

DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
February 10, 2006

The Executive Formulary Committee convened on Friday, February 10, 2006 in Room 240 - CO Building 2. The meeting was called to order by Dr. Ward, Interim Chair at 9:40 a.m.

Janet Adams, MSN, RN, CNS	√	Mike Maples	Absent
Rosha Chadwick, R.Ph.	√	Michael Woolsey	Absent
Jeanna Heidel, Pharm.D.	√	Jay Norwood, MSN, RN	Absent
J. Brett Hood, M.D.	Absent	Camille Hemlock, M.D.	Absent
Lisa Mican, Pharm.D.	√	Nina Muse, M.D.	Absent
Connie Millhollon, RN,	√	Steven P. Shon, M.D.	Absent
Victoria B. Morgan, M.D.	√	Vacant Center Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Bernardo C. Tarin-Godoy, M.D.	√	Vacant Center Position	
Robert L. Ward, D.O.	√	Vacant State School Position	
Kenny Dudley	Absent	Vacant DADS Nursing Coordinator	
Scott Schalchlin	Absent		

Guest Present: Sharon Tramonte, Pharm.D., San Antonio State School; Annah Lopez, Pharm.D. student; Quyen Ho, Pharm.D. student

Roll Call, Introductions and Announcements

Dr. Still has resigned from the San Antonio State Hospital. Dr. Lisa Mican, Clinical Pharmacologist at Austin State Hospital has been appointed to the Committee.

Approval of Minutes of October 21, 2005

On a motion of Dr. Tarin-Godoy, seconded by Ms. Millhollon, the minutes of the October 21st meeting were approved as previously distributed.

Adverse Drug Reaction Reports

The Executive Formulary Committee received four adverse drug reaction reports. In the first case, a 22-year-old male had a seizure with the addition of olanzapine (Zyprexa®) to his already established drug regimen of aripiprazole (Abilify®), sertraline (Zoloft®) and propranolol (Inderal®). The seizure occurred less than 72 hours after the addition of the olanzapine and the patient had no pre-existing history of a seizure disorder. The olanzapine was discontinued and a short course of phenytoin (Dilantin®) was added.

In the second case, a 16-year male developed galactorrhea and hypothyroidism. In this case, the patient had a TSH level of 2.83 uIU/ml on admission. The patient was started on risperidone and the dose was increased to 4 mg per day. Venlafaxine (Effexor®) XR was added. The galactorrhea and hypothyroidism (TSH 6.79 uIU/ml) developed. Both the risperidone and venlafaxine were discontinued and aripiprazole, duloxetine (Cymbalta®) and divalproex (Depakote®) were added. A follow up TSH was 2.55 uIU/ml.

A 45-year-old male was on a multivitamin with minerals, trazodone (Desyrel®), valproic acid (Depakene®), ferrous sulfate and risperidone (Risperdal®). The patient was on stable doses of valproic acid and risperidone since 10/31/05 and 11/16/05, respectively. Clozapine (Clozaril®) was added to the regimen. Five liver function tests completed in August, September, October and November were within normal limits. The patient developed a decrease in red blood cells, hemoglobin, hematocrit and sodium beginning in early December. The patient developed an increase in eosinophils starting in mid-December and hypoalbuminemia at the end of December. The patient was sent to a medical hospital on December 27th and was treated for a possible drug-induced hepatotoxicity. On December 31st, the AST was 247 U/L, the ALT was 600 U/L and albumin was 2.8 g/dl. The valproic acid was suspected and this was discontinued. Upon return to the State Hospital, the AST continued to climb to 311 U/L with an ALT of 639 U/L and a direct bilirubin of 0.3 mg/dl. At that time, the clozapine was suspected to be the offending agent and it was discontinued. In mid-January, the AST and ALT began to normalize.

In the last case, a 20-year-old female was on routine doses of lithium carbonate ER and risperidone with prns of nicotine polacrilex (Nicorette®) gum, quetiapine (Seroquel®) and acetaminophen. On January 10th the patient received medroxyprogesterone (Depo-Provera®) intramuscular for contraception. Later that afternoon, the patient developed a low-grade temperature and inflammation at the site. The patient was administered acetaminophen and an antihistamine. The next day, the inflammation and pain increased and prednisone (Deltasone®) was added along with a regularly scheduled ice pack for vasculitis. Labs obtained on January 11th showed a CPK of 8,602 IU/L, serum creatinine of 0.5 mg/dl, WBC 16.8 K/mm³ and an ANC of 14.3 K/mm³. The patient was transported to a local hospital where ceftriaxone (Rocephin®) was administered and the patient was hydrated. The CPK continued to climb and all psychotropics were discontinued. On January 14th, the CPK decreased to 8,488 IU/L with a serum creatinine of 0.6 mg/dl. The CPK and WBC continued to decrease and the patient complained of no other symptoms except for the localized reaction from the medroxyprogesterone. On January 20th, psychotropic medications were restarted.

Duloxetine (Cymbalta®) Audit Criteria/Audit Checklist

Dr. Mican presented the duloxetine audit criteria. This is an original document as this was recently added to the Formulary. The audit criteria was modified as followed:

- Under Contraindications – Use of monoamine oxidase inhibitor within 14 days
- Under Patient Monitoring Parameters – change hepatic function panel to hepatic function testing
- Under Dosing – change TDMHMR Drug Formulary to DSHS/DADS Drug Formulary

On a motion of Dr. Tarin-Godoy, seconded by Ms. Millhollon, the duloxetine audit criteria were approved as modified.

On a motion of Dr. Morgan, seconded by Dr. Heidel, it was recommended that all drug audit criteria be changed from hepatic function panel to hepatic function testing and TDMHMR Drug Formulary to DSHS/DADS Drug

Formulary.

In reviewing the SSRI audit criteria, it was decided that monitoring for suicidality should be included for all antidepressants. On a motion of Dr. Heidel, seconded by Dr. Tarin-Godoy the recommendation that the statement “Monitor for emergence of suicidal ideation or behavior” be added to all antidepressant audit criteria as a monitoring parameter.

FDA Alerts

The FDA has issued numerous alerts in the past several months.

Clozapine (Clozaril®), including generic versions made the following changes for the monitoring frequency:

- Requirement that the absolute neutrophil count (ANC) be determined and reported along with each WBC count.
- New parameters for initiation of treatment: $WBC \geq 3500/mm^3$ and $ANC \geq 2000/mm^3$.
- Initiation of monthly monitoring schedule after one year (six months weekly, six months every two weeks) of WBC counts and ANCs in the normal range ($WBC \geq 3500/mm^3$ and $ANC \geq 2000/mm^3$).
- Addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine following recovery from an initial episode of moderate leukopenia ($3000/mm^3 > WBC \geq 2000/mm^3$ and/or $1500/mm^3 > ANC \geq 1000/mm^3$). After recovering from such an episode, these patients are now required to undergo weekly monitoring for 12 months if they are re-challenged.

Additional changes in the package insert for clozapine include:

- A boxed warning about an increased risk of mortality in elderly patients with a dementia-related psychosis.
- The addition of paralytic ileus as a contraindication.
- The addition of reports of hypercholesterolemia and/or hypertriglyceridemia to the Adverse Reactions section
- The addition of citalopram (Celexa®) to the Precaution section as concomitant use of clozapine and citalopram results in clinically significant elevation of clozapine blood levels.

The FDA has concluded that the overall risk of liver toxicity from pemoline (Cylert®) and generic pemoline products outweighs the benefits of this drug. All manufacturers of pemoline have agreed to stop sales and marketing. The product is being withdrawn from the market. It is recommended that healthcare professionals who prescribe pemoline should transition their patients to an alternative therapy. Pemoline will remain available through pharmacies and wholesalers until supplies are exhausted; no additional product will be available.

Pimecrolimus (Elidel®) cream and tacrolimus (Protopic®) ointment have added a box warning about a possible risk of cancer and a Medication guide (FDA-approved patient labeling). The new labeling clarifies that these drugs are recommended for use as second-line treatments. This means that other prescription topical medicines should be tried first.

Paroxetine (Paxil®, Paxil CR®) have changed their pregnancy category from Category C to Category D. Category D is indicative of positive evidence of human fetal risk. The manufacturer recommended the following:

- If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant in these cases.
- If paroxetine is discontinued, one should refer to the Discontinuation of Treatment section in the package insert.
- For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

GlaxoSmithKline has issued a warning regarding a new onset and worsening diabetic macular edema for patients receiving rosiglitazone (Avandia® or Avandamet®). In the majority of these cases, the patients also reported concurrent peripheral edema. In some cases, the macular edema resolved or improved following discontinuation of therapy and in one case, macular edema resolved after dose reduction.

Bristol-Myers Squibb issued a warning that anyone handling bottles of hydroxyurea (Hydrea®, Droxia®) capsules must wear “impervious gloves” to minimize the risk of serious skin reactions. It was reported that gangrene, ulcerations, and other skin toxicities have occurred in patients taking hydroxyurea to treat myeloproliferative disorder. To decrease patients’ and health care workers’ risk of dermal exposure to the cytotoxic agent, instructions have been added to the labeling. In these instructions, healthcare workers are told to wear gloves whenever handling bottles of hydroxyurea capsules, whether in clinical settings, pharmacies, storerooms, or home health care settings and even when unpacking, inspecting, or transporting the bottles. Gloves must be worn when preparing or administering hydroxyurea doses. Similar instructions apply to patients and anyone else who may handle a bottle or dose of hydroxyurea. However, no where in the instructions does the company describe the gloves beyond the fact that they have to be impervious to hydroxyurea.

The FDA is changing the requirements for the package insert. The new look will make prescribing information easier to read and help healthcare professionals find the information they need more easily and quickly. The FDA’s electronic health initiative will make updated prescribing information available on the Internet, creating an even faster and more efficient way for health professionals to have current prescribing information. The new prescribing information requirements apply to:

- Prescription drugs, including those that were approved on or after the effective date of the final rule
- Drugs that have been approved in the 5 years before the effective date of the rule
- Older drugs for which there is a major change in the prescribing information (e.g., approval of a new use).

Through the implementation of the DailyMed, the FDA and the National Library of Medicine have begun to disseminate (via <http://dailymed.nlm.nih.gov>) up-to-date and comprehensive medication information for use with information systems that support patient care. The DailyMed will make current information about FDA-regulated products readily available, free of charge, to physicians, other healthcare professionals, and patients.

Clozapine Medication Audit Criteria/Audit Checklist

Dr. Mican presented the revised medication Audit Criteria for clozapine. The following changes were recommended:

- Added to Indications: Reduction in the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder

- Added to Absolute Contraindications: Uncontrolled epilepsy; Severe CNS depression; Paralytic ileus; concomitant use of agents that may cause bone marrow suppression, including carbamazepine (Tegretol®, Carbatrol®, Equetro®) (note: carbamazepine issue was moved from relative to absolute contraindication)
- Added to Relative Contraindications: History of seizure; Diabetes Mellitus
- Deleted from Precautions: diabetes mellitus, history of neuroleptic malignant disorder, diagnosis of seizure disorder
- Added to Drug Interactions of Major Significance: Concomitant use of agents that cause bone marrow suppression
- Added to Side Effects Which Require medical Attention: Hypercholesterolemia or hypertriglyceridemia
- Change TDMHMR Drug Formulary to DSHS/DADS Drug Formulary

On a motion of Dr. Heidel, seconded the Dr. Tarin-Godoy, the recommendation to approve the clozapine medication audit criteria as revised was approved. The information will be distributed to the field.

Medicare D

An update on Medicare Part D was provided. Medicare Part D went into effect on January 1, 2006. Currently, the facilities are not submitting claims. The Pharmacy software system (WORx) is scheduled to be updated to the on-line adjudication version at the end of February. A switch company is needed in order to complete the on-line adjudication process. A contract for one switch company has been signed. The switch company will need to be set up so that the communication will work with WORx. Once this is established, the claims process can be tested. Dr. Heidel is testing the upgraded version of WORx. In addition, she has completed a significant amount of research into the Medicare Part D Program. Dr. Heidel reported that even though the plans are required to contain all or almost all of the psychotropic medications, the plans still could enforce prior authorization, quantity limits and step therapy. CMS is now requiring plans to pay for drugs not on their formularies through the end of March. Dr. Tramonte has spent a significant amount of time researching the plans' drug formularies and has developed tables of specific drug categories.

Non-Formulary Drug Justification Report

The Quarterly Non-Formulary Drug Justification Report was reviewed by facility, generic name and unit cost. It was noted that many of the reports do not contain the unit cost. It appears that many of the facilities are still not reporting non-formulary requests. Since all facilities are now on the new Pharmacy software, it might be possible to pull a report of individuals on these medications.

New Drug Applications

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

flurazepam (Dalmane®) - discussed by Dr. Mican

Flurazepam is a long-acting benzodiazepine, thought to exert its action by binding to the GABA-A Receptor-Benzodiazepine Receptor-Chloride Ion Channel Complex, which increases the affinity of the receptor for GABA. It is indicated for use as a hypnotic agent for the treatment of short-term/transient insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Flurazepam has not been shown to be superior to other benzodiazepines currently available for the treatment of insomnia. Other long-acting benzodiazepines are already available on the Formulary. These include chlordiazepoxide, clonazepam, clorazepate, and diazepam. Concerns regarding the use of flurazepam include the risk of accumulation and toxicity in patients

with hepatic or renal impairment, the elderly, and those receiving concomitant medications that inhibit CYP 3A4.

Following discussion, on motion of Dr. Mican, seconded by Dr. Tarin-Godoy, the request to add flurazepam (Dalmane®) to the formulary was denied.

carisoprodol (Soma®) - discussed by Dr. Mican

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. Carisoprodol does not directly relax tense skeletal muscles in man. The mode of action has not been clearly identified in humans but may be related to its sedative properties. Carisoprodol is indicated for the discomfort associated with acute, painful musculoskeletal conditions. It should be used as an adjunct to rest and physical therapy. There are other muscle relaxants including diazepam (Valium®) and methocarbamol (Robaxin®) currently on Formulary.

Following discussion, on motion of Dr. Tarin-Godoy, seconded by Dr. Ward, the request to add carisoprodol (Soma®) to the formulary was denied.

bupropion XL (Wellbutrin XL®) - discussed by Dr. Mican

Bupropion is a weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the exact mechanism of action of bupropion for the treatment of depression is unknown, the primary mechanism is thought to be secondary to norepinephrine and dopamine reuptake inhibition. It is indicated for the treatment of major depressive disorder. Bupropion XL exhibits bioequivalence with regard to AUC and C_{max} to immediate and sustained release formulations of bupropion. Currently, it is unknown whether the XL formulation provides improved tolerability or efficacy compared to the other formulations. Once daily dosing of bupropion XL may be beneficial in patients with difficulty adhering to BID or TID dosing with the sustained release and immediate release formulations. Bupropion XL is not available as a generic and is more expensive than the immediate (approximately five times more expensive) and sustained-release (approximately two times as expensive).

Following discussion, on motion of Dr. Mican, seconded by Dr. Tarin-Godoy, the request to add bupropion XL (Wellbutrin XL®) to the formulary was denied.

valsartan (Diovan®) - discussed by Dr. Mican

Valsartan produces direct antagonism of the angiotensin II (AT₂) receptors. It displaces angiotensin II from the AT₁ receptor and produces its blood pressure lowering effects by antagonizing AT₁-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertropic responses. It is indicated for monotherapy or in combination with other antihypertensive agents for the treatment of essential hypertension; treatment of heart failure in patients intolerant to angiotensin converting enzyme (ACE) inhibitors; to reduce cardiovascular mortality in clinically stable patients with ventricular failure or left ventricular dysfunction following myocardial infarction.

Following discussion, on motion of Dr. Heidel, seconded by Dr. Morgan, the request to add valsartan (Diovan®) to the formulary was approved. The Formulary CheckList was completed.

Angiotensin II Receptor Antagonists/Blockers (ARBs) Review

Dr. Tramonte presented a class review on the ARBs. The ARBs include candesartan (Atacand®), esprosartan (Teveten®), irbesartan (Avapro®), losartan (Cozaar®), olmesartan (Benicar®), telmisartan (Micardis®), and valsartan (Diovan®). All of the ARBs have a FDA indication for the treatment of hypertension. Irbesartan and losartan have a FDA indication for nephropathy in the treatment of diabetes mellitus Type 2, valsartan has an indication in heart failure and losartan has an indication for the treatment of hypertension with left ventricular

hypertrophy. The ARBs are classified based on their AT₁-blocking capacity into two categories: insurmountable and surmountable. Insurmountable antagonism indicates suppression of agonist response despite escalations of dose. The reverse holds true for surmountable antagonism. Candesartan, valsartan and telmisartan are insurmountable AT₁ receptor antagonists. Esprosartan and losartan exert surmountable antagonism of the AT₁ receptor. Data on the antagonistic binding of irbesartan and EXP-3174, the active metabolite of losartan, appear to be less conclusive. Whether insurmountable antagonism provides superior protection from angiotensin II is not known. ARBs vary in their ability to antagonize subtype-1 receptors. Candesartan, irbesartan and telmisartan block AT-II receptors more effectively than losartan or valsartan, but the clinical significance of this has not been established. No ARB requires adjustment in patients with renal impairment. However, losartan requires an adjustment in those with hepatic impairment. The cost of the ARBs range from the cheapest olmesartan (low dose - \$1.30 to high dose - \$1.46) to the most expensive valsartan (low dose \$1.54 to high dose - \$3.31). When compared to ACE inhibitors, the ARBs demonstrated fewer adverse reactions. In recent database reviews of the medical records of more than 56,000 patients followed for 1 to 4.5 years, the rate of patient persistence with antihypertensive therapy was significantly higher with ARBS than with any other class of antihypertensives, including the ACE inhibitors, calcium antagonists, diuretics and beta blockers. Although the JNC-7 report suggests ARBs be considered as first-line therapy, these agents are currently used most often as second-line alternatives for patients, such as those with heart failure or diabetes, who would benefit from an ACE inhibitor but who suffers from an ACE-induced cough. The major drawback of ARBs is their cost. See Attachment B.

The Committee recommended adding another ARB to the Formulary. Based on cost, on a motion by Dr. Heidel, seconded by Dr. Morgan, it was recommended to add olmesartan to the Formulary. A Formulary CheckList will be completed.

Based on the expense of the ARBs, on a motion of Dr. Heidel, seconded by Dr. Tarin-Godoy, it was recommended that the ARBs (valsartan and olmesartan) be in the reserve category. The criteria for the use of the ARBs will be: Prior failure to ACE inhibitor therapy due to intolerable side effects.

Review of Dementia Agents Purchases

Dr. Tramonte presented the information on the purchases of the dementia agents for 2005. San Angelo State School (30% of purchases) had the most purchases based on dollar amount, followed by Wichita Falls (16% of purchases) component of North Texas State Hospital, San Antonio State Hospital/State School (11% of purchases) and Austin State School (7% of purchases).

Proposed Drug Deletion List -

Infectious Disease Agents

The Committee did not receive any comments from the field about the proposed deletions for the infectious disease agents. On a motion of Dr. Tarin-Godoy, seconded by Dr. Morgan, the motion to delete these agents was approved.

Drug Formulary Sectional Review-

Gastrointestinal Agents Genitourinary Agents

The sectional review was not completed. It will be presented at the next meeting.

Psychoactive Consent List

Dr. Richards presented the psychoactive consent lists. The Committee recommended the following changes to the current psychoactive consent list:

- Add Fazacllo® as a trade name for clozapine

- Add isocarboxazid (Marplan®) to the monoamine oxidase inhibitors
- Add eszopiclone (Lunesta®) - nonformulary to the anxiolytics/sedatives/hypnotics
- Add Atarax® as a trade name for hydroxyzine
- Add Equetro® as a trade name for carbamazepine
- Delete verapamil (Calan®, Isoptin®) from mood stabilizers
- Delete pemoline (Cylert®) from stimulants
- Add gabapentin (Neurontin®) to miscellaneous drugs

On a motion of Dr. Tarin-Godoy, seconded by Dr. Mican the psychoactive consent list was approved as modified.

Divalproex (Depakote®) ER

It was noted that divalproex ER has received FDA approval for a bipolar indication. Based on this, on a motion of Dr. Heidel, seconded by Ms. Millhollon, it was recommended that divalproex ER be removed from the Reserve Section of the Drug Formulary.

Next Meeting Date

The next meeting was scheduled for April 7, 2006.

Adjourn

There being no further business, the meeting was adjourned at 1:35 p.m.



Approved: _____
Robert Ward, D.O., Interim Chairman

Attachments

Attachment A – New Drug Applications

Attachment B – Angiotensin II Receptor Antagonists/Blockers (ARBs) Review

Minutes Prepared by:

Ann L. Richards, Pharm.D.

Rosha Chadwick