DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
June 12, 2009

The Executive Formulary Committee convened on Friday, June 12, 2009 in Conference Room 240 - CO Building 2. The meeting was called to order by Dr. Matthews, Chair at 9:40 a.m.

Janet Adams, MSN, RN, CNS	Absent	Fred Bibus, M.D. (non-voting)	Absent
Emilie A. Becker, M.D.	√	Nina Muse, M.D. (non-voting)	Absent
Rosha Chadwick, R.Ph.	Absent	Kenny Dudley (non-voting)	Absent
Catherine S. Hall, Pharm.D.	√	Denice Geredine (non-voting)	Absent
Jeanna Heidel, Pharm.D.	√	Mike Maples (non-voting)	Absent
J. Brett Hood, M.D.	√	Bob Burnett (non-voting)	Absent
Jeff Matthews, M.D.	√	Julie McRae, MS, RN, CDDN (non-voting)	Absent
Connie Millhollon, RN,	√	Jay Norwood, MSN, RN (non-voting)	Absent
Victoria Morgan, M.D.	√	Vacant Medical Director	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Bill Race, M.D.	√	Vacant Center Position	
Robert L. Ward, D.O.	√	Vacant Center Position	

Introductions

Dr. Emilie Becker was introduced as the new Medical Director, Behavioral Health and Substance Abuse, effective June 15th.

Approval of Minutes of March 27, 2009

The minutes of the March 27th meeting were modified to reflect the correct date under the title. On a motion of Dr. Heidel, seconded by Dr. Morgan, the minutes of the March 27th meeting were approved as modified.

Adverse Drug Reaction Reports

The Executive Formulary Committee received several adverse drug reaction reports. In the first case, a 48 year old male developed an elevated CPK secondary to aripiprazole (Abilify®). The patient received aripiprazole 15 mg daily from September 7th to September 21st. On September 22nd, the dose was increased to 20 mg daily until January 20th at which time it was increased to 30 mg daily. The aripiprazole was discontinued March 18th. The CPK increased to a peak of 723 IU/L on March 11th. Once the CPK value decreased quetiapine (Seroquel®) was initiated.

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In the second case, a 43 year old male was readmitted on 10/22/08 after being previously discharged on September 30th on olanzapine (Zyprexa®) 40 mg at bedtime, thiothixene (Navane®) 5 mg at bedtime, citalopram (Celexa®) 20 mg in the morning, amitriptyline (Elavil®) 50 mg at bedtime, zolpidem (Ambien®) 10 mg at bedtime as needed, enalapril (Vasotec®) 5 mg in the morning, omeprazole (Prilosec®) 20 mg every morning, atorvastatin (Lipitor®) 10 mg every morning and hydroxyzine (Atarax®) 50 mg three times a day. The patient reported being compliant with his medication regimen since his last discharge. Upon readmission, he reported persistent auditory hallucinations as the reason for his suicidal ideation. Baseline labs were within normal limits except: eosinophils 4.3%, hematocrit 39.8 %, hemoglobin 12.7 g/dl, MCH 21.5 pg/cell, MCV 67.4 fL, HDL 23 mg/dl, triglycerides 338 mg/dl and potassium 5.6 mmol/L. The patient's fasting blood glucose was normal at 89 mg/dl. On this admission, the patient was started on thiothixene 10 mg twice daily, atorvastatin, pantoprazole (Protonix®), multivitamin, benztropine (Cogentin®) prn EPS and diphenhydramine (Benadryl®) prn anxiety, insomnia or itching. On October 24th, the olanzapine was reinitiated at 10 mg twice a day which was increased to 30 mg/day. On November 10th, the patient's fasting blood glucose was 135 mg/dl. Metoprolol (Toprol®) XL, fenofibrate (Tricor®) and haloperidol (Haldol®) were added to his drug regimen. On December 2nd the patient's fasting blood glucose was 166 mg/dl and HgbA1c was 8.5%. After referral to the medical clinic, the patient was started on glyburide (Diabeta®) 2.5 mg every morning on December 4th for suspected new-onset Type 2 diabetes. On December 9th, the glyburide dose was increased to 5 mg due to elevated blood glucose values and pioglitazone (Actos®) was added at 15 mg/day. The pioglitazone was increased to 30 mg/day on December 16th. The patient had an elevated CPK on December 1st of 553 IU/L. The CPK was obtained due to patient complaints of myalgia in his thighs and calves while on statin therapy. The atorvastatin, fenofibrate and haloperidol were discontinued due to the high CPK. On December 27th, the patient's CPK was 743 IU/L. At this time, it was thought that olanzapine was contributing to the elevated CPK. A taper of olanzapine was initiated and it was discontinued on January 4th. On March 10th the CPK remained elevated at 704 IU/L. After the olanzapine was discontinued, the pioglitazone was also discontinued secondary to hypoglycemia. Later the glyburide was also discontinued due to hypoglycemia.

A 54 year old female was admitted on February 6th for the treatment of schizoaffective disorder. Her medical conditions included hypertension, type 2 diabetes, hyperlipidemia and a self-reported history of renal insufficiency and hypothyroidism. Her baseline labs were within normal limits with the exception of: albumin 3.3 g/dl, cholesterol 202 mg/dl, LDL 138 mg/dl, RBC 3.93 M/mm^3, HCT 34.8 % and small leukocyte esterase in urine. The patient was started on court ordered thioridazine (Mellaril®) and haloperidol (Haldol®) decanoate on February 18th. An EKG was ordered on February 26th but the patient refused the EKG until March 16th. The EKG showed a QT of 414 msec and a QTc of 511 msec. The patient's scheduled thioridazine and haloperidol were discontinued after the EKG results were known. The patient had been refusing vital signs but on March 17th the vital signs were: BP 140/88 mm Hg, P 116 bpm, RR 22, T 97.7 ^{o} F. The patient refused a follow up EKG on March 17th. The patient denied any symptoms on March 17th. On March 18th, the patient did have an EKG completed and the QTc was 382 msec. The haloperidol decanoate was restarted but the thioridazine was not.

A 19 year old male was admitted on April 28th. Prior to the admission, the patient had been at a medical hospital receiving treatment for a motor vehicle accident in which he purposely drove his car into a cement wall. The patient was diagnosed with depression and polysubstance abuse (cocaine, THC, benzodiazepines and opiates). The medical conditions from the motor vehicle accident included: resolving pneumothorax, facial lacerations, closed head injury with concussion, right ulnar/radial fracture, acetabulum fracture, right leg trauma, and generalized pain. The patient was prescribed duloxetine (Cymbalta®) 60 mg in the morning, methadone 25 mg in the morning and 30 mg at bedtime, omeprazole 20 mg at bedtime, and promethazine 50 mg at bedtime. On April 29th, the duloxetine was increased to 120 mg daily. On April 30th at 2 pm, the patient was seen in the medical clinic due to an elevated temperature of 103° F. The patient complained of myalgia and bone pain in chest, wrist, and left pelvis. He was given acetaminophen (Tylenol®) and the temperature normalized. Later on April 30th at 9:25 pm, the patient's vitals were temperature 100.8 ^{o} F, P 116 bpm, BP 140/88 mm Hg, pulse ox 72% on room air, RR 14-16 and agonal, temperature 99.7 ^{o} F and blood sugar was 120 mg/dl. The patient's skin was ashen, warm and dry, lips and nail beds were cyanotic. EMS was called and the patient was transferred to a local medical hospital. The patient became more alert after administration of IV naloxone (Narcan®) and fluids. At the medical hospital, the patient was diagnosed as having serotonin syndrome with elevated CPK, elevated transaminases, fever, altered mental status, 3+ reflexes and slight myoclonus. The duloxetine was discontinued and the methadone was reduced to 25 mg twice a day and his mental status cleared and labs normalized. The patient returned to the psychiatric hospital on May 4th and the methadone was reduced to 25 mg in the morning on May 6th and duloxetine was reinitiated at a lower dose

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of 60 mg/day on May 7th. At the time of the adverse drug reaction report (12 days after the duloxetine was restarted), the patient did not have any further complications. The adverse drug reaction report noted that upon chart review it was unlikely that the patient was receiving any methadone prior to admission to the hospital as some of the transfer paperwork indicated. Therefore, the patient received a high dose of methadone (55 mg/day) which likely resulted in opiate toxicity and CNS/respiratory depression. This is further substantiated by the response to naloxone as noted in the nursing note on May 1st. The Committee noted that the patient was also receiving promethazine which could lead to neuroleptic malignant syndrome.

A 29 year old female was admitted for the treatment of pervasive developmental disorder. Her medical conditions included: obesity, diabetes, history of migraines and knee pain. Fluoxetine (Prozac®) 20 mg daily was initiated on March 4th for depression. Two days later on March 6th, a rash was noted on the patient's wrists and hands, so the fluoxetine was discontinued. Diphenhydramine (Benadryl®) was initiated at 50 mg three times a day as needed for rash. The rash resolved after discontinuing the fluoxetine. The fluoxetine was not was not restarted.

A 49 year old African American male was admitted on March 1st for the treatment of schizoaffective disorder. The patient reported that he had been off his home medications of risperidone (Risperdal®) 4 mg at bedtime, trazodone (Desyrel®) 300 mg at bedtime for sleep/depression, and benztropine (Cogentin®) 1 mg twice a day. His baseline labs were within normal limits except for RBC 3.9 M/mm^3, Hgb 12.12 g/dl, Hct 35.6 %, blood glucose 111 mg/dl and LDL 140 mg/dl. His urine drug screen was negative. On March 1st, his home medications were restarted at the same total daily dose; however, the risperidone dose was divided. On March 5th, the patient complained of a possible problem with his penis. Upon examination, it was discovered that the patient had priapism. The patient was sent to a local medical hospital on March 5th for treatment. At the medical hospital, he received calcium channel blocker injections, which were ineffective. He then underwent penile irrigation which was successful. He was returned to the psychiatric facility on March 10th. The medications were restarted upon re-admission to the psychiatric hospital. It was noted that the patient had a diagnosis of sickle cell anemia which may have contributed to this incidence of priapism.

The Committee discussed the ability to separate adverse drug reactions from allergies in CWS so that this medical information can be accurately reported in the medical record. For example, in the case of the olanzapine induced hyperglycemia, the adverse drug reaction would have to be reported as an allergy in order to capture that information. In someone with hyperglycemia secondary to olanzapine, it probably wouldn't eliminate the possibility of using injectable olanzapine as a treatment in a psychiatric emergency. However, if this would be a true allergic reaction, then one would not consider it as a treatment option in patient needing treatment for a psychiatric emergency.

New Drug Applications

(Please refer to <u>Attachment A</u> for the monographs and applications that were considered when determining action by the committee.)

Ondansetron (Zofran®) - presented by Dr. Richards (developed by Regina Tabor and University of Incarnate Word Feik School of Pharmacy Pharm.D. students)

Ondansetron is a selective 5-HT_3 receptor antagonist. The exact mechanism of action has not been fully characterized. However, it is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action in chemotherapy-induced nausea and vomiting is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from enterochromaffin cells of the small intestine. Ondansetron is well absorbed from the gastrointestinal tract. The extent and rate of ondansetron's absorption is greater in women than men. The extent of ondansetron absorption significantly increases (17%) when administered with food. Ondansetron is extensively metabolized by the liver and undergoes some first-pass metabolism. Ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4 (predominant role). Ondansetron elimination may be affected by cytochrome P-450 inducers (i.e. carbamazepine, or phenytoin), but no dosage adjustments for

ondansetron is recommended. Ondansetron is indicated for the prevention of nausea and vomiting associated with highly or moderately emetogenic cancer chemotherapy. It is also indicated for the prevention of nausea and vomiting associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen. In addition, it is indicated for the prevention of postoperative nausea and/or vomiting. Within our system, ondansetron is being used for the treatment of nausea and vomiting associated with the drugs used to treat tuberculosis. Ondansetron is contraindicated for patients known to have hypersensitivity to the drug and should be used with caution in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. Ondansetron is considered a pregnancy category B and it is not known if it is excreted in human breast milk. In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, rifampin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

Following discussion, on motion of Dr. Ward, seconded by Dr. Becker, the request to add ondansetron (Zofran®) in solid oral dosage forms to the formulary was approved. The Formulary Drug Check List was completed.

Guidelines for drug additions/conflict of interest

With the recent changes in PhRMA Guidelines, there has been much discussion in the healthcare field regarding conflict of interest for those individuals that have influence on drug formularies for hospitals and healthcare systems. The American Society of Health-System Pharmacists (ASHP) has published "ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System" and "Principles of a Sound Drug Formulary System" found in the following references:

> Hawkins B, ed. *Best Practices for Hospital & Health-System Pharmacy.* 2006-2007 ed. Bethesda, MD: American Society of Health-System Pharmacists; 2006.
>
> Hawkins B, ed. *Best Practices for Hospital & Health-System Pharmacy.* 2008-2009 ed. Bethesda, MD: American Society of Health-System Pharmacists; 2008.

The "ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System" state the following:

> "Finally, the role of pharmaceutical company representatives and medical science liaisons in a health care organization should be carefully considered. Organizational guidelines should define appropriate relationships and interactions with such individuals. At a minimum, these guidelines should address the provision of pharmaceutical samples, indirect or direct funding support, and educational programming regarding formulary and nonformulary medications. Applications for formulary additions should be initiated and completed independently by the requesting health care provider and not by an industry representative or vendor."
>
> "The P&T committee should use formulary packets and dossiers prepared by pharmaceutical manufacturers with the utmost caution, since the objectivity of these documents may be challenged. The formulary decision-making process should instead be guided by an independent review of evidence published in the biomedical literature, applications of expert opinion, and use of internal data, and benchmarking programs."
>
> "Pharmacoeconomic analyses published in the medical literature or provided in the manufacturer's formulary dossier should be analyzed carefully before being included as part of the review process. Particular attention should be paid to the assumptions made in these studies. In many situations, assumptions made to simplify economic studies are not valid in particular institutions. Institution-specific costs are often different from the costs used in published studies, and local data should be used when incorporating their results into medication reviews."

The "Principles of a Sound Drug Formulary System" states the following:

"Formulary system policies should:

- Require P&T committee members to reveal, by signing a conflict of interest statement, economic and other relationships with pharmaceutical entities that could influence Committee decisions.
- Exclude product sponsor representatives from P&T committee membership and from attending P&T committee meetings.
- Require P&T committee members to adhere to the formulary system's policy on disclosure and participation in discussion as it relates to conflict of interest."

The Committee members discussed their support of developing a policy regarding guidelines on the addition of drugs to the Formulary and on conflict of interest.

On a motion of Dr. Becker, seconded by Dr. Ward, it was recommended that a small work group be formed to develop a policy on guidelines for the addition of drugs to the Formulary and on conflict of interest. Some suggestions for consideration are:

- Having the requestor for a new drug application complete a disclosure statement that will be submitted along with the new drug application
- Having each Executive Formulary Committee member complete a conflict of interest statement
- Recommending that each member of the local pharmacy and therapeutics committee complete a conflict of interest

Dr. Becker, Dr. Matthew, Dr. Morgan and Dr. Richards will serve on the work group.

The Committee discussed whether or not disclosing stock information was necessary and if so, the amount of investment that should be reported. Since a consensus could not be reached, the Committee recommended that the work group address this issue. In the meantime, each Committee member present at the meeting stated that in the last 12 months, they did not receive any money for serving as a speaker for any drug company.

Clonidine (Catapres®), guanfacine (Tenex®) Audit Criteria

At the last meeting, guanfacine was added to the Drug Formulary. Dr. Richards developed the audit criteria for guanfacine. In reviewing it, the Committee recommended some changes. See Attachment B. On the recommendation of Dr. Becker, seconded by Dr. Race, the clonidine and guanfacine audit criteria were approved as modified.

Possible TAC Change

The Committee is still pursuing the option of changing the TAC regarding the requirements for the completion of an evaluation for movement disorders for typical and atypical antipsychotics. At this time, a Work Group has not been formed.

FDA Alerts

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

The FDA notified healthcare providers and patients that insulin pens and insulin cartridges are never to be

shared among patients. Sharing of insulin pens may result in transmission of hepatitis viruses, HIV, or other blood-borne pathogens. Insulin pens are not designed, and are not safe, for one pen to be used for more than one patient. Even if needles are changed between patients because any blood contamination of the pen reservoir could result in transmission of already existing blood-born pathogens from the previous user.
Two prescription topical testosterone gel products, AndroGel® 1% and Testim® 1%, will include a boxed warning on the products' label due to reports of adverse effects in children who were inadvertently exposed to testosterone through contact with another person being treated with these products. Despite the currently labeled precautions, the FDA has received reports of eight cases of secondary exposure to testosterone in children ranging in age from nine months to five years. Since that time, additional reports of secondary exposure have been received by the FDA and are under review. Of the fully reviewed cases, adverse events reported in these children included inappropriate enlargement of the genitalia (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido and aggressive behavior.

Healthcare professionals are being notified of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil (PTU) in adult and pediatric patients. Reports to FDA's Adverse Event Reporting System (AERS) suggest there is an increased risk of hepatotoxicity with propylthiouracil when compared to methimazole. Although both propylthiouracil and methimazole are indicated for the treatment of hyperthyroidism due to Graves' disease, healthcare professionals should carefully consider which drug to initiate in a patient recently diagnosed with Graves' disease. Physicians should closely monitor patients on propylthiouracil therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy.

The FDA strengthened the warnings on human papillomavirus vaccine (Gardasil®) about fainting after receiving reports of "traumatic injuries" among vaccine recipients. All vaccine recipients should remain seated or lying down and be closely observed for 15 minutes following vaccination, to prevent falls and injuries.

Update Formulary Indications

Dr. Morgan requested that the audit criteria indications for the atypical antipsychotics be updated to reflect the current FDA indications for bipolar and depression as appropriate. In order to prevent the continuous challenge of keeping the indications updated, it was recommended that the statement: "Or other FDA approved indications" be added. On a motion of Dr. Ward, seconded by Dr. Becker, this recommendation to change the audit criteria was approved. Dr. Richards will update the audit criteria for review at the next meeting.

Dr. Morgan requested that the indications for valproic acid (Depakene®)/divalproex (Depakote®) and perhaps the other anticyclic medications be updated. Dr. Morgan will complete the necessary research for review at the next meeting.

New Dosage Strengths

The following dosage strengths were recommended to be added to the Formulary:

- Clonazepam (Klonopin®)
  - Oral disintegrating tablets: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg
- Vitamin D
  - Tablet: 2,000 Units
  - Capsule: 2, 000 Units
- Venlafaxine
  - Extended release tablet: 37.5 mg, 75 mg, 150 mg, 225 mg

On a motion of Dr. Ward, seconded by Dr. Race, the recommendation to add these dosage strengths to the Formulary was approved.

Quarterly Non-Formulary Drug Justification Report

In reviewing the third quarter's non-formulary drug purchases, it was noted that all of the facilities had submitted their data. Apparently, there have been fax problems which prevented the reports from being received. The top drugs listed include lansoprazole (Prevacid®) ODT, quetiapine (Seroquel®) XR, cetirizine (Zyrtec®), melatonin, levalbuterol (Xopenex®). The Committee will address the addition of some of the top non-formulary users, such as, cetirizine (Zyrtec®) and levalbuterol (Xopenex®) in the near future. Quetiapine XR is scheduled for presentation at the next meeting.

Drug Formulary Sectional Review- Anti-Parkinson Agents

Dr. Hall provided the review on the anti-Parkinson agents. In her review, she recommended the deletion of the following product:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Biperiden	Akineton	Tablet: 2 mg	None

The biperiden is being recommended for deletion because it is no longer being manufactured. On the motion of Dr. Ward, seconded by Dr. Heidel, the recommendation to delete biperiden from the Formulary was approved.

Dr. Hall recommended that rasagiline (Azilect®) be added to the Formulary.

> Rasagiline is a potent, irreversible and selective inhibitor of brain monoamine oxidase (MAO) type B, which plays a major role in the catabolism of dopamine. Inhibition of dopamine depletion in the striatum reduces the symptomatic motor deficits of Parkinson's disease. There is experimental evidence of rasagiline conferring neuroprotective effects (antioxidant, antiapoptotic); this neuroprotection may delay onset of symptoms and progression of neuronal deterioration. Rasagiline is indicated for initial monotherapy or as an adjunct to levodopa in the treatment of idiopathic Parkinson's disease. For monotherapy, the dose is 1 mg once daily. In adjunctive therapy with levodopa, the initial dose is 0.5 mg once daily; may increase to 1 mg daily based on response and tolerability. When added to levodopa therapy, a dose reduction of levodopa may be required to prevent worsening of dyskinesias. In clinical trials, levodopa doses were typically reduced approximately 9 to 13%. CYP1A2 inhibitors (e.g., amiodarone, ciprofloxacin, fluvoxamine, ketoconazole, norfloxacin, ofloxacin) may increase the levels/effects of rasagiline. Concurrent use of rasagiline in combination with amphetamines, methylphenidate, dextromethorphan, meperidine, methadone, mirtazapine, propoxyphene, tramadol, tricyclic antidepressants may result in serotonin syndrome so these combinations are contraindicated. Concurrent use of rasagiline with an SSRI or SNRI may result in mania or hypertension, so it is generally best to avoid these combinations. Combination of rasagiline with valerian, St. John's wort, SAMe, or kava kava may increase the risk of serotonin syndrome and/or excessive sedation. In addition, one should avoid supplements containing caffeine, tyrosine, tryptophan or phenylalanine as ingestion of large quantities may increase the risk of severe side effects (e.g., hypertensive reactions, serotonin syndrome). CYP1A2 inducers (e.g., aminoglutethimide, carbamazepine, phenobarbital, rifampin) may decrease the levels/effects of rasagiline. Rasagiline may be neuroprotective and it reduces off time in patients with advanced Parkinson's disease who are being treated with levodopa. Rasagiline's efficacy in managing motor fluctuations is comparable to that of entacapone (Comtan®) and the dopamine agonists (pergolide mesylate, pramipexole, and ropinirole hydrochloride). Its advantages are its once daily administration, lack

of need for titration, and lack of psychiatric effects (hallucinations, somnolence, and confusion). A disadvantage is its potential to interact with other psychotropic agents. See attachment C.

On the motion of Dr. Ward, seconded by Dr. Heidel, the recommendation to add rasagiline (Azilect®) to the Formulary was approved. The Formulary Check List was completed.

Sectional Review for Next Meeting

A decision regarding the next sectional review will be made at a later date.

Other Issues

The Committee discussed the need to develop a listing of potential websites that may be helpful for providing patient information to facilitate sharing information and obtaining consent. This would be especially helpful with individuals in DADS facilities where someone else is giving consent. It was recommended that once a list is developed, it could be added as links from our web pages. Each Committee member will attempt to find these sites and share them with other Committee members for their review. At the next meeting, it is hoped that these sites can be reviewed.

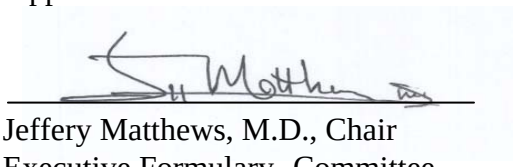
Next Meeting Date

The next meeting was scheduled for September 25, 2009.

Adjourn

There being no further business, the meeting was adjourned at 1:15 p.m.

Approved:



Jeffery Matthews, M.D., Chair
Executive Formulary Committee

Attachments
- Attachment A – New Drug Applications
- Attachment B – clonidine (Catapres®); guanfacine (Tenex®) Audit Criteria
- Attachment C – rasagiline (Azilect®) Monograph

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

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: June 11, 2009

Name of practitioner submitting the application: Ann Richards, Pharm.D., BCPP

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	Antiemetic, Serotonin Receptor Antagonist, F-HT3
Generic Name	Ondansetron
Trade Name(s)	Zofran®
Manufacturer(s)	
Dosage Form(s)	**4 mg, 8 mg tablets** & oral disintegrating tablets, 4 mg/5 ml oral solutions, 4 mg/2 ml injectable

Explain the pharmacological action or use of this drug:

Explain the advantages of this drug over those listed in the formulary:
Currently used at TCID to assist in the nausea caused by the drugs used to treat Tb.

State which drugs this new drug would replace or supplement:
Supplement.
****

☐application is approved

Ann L. Richards
signature of chairman of facility pharmacy and therapeutics committee

OR
☐application is appropriate and complete

signature of clinical/medical director or designee

Clonidine (Catapres®), Guanfacine (Tenex®)

INDICATIONS

1) Attention deficit/hyperactivity disorder

PRECAUTIONS TO CONSIDER

Contraindications

Absolute

1) Hypersensitivity to medication prescribed

Relative

Precautions

1) Avoid abrupt withdrawal (rebound hypertension)
2) Cerebrovascular disease
3) Conduction disturbance (clonidine)
4) Chronic liver disease (guanfacine)
5) Recent myocardial infarction
6) Chronic renal Impairment
7) Sedation
8) Severe coronary insufficiency

Pregnancy and Breast-Feeding

FDA Pregnancy Category B (guanfacine); Category C (clonidine)
Not known if guanfacine is excreted in human breast milk
Clonidine is excreted in human breast milk

Drug Interactions of Major Significance

1) Tricyclic antidepressants
2) Bupropion (maybe increase potential for seizures)
3) Known microsomal enzyme inducer (e.g., phenobarbital, phenytoin)
4) CNS depressants
5) Drugs that affect sinus node function or AV nodal conduction (digitalis, calcium channel blockers, beta blockers) - clonidine

Clonidine (Catapres®), Guanfacine (Tenex®)

PRECAUTIONS TO CONSIDER (continued)

Age-Specific Considerations
Safety and efficacy in pediatric patients under 12 years of age have not been demonstrated

Side Effects Which Require Medical Attention

1) Confusion
2) Depression
3) Difficulty in breathing
4) Extreme dizziness
5) Bradycardia
6) Unusual tiredness or severe weakness
7) Sodium and water retention or edema (clonidine)
8) Raynaud's phenomenon (clonidine)
9) Vivid dreams or nightmares (clonidine)

PATIENT MONITORING

Patient Monitoring Parameters

1) Blood pressure – baseline, then daily for 4 days after initiation or dose increase and as clinically indicated

Dosing

Guanfacine in the treatment of ADHD: Initial doses of 0.5 mg/day with increases of 0.5 mg every 3 to 4 days or 0.25 to 0.5 mg every 5 to 7 days as needed or tolerated
See DSHS/DADS Drug Formulary for dosage guidelines for clonidine
Exceptions to maximum dosage must be justified as per medication rule.

Rasagiline
(*Azilect)*

Classification: Anti-Parkinson's Agent

Pharmacology:

Potent, irreversible and selective inhibitor of brain monoamine oxidase (MAO) type B, which plays a major role in the catabolism of dopamine. Inhibition of dopamine depletion in the striatum reduces the symptomatic motor deficits of Parkinson's disease. There is also experimental evidence of rasagiline conferring neuroprotective effects (antioxidant, antiapoptotic); this neuroprotection may delay onset of symptoms and progression of neuronal deterioration.

Pharmacodynamics/Kinetics:

Onset of action: Therapeutic: within 1 hour

Duration: approx. 1 week (irreversible inhibition); may require approx. 14-40 days for complete restoration of brain MAO-B activity

Absorption: Rapid

Distribution: Vdss: 87 L. protein binding = 88% to 94%

Metabolism: Hepatic N-dealkylation and/or hydroxylation via CYP1A2 to multiple inactive metabolites (nonamphetamine derivatives)

Elimination: Approx. 1.3-3 hours (no correlation with biologic effect due to irreversible inhibition)

Indications:

Initial monotherapy or as an adjunct to levodopa in the treatment of idiopathic Parkinson's disease.

Dosage and Administration:

Monotherapy: 1 mg once daily

Adjunctive therapy with levodopa: Initial: 0.5 mg once daily; may increase to 1 mg once daily based on response and tolerability. When added to levodopa therapy, a dose reduction of levodopa may be required to prevent worsening dyskinesias; in clinical trials, levodopa doses were typically reduced approximately 9% to 13%.

Dose reduction with concomitant ciprofloxacin or other CYP1A2 inhibitors: 0.5 mg once daily.

Dietary Considerations:

Avoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, hearty red wine, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

Contraindications:

Hypersensitivity to rasagiline or any component of the formulation; concomitant use of amphetamine, tramadol, propoxyphene, methadone, dextromethorphan, St John's wort, mirtazapine, cyclobenzaprine, or sympathomimetic amines (eg, pseudoephedrine, ephedrine); use of meperidine or another MAO inhibitor within 14 days of rasagiline; elective surgery requiring general anesthesia, local anesthesia containing sympathomimetic vasoconstrictors; patients with pheochromocytoma.

Warnings/Precautions

Cardiovascular system: Hypertensive crisis may occur with tyramine, tryptophan, or dopamine-containing foods; avoid for at least 2 weeks following discontinuation of rasagiline. May cause orthostatic hypotension, particularly in combination with levodopa; use with caution in patients with hypotension or patients who would not tolerate transient hypotensive episodes (cardiovascular or cerebrovascular disease); orthostasis is usually most problematic during the first 2 months of therapy. Because of the potential for hemodynamic instability, patients should not undergo elective surgery requiring general anesthesia and should avoid local anesthesia containing sympathomimetic vasoconstrictors within 14 days of discontinuing rasagiline. If surgery is required, benzodiazepines, mivacurium, fentanyl, morphine, or codeine may be used cautiously.

Central nervous system: May cause hallucinations; signs of severe CNS toxicity (some fatal) including hyperpyrexia, hyperthermia, rigidity, altered mental status, seizure and coma have been reported with selective and nonselective MAO inhibitor use in combination with antidepressants; Do not use within 5 weeks of fluoxetine discontinuation; do not initiate tricyclic, SSRI or SNRI therapy within 2 weeks of discontinuing rasagiline. Addition to levodopa therapy may result in worsening dyskinesias, requiring a reduction in levodopa dosage.

Dermatologic: Risk of melanoma may be increased with rasagiline, although increased risk has been associated with PD itself; patients should have regular and frequent skin examinations.

Organ dysfunction: Use caution in mild hepatic impairment; dose reduction recommended. Do not use with moderate to severe hepatic impairment.

Safety and efficacy in pediatric patients have not been established.

Adverse Reactions: Unless otherwise noted, the following adverse reactions are as reported for monotherapy. Spectrum of adverse events was generally similar with adjunctive (levodopa)

therapy, though the incidence tended to be higher.
> 10%: CNS: Dyskinesia (18% adjunct therapy), headache (14%)
> 10%: Gastrointestinal: Nausea (10% to 12% adjunct therapy)

1% to 10%:

Cardiovascular: Postural hypotension (6% to 9% adjunct therapy; dose dependent), bundle branch block, angina, chest pain, syncope

Central nervous system: Depression (5%), hallucinations (4% to 5%, adjunct therapy), fever (3%), malaise (2%), vertigo (2%), anxiety, dizziness

Dermatologic: Bruising (2%), alopecia, skin carcinoma, vesiculobullous rash

Endocrine and metabolic: Impotence, libido decreased

Gastrointestinal: Constipation (4% to 9% adjunct therapy), weight loss (2% to 9%, adjunct therapy; dose dependent), dyspepsia (7%), xerostomia (2% to 6% adjunct therapy; dose dependent), gastroenteritis (3%), anorexia, diarrhea, gastrointestinal hemorrhage, vomiting

Genitourinary: Hematuria, urinary incontinence

Hematologic: Leukopenia

Hepatic: Liver function tests increased

Neuromuscular & skeletal: arthralgia (7%), neck pain (2%), arthritis (2%), paresthesia (2%), abnormal gait, hyperkinesias, hypertonia, neuropathy, tremor, weakness

Ocular: conjunctivitis (3%)

Renal: albuminuria

Respiratory: rhinitis (3%), asthma, cough increased

Miscellaneous: Fall (5%), flu-like syndrome (5%), allergic reaction

Monitoring Parameters: Blood pressure; symptoms of parkinsonism; general mood and behavior (increased anxiety, or presence of mania or agitation); skin examination for presence of melanoma (higher incidence in Parkinson's patients—drug causation not established).

Drug Interactions

Cytochrome P450 effect: substrate of CYP1A2 (major)

Increased effect/toxicity: CYP1A2 inhibitors may increase the levels/effects of rasagiline (example inhibitors include amiodarone, ciprofloxacin, fluvoxamine, ketoconazole, norfloxacin,

and ofloxacin). Concurrent use of rasagiline in combination with amphetamines, methylphenidate, dextromethorphan, meperidine, methadone, mirtazapine, propoxyphene, tramadol, tricyclic or tetracyclic antidepressants may result in serotonin syndrome; these combinations are contraindicated. Concurrent use of rasagiline with an SSRI or SNRI may result in mania or hypertension; it is generally best to avoid these combinations.
Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation; avoid supplements containing caffeine, tyrosine, tryptophan or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Decreased effect: CYP1A2 inducers may decrease the levels/effects of rasagiline (example inducers include aminoglutethimide, carbamazepine, phenobarbital, and rifampin).

Cost:

Azilect strength	**AWP price per 30 tabs**	**AWP price per tab**	**Purchase price per 30 tabs**	**Purchase price per tab**
0.5 mg	$343.56	$11.45	$274.85	$9.16
1.0 mg	$343.56	$11.45	$274.85	$9.16

Efficacy:

As monotherapy:

In a delayed-start, multi-center, double-blind, parallel-group clinical trial, 404 subjects with early PD (not requiring dopaminergic therapy) were randomized to one of three treatment groups: (1) rasagiline 1 mg/d for one year (2) rasagiline 2 mg/d for one year or (3) placebo for 6 months followed by rasagiline 2 mg/d for six months. The purpose of the "delayed-start" design was to determine if earlier initiation of rasagiline resulted in better functional status at 12 months, when all participants would have received rasagiline for at least six months and the medication's effect on symptoms would be balanced among groups.

The study's primary outcome was the change in total score from baseline to 12 months on the Unified Parkinson's Disease Rating Scale (UPDRS). Compared to subjects in the "delayed-start" cohort, subjects treated with rasagiline 2 mg/d for one year had a 2.29-unit smaller increase in mean adjusted total UPDRS score ($p = 0.01$). Compared to subjects in the "delayed-start" cohort, subjects treated with rasagiline 1 mg/d for one year had a 1.82-unit smaller increase in mean adjusted total UPDRS score ($p = 0.05$). Rasagiline was well tolerated; during the first six months of the study, adverse events were not more common in subjects receiving rasagiline than in those receiving placebo. The authors concluded that subjects treated for one year had less disease progression than those only treated for six months.

As adjunctive therapy:

PRESTO

The PRESTO study was a 26-week, multi-center, randomized, double-blind, parallel-group trial that evaluated the safety, tolerability, and efficacy of rasagiline (0.5 or 1.0 mg per day) versus placebo in levodopa-treated patients with Parkinson Disease (PD) and motor fluctuations. Inclusion criteria included at least 2 ½ hours of total daily "off" time despite optimized treatment with anti-PD meds.

The primary outcome measure was change from baseline in daily off time (measured by patients' home diaries). During the 26-week study, mean adjusted total daily off time decreased from baseline by 1.85 hours (29%) in individuals treated with 1.0 mg/d of rasagiline, 1.41 hours (23%) in those treated with 0.5 mg/d of rasagiline, and 0.91 hours (15%) in patients treated with placebo. Compared to placebo, patients treated with 1.0 mg/d of rasagiline had 0.94 hours less off time per day while patients treated with 0.5 mg/d of rasagiline had 0.49 hours less off time per day. Patients' daily increase in on-time corresponded to the decrease in off time. In the 0.5 mg/d rasagiline group, all of the increase in on time was without troublesome dyskinesias. In the 1.0 mg/d rasagiline group, 32% of the increase in on time included troublesome dyskinesias. The dyskinesias did not lead to early terminations.

The number of patients discontinuing for any reason was not significantly different between treatment groups. Adverse events were reported in 87% of patients receiving placebo, 91% of patients receiving 0.5 mg/d of rasagiline, and 95% of patients receiving 1.0 mg/d of rasagiline. Adverse events that were significantly more common in patients treated with rasagiline (either dose) than placebo mainly involved the gastrointestinal tract and were dose related.

LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily)

The LARGO study was an 18-week, multi-center, double-blind trial in which 687 outpatients with PD treated with levodopa were randomized to receive adjunctive therapy with either rasagiline 1 mg po qd, entacapone 200 mg with every dose of levodopa, or placebo.

The primary outcome measure was change in total daily off-time (measured by patient diaries). Both rasagiline and entacapone reduced mean total daily off-time from baseline to treatment by more than 1 hour, almost three times more than the reduction with placebo. (-1.18 h rasagiline, -1.2 h entacapone, - 0.4 h placebo; $p = 0.0001$, $p < 0.0001$ respectively for comparisons vs placebo). This effect was evident at the study's first efficacy assessment (week 6) and was sustained throughout the study. The two active treatments also increased daily on-time without troublesome dyskinesia; no change in the duration of on-time with troublesome dyskinesia was recorded.

Frequency of adverse events was similar for all treatments.

Conclusions:

Rasagiline (Azilect) may be neuroprotective and it reduces off time in patients with advanced PD who are being treated with levodopa. Rasagiline's efficacy in managing motor fluctuations is comparable to that of entacapone (Comtan) and the dopamine agonists (pergolide mesylate, pramipexole, and ropinirole hydrochloride). Its advantages are its once-daily administration, lack of need for titration, and lack of psychiatric side effects (hallucinations, somnolence, and confusion). A disadvantage is its potential to interact with other psychotropic agents.

Recommendation:

Rasagiline: recommended for addition to the formulary.

References:

Lacy CF, Armstrong LL, Goldman MP, Lance LL. Lexi-Comp. Drug Information Handbook. 17th edition, 2008-2009.

Pahwa R, Factor SA, Lyons KE, Ondo WG, Gronseth G, Bronte-Stewart H, Hallett M, Miyasaki J, Stevens J, Weiner WJ. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66: 983-995.

Parkinson Study Group. A Controlled, Randomized, Delayed-Start Study of Rasagiline in Early Parkinson Disease. *Arch Neurol*. 2004;61:561-566.

Parkinson Study Group. A Randomized Placebo-Controlled Trial of Rasagiline in Levodopa-Treated Patients with Parkinson Disease and Motor Fluctuations. The *PRESTO* Study. *Arch Neurol.* 2005;62:241-248.

Rascol O, Brooks D J, Melamed E, Oertel W, Poewe W, Stocchi F, Tolosa E, for the *LARGO* study group. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomized, double-blind, parallel-group trial. *Lancet* 2005:365: 947-54.

Suchowersky O, Gronseth G, Perlmutter J, Reich S, Zesiewicz T, Weiner WJ. Practice Parameter: Neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66: 976-982.

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