted that 400 mg could be administered weekly
- Change trifluoperazine (Stelazine®) maximum dose from 80 mg to 40 mg. This recommendation is based on the maximum dose listed in Micromedex™.

For the “Antidepressants” table:

- Change nortriptyline (Pamelor®) maximum dose from 200 mg to 150 mg based on the recommended maximum dose listed in Micromedex™ and AHFS Drug Information.

For the “Stimulants” table:

- Add “Concerta” to the 72 mg maximum dose for methylphenidate, sustained release

No other changes were made to the existing tables. Dr. Richards noted that the therapeutic serum concentration of phenobarbital varies by reference from 10 to 40 mcg/ml; 15 to 40 mcg/ml to 20 to 40 mcg/ml.

On a motion of Dr. Matthews, seconded by Dr. Morgan, the recommended changes to the tables were approved.

Reserve Drugs

There were no recommended changes to the Reserve Drugs.

2013 Drug Formulary

The 2013 Drug Formulary is tabled until January’s meeting

Deltoid Injection Volume

Most of the facilities limit the volume of medication administered in the deltoid to 1 ml. However, risperidone (Risperdal®) Consta™ products are 2 ml and their package insert states that the product can be administered in the deltoid. The following article “Intramuscular injections: a review of best practice for mental health nurses,” Journal of Psychiatric and Mental Health Nursing, 2008(15):424-434, states that 2 ml may be administered in the deltoid. One facility addressed this issue by changing its policy to state “unless the manufacturer recommends differently only 1 ml should be administered in the deltoid.” The Committee recommended that this wording be shared with the facilities.

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.

Issues from the Clinical Directors' Meeting

Dr. Becker reported that there have been some issues with slowness with CWS. This has been due to the network. She is hoping that the bandwidth will be increased to address this issue. Recently, Dr. Becker distributed an email regarding the website that physicians can use to check to see if their patients have received controlled substances from other practitioners and if there are records of their own prescribing. Dr. Becker noted that the database indicated that she had prescribed controlled substances earlier this year, yet she hasn't seen patients for years. She did notify the authorities of this issue.

New Drug Applications

(Please refer to Attachment B for the monographs and applications that were considered when determining action by the committee.)

Melatonin - presented by Dr. Duhon

Melatonin is a sleep-regulating pineal gland hormone. It is available as an over-the-counter product and is not regulated by the Food and Drug Administration. Endogenous melatonin is produced by the pineal gland during the dark hours of the day-night cycle. Serum levels of melatonin remain low during the day due to stimulatory suppression induced by light. Its secretion is regulated by the suprachiasmatic nucleus, otherwise known as the circadian clock. Three melatonin receptors have been identified (MT1, MT2, MT3) and are located in the retina, reproductive organs, vasculature, and lymphocytes, leading to hypothesized roles in immune system, reproductive cycle, and cancer cell regulation. Exogenous supplementation of melatonin is associated with a reduced body temperature, and time-dependent increases in sleepiness. Prolonged administration of melatonin induces a re-entrainment and phase-setting effect on circadian rhythms, such as the sleep-wake cycle. The bioavailability of melatonin has a wide range of 3% to 76%. The AUC and plasma levels tend to be higher and more stable when given with food. The dose is 0.5 to 5 mg daily at darkness one to five hours prior to sleep onset. Melatonin may interact with nifedipine, leading to increased blood pressure and heart rate by an unknown mechanism. Melatonin also has the potential to increase prothrombin time, leading to an associated increased risk of bleeding. Drugs with antiplatelet or anticoagulation properties should be used with caution.

Following discussion, on motion of Dr. Hall, seconded by Ms. Millhollon, the request to add melatonin to the formulary was approved. The Formulary Drug Check List was completed.

Lisdexamfetamine dimesylate (Vyvanse®) - presented by Dr. Ali

Lisdexamfetamine dimesylate is a pro-drug of dextroamphetamine. After administration, lisdexamfetamine dimesylate is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention-Deficit/Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*. In patients 6 years and older with ADHD who are either starting treatment for the first time or are switching from another medication, 30 mg once daily in the morning is the recommended dose. If an increase is necessary, the dosage may be adjusted in increments of 10 mg or 20 mg per day and at approximately weekly intervals. The maximum recommended dose is 70 mg/day. Lisdexamfetamine dimesylate was considered for addition to the

Formulary previously. At that time, it was declined due to cost issues. However, with the shortages of the Adderall® products as well as its generics, the use of lisdexamfetamine dimesylate has increased and more patients are being admitted on this drug.

Following discussion, on motion of Dr. Ward, seconded by Dr. Morgan, the request to add lisdexamfetamine dimesylate (Vyvanse®) to the formulary as a Reserve drug was approved.

The criteria for use shall be: continued therapy on admission or failed other stimulants. The Formulary Drug Check List was completed.

Citalopram (Celexa®) Label Change

Dr. Mican presented information on the citalopram labeling changes regarding QTc prolongation. See Attachment C. Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which have been observed in post-marketing reports for citalopram. Due to the risk of QTc prolongation at higher citalopram doses, it is recommended that citalopram should not be given at doses about 40 mg/day.

Based on its labeling, it is recommended that citalopram should not be used in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure. Citalopram should also not be used in patients who are taking other drugs that prolong the QTc interval. Such drugs include Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

In addition, the citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected. The maximum dose should also be limited to 20 mg/day in patients with hepatic impairment and in patients who are greater than 60 years of age because of expected higher exposure.

Electrolyte and/or ECG monitoring is recommended in certain circumstances. Patients being considered for citalopram treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QTc prolongation and arrhythmia, and should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients for whom citalopram use is not recommended, but is considered essential.

The main issue with the citalopram labeling is that antipsychotics as a class are listed as drugs that prolong the QTc interval and according to the labeling, citalopram should not be used in these patients. This becomes an issue as the majority of patients in state hospitals are on antipsychotics so if an antidepressant is needed, citalopram may not be an option. However, it is noted that if citalopram is used in patients, then the ECG should be periodically monitored.

There are different ways to assess QTc prolongation risk. Clinically significant drug-induced QTc prolongation: < 5 msec not generally associated with increased risk and is generally not of concern; 5-10 msec low risk; 10-20 msec moderate risk; ≥ 20 msec high risk of inducing an arrhythmia and of significant concern. Other markers of clinically significant concern include QTc > 500 msec or prolongation > 60 msec over baseline.

With this dilemma, Austin State Hospital completed an analysis of QTc safety with citalopram. From February 1st through May 1st, patients on citalopram were reviewed. During this time, 31 patients were on citalopram with 17 of them (54.8%) having an ECG completed. There were no cases of QTc > 500 msec. There were three cases of QTc > 450 msec; however, the hospital was unable to isolate citalopram as a causative factor in any of these cases.

After the initial drug use evaluation, the hospital completed training on the new labeling changes. After this training, a second drug use evaluation was completed from July 20th through August 20th. This evaluation involved patients that were not used in the first evaluation. During this time frame, ten patients

were on citalopram and seven of them (70%) had ECGs. There were no cases of QTc intervals > 450 msec.

The Hospital reviewed all their FDA MedWatch reports due to QTc prolongation since 2005. Six reports were identified. In two of these six reports, the patient was also taking citalopram, however, citalopram was not identified as the QT prolonging agent. In one case, the QTc prolongation resolved after quetiapine (Seroquel®) was discontinued even though the citalopram dose had been recently increased. In the second case, the QTc improved with discontinuation of quetiapine, but remained mildly prolonged after a dose increase of citalopram; however, no baseline ECG prior to medication use was available.

In reviewing the FDA Adverse Event Reporting System for Torsade de Pointes (TdP) from January 2004 to December 2007 there were 1,665 reports of TdP with 12 cases reported with citalopram which was the most prescribed antidepressant during this time period. In comparison, fluoxetine (Prozac®) had 12, paroxetine (Paxil®) 11 and mirtazapine (Remeron®) 11. The Swedish Pharmacovigilance database showed 101 reports of TdP from January 1, 1991 to February 1, 2006 with nine cases of citalopram involvement (5 cases as sole agent), two cases with fluoxetine and one each with nortriptyline and paroxetine.

Based on ASH's data combined with the available literature, there does not appear to be any strong signal of QTc prolongation with citalopram compared to other antidepressants.

Citalopram's labeling indicates that it should not be taken with drugs that prolong the QTc interval; antipsychotics as a class are included in the listing with the specific examples of thioridazine and chlorpromazine. However, not all antipsychotics have been reported to cause clinically significant prolongation in the QT interval. Antipsychotics that have a low potential for causing prolonged QTc interval include asenapine, aripiprazole, and lurasidone.

Based on all of this information, the Austin State Hospital made the following conclusions:

- Clinically significant QTc prolongation has not been observed with citalopram in the ASH patient population.
- Antipsychotics are commonly prescribed in ASH's patient population and not all antipsychotics have been attributed with clinically significant changes in QTc.
- Not all CYP2C19 inhibitors have clinically relevant drug interactions with citalopram, with most of the evidence with strong inhibitors rather than weak or moderate inhibitors.
- The revised citalopram labeling changes with regards to QTc are likely in excess of what is necessary based on currently available information.

Based on this presentation, the Committee made the following recommendations:

- Citalopram be listed separately on the psychotropic audit criteria and guidelines
- The document presented on citalopram be included in the minutes of the meeting and included on the EFC section of the website.
- A separate memo be distributed to the field on this issue

FDA Drug Safety Communications

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

In September, the FDA informed the public about a possible increased risk of heart failure with pramipexole (Mirapex®), a drug used to treat Parkinson's disease and restless legs syndrome. Results of recent studies suggest a potential risk of heart failure that needs further review of available data. The FDA evaluated a pooled analysis of randomized clinical trials and found that heart failure was more frequent with pramipexole than with placebo; however, these results were not statistically significant. The FDA also evaluated two epidemiologic studies that suggested an increased risk of new onset of heart failure with pramipexole use. However, study limitations make it difficult to determine whether excess heart failure was related to pramipexole use or other influencing factors. Because of the study limitations, the FDA was not able to determine whether pramipexole increases the risk of heart failure. The FDA is continuing to work with the manufacturer to clarify further the risk of heart failure with pramipexole and will update the public when more information is available. Health care professionals should continue to follow the recommendations in the drug label when prescribing pramipexole.

In October, the FDA reviewed new data that indicates Budeprion® XL 300 mg (bupropion hydrochloride extended-release tablets), manufactured by Impax Laboratories, Inc., and marketed by Teva Pharmaceuticals USA, Inc., is not therapeutically equivalent to Wellbutrin® XL 300 mg. The FDA has changed the therapeutic equivalence rating for this product in the Agency's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) from AB to BX, signifying that Budeprion® XL 300 mg fails to demonstrate therapeutic equivalence to Wellbutrin® XL 300 mg. Impax has requested that the Agency withdraw approval of Budeprion® XL 300 mg extended-release tablets. Impax and Teva have stopped shipping the product and are issuing detailed information to their customers. This announcement relates only to Budeprion® XL 300 mg manufactured by Impax and marketed by Teva. It does not affect the Impax/Teva Budeprion® 150 mg product or generic bupropion products made by other manufacturers. This information was previously shared with the Pharmacy Directors.

Quarterly Non-Formulary Drug Justification Report

For the fourth quarter of fiscal year 2012, all facilities reported use of non-formulary agents. The following were the top non-formulary agents that were prescribed:

- Calmoseptine® ointment
- Melatonin
- Quetiapine (Seroquel®) XR

Melatonin was added to the Formulary during this meeting.

Sectional Review for Next Meeting

The following sections 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:

According to a study published online August 6 in the Archives of General Psychiatry, "Infants with prenatal exposure to antipsychotics show significant reductions in neuromotor performance compared with other children." To arrive at this conclusion, researchers "used the Infant Neurological International Battery (INFANIB) to compare neuromotor performance among 22 infants with prenatal exposure to antipsychotics, 202 with prenatal exposure to antidepressants, and 85 infants with no prenatal exposure to such medications."

In a review published in the Aug. 14 issue of the Annals of Internal Medicine, "Newer, more expensive schizophrenia medications are not noticeably better than their older, cheaper counterparts." Researchers at the US Agency for Healthcare Research and Quality reviewed 114 studies involving 22 comparisons between the two classes of medications, first- and second-generation antipsychotics. "The review found that the second-generation antipsychotics are not much better than the earlier incarnations at treating positive symptoms associated with schizophrenia."

According to research published online Aug. 5 in the journal Nature Neuroscience, "Scientists have discovered a molecular mechanism for resistance to antipsychotic medications." Researchers from the Mount Sinai School of Medicine in New York City found that "long-term administration of atypical

antipsychotic drugs selectively upregulates expression of the enzyme histone deacetylase 2 (HDAC2) in both mouse and human frontal cortex." That "epigenetic change, which is dependent on serotonin 5-hydroxytryptamine 2A (5-HT2A) upregulation, leads to lower expression of the metabotropic glutamate 2 receptor (mGlu2), thereby limiting the therapeutic effects of atypical antipsychotic therapy, often leading to a recurrence of psychotic symptoms."

An Associated Press story in August focused on a growing trend among drug manufacturers to offer coupons when their brand-name patents expire. Commercial insurers say the coupons "throw a wrench" into their efforts to "get as many patients as possible to take generic drugs, which account for about 80 percent of all prescriptions filled in the US." Some insurers are "fighting back." According to Express Scripts Holding Co., "more than half the insurance plans it services have policies requiring patients to pay an extra fee for staying on the brand-name drug," and the fee is high enough to "make use of coupons unattractive." But brand-name drug makers say coupons "give loyal patients savings of as much as \$100 a month." For example, under Pfizer's "Lipitor For You" coupon program, Pfizer "absorbs up to \$75 of the off each prescription."

In September, the Food and Drug Administration issued a Consumer Warning cautioning that use of over-the-counter topical pain reliever products, which contain menthol, methyl salicylate, or capsaicin as active ingredients, may cause mild to severe skin burns. FDA regulators "say they have received reports of skin injuries ranging from first- to third-degree chemical burns" caused by the OTC products; and in some cases, the "burns have required hospitalization." The agency "says consumers should stop using the pain relievers if they experience signs of skin injury, such as pain, swelling or blistering of the skin."

The Daily Mail (UK) reports that "regular use of household painkillers including ibuprofen and paracetamol can lead to an increased risk of hearing loss in women, according to a study." According to the article, "scientists from Brigham and Women's Hospital in Boston, Massachusetts, examined data from 62,261 women aged between 31 to 48 years." The report adds that "the researchers concluded that women who used ibuprofen two or three days a week showed a 13 percent increase in hearing loss."

According to a study published in the journal Health Services Research, over the past 10 years, the use of antipsychotic medications off-label "has increased among children enrolled in Medicaid." In the study, researchers from the Children's Hospital of Philadelphia found a 62 percent jump in the number of publicly insured children between the ages of three and 18 taking antipsychotics. In 2007 alone, 65 percent of the 354,000 children on these drugs were taking them for uses that have not been approved by the FDA, the investigators pointed out."

Procter & Gamble is "adding a blast of fruit flavor to a pill that you swallow whole - a first for the world's largest consumer products maker. In the biggest change to heartburn medication Prilosec [omeprazole] since it became an over-the-counter drug in 2003." P&G announced it is adding a "berry flavor to the pill - even though the pill meant to be is swallowed, not chewed. It's a marketing gimmick more in line with the grocery aisles than the more staid medicine aisle and helps the pill compete more directly with flavored traditional antacids," such as Tums (calcium carbonate).

MedPage reported that the FDA has "tracked about 100 drug shortages this year, down almost half from this time last year," an agency official said. Capt. Valerie Jensen, RPh, associate director at the FDA's Center for Drug Evaluation and Research, said last week that the agency "tracked 251 shortages all of last year and 181 in 2010." MedPage adds that Jensen "credited the drop in shortages to drug manufacturers improving quality, reducing the need for FDA action and recalls."

According to a new study presented at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy reports, "Patients taking ritonavir-boosted atazanavir (ATV/r) are 10 times more likely to develop kidney stones than patients taking other protease inhibitors." Being that "kidney stones were likely

to recur if the patients continued taking ATV/r, lead author Yohei Hamada, MD, a clinical fellow at the National Center for Global Health and Medicine in Tokyo, Japan, and colleagues recommend discontinuing the drug in any patient with kidney stones." The researchers reported that "median time from the commencement of ATV/r to the diagnosis of a kidney stone was 24.5 months (interquartile range, 14.7 to 34.6 months) in the 31 patients on ATV/r who developed stones" in the study.

Modern Healthcare reports that a "user-fee program intended to speed the approval of generic drugs is expected to begin Oct. 1 as planned" despite the fact that Congress and the President "failed to reach a spending agreement that reflected the new initiative." Legislation, which both the House and Senate passed before adjourning until "after the election would allow the Food and Drug Administration to begin collecting user fees from the generic drug industry next year." The bill, which Obama is "expected to sign, relieved the industry's concern that the program would be delayed because lawmakers resorted to another stopgap funding measure to fund the government." However, as part of the "user-fee agreement reached with the FDA, the generic drug industry is expected to pay \$299 million each year to help fund generic drug approvals and facility inspections."

According to a study published online in the BMJ, "Older patients who used benzodiazepine anti-anxiety drugs were at substantially higher risk of developing dementia than nonusers," the study found. "Among 1,063 randomly selected individuals 65 and older in southwest France who agreed to participate in a long-term observational study, the risk of new-onset dementia during follow-up was 60% greater (adjusted odds ratio 1.60, 95% CO 1.08 to 2.38) for those who had used benzodiazepines relative to never-users." The study authors concluded, "Considering the extent to which benzodiazepines are now prescribed, physicians and regulatory agencies should consider the increasing evidence of the potential adverse effects of this drug class for the general population."

According to a Nov. 24, 2011, study in the New England Journal of Medicine, "Adverse drug events send at least 265,000 seniors to US emergency departments every year and hospitalize nearly 100,000 patients 65 and older." Experts are particularly struck by "the study's finding that four kinds of medications -- warfarin, insulins, oral antiplatelet agents and oral hypoglycemic agents -- together account for seven in 10 emergency hospitalizations among seniors." The article adds, "For primary care physicians faced with helping their senior patients avoid the ED, the call to action goes beyond properly counseling patients on the absolute necessity of taking their medications exactly as directed and avoiding drug-drug and drug-food interactions, experts say."

According to a study published in the October issue of the journal Ophthalmology, the risk of developing open-angle glaucoma "was eight percent lower among those who took statins for at least two years, compared to those who did not take them." Researchers "discovered the association after looking at results from more than 300,000 Americans over 60." Although the study does not prove that statins actually decrease the risk for glaucoma, the study authors theorize that "statins could improve blood flow to parts of the eye and reduce high pressure inside the eye, which can trigger glaucoma."

H. Lundbeck A/S and Takeda Pharmaceutical Co. announced they have submitted an application to the Food and Drug Administration seeking approval of their antidepressant, vortioxetine. Lundbeck has been seeking a replacement for its blockbuster anti-depressant, CipraleX (escitalopram), which is sold under the brand name Lexapro in the US and Japan, because its patent is about to expire.

The Baltimore Sun's "Picture of Health" blog reports that the anti-retroviral medication efavirenz, "a drug commonly used by patients with HIV, may be damaging nerve cells and causing memory loss, Johns Hopkins researchers have found." Physicians "have long thought the brain damage and memory loss long-term survivors of HIV suffer was caused by the disease." However, "scientists now believe a large cause is the" drug itself, which appears to attack and then damage brain cells. Researchers now hope that by

tweaking the structure of the drug itself, the medication will still suppress the HIV virus and not be so toxic to brain cells.

The Associated Press reports, "Dozens of weight loss and immune system supplements on the market are illegally labeled and lack the recommended scientific evidence to back up their purported health claims, government investigators warn in a new review of the \$20 billion supplement industry." The report, which released by HHS' Office of Inspector General, found that "20 percent of the 127 weight loss and immune-boosting supplements investigators purchased online and in retail stores across the country carried labels that made illegal claims to cure or treat disease." Notably, Federal regulations do not require the FDA to "review supplement companies' scientific evidence for most of their products' purported health benefits before they hit the market" and the OIG "found that in numerous cases, when companies did submit evidence to back up their health claims, it fell far short of government recommendations.

The Food and Drug Administration issued a statement, saying it has been receiving reports from consumers who experienced a reduction in efficacy after substituting GlaxoSmithKline's Wellbutrin XL (bupropion hydrochloride) with the generic Budeprion XL 300 that is manufactured by Impax Laboratories Inc. and marketed by Teva Pharmaceuticals USA Inc. The agency said, however, that it has asked four other pharmaceutical companies that make generic versions of Wellbutrin XL to conduct additional Phase III trials, comparing the 300-milligram dosage generic with the brand-name formulation.

The FDA has approved a once-daily liquid medication for the treatment of attention-deficit/hyperactivity disorder (ADHD). Qullivant XR (methylphenidate hydrochloride) is an oral suspension made by NextWave Pharmaceuticals. The product is designed for use with patients who have difficulty swallowing tablets or capsules. It will be available commercially in January, 2013.

A study published Oct. 9 in Neurology suggest "an increased risk for Parkinson's disease (PD) in elderly people who have past exposure to neuroleptic" medications. The 2,991-patient study led researchers to conclude that "about one in five cases of PD could be avoided by restricting use of antipsychotics. Most patients in their study received the drugs for nonpsychiatric indications, including insomnia, anxiety, vertigo, and gastrointestinal problems, despite such use being discouraged."

Government Health IT reports, "The National Institutes of Health (NIH) has launched a database of pharmaceutical drugs associated with liver damage." The new "database, called LiverTox, is free for healthcare researchers and providers and has information on more than 700 pharmaceuticals, with another 300 set to be added in the coming years." In a press release, Jay Hoofnagle, MD, lead creator of the new database and director of the Liver Disease Research Branch at NIH's National Institute of Diabetes and Digestive and Kidney Diseases, explained why the database is necessary. He said, "Because drug-induced liver disease is not a single, common disease, it is very difficult to diagnose, with each drug causing a somewhat different pattern of liver damage."

According to a meta-analysis published online Oct. 17 in the journal Neurology, the use of selective serotonin reuptake inhibitor (SSRI) antidepressants appears to be associated with somewhat increased chances of a hemorrhagic stroke. For the study, investigators analyzed the results of 16 studies encompassing some 500,000 individuals.

Next Meeting Date

The next meeting was scheduled for January 25, 2013. Dr. Morgan has agreed to serve as Chair for the meeting scheduled in January.

Adjourn

There being no further business, the meeting was adjourned at 2:02 p.m.

Approved: *Emilie A. Becker, MD*

Emilie Attwell Becker, M.D., Acting Chairman

Attachments

Attachment A – Infectious Disease Agents Sectional Review

Attachment B – New Drug Applications

Attachment C – Citalopram labeling changes regarding QTc prolongation

Minutes Prepared by:

Ann L. Richards, Pharm.D., BCPP

MEMORANDUM

To: Executive Formulary Committee
From: Catherine S. Hall, Pharm.D., BCPP
Through: Ann L. Richards, Pharm.D., BCPP
Subject: Class Review – Infectious Disease Agents
Date: October 19, 2012

Recommended for deletion: ticarcillin (Ticar), ticarcillin/clavulanate (Timentin), cefoperazone (Cefobid), mebendazole (Vermox), cloxacillin (Cloxapen, Tegopen), oxacillin (Prostaphlin)

Recommend that we delete the “Urinary Anti-Infectives” subsection and move nitrofurantoin to “Miscellaneous Antibiotics”. Also recommend that we move pentamidine to “Miscellaneous Antibiotics”.

Infectious Disease Agents**Antibiotics**

Penicillins

Amoxicillin (Amoxil, Polymox)	\$ - \$\$\$\$
Amoxicillin/Clavulanate (Augmentin)	\$\$
Ampicillin (Polycillin, Omnipen)	\$ - \$\$\$\$
Cloxacillin (Cloxapen, Tegopen) or Dicloxacillin (Dycill, Dynapen, Pathocil)	\$ - \$\$\$\$\$\$
Nafcillin (Unipen) or Oxacillin (Prostaphlin)	\$ - \$\$\$\$\$\$
Penicillin G Benzathine (Bicillin)	\$\$\$ - \$\$\$\$\$\$\$
Penicillin G Benzathine/Penicillin G Procaine (Bicillin C-R)	\$\$\$\$
Penicillin G Procaine (Wycillin)	\$\$ - \$\$\$\$\$\$
Penicillin G Sodium	\$\$ - \$\$\$\$
Penicillin V Potassium (Pen-Vee K, V-Cillin K)	\$ - \$\$
Piperacillin/Tazobactam (Zosyn)	\$\$\$\$\$\$\$
Ticarcillin (Ticar)	\$\$\$\$\$ - \$\$\$\$\$\$\$
Ticarcillin/Clavulanate (Timentin)	\$\$\$\$\$\$\$

Cephalosporins

Cefazolin (Kefzol, Ancef)	\$\$\$\$ - \$\$\$\$\$
Cefepime (Maxipime)	\$\$\$\$\$\$ - \$\$\$\$\$\$\$
Cefoperazone (Cefobid)	\$\$\$\$\$\$\$
Ceftriaxone (Rocephin)	\$\$\$\$\$\$\$
Cefuroxime Axetil (Ceftin) - Oral form only - RESERVE USE	\$\$\$ - \$\$\$\$\$
Cephalexin (Keflex)	\$ - \$

Macrolides

Azithromycin (Zithromax)	\$\$\$\$
Clarithromycin (Biaxin)	\$
Erythromycin (Erythrocin)	\$ - \$
Erythromycin Ethylsuccinate/Sulfisoxazole Suspension (Pediazole)	\$ - \$\$
Tetracyclines	
Doxycycline (Vibramycin)	\$ - \$\$\$\$\$\$
Minocycline	\$\$ - \$\$\$\$
Tetracycline (Achromycin, Panmycin)	\$ - \$\$
Quinolones	
Ciprofloxacin (Cipro)	\$ - \$\$\$\$\$\$\$\$
Levofloxacin (Levaquin)	\$\$\$\$\$ - \$\$\$\$\$\$\$\$
Moxifloxacin (Avelox)	\$\$\$\$\$ - \$\$\$\$\$\$\$\$
Aminoglycosides	
Amikacin (Amikin)	\$\$\$\$\$
Gentamicin (Garamycin)	\$\$
Neomycin (Mycifradin)	\$\$ - \$\$\$
Tobramycin (Nebcin)	\$\$\$ - \$\$\$
Miscellaneous Antibiotics	
Clindamycin (Cleocin)	\$ - \$\$\$\$\$\$\$\$
Cycloserine (Seromycin)	\$\$\$\$
Linezolid (Zyvox)	\$\$\$\$\$\$\$
Metronidazole (Flagyl)	\$ - \$\$\$\$\$\$\$\$
Trimethoprim/Sulfamethoxazole (Co-Trimoxazole, Bactrim, Septra)	\$ - \$\$\$\$\$\$\$\$
Vancomycin (Vancocin)	\$\$\$\$\$ - \$\$\$\$\$\$\$\$

Antifungals

Fluconazole (Diflucan)	\$ - \$\$\$\$\$
Griseofulvin (Fulvicin)	\$
Ketoconazole (Nizoral)	\$\$ - \$\$\$
Nystatin (Mycostatin)	\$\$ - \$\$
Terbinafine (Lamisil)	\$\$\$\$

Antimalarials

Chloroquine (Aralen)	\$\$\$
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Antituberculars

Cycloserine (Seromycin)	\$\$\$\$
Ethambutol (Myambutol)	\$\$ - \$\$\$
Ethionamide	\$\$\$
Isoniazid (INH)	\$
Pyrazinamide	\$ - \$\$\$
Rifabutin (Mycobutin)	\$\$\$\$\$
Rifampin (Rifadin)	\$\$ - \$\$\$\$\$\$\$\$
Rifampin/Isoniazid (Rifamate)	\$\$

Antivirals

All commercially available antiviral agents used in the treatment of AIDS/HIV are considered to be formulary agents

Acyclovir (Zovirax)	\$\$ - \$\$\$\$
Amantadine (Symmetrel)	\$\$ - \$\$
Oseltamivir (Tamiflu)	\$\$\$\$\$\$\$
Valacyclovir (Valtrex)	\$\$\$\$ - \$\$\$\$\$\$
Zanamivir (Relenza)	\$\$\$\$\$\$\$

Anthelmintics

Ivermectin (Stromectol)	\$\$\$ - \$\$\$\$\$\$
Mebendazole (Vermox)	\$\$\$ - \$\$\$\$\$
Pyrantel (Antiminth)	\$ - \$\$\$\$
Thiabendazole (Mintezol)	\$\$\$\$

Urinary Anti-Infectives

Nitrofurantoin (Macrochantin)	\$\$ - \$\$\$\$
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Miscellaneous Anti-Infectives

Pentamidine (Pentam) - RESERVE USE	\$\$\$\$\$
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Amoxicillin (Amoxil, Polymox)

- Capsule: 250 mg, 500 mg
- Powder for oral suspension: 50 mg/mL, 125 mg/5 mL, 250 mg/5 mL
- Tablet: 500 mg, 875 mg
- Tablet, chewable: 125 mg, 250 mg

Amoxicillin/Clavulanate (Augmentin)

- Suspension, oral: 400mg (contains 57mg Clavulanate) per 5ml, 600mg (contains 42.9mg Clavulanate) per 5ml
- Tablet:
 - 200 mg (contains 28.5 mg Clavulanate)
 - 250 mg (contains 125 mg Clavulanate)
 - 400 mg (contains 57 mg Clavulanate)
 - 500 mg (contains 125 mg Clavulanate)
 - 875 mg (contains 125 mg Clavulanate)
- Tablet, chewable: 125 mg (contains 31.25 mg Clavulanate)
250 mg (contains 62.5 mg Clavulanate)
- Tablet, extended release: 1000 mg

Ampicillin (Polycillin, Omnipen)

- Capsule, as anhydrous: 250 mg, 500 mg
- Capsule, as trihydrate: 250 mg, 500 mg
- Powder for injection: 125 mg, 250 mg, 500 mg, 1 g, 2 g, 10 g
- Powder for oral suspension, as trihydrate: 125 mg/5 mL, 250 mg/5 mL

Cloxacillin (Cloxapen, Tegopen)

Capsule: 250 mg, 500 mg
Powder for oral suspension: 125 mg/5 mL

Dicloxacillin (Dycill, Dynapen, Pathocil)

Capsule: 125 mg, 250 mg, 500 mg
Powder for oral suspension: 62.5 mg/mL

Nafcillin (Unipen)

Capsule: 250 mg
Powder for injection: 500 mg, 1 g, 2 g, 4 g, 10 g
Solution: 250 mg/5 mL
Tablet: 500 mg

Oxacillin (Prostaphlin)

Capsule: 250 mg, 500 mg
Powder for injection: 250 mg, 500 mg, 1 g, 2 g, 4 g, 10 g
Powder for oral solution: 250 mg/5 mL

Penicillin G Benzathine (Bicillin)

Injection: 300,000 units/mL, 600,000 units/mL

Penicillin G Benzathine/Penicillin G Procaine (Bicillin C-R)

Injection: 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, 600,000 units/mL

Penicillin G Sodium

Injection: 5 million units

Penicillin V Potassium (Pen-Vee K, V-Cillin K)

Powder for oral solution: 125 mg/5 mL, 250 mg/5 mL
Tablet: 125 mg, 250 mg, 500 mg

Piperacillin/Tazobactam (Zosyn)

Injection: 2.25 g, 3.375 g and 4.5 g

Ticarcillin (Ticar)

Powder for injection: 1 g, 3 g, 6 g, 20 g, 30 g

Ticarcillin/Clavulanate (Timentin)

Powder for injection: 3.1 g

Cefazolin (Kefzol, Ancef)

Injection: 500 mg, 1 g

Cefepime (Maxipime)

Injection: 500 mg, 1 g, 2 g

Cefoperazone (Cefobid)

Infusion, premixed in dextrose: 1 g, 2 g
Powder for injection: 1 g, 2 g

Ceftriaxone (Rocephin)

Infusion, premixed in dextrose: 1 g, 2 g

Powder for injection: 250 mg, 500 mg, 1 g, 2 g, 10 g

Cefuroxime Axetil (Ceftin) - Oral form only - RESERVE USE

Powder for oral suspension: 125 mg/5 mL, 250 mg/5 mL

Tablet: 125 mg, 250 mg, 500 mg

Cephalexin (Keflex)

Capsule: 250 mg, 500 mg

Powder for oral suspension: 100 mg/mL, 125 mg/5 mL, 250 mg/5 mL

Tablet: 250 mg, 500 mg, 1 g

Tablet: 500 mg

Azithromycin (Zithromax)

Powder for oral solution: 200 mg/5 mL, 400 mg/5 mL

Tablet: 250 mg, 500 mg, 600 mg

Clarithromycin (Biaxin)

Granules for oral suspension: 125 mg/5 mL, 250 mg/5 mL

Tablet, film coated: 250 mg, 500 mg

Erythromycin (Erythrocin)**Erythromycin base (Eryc, E-Mycin, Ery-Tab, E-Base, PCE):**

Capsule, delayed release: 250 mg

Tablet, enteric coated: 250 mg, 333 mg, 500 mg

Tablet, film coated: 250 mg, 500 mg

Tablet, polymer coated particles: 333 mg, 500 mg

Erythromycin Ethylsuccinate (EryPed, E.E.S.):

Granules/Powder for oral suspension: 200 mg/5 mL, 400 mg/5 mL

Suspension, oral: 200 mg/5 mL, 400 mg/5 mL

Suspension, oral (drops): 100 mg/2.5 mL

Tablet: 400 mg

Tablet, chewable: 200 mg

Ointment, ophthalmic: 5%

Erythromycin Ethylsuccinate/Sulfisoxazole Suspension (Pediazole)

Suspension, oral: Erythromycin ethylsuccinate 200 mg/Sulfisoxazole 600 mg per 5 mL

Doxycycline (Vibramycin, Periostat)

Capsule: 50 mg, 100 mg

Powder for injection: 100 mg, 200 mg

Powder for oral suspension: 25 mg/5 mL

Syrup: 50 mg/5 mL

Tablet: 20 mg, 50 mg, 100 mg

Minocycline

Capsule: 50 mg, 75 mg, 100 mg

Capsule, pellet filled: 50 mg, 100 mg

Tetracycline (Achromycin, Panmycin)

Capsule: 100 mg, 250 mg, 500 mg

Suspension, oral: 125 mg/5 mL

Tablet: 250 mg, 500 mg

Ciprofloxacin (Cipro, Ciloxan)

Injection: 200 mg, 400 mg

Ointment, ophthalmic: 0.3%

Solution, ophthalmic: 0.3%

Suspension, oral: 5 gm/100 mL, 10 gm/100 mL

Tablet: 100 mg, 250 mg, 500 mg, 750 mg

Levofloxacin (Levaquin)

Infusion: 250 mg, 500 mg

Tablet: 250 mg, 500 mg, 750 mg

Moxifloxacin (Avelox)

Infusion: 400 mg/250 mL

Tablet: 400 mg

Amikacin (Amikin)**Injection: 50 mg/mL, 250 mg/mL****Gentamicin (Garamycin)**

Cream, topical: 0.1%

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

Ointment, ophthalmic: 0.3% [3 mg/g]

Ointment, topical: 0.1%

Solution, ophthalmic: 0.3% [3 mg/mL]

Neomycin (Mycifradin)

Tablet: 500 mg

Tobramycin (Nebcin, Tobrex)

Injection: 10 mg/mL, 40 mg/mL

Ointment, ophthalmic: 0.3%

Powder for injection: 40 mg/mL

Solution, ophthalmic: 0.3%

Clindamycin (Cleocin, Cleocin T)

Capsule: 75 mg, 150 mg, 300 mg

Gel, topical: 1% [10 mg/g]

Granules for oral solution: 75 mg/5 mL

Injection: 150 mg/mL

Lotion: 1% [10 mg/mL]

Solution, topical: 1% [10 mg/mL]

Cycloserine (Seromycin) - RESERVE USE

Capsule: 250mg

Linezolid (Zyvox)

Suspension: 100 mg/5ml

Tablet: 600 mg

Metronidazole (Flagyl, Noritate, MetroGel)

Capsule: 375 mg

Cream, topical: 0.75%, 1%

Gel, topical: 0.75% [7.5 mg/mL]

Gel, vaginal: 0.75%

Injection: 5 mg/mL

Powder for injection: 500 mg

Tablet: 250 mg, 500 mg

Trimethoprim/Sulfamethoxazole (Co-Trimoxazole, Bactrim, Septra)

The 5:1 ratio of Sulfamethoxazole (SMX) to Trimethoprim (TMP) is constant in all dosage forms

Injection: 80 mg SMX/16 mg TMP per mL

Suspension, oral: 200 mg SMX/40 mg TMP per 5 mL

Tablet: 400 mg SMX/80 mg TMP, 800 mg SMX/160 mg TMP

Vancomycin (Vancocin)

Capsule: 125 mg, 250 mg

Powder for oral solution: 1 g, 10 g

Powder for injection: 500 mg, 1 g, 2 g, 5 g, 10 g

Fluconazole (Diflucan)

Tablet: 100 mg, 150 mg, 200 mg, 250 mg, 500 mg

Griseofulvin (Fulvicin)

Microsize:

Capsule: 125 mg, 250 mg

Suspension, oral: 125 mg/5 mL with 0.2% alcohol

Tablet: 250 mg, 500 mg

Ultramicronize:

Tablet: 125 mg, 165 mg, 250 mg, 330 mg

Ketoconazole (Nizoral)

Cream, topical: 2%

Shampoo: 2%

Tablet: 200 mg

Nystatin (Mycostatin)

Cream, topical: 100,000 units/g

Ointment, topical: 100,000 units/g

Powder for oral suspension: 50 million units, 1 billion units, 2 billion units, 5 billion units

Powder, topical: 100,000 units/g

Suspension, oral: 100,000 units/mL

Tablet, oral: 500,000 units

Troche: 200,000 units

Terbinafine (Lamisil)

Cream, topical: 1%

Tablet: 250 mg

Chloroquine (Aralen)

Tablet: 250 mg, 500 mg

Cycloserine (Seromycin) - RESERVE USE

Capsule: 250mg

Ethambutol (Myambutol)

Tablet: 100 mg, 400 mg

Ethionamide

Tablet, sugar coated: 250 mg

Isoniazid (INH)

Injection: 100 mg/mL

Syrup: 50 mg/5 mL

Tablet: 50 mg, 100 mg, 300 mg

Pyrazinamide

Tablet: 500 mg

Rifabutin (Mycobutin)

Capsule: 150 mg

Rifampin (Rifadin)

Capsule: 150 mg, 300 mg

Injection: 600 mg

Rifampin/Isoniazid (Rifamate)

Capsule: Rifampin 300 mg/Isoniazid 150 mg

Acyclovir (Zovirax)

Capsule: 200 mg

Cream: 0.5%

Powder for injection: 500 mg, 1000 mg

Ointment, topical 5% [50 mg/g]: 3 gm, 15 gm

Suspension, oral: 200 mg/5 mL

Tablet: 400 mg, 800 mg

Amantadine (Symmetrel)

Capsule: 100 mg

Syrup: 50 mg/5 mL

Oseltamivir (Tamiflu)

Capsule: 75 mg

Valacyclovir (Valtrex)

Caplets: 500 mg, 1 g

Zanamivir (Relenza)

Powder for Inhalation: 5 mg

Ivermectin (Stromectol)

Tablet: 3 mg

Mebendazole (Vermox)

Tablet, chewable: 100 mg

Pyrantel (Antiminth)

Capsule: 180 mg

Liquid, oral: 50 mg/mL

Suspension, oral: 50 mg/mL

Thiabendazole (Mintezol)

Suspension, oral: 500 mg/5 mL

Tablet, chewable: 500 mg

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/mL

Pentamidine (Pentam) - RESERVE USE

Inhalation: 300 mg

Powder for injection: 300 mg

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

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

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

Date: 9/27/12

Name of practitioner submitting the application: Dr. Bayliss

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)):
Austin State Hospital

Information regarding new drug:

Therapeutic Classification	Dietary Supplement/Sedative
Generic Name	Melatonin
Trade Name(s)	Varrious
Manufacturer(s)	Nature's Bounty, Major, and others
Dosage Form(s)	1 mg and 3 mg tablets

Explain the pharmacological action or use of this drug: Melatonin is a natural product used for insomnia to decrease time to sleep onset and for disturbances in sleep-wake cycle due to shift work, jet lag or other causes

Explain the advantages of this drug over those listed in the formulary: This is not a controlled substance and is relatively inexpensive and likely the most well studied medication for insomnia in the child and adolescent population

State which drugs this new drug would replace or supplement: Possibly benzodiazepines, nonbenzodiazepine sedative hypnotics, chloral hydrate, diphenhydramine, or other sedative agents used for insomnia

application is approved


signature of chairman of facility pharmacy and therapeutics committee

OR

application is appropriate and complete

signature of clinical/medical director or designee

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION

(for inclusion in the DSHS/DADS Drug Formulary)

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

Date: 7/19/12

Name of practitioner submitting the application: Dr. Bayliss

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)):
Austin State Hospital

Information regarding new drug:

Therapeutic Classification	Stimulant
Generic Name	lisdexamfetamine dimesylate
Trade Name(s)	Vyvanse
Manufacturer(s)	Shire
Dosage Form(s)	Capsules

Explain the pharmacological action or use of this drug: Stimulant for ADHD

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

product, Adderall (MAS) shortages and more patients being admitted on this product

State which drugs this new drug would replace or supplement:

Adderall (mixed amphetamine salts)

application is approved

OR

application is appropriate and complete

J Bayliss, MD
signature of chairman of facility pharmacy and therapeutics committee

signature of clinical/medical director or designee

Citalopram labeling changes regarding QTc prolongation

QT-Prolongation and Torsade de Pointes

Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which have been observed in postmarketing reports for citalopram.

Individually corrected QTc (QTcNi) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (upper bound of the 95% one-sided confidence interval) difference from placebo were 8.5 (10.8) and 18.5 (21.0) msec for 20 mg and 60 mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNi change from placebo (upper bound of the 95% one-sided confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) msec.

Because of the risk of QTc prolongation at higher citalopram doses, **it is recommended that citalopram should not be given at doses above 40 mg/day.**

It is recommended that **citalopram should not be used in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure.** Citalopram should also not be used in patients who are taking other drugs that prolong the QTc interval. Such drugs include Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

The citalopram dose should be limited in certain populations. **The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor,** since higher citalopram exposures would be expected. **The maximum dose should also be limited to 20 mg/day in patients with hepatic impairment and in patients who are greater than 60 years of age** because of expected higher exposures.

Electrolyte and/or ECG monitoring is recommended in certain circumstances. **Patients being considered for citalopram treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring.** Hypokalemia (and/or hypomagnesemia) may increase the risk of QTc prolongation and arrhythmia, and should be corrected prior to initiation of treatment and periodically monitored. **ECG monitoring is recommended in patients for whom citalopram use is not recommended (see above), but, nevertheless, considered essential. These include those patients with the cardiac conditions noted above, and those taking other drugs that may prolong the QTc interval.**

Citalopram should be discontinued in patients who are found to have persistent QTc measurements >500 ms. If patients taking citalopram experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

Data behind the labeling change (<http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm>)

The FDA evaluated results of thorough QTc studies, assessing the effects of doses of citalopram and its active S-isomer escitalopram (Lexapro), on the QTc interval in adults. Both studies were randomized, double-blind, placebo-controlled, crossover studies. In the citalopram study, 119 subjects received citalopram 20 mg/day and 60 mg/day, moxifloxacin 400 mg/day, and placebo. In the escitalopram study, 113 subjects received escitalopram 10 mg/day and 30 mg/day, moxifloxacin 400 mg/day, and placebo.

Table 1: Citalopram and Escitalopram: Dose-dependent Change in Corrected QT Interval (QTc)

Citalopram		Escitalopram	
Dose	Change in QTc (90% Confidence Interval) (ms)	Dose	Change in QTc (90% Confidence Interval) (ms)
20 mg	8.5 (6.2, 10.8)	10 mg	4.5 (2.5, 6.4)
40 mg*	12.6 (10.9, 14.3)	20 mg*	6.6 (5.3, 7.9)
60 mg	18.5 (16.0, 21.0)	30 mg	10.7 (8.7, 12.7)
Moxifloxacin 400 mg	13.4 (10.9, 15.9)	Moxifloxacin 400 mg	9.0 (7.3, 10.8)

* Estimate based on the relationship between citalopram (and escitalopram) blood concentrations and QTc interval

No explanation as to why active control moxifloxacin 400 mg had QTc 4.4 msec higher in citalopram study vs. escitalopram study.

Didesmethylcitalopram (DDCT) and potential clinical implications

- Minor metabolite produced through CYP2D6 metabolism of major metabolite; <10% of steady-state citalopram metabolites in humans.
- Considered cardiotoxic and is theorized to be of concern in humans as its total amount increases (i.e. in overdose).
- Of 12 published case reports of citalopram and QTc prolongation, 9 of the 12 involved citalopram overdose. Of the 3 case reports not involving overdose, 1 patient was elderly with ESRD on dialysis, the second had significant hypokalemia electrolyte disturbance on furosemide, and the third was suspected of having LQTS unmasked by citalopram but refused genetic testing (still had mild QTc prolongation after citalopram discontinued).

There are different ways to assess QTc prolongation risk

Clinically significant drug-induced QTc prolongation: < 5 ms not generally associated with increased risk and is generally not of concern, 5-10 ms low risk, 10-20 ms moderate risk, ≥ 20 ms high risk of inducing an arrhythmia and of significant concern.

Other markers of clinically significant concern include QTc >500 msec or prolongation >60 msec over baseline.

Some potential risk factors for QTc prolongation outside of medication may include electrolyte imbalance (primarily K, Mg, and possibly Ca), cardiac disease, elderly, bradycardia, females, anorexia nervosa.

Citalopram Analysis of QTc Safety

ASH Medication Use Evaluation Data (Time frame evaluated 2/1/12-5/1/12)

17/31 patients on citalopram with EKGs (54.8%).

No cases of QTc > 500 msec.

Three cases of QTc > 450 msec; however unable to isolate citalopram as causative factor in any of these cases.

- 1) QTc 463 at baseline for female (QTc up to 470 msec considered wnl for females) with cardiovascular risk factors, and numerous meds with QT prolongation potential; **not taking citalopram at baseline**. No f/u EKG.
- 2) QTc 476 at baseline for female with obesity/on HRT. Taking citalopram 40mg/day prior to admission. No concomitant DDI. No f/u EKG.
- 3) QTc 456 at baseline for male with multiple cardiovascular risk factors (pacemaker, etc.). Taking furosemide only prior to admission. Started on citalopram 20mg/day. EKG done after on citalopram x2 days. No f/u EKG done.

ASH Medication Use Evaluation Follow-up Data (Time frame evaluated 7/20/12-8/20/12)

7/10 patients on citalopram with EKGs (70%). No cases of QTc > 500 msec. No cases of QTc > 450 msec while on citalopram.

- 1) Baseline QTc 449 msec prior to medication start. QTc 439 msec on citalopram 40mg/day + quetiapine 400mg QHS. No known medical comorbidities.
- 2) Baseline QTc 406 msec prior to citalopram start (from a previous admission not on citalopram). EKG on citalopram 30mg/day x7 days, QTc 427 msec. Concomitantly on mirtazapine 15 mg QHS.
- 3) No EKG at baseline. QTc 400 msec on citalopram 40mg/day x7 days. No concomitant drug interactions. Female with cardiovascular risk factors.
- 4) No EKG at baseline. QTc 416 msec on citalopram 20mg/day, 3 days after dose reduction from 40mg/day. Patient concurrently on ziprasidone 140mg/day.
- 5) QTc on citalopram 30mg/day x5 months 447 msec. No baseline for comparison. Concomitantly on lithium 1500mg/day, clozapine 250mg/day, and haloperidol 10mg PO PRNs.
- 6) QTc on citalopram 40mg/day x 8 months 431 msec. No baseline for comparison. Concomitantly on oxcarbazepine 1800mg/day.
- 7) Baseline EKG showed QTc 454 msec, admitted on no psych or QT prolongation potential meds. F/u QTc 426 msec 2 weeks later on citalopram 20mg/day + ziprasidone 80mg/day. Male with cardiovascular risk factors.

ASH Pharmacovigilance Analysis

All FDA medwatch reports filed due to QTc prolongation since 2005 were reevaluated and 6 reports were identified. In two of the six reports, the patient was also taking citalopram, however citalopram was not identified as QT prolonging agent. In one case, the QTc prolongation resolved after quetiapine was discontinued even though citalopram dose had recently been increased. In the second case, the QTc improved with discontinuation of quetiapine, but remained mildly prolonged after a dose increase of citalopram; however, no baseline EKG prior to medication use was available.

- 1) 43 years old female EKG: QTc 437 (10/10/08 – baseline at admission- n/c with outpatient meds) QTc 504 (10/14/08) on quetiapine 700 mg daily, cyclobenzaprine 10 mg three times daily and citalopram 20 mg daily, QTc 418 (10/20/2008) after quetiapine discontinued and citalopram increased to 30 mg daily along with cyclobenzaprine
- 2) 18 year old female EKG: QTc 510 (12/28/09) on quetiapine 600 mg daily, albuterol 2 puffs q 4 hours prn, and citalopram 20 mg daily. QTc 472 (12/31/09) after quetiapine discontinued and citalopram increased to 40 mg daily on 12/30/09.

FDA Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf. 2009 Jun;18(6):512-8

Reports of TdP from January 2004 to December 2007

-1665 reports of TdP with highest for amiodarone (113), methadone (83), levofloxacin (61), fluconazole (48), sotalol (46) and moxifloxacin (41)

-Only 12 cases reported with citalopram which was the most prescribed antidepressant during

this time period. Fluoxetine (12), paroxetine (11) and mirtazapine (10)

Swedish Pharmacovigilance database. *Pharmacoepidemiol Drug Saf.* 2008 Jun;17(6):587-92
Reports of TdP from January 1, 1991-February 1, 2006

-101 reports of TdP with citalopram implicated in 9 cases, 5 cases as sole agent, fluoxetine (2), nortriptyline (1), paroxetine (1)

-85% of the cases had 2 or more risk factors for TdP (heart disease 78, elderly 63, and female 62)

Clinical toxicology of citalopram after acute ingestion. *Ther Drug Monit.* 2008 Jun;30(3):365-71
Includes intentional intoxication of citalopram alone or in combination with other medications from Jan 1997-Dec 2006 from Central Hospital in Hague, Netherlands

-QTc prolongation > 450 msec occurred in 8 of 26 cases with no severe arrhythmias noted including TdP

-Amount of citalopram ingested with elevated QTc interval was 200 mg up to 2700 mg

-One fatality occurred and was with coingestion of verapamil at toxic concentrations

Cardiac safety and prospective and retrospective trial analysis. *J Clin Psychopharmacol.* 1999 Oct;19(5):407-15

Prospective randomized double-blind placebo-controlled study in healthy volunteers, citalopram 60 mg daily (n=12) and placebo (n=11)

-No significant difference in mean QTc between placebo and citalopram at steady state

-No relationship was found between QTc intervals and DCCT plasma levels

Three pooled prospective randomized controlled studies in ill patients with citalopram doses ranging from 10-60 mg

-No difference in proportion of patients with QTc >435 msec

-No relationship found between QTc and citalopram dose used

Retrospective analysis of clinical trials (open, double-blind) from 1978-1996 with citalopram doses ranging from 20-60 mg

-No clinically significant effect on mean QTc was seen. The only clinically significant EKG change was 4-8 bpm reduction in heart rate with citalopram vs. placebo

Antipsychotics and Analysis of QTc Safety

Citalopram labeling indicates citalopram should not be taken with other drugs that prolong the QTc interval, such as antipsychotics, and lists thioridazine and chlorpromazine as specific examples. Although antipsychotics as a class have been implicated in QTc prolongation, not all antipsychotics have been reported to contribute to clinically significant changes in QT interval.

CATIE QT change findings risperidone (+0.2), olanzapine (+1.2), Ziprasidone (+1.3), perphenazine (+1.4), quetiapine (+5.9) (NEJM 2005;353:1209-1223).

In the Pfizer project "054" that compared the QTc prolongation between six antipsychotics, the following medications increased the QTc: haloperidol 4.7 msec < olanzapine 6.4 msec < risperidone 10 msec < quetiapine 14.5 msec < ziprasidone 20.6 msec < thioridazine 35.8 msec. (Psych Quart 2003;74(3):291-306)

Iloperidone may cause QTc prolongation and risk may increase if combined with other QTc prolonging drugs or significant CYP 2D6 or 3A4 inhibitors. The least squares mean changes in QTc using Fridericia's QTc interval correction from baseline to end point were 2.9 msec, 3.9 msec, and 9.1 msec in the iloperidone 4-8 mg/d, 10-16 mg/d, and 20-24 mg/d treatment groups respectively (all significant at p < 0.05).

Clozapine has been implicated in cardiac problems such as cardiomyopathy, but according to a

ranking of relative risk of QTc interval prolongation, clozapine had little or no risk (Primary Care Companion J Clin Psychiatry 2003;5:205-215).

Antipsychotics that have a low potential for causing prolonged QTc interval include asenapine, aripiprazole, and lurasidone.

Asenapine at doses of 5-20 mg bid increased QTc interval from 2 to 5 msec compared to placebo in clinically stable schizophrenia patients (N=151). In a study solely evaluating QTc, no patients on asenapine had QTc increases \geq 60 msec. There is caution to avoid concomitant use with other drugs that prolong the QTc interval or drugs that significantly inhibit CYP 2D6 or 1A2 isoenzymes with asenapine (Asenapine prescribing information).

The labeling for lurasidone indicates no significant prolongation of the QTc interval.

Aripiprazole has not been shown to contribute to significant increases in QTc and some reports indicate slight decreases in QTc interval may be seen. Aripiprazole has not been reported to have clinically significant effects on QT interval and possibly better tolerated in this regard than other antipsychotic agents ([Cochrane Database Syst Rev.](#) 2009 Oct 7;(4):CD006569. [J Emerg Med.](#) 2005 Apr;28(3):311-3).

CYP 2C19 Inhibitors

The labeling notes the maximum citalopram dose should be limited to 20 mg/day in those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor. The only other specific strong CYP 2C19 inhibitor listed in the labeling is omeprazole.

Cimetidine **strong** inhibitor of CYP2C19 - In subjects who had received 21 days of 40 mg/day citalopram, with combined administration of 400 mg/day cimetidine for 8 days, resulted in an increase in citalopram AUC and Cmax of 43% and 39%, respectively.

There are many CYP 2C19 inhibitors that vary in degree of inhibition with little evidence on clinical relevance in this situation. Medications which may inhibit CYP 2C19 (moderate or strong indicated if available) but not mentioned specifically in the labeling include:

-PPIs lansoprazole (moderate), pantoprazole (moderate), rabeprazole (moderate)

-fluoxetine (moderate), fluvoxamine (strong), oxcarbazepine (?), modafinil (strong)

-Ketoconazole **moderate** inhibitor of CYP2C19 and strong inhibitor of CYP 3A4- Combined administration of citalopram (40 mg) and ketoconazole (200 mg) decreased the Cmax and AUC of ketoconazole by 21% and 10%, respectively, and DID NOT significantly affect the pharmacokinetics of citalopram (citalopram product information). *In vitro* studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Clinical relevance of mild CYP 2C19 inhibition (probenecid, topiramate) is unknown; however, if a moderate inhibitor (ketoconazole) failed to significantly affect the PK of citalopram, then the clinical relevance would likely be negligible.

Conclusions:

- 1) Clinically significant QTc prolongation has not been observed with citalopram in our patient population.
- 2) Antipsychotics are commonly prescribed in our patient population and not all antipsychotics have been attributed with clinically significant changes in QTc.
- 3) Not all CYP2C19 inhibitors have clinically relevant drug interactions with citalopram, with most of the evidence with strong inhibitors rather than weak or moderate inhibitors.
- 4) The revised citalopram labeling changes with regard to QTc are likely in excess of what is necessary based on currently available information.