NOTE: Amended version (section 7A, table 2: Prime Vendor Cost for Transdermal Estrogen Systems - Average Monthly Cost for Estraderm corrected from $7.84 to $15.68) approved by the DoD P&T Executive Council at their regularly scheduled meeting, 5 August 2003.

Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **6 May 2003**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1500 hours on 6 May 2003 at the DoD Pharmacoeconomic Center, Fort Sam Houston, Texas.

2. VOTING MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
COL Joel Schmidt, MC	Army
COL Doreen Lounsbery, MC	Army
MAJ Travis Watson, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (For COL Bill Sykora, MC)	Air Force
LtCol Ed Zastawny, BSC (For LtCol George Jones, BSC)	Air Force
CDR (sel) Debra Arsenault, MC (For CAPT Matt Nutaitis, MC)	Navy
CDR Mark Richerson, MSC	Navy
CAPT Robert Rist	Coast Guard
Mike Valentino	Department of Veterans Affairs

VOTING MEMBERS ABSENT

None	

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC (via VTC)	Navy Pharmacy Specialty Leader
COL Mike Heath, MS (via VTC)	Army Pharmacy Consultant Chair, DoD Pharmacy Board of Directors
COL Ardis Meier, BSC (via VTC)	Air Force Pharmacy Consultant
MAJ John Howe, BSC	Defense Supply Center Philadelphia
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LTC Don DeGroff, MS	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
CDR (sel) Ted Briski, MSC	DoD Pharmacoeconomic Center
LtCol Dave Bennett, BSC	DoD Pharmacoeconomic Center
LtCol Barb Roach, MC	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
MAJ Mike Terry, BSC	TRICARE Southwest
Mark Geraci	Department of Veterans Affairs, PBM
LTC Marc Caouette, MS	Joint Readiness Clinical Advisory Board

3. REVIEW MINUTES OF LAST MEETING

The Council approved the minutes of the last meeting with a correction in the last sentence of the fourth paragraph in section 9A:

- Incorrect sentence: MTFs are currently spending nearly $100,000 per month on cholinesterase inhibitors.
- Corrected sentence: MTFs are currently spending nearly $326,000 per month on cholinesterase inhibitors.

4. ADMINISTRATIVE ISSUES

None

5. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENT (BPA) AWARD, RENEWALS AND TERMINATIONS

A. The next option years were exercised for the following contracts: oral contraceptives, ticlopidine, valproic acid, nicotine patches, insulin syringes, isosorbide mononitrate, and capsaicin cream.

B. Proposals are being evaluated for the awarding of contracts to procure a sole source of isosorbide dinitrate, tramadol, ketoconazole cream, midazolam, and pamidronate injection.

C. DoD accepted an incentive agreement for methylphenidate (Concerta) that will reduce the price below FSS if performance incentives are met by the government.

6. PROCUREMENT INITIATIVES

A. *Ophthalmic Prostaglandins* – The Council had previously authorized the addition of an ophthalmic prostaglandin to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contracting strategy competing latanoprost, bimatoprost and travoprost, which would not require patients to be switched from one agent to another. The Federal Pharmacy Executive Steering Committee's (FPESC) subcommittee for contracting determined that a joint DoD/VA closed class contract would not meet the needs of both agencies. Each agency will pursue its own procurement strategy.

B. *Second Generation Antihistamines* –The availability of loratadine to MTFs at $0.38 per dose compared to fexofenadine at $0.60 per dose under a joint DoD/VA contract precipitated the decision to not renew the next option year of the fexofenadine contract. Although fexofenadine currently remains on the BCF, the termination of the fexofenadine contract allows MTFs to have additional non-sedating antihistamines on their formularies. Since loratadine is significantly less expensive than all other second generation antihistamines, MTFs are encouraged to add loratadine to their formularies and maximize the use of loratadine consistent with the clinical needs of patients. [Note: The Council could not add loratadine to the BCF because over-the-counter (OTC) products are generally not allowed on the BCF.]

C. *Thiazolidinediones (TZDs, "Glitazones")* – The Council had previously authorized the addition of a single thiazolidinedione to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contracting strategy competing rosiglitazone and pioglitazone. The contracting subcommittee of the Federal Pharmacy Executive Steering Committee is evaluating which procurement strategy would be the most cost-effective and meet each agency's requirements.

D. *Oral Fluoroquinolones* – The Council previously voted to support a joint DoD/VA contract for a "workhorse" fluoroquinolone that would compete levofloxacin and gatifloxacin. Two changes have occurred since that time:

   1) Ortho McNeil raised the price of levofloxacin by almost 40% effective 1 May 2003, and then repealed the price increase. Levofloxacin has been the only oral fluoroquinolone on the BCF for the past several years.

   2) Moxifloxacin recently gained FDA approval for treatment of community acquired pneumonia (CAP).

   The Council reviewed the most current clinical data including efficacy and safety/tolerability of levofloxacin, gatifloxacin and moxifloxacin.

   Efficacy – CAP and urinary tract infections (UTIs) are the primary indications for which fluoroquinolones are currently used. Gatifloxacin and moxifloxacin have broader gram-positive coverage and reduced gram-negative coverage than levofloxacin. All three agents are indicated for the treatment of CAP, chronic bronchitis, acute sinusitis and uncomplicated skin and skin structure infections. In addition, levofloxacin and gatifloxacin have an FDA indication for UTIs (however gatifloxacin will normally only cover approximately 80% of UTI infections because it has less gram-negative coverage). Moxifloxacin is not indicated for treatment of UTIs, which is attributed to less gram-negative coverage and extensive metabolism prior to excretion.

Safety/Tolerability – Adverse events of note include:

1) QTc prolongation with the subsequent potential for *torsade de pointes*. *Torsade de pointes* has been reported in 2 of 1,300,000 gatifloxacin patients, and 1 of 1,000,000 levofloxacin patients. Phase II-IV studies of moxifloxacin treatment in over 7,900 patients resulted in no cardiovascular morbidity attributable to QTc prolongation.
2) Dysglycemia has been associated with the use of gatifloxacin in diabetic patients receiving oral hypoglycemic agents or insulin, and elderly patients (>75yrs) with underlying disease states that increase the risk for dysglycemia.

Infectious Disease consultants stated the concerns regarding QTc prolongation and dysglycemia are probably "over-stated." However, providers should exercise caution when using fluoroquinolones in specific patients with underlying risk factors.

The Council concluded that fluoroquinolones are not sufficiently interchangeable to support a closed class contract. Differences in coverage and safety/tolerability concerns prevent the use of a single agent for all patients. All three fluoroquinolones will provide adequate clinical coverage for the majority of CAP and acute sinusitis infections.

The Council unanimously voted to authorize a procurement strategy that could include up to a joint DoD/VA open class contract competing moxifloxacin, gatifloxacin, and levofloxacin as a "workhorse" fluoroquinolone for the treatment of CAP and acute sinusitis.

E. *5HT1 Agonists (Triptans)* – The joint DoD/VA solicitation closed on 20 December 2002. The Government Accounting Agency (GAO) resolved a protest by ruling in favor of the Government. Detailed MTF guidance will be available on the PEC website when the contract award is announced.

F. *Angiotensin Receptor Blockers (ARBs)* – The Council had previously authorized the addition of a single ARB to the BCF using a procurement strategy that could include up to a joint DoD/VA closed class contract. The VA has determined that two ARBs should be on the VA National Formulary (VANF). The Council voted unanimously to accept two contracted ARBs for inclusion on the BCF. The change is expected to have minimal economic impact to DoD, while enhancing the ability of MTFs to effectively treat a wider range of patients using formulary ARBs.

G. The Council was updated on the progress of the bisphosphonate and insulin pen procurements.

7. DRUG/DRUG CLASS EVALUATIONS

A. *Transdermal Estrogen Preparations* – Short-term estrogen therapy remains the gold standard for relief of menopausal symptoms. Oral and transdermal routes are the most frequently used, with oral conjugated estrogens as the most popular estrogen formulation in the DoD and United States. Seven estrogen patches, all containing estradiol in varying strengths, are available in the United States (see Table 1). Currently the BCF contains oral conjugated estrogen, medroxyprogesterone, combination conjugated estrogen/medroxyprogesterone (Prempro), and an estrogenic vaginal cream (MTFs' choice). The BCF does not include an estrogen patch.

Table 1: Estradiol Transdermal Systems Available in the U.S.

Product/ Distributor	Release rate (mg/24 hr)	*Surface area (cm^2)	Delivery System/ Frequency of Administration
Vivelle-Dot Novartis	0.025; 0.0375; 0.05; 0.075; 0.1	2.5; 3.75; 5; 7.5; 10	Matrix Twice weekly
Vivelle Novartis;	0.025; 0.0375; 0.05; 0.075; 0.1	7.25; 11; 14.5; 22; 29	Matrix Twice weekly
Esclim Women First Health	0.025; 0.0375; 0.05; 0.075; 0.1	11; 16.5; 22; 33; 44	Matrix Twice weekly
Alora Procter & Gamble	0.05; 0.075; 0.1	18; 27; 36	Matrix Twice weekly
Climara Berlex	0.025; 0.05; 0.075; 0.1	6.5; 12.5; 18.75; 25	Matrix Once a week
♦**Estraderm** Ciba	0.05; 0.1	10; 20	Alcohol reservoir Twice weekly
Estradiol Mylan	0.05; 0.1	15.5; 31	Matrix Once a week
CombiPatch Aventis	0.05 mg estradiol/ 0.14 mg norethindrone acetate; 0.05 mg estradiol/ 0.25 mg norethindrone acetate	16	Twice weekly

*patch size increases with strength;
♦all drug delivery systems are matrix with the exception of Estraderm which uses an alcohol reservoir

Efficacy – All transdermal estrogen systems substantially decrease the number of hot flashes per week. There is no evidence that one estrogen compound is more effective than another. For relief of postmenopausal vasomotor symptoms, any patch can cover the clinical needs of patients; however, those providing the lowest dose with a wide range of dosing options are preferred by providers.

Safety/Tolerability – All estrogen-containing product package inserts carry an identical safety warning for the risk of heart disease, stroke, and cancer. Oral estrogen requires higher doses than transdermal estrogen. A recent trial assessing changes in C-reactive protein (CRP), a marker for inflammation in blood vessels and cardiovascular risk, suggested that transdermal systems might decrease cardiovascular adverse effects of estrogen. Patients using transdermal systems showed no elevation in CRP levels, while oral estrogens increased CRP levels two-fold.

Tolerability issues associated with the systemic effects of estrogen are similar for patches and oral estrogen. Local reactions due to transdermal patches include burning, erythema, irritation, pruritis, and rash. Reactions to the application site occur in about 10% of women who use reservoir (alcohol-based) patches and in 5% of women utilizing the matrix system. The incidence of skin irritation diminishes when the application site is rotated.

Table 2: Prime Vendor Cost for Transdermal Estrogen Systems

	Vivelle-Dot Novartis	**Vivelle** Novartis	**Alora** P&G	**Climara** Berlex	**Estraderm** Ciba	**Estradiol** Mylan
Prime Vendor Weighted Average Acquisition Cost/Patch	$2.20	$1.81	$1.40	$1.92	$1.96	$2.93
Dosage Frequency	Twice a week	Twice a week	Twice a week	Once a week	Twice a week	Once a week
Monthly Cost	$17.60	$14.48	$11.20	$7.68	$15.68	$23.44

Cost – Table 2 displays the prime vendor cost for various transdermal estrogen systems. Women's First Healthcare has offered a blanket purchase agreement that will make their estradiol patch (Esclim) available at a significantly lower monthly cost than other transdermal estrogen products if Esclim is added to the BCF.

Other factors – Esclim has better adhesiveness than Estraderm, which is currently on 75% of MTF formularies. The percentage of transdermal systems that became detached in the Esclim group was 6% compared to 11.3% in the Estraderm group ($p< 0.001$). (Maturitas 1996; 25)

The Council voted unanimously to add Esclim to the BCF. This will result in uniform availability of a transdermal estrogen product at a substantially reduced monthly cost per patient.

B. *Atypical Antipsychotics*

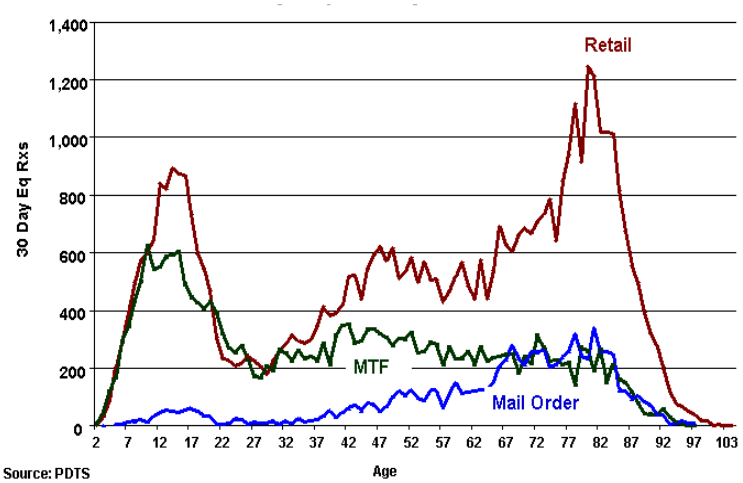
The Council considered a PEC drug class review of five atypical antipsychotics: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon). The review did not include clozapine (since its significant risk of agranulocytosis and requirement for routine white blood cell monitoring limit its use) or the injectable formulation of ziprasidone (an immediate release medication not intended for chronic use).

All five agents are indicated for schizophrenia; olanzapine is also indicated for acute bipolar mania. Other uses include depression with psychosis; symptoms of dementia including agitation, hyperactivity, hallucinations, suspiciousness, hostility and uncooperativeness; anxiety disorders; developmental disorders; autism; aggression/self injurious behavior; and Tourette's syndrome. Many of the atypical antipsychotics have been studied in pediatric as well as adult populations, although none of the drugs have pediatric indications. The review categorized the uses for atypical antipsychotics into four groups: schizophrenia and related psychoses, behavioral and psychological symptoms of dementia (BPSD), bipolar mania, and psychiatric and behavioral disorders in children and adolescents.

The onset of both schizophrenia and bipolar disorder is typically in early adulthood, between the late teens and mid-30s for schizophrenia, and in the early 20s for bipolar disorder. Based on the age distribution of usage in DoD (see Figure 1) and the likelihood that individuals with severe psychiatric illnesses will be required to leave the military, it

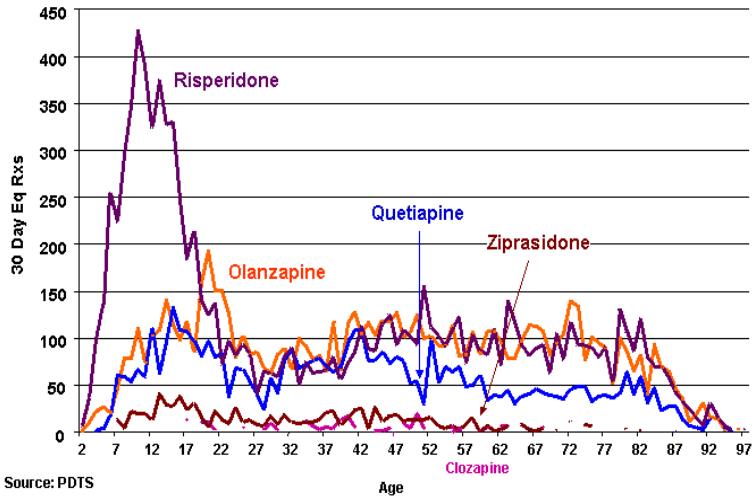
appears probable that uses other than schizophrenia or bipolar disorder represent a substantial proportion of atypical antipsychotic prescriptions in all three points of service.

Figure 1: Age Distribution of Atypical Antipsychotics in DoD
By 30 Day Equivalent Rxs, Oct 02 – Dec 02



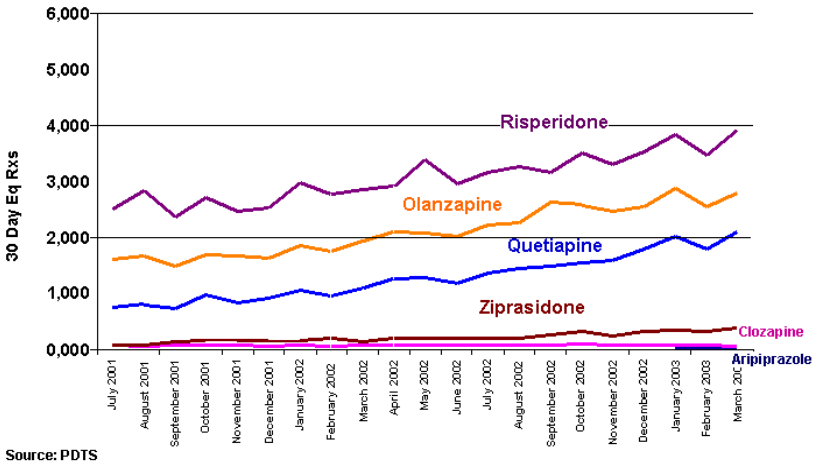
Individual atypical antipsychotics show distinctly different patterns of use at MTFs. As shown in Figure 2 below, risperidone is by far the most commonly prescribed agent in the pediatric population, although there is some usage of other atypical antipsychotics. Olanzapine, quetiapine, and risperidone show similar patterns of use in adult patients, although there is less use of quetiapine overall. Ziprasidone use appears to be less frequent in older patients. Aripiprazole was not yet available during the time period studied.

Figure 2: Age Distribution of Atypical Antipsychotics in MTFs
By 30 Day Equivalent Rxs, Oct 02 – Dec 02



Overall, the most commonly used atypical antipsychotic in MTFs is risperidone, followed by olanzapine and quetiapine (see Figure 3). There is low but increasing use of ziprasidone. Aripiprazole has not been on the market a sufficient period of time to assess its potential use.

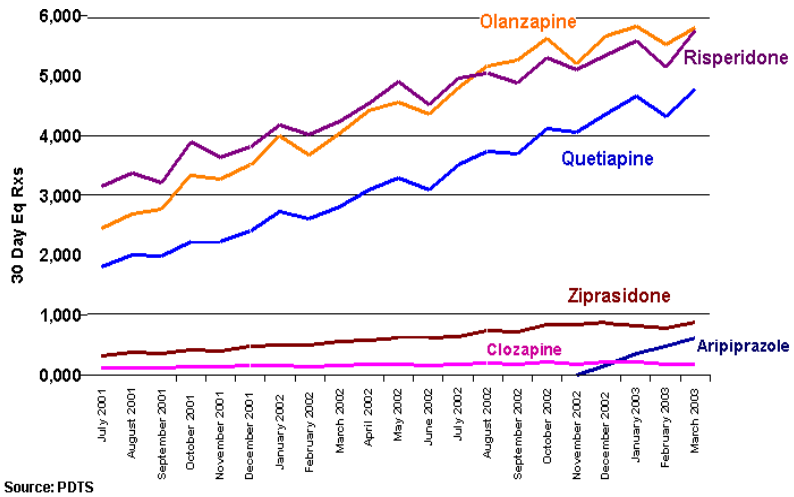
Figure 3: MTF 30 Day Equivalent Prescriptions for Atypical Antipsychotics
Jul 01 – Mar 03



Source: PDTS

In the retail network, olanzapine and risperidone are the most commonly used atypical antipsychotics, followed by quetiapine (see Figure 4). Ziprasidone use is again relatively low, but increasing. Aripiprazole use is increasing at a faster rate than in MTFs.

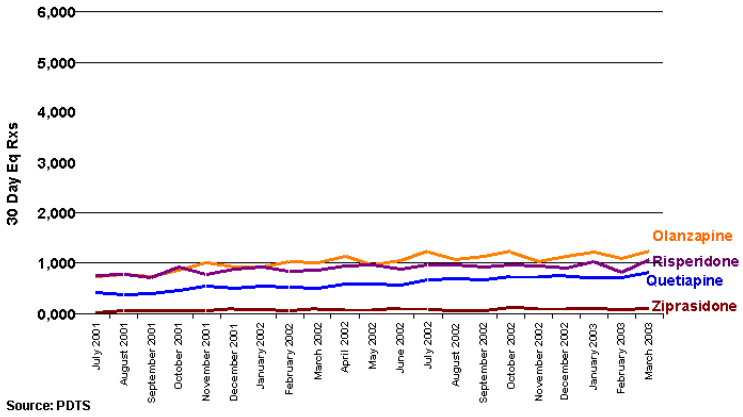
Figure 4: Retail Network 30 Day Equivalent Prescriptions for Atypical Antipsychotics
Jul 01 – Mar 03



Source: PDTS

In the mail order program, olanzapine, risperidone, and quetiapine are the most commonly used atypical antipsychotics (Figure 5). Aripiprazole was not added to the mail order formulary until March 03 and does not show on this graph.

Figure 5: Mail Order 30 Day Equivalent Prescriptions for Atypical Antipsychotics
Jul 01 – Mar 03



Efficacy

- *Schizophrenia and related psychoses* – There do not appear to be any clinically relevant differences among the atypical agents with respect to overall efficacy and treatment of positive symptoms (e.g., delusions and hallucinations), although individual patients may respond better to one than another. There is stronger evidence with olanzapine than with other atypical antipsychotics to support efficacy in treating negative symptoms (e.g., apathy, lack of motivation, lack of interpersonal and social interaction), based on olanzapine's demonstrated superiority to a typical antipsychotic (haloperidol) in reducing negative symptom scores in both individual short-term and long-term trials. Risperidone has also demonstrated superiority to haloperidol in reducing negative symptom scores based on long-term trials and pooled data from short-term trials. Less clinical evidence is available for quetiapine, ziprasidone, and aripiprazole.

  Atypical antipsychotics have also been shown to have positive effects on neurocognitive functioning (e.g., memory and attention) and mood symptoms (e.g., depressed mood) in patients with schizophrenia or related psychoses; however, the relative efficacy of specific atypical antipsychotics in these domains is still unclear.

- *Dementia* – Dementia is generally defined as a progressive decline in intellectual functioning that impedes normal activities; Alzheimer's dementia is the most common type. The FDA has not yet approved any drugs specifically for the "behavioral and psychological symptoms of dementia" (BPSD). Consensus statements from various national groups recommend antipsychotics as the only available pharmacological treatment for psychotic symptoms of *BPSD*. There is no evidence that any one atypical antipsychotic is more efficacious in one type of dementia than another. Risperidone and olanzapine have been shown to be

efficacious in reducing BPSD in published randomized controlled trials. Other atypical antipsychotics lack published data.

- *Bipolar mania* – According to the American Psychiatric Association Guideline for the Treatment of Patients with Bipolar Disorder (2000), first line treatment for more severe manic or mixed episodes of bipolar disorder is the initiation of lithium or valproate plus an antipsychotic. For less ill patients, monotherapy with lithium, valproate, or an antipsychotic may suffice. The guidelines state that atypical antipsychotics are preferred over typical antipsychotics due to their side effect profile. Olanzapine is the only atypical antipsychotic with an FDA-approved indication for the treatment of bipolar mania. It has been shown to be of comparable efficacy to lithium in the reduction of manic symptoms in one clinical trial and superior to divalproex in another. Olanzapine has also been shown to be superior to placebo as adjunctive therapy with a mood stabilizer (lithium or divalproex). Risperidone has been shown to be superior compared to placebo both as monotherapy and as adjunctive therapy with a mood stabilizer. A recently published trial (April 2003) with ziprasidone showed efficacy for monotherapy. Large trials with aripiprazole and quetiapine (either as monotherapy or as adjunctive therapy) have been performed, but results are not yet available as full publications.
- *Psychiatric and behavioral disorders in children and adolescents* – None of the atypical antipsychotics are currently approved for the treatment of children and adolescents. Multiple small trials, uncontrolled trials, case reports, and case series focus on the use of atypical antipsychotics (most commonly risperidone) in pediatric patients for the treatment of a wide variety of conditions. In large ($n \geq 30$) controlled trials, risperidone has been shown to be efficacious for the treatment of conduct disorder in children with mental retardation (two trials) and for the treatment of aggressive behavior in autistic children (one trial). Quetiapine has been shown to be efficacious as adjunctive therapy for bipolar mania with divalproex in adolescents 12-18 years of age.

Safety/Tolerability

Adverse effect profiles differ substantially among atypical antipsychotics. Provider comments with respect to the safety and/or tolerability of specific agents identified the following concerns: olanzapine (weight gain, diabetes, cholesterol/triglyceride elevations, sedation), quetiapine (weight gain, diabetes, cholesterol/triglyceride elevations), risperidone (EPS, prolactin), ziprasidone (cardiac effects, "emerging case reports of EPS"). Providers commented favorably on the ease of dosing olanzapine compared to quetiapine, and their tendency to use once daily drugs first line. Of the agents, olanzapine and aripiprazole are generally dosed once daily, risperidone can be dosed once or twice daily; and ziprasidone and quetiapine are typically dosed twice daily. Aripiprazole was not yet approved when the survey was completed and was not mentioned by survey responders.

- *Extrapyramidal symptoms* (EPS) are abnormal, involuntary movements associated with antipsychotic treatment. Their occurrence is related to D2 receptor binding in the nigrostriatal pathway; atypical antipsychotics have a higher 5-HT-2 / D2

binding ratio than typical antipsychotics, and thus a lower risk of EPS. This lower risk of EPS is considered to be the defining characteristic of "atypicality." Both olanzapine and risperidone may have increased binding affinity for D2 receptors at higher doses, but in the case of olanzapine, high antimuscarinic activity may limit EPS symptoms.

Of the atypical antipsychotics, risperidone in general appears to have a higher risk of EPS than other agents, although at lower doses (<6 mg/day) this may not be true. Tarsy et al (2002) provide a tentative ranking of EPS risk (from highest to lowest) as follows: Risperidone > olanzapine = ziprasidone > quetiapine > clozapine. Aripiprazole was not included in this review; EPS risk appears low in published trials to date. Accurate determination rates of EPS may be complicated by the presence of carryover EPS effects from previous antipsychotic treatment, particularly in short trials with minimal or no washout periods.

- *Tardive dyskinesia* (TD) is a late-appearing and generally irreversible complication of treatment with long-term antipsychotics, consisting of abnormal postures and involuntary movements of the face, eyes, tongue, trunk, or limbs. Up to 25% of patients may develop TD with cumulative use of typical antipsychotics. Sustained EPS is thought to be a risk factor for the development of TD. In general, atypical antipsychotics appear to have a lower risk of TD than typical antipsychotics. Both olanzapine and risperidone have been shown to be associated with a lower risk of TD than haloperidol. There are no long-term head-to-head studies between atypical antipsychotics addressing the risk of TD and limited long-term data with other atypical antipsychotics.
- *Weight gain* has been reported with a number of atypical antipsychotics, including olanzapine, quetiapine, and risperidone. Allison et al (1999) analyzed clinical trials with atypical antipsychotics and made the following estimates of mean weight gain at 10 weeks (6 weeks for quetiapine, which lacked longer trials; all estimates at midpoint of the standard dosing range): 4.15 kg olanzapine, 2.18 kg quetiapine, 2.10 kg risperidone, 1.08 kg haloperidol, 0.04 kg ziprasidone, -0.74 kg placebo. Aripiprazole was not included in this analysis: the mean weight gain in 4- to 6-week placebo-controlled trials with aripiprazole was 0.71 kg. Later studies and other analyses typically show the same rank order; head-to-head studies comparing olanzapine and risperidone typically demonstrate more weight gain with olanzapine. Weight gain is problematic not only because of adverse health consequences, but because it is frequently associated with lack of adherence to medication.
- *Hyperlipidemia* has been reported with atypical antipsychotics, most commonly with olanzapine, but also with risperidone and quetiapine. Olanzapine and risperidone have been most commonly compared. Increases in total cholesterol appear less frequent with risperidone than with olanzapine; there is little published data from large trials focusing on specific lipid effects (e.g., LDL, HDL, or triglycerides).
- *Treatment-emergent diabetes* has also been reported with atypical antipsychotics. The mechanism is unclear, as is the relationship of treatment-emergent diabetes

with weight gain and hyperlipidemia. In general, schizophrenic patients are at increased risk for hyperglycemia and/or diabetes compared to the general population, whether due to lifestyle factors or as a consequence of the disease process. Diabetes appears to occur more frequently in schizophrenic patients receiving atypical antipsychotics than those receiving typical antipsychotics.

Olanzapine has been associated with the greatest increase in risk of hyperglycemia and diabetes among the atypical antipsychotics reviewed, based on epidemiological studies. Risperidone has also been associated with increased risk, but less consistently and at an apparently lower rate than olanzapine. In one large case-control study (19,637 patients diagnosed and treated for schizophrenia between 1987 and 2000) the incidence of treatment-emergent diabetes per 1000 person-years was 10 for olanzapine (95% CI 5.2 – 19.2), 5.4 for risperidone (95% CI 3.0 – 9.8), and 5.1 for typical antipsychotics (95% CI 4.5-5.8) [Koro et al, 2002]. Data with other atypical antipsychotics is limited.

- *QT interval prolongation* – Labeling for ziprasidone contains a warning about the drug's potential for QTc-interval prolongation and risk of *torsade de pointes* (a potentially fatal arrhythmia) based on the occurrence of prolonged QTc intervals in Phase 2/3 clinical trials. Data from an FDA-requested study assessing the effect of maximum recommended doses of oral ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QTc interval in patients with schizophrenia is available from the FDA Psychopharmacological Drugs Advisory Committee Briefing Document for ziprasidone, July 19, 2000 (available at: www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1.htm). In this open-label, parallel group trial, mean changes in QTc interval occurred in the following rank order, from greatest to least: thioridazine > ziprasidone > quetiapine > risperidone > olanzapine > haloperidol. While ziprasidone was associated with the greatest increase in QTc interval among the atypical antipsychotics studied, no patients had a QTc > 500 msec. The study also included an analysis of the effect of co-administration of metabolic inhibitors for each product. Co-administration of ziprasidone with its metabolic inhibitor, ketoconazole, did not lead to any further prolongation of the QTc despite an increase in serum concentration. According to the manufacturer, there have been no reports of *torsades de pointes* during post-marketing experience with ziprasidone. Ziprasidone has been taken by approximately 150,000 patients since it was approved (Weiden et al, 2002).

  Product labeling for risperidone reports lengthened QTc intervals in some patients but no mean increase even at higher than normal doses. No increases in QTc interval are reported in product labeling for aripiprazole, olanzapine, or quetiapine.

- *Cerebrovascular events* – Results of an analysis of 4 placebo-controlled trials (4-12 weeks in duration) in more than 1200 patients with Alzheimer's disease or vascular dementia receiving risperidone were recently released. The overall risk of cerebrovascular adverse events was 4% in the risperidone-treated group compared to 2% in the placebo group; four patients died in the risperidone group vs. one patient in the placebo group. A further search of postmarketing databases

revealed 37 cases of cerebrovascular adverse events in elderly dementia patients taking risperidone, of which 16 (43%) were fatal.

The manufacturer of risperidone recently stated that it intends to send letters to U.S. physicians advising them of the possibility of increased risk of stroke among elderly patients taking risperidone and to make changes to product labeling more clearly outlining available information about risk in elderly patients. A similar warning was released in Canada last October, with a summary and review of available information published in the November 2002 issue of the Canadian Medical Association Journal (Wooltorton, 2002). The Canadian letter to physicians is available at: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/risperdal1_e.pdf.

Whether other atypical antipsychotic agents are associated with similar cerebrovascular risks is unknown.

- *Prolactin elevation* - Blockade of D2 receptors in the hypothalamus can result in increased prolactin secretion, which can lead to breast swelling, tenderness, and discharge; menstrual cycle irregularity or amenorrhea; sexual dysfunction; anovulation; and osteoporosis. Elevated prolactin levels do not always correlate with the presence of symptoms; long-term consequences of elevated prolactin are unclear. Atypical antipsychotics have a lower risk for causing prolactin elevation than typical antipsychotics, due to selectivity in the limbic system and higher 5-HT2 to D2 binding ratios. Of the atypical antipsychotics, risperidone has been associated with the largest increases in prolactin levels.
- *Other adverse effects* considered by the Council included the risk of orthostatic hypotension, anticholinergic effects, somnolence, cataracts, sexual dysfunction, priapism, and seizure.

Cost

MTFs spent about $11.3 million on atypical antipsychotics in FY 02: $5.6M for olanzapine, $3.8M for risperidone, $1.4M for quetiapine, $0.4M for ziprasidone, and $0.1M for clozapine. The average cost per day (tabs/caps only) is given in Table 3 below:

Table 3 - Average cost per tab/cap, tab/caps per day, and average cost per day for atypical antipsychotics in MTFs

	Average cost per tab/cap (PV data Dec 02-Feb 03)	Average tabs/caps per day** (PDTS data Jan 03-Mar 03)	Average cost per day
Aripiprazole*	$7.13	1.01	$7.21
Olanzapine	$4.22	1.33	$5.61
Quetiapine	$1.23	2.14	$2.64
Risperidone	$1.88	1.60	$3.01
Ziprasidone	$2.32	1.97	$4.56

* Limited data for aripiprazole
** Based on days supply. Results are consistent with those calculated for the retail network and mail order and with an older analysis based on directions for use.

The Council considered BPAs or incentive purchase agreement offers from the manufacturers of olanzapine, quetiapine, and risperidone. Offers differed considerably regarding the basis for price discounts and the considerations required by the manufacturers. A cost impact analysis by LCDR Ted Briski showed that annual cost avoidance ranging from $0.7 million to $1 million (based on current usage) could be attained by accepting two of the three offers.

After weighing relative usage, clinical factors, and economic factors, the Council voted to add risperidone and quetiapine to the BCF. The Council noted the following:

- Risperidone is by far the most commonly used atypical antipsychotic in the pediatric population, an age group in which use of this drug class is relatively high. Ensuring uniform availability of this agent across the system may benefit military personnel with children, who commonly move from MTF to MTF.
- The recent reports of an increased incidence of stroke in elderly patients with dementia receiving risperidone may lead to preferential use of other atypical antipsychotics in elderly patients (although there are no data indicating whether the same effect occurs with other atypical antipsychotics). Taken along with the general inter-patient variability in this drug class and the higher incidence of EPS and prolactin elevation with risperidone, this argues for the presence of a second agent on the BCF.
- Data for differences in efficacy among the various agents are not compelling, particularly considering the likelihood of use in conditions other than schizophrenia. However, adverse effect profiles differ considerably. All of the most commonly used medications have adverse effect concerns. Data on the newer agents, ziprasidone and aripiprazole, which may avoid some common adverse affects, are limited, and usage is low.
- Quetiapine and risperidone are the least costly agents on a cost per day basis.
- MTFs are free to add or retain additional atypical antipsychotics on their formularies if required locally.

C. *Topical Immunomodulators (TIMS)*

In November 2002, the DoD P&T Executive Council agreed that TIMS are a unique class and have a substantial place in therapy for the treatment of atopic dermatitis (AD), however there was concern regarding the cost of these agents and the potential for overuse. The Council agreed to consider one or both of these medications for addition to the BCF after procurement options were explored.

Efficacy – Randomized controlled clinical trials demonstrate that both agents are more efficacious than placebo in the treatment of AD. Tacrolimus, an ointment, appears to be as efficacious as a medium potency topical corticosteroid (TCS) whereas pimecrolimus, a cream, is as efficacious as a low potency TCS. Tacrolimus is indicated for moderate to severe AD while pimecrolimus is indicated for mild to moderate AD. Ninety percent of patients have mild to moderate AD and the rest are moderate to severe. Most of the use is in the very young (ages 0-4) and elderly (ages 65+).

Safety/Tolerability – Neither drug has clinically significant adverse effects that cause the patients to discontinue use. The drugs are not systemically absorbed, so they can be used long term without potential problems associated with long-term TCS use. TIMS can also be used on sensitive body areas such as the face and intertriginous regions where one would not want to use a TCS. Because pimecrolimus is a cream and less occlusive, it is preferred over tacrolimus for areas like the face, perioribital eyelids, and flexural and groin areas.

Other – Provider response was markedly positive regarding the prospect of having an alternative to TCSs on MTF formularies. At the same time, providers noted that these would not take the place of the low potency TCSs or other initial therapies for mild AD. Of 68 provider responses, 60 recommended adding one or both agents to the BCF. Of these 60 responses, 33 preferred pimecrolimus, 6 preferred tacrolimus, and the rest either had no preference or wanted both agents on the BCF. Pimecrolimus prescription fills are increasing at all points of service (MTF, TMOP, and retail). Pimecrolimus is currently on 49 percent of all MTF formularies. Tacrolimus is on 25 percent of MTF formularies; tacrolimus prescription fills for all points of service have leveled off at a point well below pimecrolimus.

Cost – Novartis offered an incentive agreement contingent on pimecrolimus being added to the BCF. The agreement provides a discount on all future purchases.

The Council voted unanimously to add pimecrolimus to the BCF. After being reviewed by dermatologists, a place in therapy (PIT) guide will be disseminated to the MTFs as a tool to help reduce potential inappropriate use.

8. REQUESTS FOR BCF CHANGES

A. *Nitroglycerin Products on the BCF*

The American College of Cardiology/American Heart Association currently considers nitroglycerin as third-line treatment for *chronic* symptoms of angina. Despite this third-line consideration for use, nitroglycerin transdermal systems currently account for approximately 8,000 prescriptions monthly in the MHS, second only to the sublingual tablets (approximately 15,000 prescriptions/month). Other nitroglycerin preparations (translingual spray, sustained release capsules, and ointment) combined account for approximately 6,000 prescriptions/month. Current BCF nitroglycerin products include sublingual nitroglycerin tablets, translingual spray, and isosorbide dinitrate oral. The BCF does not contain a long acting nitroglycerin product.

Transdermal nitroglycerin systems are on 75% (86/114) of local MTF formularies. A DoD/VA joint contract for nitroglycerin transdermal systems from Schering provides the patches at a cost of $0.16/day ($4.89/month).

An analysis of MHS prescription data revealed a steadily increasing number of prescriptions for isosorbide mononitrate oral for all three points of service in the MHS (approximately 16,000 prescriptions/month combined). Isosorbide mononitrate oral is on 43% (49/114) of local MTF formularies. The DoD/VA currently has a joint contract for a generic once daily isosorbide mononitrate oral tablet at a cost ranging between $0.04 to $0.06/day, depending on strength.

The Council voted unanimously to add the contracted nitroglycerin transdermal system and the contracted once daily preparation of isosorbide mononitrate oral to the BCF, due to wide usage in the MHS and low cost.

B. *Administrative Changes Concerning the Process for Requests from the Field for BCF Changes*

In order for the PEC to provide support materials for agenda items to the Council members three weeks prior to the meeting, a deadline needs to be established for submission or requests for BCF changes. To allow sufficient time to complete an analysis and prepare a recommendation for any submitted request, the PEC recommended that the deadline for BCF change requests should be 6 weeks prior to the next regularly scheduled meeting. The Executive Council concurred with this recommendation.

A second issue concerned the potential need for individuals requesting the addition of an agent to the BCF to disclose whether they have a financial interest or other relationship with the manufacturer of the product that could be perceived as a conflict of interest. The purpose of this disclosure would not be to prevent the consideration of the request, but to provide the Council with information that would allow it to make a more informed and credible decision. It was initially proposed that a disclosure form should be required to accompany a request for a BCF change. Some Council members suggested that if disclosure forms are required for BCF change requests, the same type of disclosure should be required for input regarding other P&T actions. Council members were concerned that the paperwork burden would degrade the ability of the PEC to obtain input from providers. The Council voted to table this issue and tasked the PEC to clarify the necessary scope and process for obtaining disclosure statements on any input related to formulary decisions making. The PEC is to present a revised recommendation at the next meeting.

9. ADJOURNMENT

The meeting adjourned at 1500 hours. The next meeting will be held at TRICARE Management Activity (TMA), conference room 815, Skyline Building 6, 5111 Leesburg Pike, Falls Church, VA at 0800 on Tuesday, 5 August 2003. All agenda items should be submitted to the co-chairs no later than 18 July 2003.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair