

**DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES**  
**July 29, 2016**

The Executive Formulary Committee convened on Friday, July 29, 2016 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Wright, Chair at 9:40 a.m.

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

**Guests Present:** Lisa Mican, Pharm.D., Austin State Hospital; Brent Curry, Pharm.D., Resident ASH; Haemy Chung, Pharm.D. Student, ASH

**Introduction and Other Information**

Dr. Scott Murry has been appointed to the Committee as a psychiatrist representative from a DADS facility. In addition, Dr. Victoria Morgan has been added to the Committee as an ex-officio (non-voting) member. Dr. Morgan was unable to attend today's meeting due to previous commitments.

**Approval of Minutes of April 29, 2016**

On a motion of Ms. Millhollon, seconded by Dr. Messer, the minutes of the April 29<sup>th</sup> meeting were approved as previously distributed.

**Conflict of Interest**

Dr. Murry completed his conflict of interest form. He had no conflicts to report. Dr. Mican noted that she attended two drug company sponsored luncheons. The Committee did not feel that the luncheons reported by Dr. Mican would be an issue.

## Adverse Drug Reaction Reports

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

A 71 year old Caucasian male was admitted to the psychiatric hospital diagnosed with depression unspecified and major vascular neurocognitive disorder. Medical diagnosis include hypertension, diabetes, hyperlipidemia, sleep apnea, benign prostatic hypertrophy, GERD, left ventricular hypertrophy with diastolic dysfunction (ejection fraction > 40%), neuropathy, hearing impairment, seborrheic dermatitis, and a remote history of seizure. Baseline labs were within normal limits except lymphocyte 19.4%, glucose 150 mg/dl (high), total protein 6.1 g/dl (low), Alk phos 130 U/L (high), and TG 196 mg/dl (high). The TSH was within normal limits. Repeat labs two weeks later showed normal ALK phos, glucose, and total protein. A CBC, CMP (except for glucose 115 mg/dl), magnesium, potassium and BNP were within normal limits at the time of the abnormal EKG. Medications at the time of QTc prolongation include: risperidone 0.5 mg at bedtime, escitalopram 10 mg daily, tamsulosin 0.8 mg at bedtime, oxybutynin 10 mg daily, glipizide 10 mg daily, simvastatin 40 mg daily, aspirin 81 mg daily, and omeprazole 20 mg daily. The EKG was performed 6 and 4 months after starting escitalopram and risperidone, respectively, and it showed a severely prolonged QTc interval at 513 msec, HR 83 beats/minute with left bundle branch block (LBBB). Baseline EKG showed moderate QTc interval prolongation at 477 msec, HR 61 beats/minute with LBBB. Risperidone and escitalopram were both discontinued due to their potential for prolonging the QTc interval. Risperidone was discontinued and escitalopram was tapered and discontinued 3 days later. No changes were made to other medications. Repeat EKG one week after discontinuation of risperidone showed a normal QTc interval of 396 msec, HR 71 beats/minute with LBBB.

A 21 year old Asian female was taking linezolid since 4/15/16. On June 29<sup>th</sup>, the patient reported blurry/double vision and could see "spots" in her right eye. On June 30<sup>th</sup>, the linezolid was discontinued and she was sent to optometry. The optometrist reported optic nerve edema bilaterally, choked discs, and multiple hemorrhages around the optic nerves. She was transferred to a medical hospital on July 1<sup>st</sup>, where ophthalmology found the patient to have a disconjugate gaze with esotropia of her right eye. The diplopia finally resolved July 4<sup>th</sup>.

A 33 year old white male was admitted to the psychiatric facility from jail. Prior to admission, his medications were carbamazepine, escitalopram, and topiramate. Medical conditions include history of TBI, GERD, and osteoarthritis of the knees. Admission labs were within normal limits including CMP, UA, TSH, and a negative UDS. The CBC was within normal limits except RBC 4.28 M/mm<sup>3</sup>, hemoglobin 13.1 g/dl and hematocrit 40.1%. At 2:05 pm on the day of admission, vitals were within normal limits with BP 102/67 mmHg and P 65 beats/minute. EKG showed normal sinus rhythm with QTc 408 msec. At 8:29 pm on the night of admission, he was administered olanzapine ODT 10 mg at bedtime for psychosis and prazosin 1 mg at bedtime for PTSD. The following morning at 7:58 a.m., he was noted to be hypotensive with a blood pressure of 77/54 mmHg, P 71 bpm, O<sub>2</sub> Sat 98%. Approximately 1 hour later, he had a syncopal episode in the bathroom while trying to urinate and fell hitting his left hip and head and sustaining a laceration to the head. Vitals were obtained after the incident and BP was 96/63 mmHg and P 71 beats/minute. He was transferred to a local medical hospital and treated for syncopal episode with head injury and laceration as well as traumatic bursitis. The CT of his head was negative at the local medical hospital and he was sent back later that day with a BP 100/67 mmHg and P 76 beats/minute. The dose of olanzapine was resumed at 2.5 mg at bedtime titrated during admission to 5 mg and prazosin at 0.5 mg at bedtime titrated during admission to 1 mg without further syncope or hypotension.

A 24 year old Hispanic male was admitted to the psychiatric facility in mid-December 2015, on emergency detainment from jail after being witnessed responding to internal stimuli and refusing psychotropic medication. He has a current diagnosis of schizophrenia with a history of cannabis abuse. This is the patient's first admission to the facility with no previous psychiatric history. Baseline labs were never drawn at the facility due to an emergency transfer to a medical facility on day 2 of admission for suspected seizure activity. At the medical facility, labs were obtained and showed normal liver function test (LFT); aspartate aminotransferase (AST) 19 U/L, alanine aminotransferase (ALT) 16 U/L alkaline phosphatase (ALP) 60 U/L, and total bilirubin (T. Bili) 0.9 mg/dL. Upon return to the facility, the patient consistently refused medications, until court ordered medications were approved, at which time he routinely took risperidone ODT and the dose was titrated to 6 mg per day. Once discharge discussions began, the patient agreed to have his labs drawn, and results showed an elevated AST of 57 U/L [1.5 times the upper limit of normal (ULN)] ALT of 151 U/L (2.5 times the ULN) and ALP 87 U/L. Repeat labs were obtained a week later and revealed further elevations in AST of 72 U/L (two times the ULN), ALT of 202 U/L (3.5 times the ULN) and ALP 81 U/L. The patient received limited PRNs (9 doses from Day 2 to Day 36) of olanzapine, lorazepam, haloperidol and diphenhydramine and no other scheduled medications. The patient was switched from risperidone to olanzapine and eventually was switched

to paliperidone.

A 37 year old black male with a history of Bipolar I disorder was admitted to a psychiatric hospital from jail. He has a history of drug use including marijuana and cocaine and smokes 5-6 cigarettes per day, although he has been smoke and drug free for at least the past 4 months since incarceration. Medications prescribed while in jail were noted to be risperidone 6 mg daily, divalproex 1,000 mg daily and melatonin. Admission labs were within normal limits including potassium, sodium and calcium except for mild anemia noted on CBC, low VPA level of 40.4 mcg/mL and TSH 7.56 mIU/L with normal fT4. Uncontrolled hypertension was observed on vitals. After admission, the dose of risperidone was reduced to 2 mg twice daily, olanzapine 10 mg at bedtime was added and trazodone 100 mg at bedtime was prescribed instead of melatonin for insomnia. Medical medications included the addition of lisinopril 20 mg daily for hypertension, vitamin D 2,000 units dietary supplement and fish oil 1,200 mg at bedtime dietary supplement were also prescribed. One day after admission, an EKG noted severely prolonged QTc of 504 msec with LVH noted. Prior to the EKG, he had received a bedtime dose of trazodone and olanzapine as well as a bedtime and morning dose of risperidone. A subsequent STAT repeat EKG was obtained the following day which was almost identical with a QTc of 507 msec on the same medications. Subsequently, risperidone, olanzapine and trazodone were all discontinued and the dose of divalproex ER was increased to 2,000 mg at bedtime. A follow-up EKG obtained the following day off of risperidone, olanzapine and trazodone showed significant improvement of the QTc at 456 msec. A follow-up EKG a week later was similar with QTc of 454 msec. Diphenhydramine 50 mg at bedtime was prescribed for insomnia and he was subsequently switched to aripiprazole and titrated up to 15 mg daily with a QTc of 462 msec on June 22<sup>nd</sup> and was discharged from the hospital on this medication. Possible known risk factors for QT prolongation in addition to medications prescribed include: history of drug use (particularly stimulant use), preexisting CVD (QTc prolongation noted on 2 past admissions and LVH also noted on last admission in 2011), possible thyroid disorder (elevated TSH), uncontrolled hypertension, and obesity (137% of IBW per dietary).

#### **Texas Foster Care Guidelines CORRECTION**

A correction to the Texas Foster Care Guidelines has been published. In the original document, Dyanavel® XR and Adzenys®-ODT were listed as amphetamine mixed salts instead of amphetamine base. In addition, the dosing of these products were updated to reflect the product labeling. The updated guidelines can be found at: [https://www.dfps.state.tx.us/Child\\_Protection/Medical\\_Services/documents/reports/2016-03\\_Psychotropic\\_Medication\\_Utilization\\_Parameters\\_for\\_Foster\\_Children.pdf](https://www.dfps.state.tx.us/Child_Protection/Medical_Services/documents/reports/2016-03_Psychotropic_Medication_Utilization_Parameters_for_Foster_Children.pdf)

Neither of the products updated are on our Formulary and are not included in our table of stimulants.

#### **Drug Formulary Sectional Review- *Dermatologicals (Acne Agents to Anti-Infectives Antiseptic & Germicides)***

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

For this Dermatological section the following changes were recommended:

##### Acne Section

- Benzoyl Peroxide
  - Delete:
    - Bar: 5%
    - Cream, topical 10%
    - Gel, topical: 2.5%
    - Lotion: 10%
    - Pads: 9%
- Erythromycin-Benzoyl Peroxide (Benzamycin®)
  - Change listing to: Gel, topical: Erythromycin 3% - Benzoyl Peroxide 5% (with 20% alcohol)
- Salicylic Acid – Sulfur
  - Delete:
    - Bar
    - Cream
    - Gel

- Sulfacetamide Sodium
  - Delete trade name Sebizon®
  - Delete – Gel: 10%
- Tretinoin Gel
  - Delete “Gel” from the listing
  - Delete:
    - Gel, topical: 0.01%
    - Liquid, topical: 0.05%

#### Anesthetics, Local

- Benzocaine
  - Delete – Spray: 5%
- Ethyl Chloride
  - Delete all sizes
- Lidocaine
  - Delete:
    - Gel, topical: 2.5%
    - Liquid, topical: 2.5%, 4%
    - Ointment, topical: 2.5%
  - Move Liquid, viscous 2% to mouth and throat section
- Pramoxine
  - Delete trade name Tronothane®
  - Delete - Ointment, topical: 1%

#### Anti-Histamine Agents

- Delete bottle sizes from the following products:
  - Calamine-Zinc Oxide-Glycerin
  - Calamine-Pramoxine
- Delete diphenhydramine lotion: 1%

#### Anti-Infectives – Antibiotics

- Bacitracin-Polymyxin B
  - Delete – Powder, topical: Bacitracin 500 units – Polymyxin B 10,000 units/g
- Polymyxin B-Neomycin
  - Delete – Cream: Polymyxin B 10,000 units – Neomycin 3.5 mg
  - Deletion removes Polymyxin B-Neomycin from the formulary as there are no products with this combination

#### Anti-Infectives – Antiviral

- Acyclovir
  - Change cream listing from 0.5% to 5%
  - Ointment, topical 5% [50 mg/g] – delete all sizes

#### Anti-Infectives – Antifungals

- Delete all trade names listed in this section
- Clotrimazole
  - Delete – Lotion: 1%
- Miconazole
  - Delete – Lotion: 2%

#### Anti-Infectives – Antipsoriatics

- Coal Tar
  - Delete trade names Ionil-T®, Tegrin®, Pentrax®, Polytar®
  - Delete the following products:
    - Cream, topical: 2%
    - Liquid, topical: 30%
    - Shampoo: 5%

- Solution, topical: 120 ml, 480 ml
  - Add Shampoo: 0.5%
- Selenium Sulfide
  - Delete trade name Selsun®

#### Anti-Infectives – Antiseborrheic Agents

- Coal Tar
  - Delete trade names Ionil-T®, Tegrin®, Pentrax®, Polytar®
  - Delete the following products:
    - Cream, topical: 2%
    - Liquid, topical: 30%
    - Shampoo: 5%
    - Solution, topical: 120 ml, 480 ml
  - Add Shampoo: 0.5%
- Salicylic Acid-Sulfur
  - Delete the following products:
    - Bar
    - Cream
    - Gel
- Selenium Sulfide
  - Delete trade name Selsun®
- Sulfacetamide Sodium
  - Delete trade name Sebizon®

#### Anti-Infectives – Antiseptics & Germicides

- Chlorhexidine – delete trade names Hibiclens®, Bactoshield®
- Hexachlorophene – delete trade name pHisoHex®
- Povidone-Iodine
  - Delete all package sizes
  - Delete – Cleanser, topical
  - Change Solution, prep to Surgical Scrub: 7.5%

#### Burn Agents

- Bacitracin – delete trade name Baciguent®

#### Corticosteroids

- Betamethasone dipropionate
  - Delete –Gel: 0.05%
- Fluocinonide
  - Delete trade name Lidex®
  - Delete the following products:
    - Cream, topical: 1%, 2.5%
    - Lotion, topical: 1%, 2%, 2.5%
    - Ointment, topical: 1%, 2.5%
- Betamethasone valerate
  - Delete – Cream, topical: 0.01%
- Triamcinolone
  - Delete trade names Aristocort®, Kenacort®
- Desonide
  - Delete trade name Lokara®
- Hydrocortisone
  - Delete trade names Lanacort®, Corticaïne®
  - Delete – Lotion, topical: 0.5%

#### Diaper Rash Agents

- For the diaper rash section, no specific products will be listed.
- Any product used as a Diaper Rash product will be considered Formulary

#### Emollients

- Emollient Gel – delete trade name Clinac O.C.®
- Emollient Lotion – delete trade names Allercreme®, Lac-Hydrin®

#### Keratolytics

- Salicylic Acid
  - Delete individual listings of products
  - Add statement: “All available salicylic acid products as a single agent are considered to be on formulary.”
- Urea
  - Delete percentages off the listing which makes all percentages on formulary
  - Delete – Shampoo

#### Ointments & Lotion Bases

- Change section title to “Ointments”
- Petrolatum, white
  - Delete package size from Ointment, topical

#### Rubs and Liniments

- Menthol
  - Menthol is rarely found as a single ingredient
  - List menthol only with no products listed
- Menthol-Methyl salicylate
  - Delete the strength (30%) from the Cream, topical listing
  - Add: Ointment, topical

#### Skin Cleansers

- Abrasive Cleanser
  - Delete the “Abrasive Cleanser” section as many of these contain salicylic acid which is listed separately
- Salicylic Acid-Sulfur
  - Delete the product listings and add the following statement: “All commercially available forms are on formulary.”

#### Scabicides & Pediculicides

- Permethrin
  - Delete trade name Acticin®
  - Change Shampoo to Cream Rinse
- Pyrethins 0.33%-Piperonyl Butoxide 4%
  - Delete – Shampoo: 0.3%

#### Skin Protectants

- Benzoin, Compound Tincture
  - Delete sizes from the listing
  - Change the “also contains” to “may also contain”
- Zinc Oxide
  - Delete the percentages from the ointment and paste entries which makes all percentages on formulary

#### Tar-Containing Agents

- Coal tar
  - Delete trade names Ionil-T®, Tegrin®, Pentrax®, Polytar®
  - Delete the following products:
    - Cream, topical: 2%
    - Liquid, topical: 30%
    - Shampoo: 5%
    - Solution, topical: 120 ml, 480 ml
  - Add Shampoo: 0.5%

## Wound Agents

- Collagenase
  - Delete the strengths from the ointment, topical listing
- Trypsin-balsam Peru-Castor Oil
  - Delete the following trade names GranuloDerm®, Vasolex®, Xenaderm®
  - Change listings to:
    - Aerosol
    - Ointment
- Wound Cleanser
  - Change trade name to Karrington Clara-Klenz®

## Miscellaneous Dermatologicals

- Trypsin-balsam Peru-Castor Oil
  - Delete the following trade names GranuloDerm®, Vasolex®, Xenaderm®
  - Change listings to:
    - Aerosol
    - Ointment

On a motion of Dr. Messer, seconded by Ms. Millhollon, the recommended changes to the dermatological section were approved.

## Novel Oral Anticoagulant Review

Dr. Hall provided a review of the NOACs or novel oral anticoagulant medications dabigatran, rivaroxaban, apixaban, and edoxaban. The following is a brief summary of the available oral anticoagulants on the market.

### Warfarin

- Inhibits formation of vitamin K-dependent clotting factors (II, VII, IX, X) and proteins C & S
- Approved indications
  - Prophylaxis and treatment of thromboembolic disorders (e.g., venous, pulmonary) and embolic complications arising from atrial fibrillation or cardiac valve replacement
  - Adjunct to reduce risk of systemic embolism (e.g., recurrent MI, stroke) after myocardial infarction
- Substrate of CYP 2C9 (major), CYP 1A2 (minor), CYP 3A4(minor) and CPY 2C19 (minor)
- Monitoring parameters include PT/INR
- Has drug/vitamin K food interactions; takes 5-7 days for full effect, half-life is approximately 40 hours
- Vitamin K is used for reversing the effects of warfarin when INR > 10
- Pre-op management requires that warfarin be held at least 5 days before surgery

### Dabigatran (Pradaxa®)

- Directly inhibits thrombin
- Approved indications
  - Deep venous thrombosis and pulmonary embolism treatment and prevention (in patients treated with parenteral anticoagulants for 5-10 days)
  - Nonvalvular atrial fibrillation (decrease risk of stroke, systemic embolism)
  - Postoperative thromboprophylaxis (hip replacement)
- Metabolism is through hepatic glucuronidation; P-gp
- Routine lab monitoring, other than renal function, is not required. Activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), thrombin time (TT) may be used to assess bleeding risk.
- Requires twice a day dosing so compliance could be an issue; dosing is based on renal function; use is contraindicated if CrCl ≤ 30 ml/min, P-gp drug interactions
- Per product labeling, “use with extreme caution or consider other treatment options in patients > 75 kg”
- Dabigatran is the only NOAC that currently has a specific antidote - idarucizumab (Praxbind®). Idarucizumab is an IV monoclonal antibody that binds to dabigatran to reverse anticoagulation. It costs about \$3,500 per dose and is indicated for life threatening bleeding or the need for emergency surgery within eight hours. Other reversal strategies include dialysis (60% dialyzable) and activated charcoal if ingestion is < 2 hours before presentation

- Pre-op management include: CrCl  $\geq$  50 ml/min  $\rightarrow$  hold 1-2 days; CrCl  $<$  50 ml/min  $\rightarrow$  hold 3-5 days; Consider holding  $>$  5 days for major surgery, spinal puncture/catheter/port insertion

#### Edoxaban (Savaysa®)

- Directly inhibits factor Xa
- Approved indications
  - Deep vein thrombosis and pulmonary embolism (patients treated with parenteral anticoagulants for 5 to 10 days)
  - Nonvalvular atrial fibrillation
- Metabolism is through P-gp, CYP 3A4 (minor); hydrolysis (minimal)
- Routine labs not required
- Administered daily; For DVT/PE - decrease dose if:  $<$  60 kg, concomitant P-gp inhibitor, or CrCl 15-50 ml/min. Do not use if CrCl  $<$  15 ml/min. For nonvalvular atrial fibrillation – **Don't use if CrCl  $>$  95 ml/min.** Decrease dose if CrCl 15-50 ml/min. Don't use if CrCl  $<$  15 ml/min.
- No specific antidote; not dialyzable
- Discontinue at least 24 hours prior to elective surgery or invasive procedure

#### Rivaroxaban (Xarelto®)

- Directly inhabits factor Xa
- Approved Indications
  - Deep vein thrombosis prophylaxis (knee or hip replacement surgery)
  - DVT treatment
  - PE treatment
  - Nonvalvular atrial fibrillation
  - Reduction in the risk (secondary prevention) of recurrent deep vein thrombosis and/or pulmonary embolism
- Metabolism through CYP 3A4, P-gp, 3A5 (minor), CYP 2J2 (minor)
- Routine labs not required; may use PT or antifactor Xa activity to detect presence of rivaroxaban; monitor renal and hepatic function
- If dose  $\geq$  15 mg/day then give with food; dosing frequency depends on indication; renal dosing; avoid moderate to severe hepatic impairment; watch for CYP 3A4, P-gp drug interactions
- No specific antidote; for major bleeding consider prothrombin complex concentrate (PCC), activated PCC or recombinant factor VIIa; not dialyzable; new antidote is in the pipeline
- Hold at least 24 hours before surgery

#### Apixaban (Eliquis®)

- Directly inhibits factor Xa
- Approved indications
  - Deep vein thrombosis: treatment of DVT, to reduce risk of recurrent DVT following initial treatment
  - Nonvalvular atrial fibrillation
  - Postoperative venous thromboprophylaxis following hip or knee replacement
  - Pulmonary embolism: treatment of PE, to reduce risk of recurrent PE following initial treatment
- Metabolism CYP 3A4; P-gp
- Routine labs not required: PT, INR, aPTT may detect presence of apixaban
- Twice a day dosing; renal dosing; avoid CrCl  $<$  25 ml/min; avoid in severe liver impairment; watch for CYP 3A4, P-gp drug interactions
- No specific antidote; may consider PCC, activated PCC or recombinant factor VIIa; not dialyzable; activated charcoal if ingestion within 2-6 hours of presentation
- Hold at least 24 to 48 hours before surgery

The novel oral anticoagulants (NOAC) have no required lab monitoring. Before starting a NOAC, obtain PT, aPTT, serum creatinine and platelets. Compared to vitamin K antagonists, there is less variability in drug effect for a given dose. A single missed dose of a NOAC is more likely to lead to inadequate anticoagulation than single missed dose of warfarin because NOACs have a shorter half-life. Therefore, compliance is needed with these medications.

Overall, the risk of bleeding with NOACs is similar to that of the vitamin K antagonists. The risk for intracranial bleeding is less with NOACs.

NOACs are not appropriate in:

- Severe renal insufficiency
  - A-fib trials excluded patients eCrCl < 30 ml/min
  - Per ACCP, dabigatran is contraindicated in patients with CrCl ≤ 30 ml/min
- Lack of clinical experience in pregnancy, therefore LMW heparin should be used
- With prosthetic heart valves there is a greater risk of valve thrombosis compared to vitamin K antagonists, therefore warfarin should be used in these cases
- For BMI > 40 kg/m<sup>2</sup>, weight > 120 kg, the Intl Soc. On Thrombosis and Haemostasis 2016 guidelines suggests avoiding due to lack of data. Rivaroxaban product label states “extremes of body weight (<50 kg or > 120 kg) do not significantly influence rivaroxaban exposure.”

Rivaroxaban is usually given once daily and does not need to be dose adjusted for extremes of body weight. In reviewing purchase histories for the state hospitals and the state supported living centers, it was noted that rivaroxaban is the most purchased NOAC. On a recommendation of Dr. Messer, seconded by Ms. Millhollon, it was recommended that rivaroxaban be added to the Formulary.

### New Drug Applications

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

#### **Naltrexone Extended Release Injection (Vivitrol®) - presented by Haemy Chung, Pharm.D. Student**

Naltrexone is an opioid antagonist which has the highest affinity for the mu-opioid receptor. Minimal to no opioid agonist activity is seen with naltrexone. However, it does produce some pupillary constriction by an unknown pathway. Naltrexone is indicated in:

- the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation
- prevention of relapse to opioid dependence, following opioid detoxification

The dose is 380 mg IM gluteal injections (alternating) every 4 weeks or once a month. The patient should be opioid free for a minimum of 7 – 10 days prior to initiation of therapy and should not be actively drinking at the time of therapy initiation.

The use of naltrexone extended release injection requires a REMS program. The goal of the REMS program is to:

- inform patients and healthcare providers about severe injection site reactions associated with the use of naltrexone extended release injection
- inform healthcare providers about the importance of counseling their patients about severe injection site reactions associated with the use of naltrexone extended release injection

The Medication Guide must be provided to patients before each administration of naltrexone extended release injection. The advantage of naltrexone extended release injection is higher patient adherence in the outpatient setting. In the inpatient setting, the oral administration of naltrexone can be supported by staff. The studies in establishing efficacy of naltrexone extended release injection excluded patients with many psychiatric co-morbidities and psychiatric medication. The Pharmacy system (WORx™) shows that San Antonio State Hospital and Lufkin State Supported Living Center have used this product. It is unlikely, that the Supported Living Centers' new pharmacy system has this product listed.

**After a discussion, on a motion of Dr. Heidel, seconded by Ms. Millhollon, the request to add naltrexone long acting injection was denied.** It was recommended that its use (purchase history) be tracked and if the use increases, then the application to add naltrexone extended release injection will be reconsidered. If facilities need this product for their patients, then they are encouraged to use it as well as following the REMS program and working with the outpatient clinic to determine accessibility of the drug once the patient is discharged.

## Drug Deletion

The Committee did not receive any feedback from field regarding the deletion of the following items from the DADS/DSHS Drug Formulary:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Aminophylline		Injection: 25 mg/ml Suppository, rectal: 250 mg Tablet: 200 mg	None
Salmeterol	Serevent®	Aerosol, inhalation: 25 mcg/dose	Powder, inhalation: 50 mcg
Terbutaline		Aerosol, oral: 0.2 mg/actuation	Injection: 1 mg/ml Tablet: 2.5 mg, 5 mg
Theophylline		Capsule, timed release (12 hour): 130 mg, 260 mg Capsule, timed release (24 hour); 100 mg, 200 mg, 300 mg Solution, oral: 80 mg/15 ml, 150 mg/15 ml Tablet, immediate release (Slo- phyllin®): 100 mg, 125 mg, 200 mg, 250 mg, 300 mg Tablet, timed release: Theolair® SR (8-12 hour): 100 mg, 200 mg, 250 mg, 300 mg, 500 mg Theo-Dur (8-24 hour): 100 mg, 200 mg, 300 mg, 450 mg Theophylline SR (12-24 hour): 100 mg, 200 mg, 300 mg Uniphyll (24 hour): 400 mg Tablet, timed release (12 hour): 100 mg, 200 mg, 300 mg	None
Triamcinolone		Aerosol, oral, inhalation: 100 mcg/metered spray	Aerosol, topical: 0.2/2 second spray Cream, topical: 0.025%, 0.1%, 0.5% Lotion, topical: 0.25%, 0.1% Ointment, topical: 0.25%, 0.1%, 0.5% Spray, intranasal: 55 mcg/actuation [100 sprays/canister]
Brompheniramine- pseudoephedrine		Capsule: Brompheniramine 12 mg – pseudoephedrine 20 mg Elixir: brompheniramine 4 mg – pseudoephedrine 30 mg Liquid: brompheniramine 12 mg –pseudoephedrine 1 mg per 5 ml Syrup: brompheniramine 2 mg – pseudoephedrine 30 mg Tablet, sustained release: brompheniramine 8 mg – pseudoephedrine 120 mg	Liquid: brompheniramine 15 mg –pseudoephedrine 1mg per 5 ml Tablet: brompheniramine 4 mg –pseudoephedrine 60 mg
Chlorpheniramine		Capsule: 12 mg Tablet: 8 mg, 12 mg	Syrup: 2 mg/5 ml Tablet: 4 mg

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
		Tablet, chewable: 2 mg Tablet, timed release: 8 mg	Tablet, timed release: 12 mg
Diphenhydramine		Tablet: 50 mg	Capsule: 25 mg, 50 mg Cream, topical: 2% Injection: 50 mg/ml Liquid, oral: 12.5 mg/5 ml Lotion: 1%
Phenylephrine		Solution, nasal, drops: 0.25%, 0.5%	Solution, nasal, drops: 0.125% Solution, nasal, spray: 0.25%, 0.5%, 1% Solution, ophthalmic: 2.5%, 10%
Pseudoephedrine		Tablet, timed release: 120 mg Tablet, extended release: 240 mg	Liquid, oral: 15 mg/5 ml, 30 mg/5 ml Tablet, immediate release: 30 mg, 60 mg Tablet, extended release: 120 mg
Triprolidine- pseudoephedrine		Capsule, extended release: Triprolidine 5 mg – pseudoephedrine 120 mg Syrup: Triprolidine 1.25 mg – pseudoephedrine 30 mg per 10 mg	Tablet: Triprolidine 2.5 mg – pseudoephedrine 60 mg
Guaifenesin		Caplet, sustained release: 600 mg Liquid, oral: 200 mg/5 ml Tablet: 100 mg	Liquid, oral: 100 mg/5 ml Tablet: 200 mg, 400 mg Tablet, sustained release: 600 mg
Potassium iodide		Solution, oral: 100 mg/ml	Solution, oral: 1 g/ml
Cetirizine		Tablet, chew: 5 mg, 10 mg	Syrup: 1 mg/ml Tablet: 5 mg, 10 mg
Hydroxyzine		Suspension: 25 mg/5 ml Tablet: 100 mg	Capsule: 25 mg, 50 mg, 100 mg Injection, as hydrochloride: 25 mg/ml, 50 mg/ml Syrup, as hydrochloride: 10 mg/5 ml Tablet: 10 mg, 25 mg, 50 mg

With the removal of terbutaline from the respiratory section at April's meeting, terbutaline is no longer listed in a section. The injection and tablets are still listed in the Formulary. Since terbutaline is occasionally used for the treatment of priapism, it is recommended that terbutaline be moved to the Genitourinary Section.

On a motion of Dr. Wright, seconded by Dr. Messer, the products were deleted from the Formulary and terbutaline was moved to the Genitourinary Section.

### New Dosage Strengths

It was recommended that pramoxine 1%-hydrocortisone 1% foam (Proctofoam® HC) be added to the Formulary as other combinations of pramoxine and hydrocortisone are on Formulary.

On a motion of Ms. Millhollon, seconded by Dr. Messer, the recommendation to add pramoxine 1%-hydrocortisone 1% foam to the Formulary was approved.

### Psychotropic Audit Criteria & Guidelines - Antidepressants

The Antidepressant Audit Criteria and Guidelines have not been reviewed.

## **Psychotropic Audit Criteria & Guidelines – Chemical Dependence Adjunct**

The Chemical Dependence Adjunct Audit Criteria and Guidelines have not been developed.

### **Brexpiprazole (Rexulti®) Review**

Brexpiprazole was added to the Formulary in January. Since it is a newly marketed agent, its use, adverse effects and medication errors are being reviewed. Since October 1, 2015 to current, two facilities (San Angelo State Supported Living Center and San Antonio State Hospital) have used brexpiprazole. San Angelo has had eleven individuals on brexpiprazole and currently, there are 5 individuals on this drug. San Antonio has had two patients try brexpiprazole. Both patients are currently at the hospital but not on brexpiprazole. Neither facility reported any adverse drug reactions or medication errors with this drug.

### **Brexpiprazole (Rexulti®) Audit Criteria**

Brexpiprazole was added to the Atypical Antipsychotic Audit Criteria. For the indication section, it was noted that brexpiprazole is not indicated for bipolar disorder but is indicated for adjunctive treatment in depression for patients who are on antidepressants. For brexpiprazole, the major metabolic pathways are CYP3A4 and 2D6.

In reviewing the audit criteria, it was noted that lurasidone has an indication for bipolar disorder, so this change was made to the audit criteria.

On a motion of Dr. Messer, seconded by Dr. Balfanz, the Atypical Antipsychotics Audit Criteria were approved as modified. See Attachment B.

### **Aripiprazole lauroxil (Aristada™) Review**

At January's meeting, the Committee tabled the request to add Aristada® to the Formulary with the plan to review its use in six months. Since Aristada™ was added to WORx, four patients have been tried on this drug. San Antonio State Hospital and Terrell State Hospital each had two patients on the drug. Each hospital has one patient currently on Aristada™ and one was discharged on it.

It was recommended to review its use in six months.

### **Antipsychotic Tier Schedule**

Dr. Richards presented an updated Antipsychotic Tier Schedule. The major changes were:

- Adding aripiprazole LAI (Aristada) with 15 dollar signs to Tier 2
- Adding "Maintena" to the current Aripiprazole LAI listing in order to distinguish between the two LAI products for aripiprazole
- Adding brexpiprazole with seven dollar signs to Tier 2
- Adding cariprazine with seven dollar signs to Tier 3

A pricing update was completed for the relative cost. The cost is based on average dosing. The price changes are as follows:

- Decrease aripiprazole from 8 dollar signs to 1 dollar sign
- Increase asenapine from 5 dollar signs to 6 dollar signs
- Increase chlorpromazine from 1 dollar sign to 3 dollar signs
- Increase fluphenazine from 1 cent sign to 1 dollar sign
- Decrease haloperidol from 1 dollar sign to 1 cent sign
- Increase lurasidone from 8 dollar signs to 10 dollar signs
- Decrease perphenazine from 3 dollar signs to 2 dollar signs
- Increase aripiprazole LAI (Maintena®) from 10 dollar signs to 12 dollar signs
- Increase clozapine tablets, oral disintegrating tablets from 2 to 7 dollar signs to 2 to 10 dollar signs

- Increase iloperidone from 11 dollar signs to 13 dollar signs
- Decrease paliperidone from 10 dollar signs to 6 dollar signs
- Increase paliperidone palmitate from 11 dollar signs to 12 dollar signs
- Increase risperidone microspheres LAI from 10 dollar signs to 12 dollar signs
- Increase clozapine suspension from 15 dollar signs to 16 dollar signs
- Decrease thioridazine from 2 dollar signs to 1 dollar sign

On a motion of Dr. Wright, seconded by Ms. Millhollon, the changes in the Antipsychotic Tier Schedule were approved. See Attachment C.

### **Monitoring Parameters Children/Adolescent**

At the previous meeting, Dr. Shishko provided a review on the diagnosing of metabolic syndrome in children and adolescents. The ADA and APA recommendations for monitoring vary slightly from the current psychotropic audit criteria. Obvious differences include: obtaining personal/family history and blood pressure monitoring. The psychotropic audit criteria do not require these items, however, this information is obtained through other sources/requirements. The other differences were in timing of the sampling. The Committee did not feel that the differences truly warranted a change in the psychotropic audit criteria. On a motion of Dr. Wright, seconded by Ms. Millhollon, it was recommended that the psychotropic audit criteria monitoring parameters for metabolic syndrome remain the same.

### **Issues from the Medical Executive Committee**

Dr. Muse reported that the Medical Executive Committee did not have any issues for this Committee.

### **Medical Director for Behavioral Health**

Dr. Muse reported that effective September 1<sup>st</sup>, she will be moving to HHSC and will be working with the Community programs and will no longer be involved with the state hospitals. Her current position is posted.

### **Antipsychotics Use Review Group (Hospital Section)**

Dr. Muse requested that the Executive Formulary Committee form a sub-committee of Hospital members that would review the use of atypical antipsychotics for the state hospitals. Currently, cost data is being obtained and distributed to hospital administrations. She would like an overall review of this information. The following individuals volunteered to work on this sub-committee:

- Ann Richards
- Catherine Hall
- Connie Millhollon
- Jeanna Heidel
- Jennifer Wright
- Mark Messer

Dr. Richards will coordinate the sub-committee.

### **FDA Drug Safety Communications**

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

The FDA has approved a brand name change for the antidepressant Brintellix (vortioxetine) to decrease the risk of prescribing and dispensing errors resulting from name confusion with the blood-thinning medicine Brilinta (ticagrelor). The new brand name of the drug will be Trintellix, and it is expected to be available starting in June 2016. No other changes will be made to the label or packaging, and the medicine is exactly the same.

The FDA is warning that compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with the use of the antipsychotic drug aripiprazole (Abilify, Abilify Maintena, Aristada, and generics). These uncontrollable urges were reported to have stopped when the medicine was discontinued or the

dose was reduced. These impulse-control problems are rare, but they may result in harm to the patient and others if not recognized. Although pathological gambling is listed as a reported side effect in the current aripiprazole drug labels, this description does not entirely reflect the nature of the impulse-control risk that the FDA identified. In addition, FDA has become aware of other compulsive behaviors associated with aripiprazole, such as compulsive eating, shopping, and sexual actions. These compulsive behaviors can affect anyone who is taking the medicine. As a result, FDA is adding new warnings about all of these compulsive behaviors to the drug labels and the patient Medication Guides for all aripiprazole products. Health care professionals should make patients and caregivers aware of the risk of these uncontrollable urges when prescribing aripiprazole, and specifically ask patients about any new or increasing urges while they are being treated with aripiprazole. Closely monitor for new or worsening uncontrollable urges in patients at higher risk for impulse-control problems. These include those with a personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse, or other addictive behaviors. Consider reducing the dose or stopping the medicine if such urges develop.

The FDA is warning that the antipsychotic medicine olanzapine can cause a rare but serious skin reaction that can progress to affect other parts of the body. The FDA is adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). A search of the FDA Adverse Event Reporting System (FAERS) database identified 23 cases of DRESS reported with olanzapine worldwide since 1996, when the first olanzapine-containing product was approved. FAERS includes only reports submitted to FDA, so there are likely to be additional cases about which FDA is unaware. One patient taking olanzapine experienced DRESS and died; however, this patient was taking multiple medicines that could also have contributed to death. DRESS may start as a rash that can spread to all parts of the body. It can include fever and swollen lymph nodes and a swollen face. It causes a higher-than-normal number of infection-fighting white blood cells called eosinophils that can cause inflammation, or swelling. DRESS can result in injury to organs including the liver, kidneys, lungs, heart, or pancreas, and can lead to death. DRESS is a potentially fatal drug reaction with a mortality rate of up to 10%. Health care professionals should immediately stop treatment with olanzapine if DRESS is suspected. There is currently no specific treatment for DRESS. The important ways to manage DRESS are early recognition of the syndrome, discontinuation of the offending agent as soon as possible, and supportive care. Treatment with systemic corticosteroids should be considered in cases with extensive organ involvement. When prescribing the medicine, explain the signs and symptoms of severe skin reactions to your patients and tell them when to seek immediate medical care.

The FDA is warning that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium®), including through abuse or misuse of the product, can cause serious heart problems that can lead to death. The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medicines that interact with loperamide. The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria.

The FDA is alerting health care professionals that PharmaTech LLC, Davie, Florida, is voluntarily recalling all non-expired lots of Diocto Liquid, a docusate sodium solution distributed by Rugby Laboratories, Livonia, Michigan. The agency confirmed the product has been contaminated with *Burkholderia cepacia*, a bacteria linked to an outbreak in five states. In addition, FDA has received several adverse event reports of *B. cepacia* infections in patients. Some of these reports identify liquid docusate sodium products manufactured by companies other than PharmaTech. FDA and the Centers for Disease Control and Prevention continue to investigate the extent of this issue in order to identify other potentially contaminated liquid docusate sodium products. The FDA joins CDC in recommending that clinicians not use any liquid docusate sodium product as a stool softener or for any other medical purpose.

The FDA approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection). These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, FDA revised the Boxed Warning, FDA's strongest warning, to address these serious safety issues. In addition, FDA updated other parts of the drug label including the Warnings and Precautions and Medication Guide sections. The FDA has determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and

uncomplicated urinary tract infections because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option. FDA is continuing to assess safety issues with fluoroquinolones as part of FDA's usual ongoing review of drugs and will update the public if additional actions are needed.

### **Probiotic Purchases**

At the last meeting, it was suggested that purchases of probiotic agents be reviewed. The following are the probiotic agents' purchases from January 1, 2016 through June 30, 2016:

DADS	\$51,485.83
DSHS	\$4,149.61

Based on the amount of purchases, it was recommended that a review of probiotics be presented at the next meeting.

### **Donepezil Purchases**

At the previous meeting, the Committee suggested that the purchases of donepezil be reviewed. For January 1, 2016 through June 30, 2016, the purchases for donepezil were:

DADS	\$6,178.19
DSHS	\$390.50

The Committee noted that the purchases for donepezil were minimal.

### **Quarterly Non-Formulary Drug Justification Report**

For the third quarter of fiscal year 2016, all facilities reported use of non-formulary agents. The DADS facilities submitted 1,137 non-formulary requests and the DSHS facilities had 386 requests. The following were the top non-formulary agents that were prescribed:

- Cariprazine (Vraylar)
- Omega 3 acid ethyl esters (Lovaza®)
- Losartan (Cozaar)
- Phenazopyridine liquid (Uti-STAT)
- Magnesium oxide

### **Sectional Review for Next Meeting**

The following sections will be reviewed at the next meeting:

- Dermatologicals (Scabicides to Wound Agents)
- Irrigation solutions
- Immunological agents
- Table Review (Psychotropics)
- Reserve Drug Review

### **Other Issues**

The following information was shared with the Committee members:

The Wall Street Journal reported that the Food and Drug Administration approved Acadia Pharmaceuticals' Nuplazid (pimavanserin), the first FDA-approved drug to treat Parkinson's-related psychosis. Like other atypical antipsychotic drugs, Nuplazid will carry a boxed warning that it can increase the risk of death for older patients with dementia-related psychosis.

HCP Live reports that on May 2, the Food and Drug Administration approved a new oral “formulation of perampanel (Fycompa),” a medication developed by Eisai Inc. for the treatment of epileptic seizures. The FDA has approved the drug “as an adjunctive therapy to treat partial-onset seizures (POS) with or without secondarily generalized seizures and primary generalized tonic-clonic (PGTC) seizures.”

In “To Your Health,” the Washington Post (5/3, Cha) reports officials with the Centers for Disease Control and Prevention are now “urging parents of preschoolers with attention-deficit/hyperactivity disorder (AD/HD) to try behavior therapy first before trying” medications. In addition, the CDC is “calling on insurers to cover the treatments.” Currently, about 75 percent of children with AD/HD are receiving medication for treatment. CDC principal deputy director Anne Schuchat, MD, MPH, said in a call with reporters yesterday, “Until we know more, the recommendation is to first refer parents of children under six years of age who have AD/HD for training and behavior therapy.”

TIME (5/18, Park) reports that Lyrica (pregabalin), a medication “approved in the US to treat nerve pain, including fibromyalgia and pain caused by shingles and diabetes, as well as for seizures,” may also “contribute to birth defects,” a study published online May 18 in *Neurology* suggests.

The safe use of the CredibleMeds® lists of medications requires that the user have the most up-to-date lists and be aware when changes are made to the lists. Therefore, we wish to inform you of the following changes. **Buprenorphine**, an opiate used to treat addiction, (brand names Butrans®, Belbuca®, Bunavail®, Buprenex®, Suboxone®, Zubsolv®): Substantial evidence associates it with QT prolongation but we found no convincing evidence of torsades de pointes arrhythmia (TdP) at this time. Therefore, it has been added to the list with **Possible Risk (PR) of TdP**. **Loperamide** (Imodium® and many OTC and Rx brand names), an over-the-counter drug used to treat diarrhea: It is associated with TdP when taken in very high dosages, most often by people addicted to narcotics. Therefore, it was added to the **Conditional Risk (CR) of TdP list** (Condition = excessive dose). These drugs are also now included in the list of **Drugs to Avoid in patients with Congenital Long QT Syndrome** (if at all possible).

The Washington Post (5/26, McGinley) reports in “To Your Health” that the Food and Drug Administration “on Thursday approved the first implantable drug to deliver long-lasting medication to people addicted to opioids.” The implant, known as Probuphine, “administers the anti-addiction drug buprenorphine in a continuous dose for six months.” It is “intended for people who are already stable on low doses of the drug.”

The AP (5/29) reported that on Friday, US District Court Judge John C. Coughenour “ordered Washington Medicaid to provide an expensive drug to all hepatitis C patients, not just the sickest ones.” He granted a preliminary injunction which compels the state’s Medicaid agency “to stop a 2015 policy that restricted access to the drugs based on a measure of liver scarring.” Two Medicaid recipients sued the state in February, and the injunction is a result of that class-action suit. The AP said the two and others were denied coverage to Harvoni (ledipasvir/sofosbuvir) to treat their hepatitis C infections.

HealthDay (6/1, Thompson) reports that research suggests the AD/HD medication methylphenidate may “increase the risk of an abnormal heart rhythm shortly after a young person starts taking it.” Investigators, after looking at data on more than 114,600 kids, found that “children and teens who were prescribed methylphenidate – sold under the brand names Ritalin, Daytrana and Concerta – had a 61 percent increased risk of arrhythmias during the first two months of use.” The findings were published in *BMJ*.

Medscape (6/7, Lowry) reports, “The use of atypical antipsychotics during pregnancy is associated with a modest level of risk for fetal malformations,” research suggests. The findings of the analysis of data on 351 women were presented June 2 at the American Society of Clinical Psychopharmacology’s annual meeting.

TIME (6/8, Park) reports that in order to find out “how effective” antidepressants “are in treating depression among younger people,” researchers from Oxford University “conducted an analysis of 34 trials of antidepressants involving more than 5,000 children or teens taking 14 different antidepressants.” In a meta-analysis published online June 8 in *The Lancet*, investigators found that “ratings of the depression before and after taking the medications did not change significantly.” Just one medication, fluoxetine, which is already approved by the Food and Drug Administration for children and adolescents, “improved their depression.”

Medscape (6/13, Lowry) reports that a study published in the American Journal of Psychiatry found that a Food and Drug Administration safety warning “advising clinicians not to prescribe the antidepressant citalopram (multiple brands) at dosages higher than 40 mg/day resulted in worsening depressive symptoms and more psychiatric hospitalizations among patients whose conditions had previously been stabilized with higher doses of the drug.” Researchers studied VA Health Administration electronic medical records and “compared rates of hospitalizations and mortality in an at-risk veteran population whose prescribed dosages of citalopram were >40 mg/day at the time the safety warning was issued and whose dosages were either reduced to ≤40 mg/day after the warning or were not reduced.”

The AP (6/14, Tanner) reports that research suggests “powerful prescription” pain medications may “contribute to heart-related deaths and other fatalities.” The findings were published in the Journal of the American Medical Association. Investigators found that “among more than 45,000 patients in the study, those using opioid” pain medications “had a 64 percent higher risk of dying within six months of starting treatment compared to patients taking other prescription pain medicine.” The study indicated “unintentional overdoses accounted for about 18 percent of the deaths among opioid users, versus 8 percent of the other patients.”

Fox News (6/21, Carstensen) reports that researchers “identified a dose and administration method” of TNX-102 SL, an experimental medication containing “the same chemical property as” the muscle relaxant Flexeril (cyclobenzaprine), “that statistically improved participants” post-traumatic stress disorder “symptoms among several mental health indices.” The findings of the 230-patient, phase II study were presented at a medical meeting.

MedPage Today (6/23, Fiore) reports that typical antipsychotics appear to be associated with an increased risk of “movement disorders” in patients with depression and schizophrenia, research suggests. That risk “was not increased,” however, among patients taking atypical antipsychotics, researchers observed. The findings of the 814-patient study were presented at the International Congress of Parkinson’s Disease and Movement Disorders.

MedPage Today (6/23, Fiore) reports that ADS-5102, “an extended-release formulation of amantadine for levodopa-induced dyskinesia, is well tolerated in the long run,” research suggests. In the “interim analysis of data from an ongoing open-label safety study, adverse event rates for those on ADS-5102 were similar to those in earlier studies over a total of 41 weeks, with the most common being falls (20%) and hallucinations (11%),” researchers reported at the International Congress of Parkinson’s Disease and Movement Disorders.

The Wall Street Journal (6/28, Stynes, Rockoff, Subscription Publication) reports that the Food and Drug Administration has approved Gilead Sciences Inc.’s Epclusa (sofosbuvir/velpatasvir), the first drug that treats all six strains of hepatitis C. According to Gilead, the drug’s list price will be \$74,760 for a course of treatments, which is lower than its older hepatitis C treatments.

HCP Live (6/28, Fitzpatrick) reports that in research published in the June issue of Value in Health, researchers “calculated the incremental cost-effectiveness ratio and compared the costs and public health effects of” restricting hepatitis C treatment “to people with advanced” disease (the current Medicaid approach) to “unrestricted access to medications that have proven to cure the disease.” The study revealed that “restricting hepatitis C treatment to those with advanced disease results in higher costs and less effectiveness.”

The Washington Post (7/6, Eilperin) reports that on Wednesday, HHS said “it is raising the limit on how much of an opioid addiction medication, buprenorphine, qualified health-care providers can prescribe.” Until now, “providers could prescribe buprenorphine to no more than 100 patients at once,” but HHS is raising that limit to 275.

USA Today (7/12, Blumenthal) reports that Sage Therapeutics announced that patients in a mid-stage clinical trial of its experimental drug, SAGE-547, saw a statistically significant decrease in symptoms of postpartum depression compared to a placebo. Patients enrolled in the trial “needed to have had a major depressive episode that began no earlier than the third trimester and no later than the first four weeks following delivery.” They also “needed to be less than six months postpartum at the time of enrollment.”

Healthcare Finance News (7/20, Lagasse) reports that “the more generic alternatives there are to brand-name drugs, the more likely they will drive down costs for patients and providers.” According to a study published in

JAMA Internal Medicine, the availability of four or more generic versions of a medicine is correlated with a price decrease of about 60%, compared to markets with three or fewer generic alternatives. Healthcare Finance explains that many treatment areas have fewer than four generic versions available. For example, “only two-thirds of cancer drugs...have at least one generic.”

### **Next Meeting Date**

The next meeting was scheduled for October 21, 2016.

### **Adjourn**

There being no further business, the meeting was adjourned at 2:00 p.m

Approved: *Jennifer Wright, MD*  
Jennifer Wright, M.D., Chairman

### **Attachments**

- Attachment A – New Drug Application – Naltrexone Extended Release (Vivitrol®)
- Attachment B – Atypical Antipsychotics Psychotropic Audit Criteria
- Attachment C – Antipsychotic Tier Schedule

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: 4/15/16

Name of practitioner submitting the application: Mark Messer DO, Clinical Director @ TSH

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	Opiate Antagonists
Generic Name	Naltrexone
Trade Name(s)	Vivitrol
Manufacturer(s)	Alkermes
Dosage Form(s)	380mg IM q4wk

Explain the pharmacological action or use of this drug:

Mu receptor blockade

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

it is an LAI that only req. q4wks dosing

State which drugs this new drug would replace or supplement:

oral naltrexone

\*\*\*\*\*

application is approved

OR

application is appropriate and complete

Mark Messer  
signature of chairman of facility pharmacy and therapeutics committee

\_\_\_\_\_  
signature of clinical/medical director or designee

**Naltrexone for extended-release injectable suspension**  
(Vivitrol®, Alkermes, Inc.)

**Classification:**

Opioid receptor competitive antagonist

**Description:**

Vivitrol® is supplied in single-use cartons which contain: one 380 mg vial of Vivitrol® microspheres, one vial of 4 mL diluent (to deliver 3.4 mL) for suspension, one 5-mL prepackaged syringe, and needles (with protection device) for injection and administration. Vivitrol® must be administered by a healthcare provider.

**Pharmacology:**

Naltrexone is an opioid antagonist for the mu opioid receptor with the highest affinity. Minimal to no opioid agonist activity is seen with naltrexone. However, it does produce some pupillary constriction by an unknown pathway.

**Pharmacodynamics/Pharmacokinetics:**

- Absorption: Initial peak occurs in approximately 2 hours after injection, followed by a second peak observed approximately 2-3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measureable levels for greater than 1 month. Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 2-4 fold higher following administration of a single dose of Vivitrol® 380 mg. Steady state is reached at the end of dosing interval following the first injection. There is minimal accumulation (<15%) of naltrexone or 6-beta-naltrexol (primary metabolite) upon repeat administration of Vivitrol®.
- Distribution: Vd ~1350 L; widely throughout the body but considerable inter-individual variation exists; Protein binding 21%
- Metabolism: Extensively metabolized via noncytochrome-mediated dehydrogenase conversion to 6-beta-naltrexol and related minor metabolites; glucuronide conjugates are also formed from naltrexone and its metabolites
- Elimination: half-time elimination of naltrexone and 6-beta-naltrexol is 5-10 days (dependent upon erosion of polymer). Excretion is primarily through urine as metabolites and small amounts of unchanged drug

**Indications:**

- Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation
- Prevention of relapse to opioid dependence, following opioid detoxification

**Dosage:**

Injectable suspension containing 380 mg naltrexone in a microsphere formulation and diluent

**Administration:**

- IM alternating gluteal injection by health care provider. **Do not administer IV or SubQ**

**Storage:**

Entire dose pack should be stored in refrigerator (2-8°C; 36-46°F). Kit may be kept at room temperature of ≤25°C; 77°F) for ≤7 days prior to use; must not be frozen

**Contraindications:**

- Patients with acute hepatitis or liver failure
- Patients receiving opioid analgesics
- Patients with current physiologic opioid dependence
- Patients in acute opioid withdrawal
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

**Precautions:**

- **Hepatotoxicity** – may cause hepatocellular injury when given in excessive doses. Discontinue when signs or symptoms of acute hepatitis is seen
- **Injection Site Reaction** – in some cases may be severe and require surgical intervention; includes induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis
- **Eosinophilic pneumonia** – patients should be advised to seek medical attention should they develop symptoms of pneumonia
- **Hypersensitivity** – risk of hypersensitivity, including anaphylaxis
- **Unintended Precipitation of Opioid Withdrawal** - Opioid-dependent and opioid-using patients, including those being treated for alcohol dependence, must be opioid-free for a minimum of 7-10 days before starting Vivitrol® treatment
- **Opioid Overdose at the End of a Dosing Interval, After Missing a Dose and Following an Attempt to Overcome Opioid Blockade** – use of lower doses of opioids after Vivitrol® treatment is discontinued, at the end of a dosing interval, or after missing a dose could result in life-threatening opioid intoxication. Any attempt by a patient to overcome the blockade produced by Vivitrol® by taking opioids is very dangerous and may lead to fatal overdose
- **Depression and Suicidality** – patients should be monitored for depression or suicidal thinking
- **Intramuscular injection** – should be administered with caution to patients with thrombocytopenia or any coagulation disorder
- **Pain Management** – regional analgesia or use of non-opioid analgesics is suggested for pain management<sup>1,2</sup>

**Interactions:**

Naltrexone antagonizes the effects of opioid containing medicines, such as cough and cold medicines, antidiarrheal preparations and opioid analgesic. In contrast to methadone and buprenorphine, naltrexone is not metabolized by CYP3A4 thus avoiding any CYP3A4 metabolized drug interactions. Naltrexone may be used in combination with psychiatric medications. There are

no known CYP 450 drug interactions.<sup>3</sup>

### **Adverse Reactions:**

- **Most frequent in association with Vivitrol® therapy for alcohol dependence (>5% and at least twice as frequently with Vivitrol® than placebo)** – nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders
- **Most frequent in association with Vivitrol® therapy in opioid-dependent patients (>2% and at least twice as frequently with Vivitrol® than placebo)** – hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache

### **Use in Special Populations:**

- PK has not been evaluated in subjects with severe hepatic impairment
- Caution is recommended in administering Vivitrol® to patients with moderate to severe renal impairment
- Pregnancy: Risk Factor C; adverse events observed in animal reproduction studies
- Nursing: Naltrexone is excreted in breast milk. Manufacturer recommends either discontinuing nursing or discontinue the drug<sup>1,2</sup>

### **Hospital costs:**

For Alcohol Dependence:

Acomprosate ≤666 mg 3 times daily ≤\$98.45/28 days

Oral naltrexone 50 mg 1 times daily \$58.80/28 days

Vivitrol® 380 mg 1 time \$1,124.44/28 days

Substance Dependence:

Methadone ≤60-120mg 1 time daily ≤\$17.47-\$20.83/28 days

Buprenorphine SL tablet ≤8-24 mg 1 time daily ≤\$46.56-\$139.69/28 days

Buprenorphine/naloxone SL tablet ≤8-24 mg 1 time daily ≤\$176.12-\$528.36/28 days

Oral naltrexone 50 mg 1 times daily \$58.50/28 days

Vivitrol® 380 mg 1 time \$1,124.44/28 days

### **Monitoring:**

#### **REMS- Requires Medication Guide and Communication Plan**

The Vivitrol® Risk Evaluation and Mitigation Strategy (REMS) program was modified May 17, 2016. The Medication Guide must be provided to patients before each administration of Vivitrol®

Vivitrol®, when used as a comprehensive management program, is indicated for the following:

- Treatment of alcohol dependence who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol®
- Prevention of relapse to opiate dependence following opiate detoxification

Providers and Patients should be aware of the following risks of Vivitrol®:

- Risk of opioid overdose
- Severe injection site reactions
- Precipitation of opioid withdrawal during initiation and reinitiation of Vivitrol®
- Hepatotoxicity
- Patients may not feel the therapeutic effects of opioid containing medicines for pain cough or cold or diarrhea while taking Vivitrol®

- The REMS program for Vivitrol® includes a patient counseling tool that reviews these risks
- There is also an education tool available for providers on techniques to reduce severe injection site reactions.

More information and materials can be found on the FDA REMS website:

<http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>

- Safety bracelets and wallet cards can be obtained by contacting the manufacture of Vivitrol® at 1-800-848-4876

### Other

- Monitor Liver function tests (baseline and periodic); signs and symptoms of opioid withdrawal; injection site reactions with IM administration; and depression and/or suicidal thinking.<sup>4</sup> Contraindicated in those that fail the naloxone challenge test or have a positive urine screen for opioids.

### Efficacy:

Alcohol Dependence:

**A 24-week, multi-center, double-blind, randomized, placebo-controlled trial was conducted at 24 US public hospitals, private and Veterans Administration clinics, and tertiary care medical centers.** Of the 899 individuals screened, 627 who were diagnosed as being actively drinking alcohol-dependent adults were randomized to receive treatment and 624 received at least 1 injection. The participants were randomly assigned to naltrexone 190 mg injection every 4 weeks (n=210), naltrexone 380 mg injection every 4 weeks (n=205), or a placebo injection (n=209) and no participants were given oral naltrexone prior to initial or subsequent injections. Participants were men or nonpregnant nonlactating women aged 18 years or older with a current diagnosis of alcohol dependence defined by DSM IV. Patients also had a minimum of 2 episodes of heavy drinking ( $\geq 5$  standard drinks/d for men and  $\geq 4$  standard drinks/d for women) per week during the 30 days before screening. **Inclusion did not require intent to abstain and ongoing active drinking was not a cause for exclusion.** A subpopulation (8.3%) of lead-in abstinent patients were defined as those who reported no drinking during the 7 consecutive days preceding the first dose of study medication. **Exclusion included** evidence of liver failure (ALT, AST elevation); any clinically significant medical condition that in the opinion of the investigator would adversely affect safety or study participation; **major depression with suicidal ideation, psychosis, or bipolar disorder (patients with treated depression and stable pharmacotherapy for at least 8 weeks were not excluded); dependence within the past year on benzodiazepines, opiates or cocaine;** more than 7 days of inpatient treatment for substance abuse in the month before screening; or use of opiates, oral naltrexone, or disulfiram in the 2 weeks before screening. Detoxification prior to randomization was performed only if medically indicated. The randomization procedure based on the biased coin principle was utilized to optimally balance the allocation of participants based on sex, patient-specified goal of total abstinence, self-reported abstinence for the 7-day lead-in period prior and study site. Injection was made every 4 weeks. 12 sessions of low-intensity psychosocial support was provided to participants in each of the three study groups. At each study visit, patients were systematically asked whether any adverse events had occurred and injection sites were inspected. The number of standard drinks consumed per day was recorded using calendars and recall of drinking patterns. Such data were collected only when breath alcohol levels were 0.02g/dL or less. Patients who discontinued study drug treatment prematurely were allowed to remain in the study, continue to follow the established visit and procedure schedule, and receive the psychosocial therapy. **The primary efficacy end point was the event rate, number of heavy drinking days**

**divided by the number of days at risk for heavy drinking.** Every day, treatment group event rate was contrasted with the placebo group event rate by forming the event rate ratio. Secondary end points included the event rate of “risky” drinking days (>2 drinks per day for men and >1 drink per day for women). Serious adverse events were defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. The primary analysis for the primary and secondary end points were performed on the intention-to-treat population. Primary analysis for end point was performed using a stratified Andersen-Gill recurrent-event Cox model with robust variance estimation. The analysis was performed on all heavy drinking events between the first treatment and 30 days following the last dose. In dropouts, last-day drinking data were collected. No imputations were performed for days in which drinking data were unavailable. Retention rate comparability between treatment groups was evaluated by generating Kaplan-Meier curves for the time-to-study discontinuation. A log-rank test was used to examine treatment group differences.  $P < 0.05$  (2-tailed) was considered for statistical significance.

401 patients (64%) received all 6 injections, 463 (74%) received at least 4 injections. Time to discontinuation was similar among groups. **The number of therapy sessions and the percentage of patients attending all sessions were similar among treatment groups. Compared to the placebo, 380 mg of extended-release naltrexone resulted in a 25% decrease in the event rate of heavy drinking days ( $P = 0.02$ ; significant), and 190 mg of naltrexone resulted in a 17% decrease ( $P = 0.07$ ; not significant). Sex and pretreatment abstinence showed significant interaction with the medication group on treatment outcome, with men and those with lead-in abstinence both exhibiting greater treatment effects. A significant decrease in event rate of heavy drinking was not observed in women but the study notes the study was not designed to answer this question and that the women who participated may not be representative of women in the general population, and the number of women studied was small.** Results indicated that the treatment effect among men taking 380 mg naltrexone vs placebo was highly significant (hazard ratio [HR] 0.56;  $P < 0.001$ ), whereas the treatment effect was not significant in women (HR 1.23;  $P = 0.28$ ). Neither the rate of “risky” drinking nor the rate of any drinking was significantly lower with either dose of long-acting naltrexone. **Treatment x factor interactions with long-acting naltrexone demonstrated significant effects for sex ( $P = 0.002$ ) and lead-in abstinence ( $P = 0.02$ ). The treatment goal of abstinence did not demonstrate a significant interaction with treatment.** The number of patients who maintained complete abstinence during the trial was 14 (7%) in the 380 mg naltrexone group, 13 (6%) in the 190 mg naltrexone group, and 11 (5%) in the placebo group. **Significant treatment effects were observed with long-acting naltrexone 380 mg vs placebo irrespective of whether patients were abstinent during lead-in; however, treatment effects were greater for patient with lead-in abstinence (HR 0.20;  $P = 0.005$ ) compared with patients who drank during the lead-in period (HR 0.79;  $P = 0.05$ ).** The subset of patient with lead-in abstinence also showed a significant treatment effect with long-acting naltrexone 190 mg vs placebo (HR 0.05;  $P < 0.001$ ). However due to the small numbers, this analysis should be interpreted with caution. The patients enrolled in this study predominantly were actively drinking, with only 8.3% abstinent for the 7-day lead-in period. **Among the patient with lead-in abstinence, the rate of total abstinence was 41% in the 380 mg naltrexone group, 35% in the 190 mg naltrexone group, and 17% in the placebo group. Group differences on the measured did not reach significance.** Limitations include study likely including more motivated people compared to the general population, and dropouts reducing extent to which findings generalize to population of all alcoholics. Also, drinking data for dropouts were not obtained once they left the study.<sup>5</sup>

In a meta-analysis of 5 observational studies observing 6 months after initiation of pharmacotherapy, extended release naltrexone had as low or lower healthcare costs, with the longest medication persistence and the least inpatient utilization (detoxification facility, substance-abuse related inpatient, and emergency department).<sup>6</sup>

#### Opioid Dependence:

**A 24 week, placebo-controlled, multi-center, double-blind, randomized trial was conducted at 13 clinical sites in Russia.** Men and women aged 18 years or over who met the DSM IV criteria for opioid dependence disorder, **who had 30 days or less of inpatient detoxification and 7 days or more off all opioids were recruited into the study. Patients were voluntarily seeking treatment and were excluded if they were under justice system coercion ie, parole or probation, or pending legal proceedings with potential for incarceration. Every patient also had a significant other who supervised their compliance with the visit schedule and study procedures.** Women of childbearing potential agreed to use contraception during the study. Other exclusion criteria were pregnancy or breastfeeding; significant medical conditions (ex. acute renal failure, endocarditis, and tuberculosis); positive naloxone challenge (increases in vital signs or opioid withdrawal symptoms); hepatic failure; past or present history of an AIDS-indicator disease; active hepatitis or AST and ALT more than three times the upper limit of normal; known intolerance or hypersensitivity to naltrexone, carmellose, or polylactide-co-glycolide; **psychosis, bipolar disorder, major depressive disorder with SI or present dependence on substances other than opioids or heroin, including alcohol;** positive urine test for cocaine or amphetamines; and naltrexone use within the past 6 months. 335 candidates were screened, 250 of whom were randomly assigned (1:1) to either 380 mg extended-release naltrexone (n=126) or placebo (n=124) by an interactive voice response system, stratified by site and gender in a centralized, permuted-block method. Patients received an injection of extended-release naltrexone or placebo within 1 week after detoxification and then every 4 weeks thereafter, for a total of six injections over 24 weeks. Upon completion of the 24-week treatment period, all patients were offered open-label extended-release naltrexone treatment for an additional year. Urine drug testing for opioids (immunochemistry-based one-step in-vitro tests) was done weekly for 24 weeks and detected urine morphine and methadone at concentrations greater than 300 ng/mL. **The following drugs were prohibited during the study:** naltrexone, buprenorphine, levacetylmethadol, methadone, other prescription opioids, **antipsychotics, anticonvulsants, antidepressants, and anxiolytics. Permitted drugs were anticonvulsants if dosing was stable and short-acting insomnia drugs, such as zopiclone, as required.** Standardized, manual-based psychosocial support was provided on a biweekly basis to all subjects in addition to medication. **The primary endpoint was the response profile for confirmed abstinence during weeks 5-24, assessed by urine drug tests and self report of non-use. Weeks 1-4 were omitted because participants might challenge the blockade during this period, after which abstinence should stabilize.** Confirmed abstinence was defined as a negative urine drug test and no self-reported opioid use on a survey using calendars and daily recall of substance use on specific days to record quantity or frequency of opioid use. Omission of any of these criteria resulted in failure to confirm abstinence for the week. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days or retention, and relapse to physiological opioid dependence (via naloxone challenge). Physiological dependence was assessed at baseline, upon any positive urine drug screen, at treatment discontinuation, and at week 24. Patients were removed from the study if the naloxone challenge test was positive, and if there was concern for their health according to the health outcome assessments.

Sample size of 125 patients per treatment group provided 85% and 96% power to detect an effect

size of Cohen's  $d$  0.4 and 0.5, respectively, by Wilcoxon rank-sum test at a two-sided significance level of 0.05. Analyses were by intention to treat. **Response profiles were created by calculating the number of confirmed abstinence weeks for weeks 5-24 for each patient and then dividing by the number of scheduled tests.** For between-group comparisons we used a two-sided Van der Waerden test (non-parametric test of whether  $k$  population distributions are equal). The rate of opioid negative urine drug tests were analyzed with ANCOVA, containing factors for treatment group, sex, and sex-by-treatment interaction, and with age, duration of opioid dependence, and duration of last pre-study inpatient detoxification as covariates. Consistency of the effects of treatment on opioid-free weeks across subgroups defined by baseline characteristics such as sex, age, duration of opioid dependence and duration of pre-study detoxification and site was measured with ANCOVA models. Retention was assessed with Kaplan-Meier curves and a log-rank test. Missing urine drug test results were imputed as positive for opioids; retention was censored upon discontinuation, craving was imputed using last observation carried forward, and missing self-reported opioid-free days data were imputed using patients' rates of opioid-free days during the 30 pre-detoxification days. For all other endpoints, all available data were included in analyses. The primary endpoint was tested with a two-sided  $\alpha=0.05$ . For craving and retention outcomes  $p$  values were adjusted for multiplicity using the Bonferroni-Holm method to preserve family-wise type 1 error at 0.05. A full statistical analysis was also done by an independent academic statistician who came to the same conclusions.

Of 4285 urine drug tests and self-reported responses obtained, 4178 (97.5%) were in agreement. On 53 (1.2%) of 4285 occasions, participants self-reported using opioids despite opioid-negative urine tests. Attendance at the scheduled counselling sessions were similar. **Total abstinence was reported in 45 (36%) of patients in the extended-release naltrexone group compared with 28 (23%) in the placebo group ( $p=0.0224$ ).** When efficacy was analyzed on the basis of the full 24-week period, including weeks 1-4, results were still significant ( $p=0.0001$ ). 119 (94%) of 126 patients in the extended-release naltrexone group were opioid free compared with 96 (77%) of 124 in the placebo group by week 2, and this separation persisted through to the end of the trial. **No significant relation was noted between age, sex, or duration of opioid dependence and the rate of opioid-free urine tests (data not shown).** The treatment effect was consistent across baseline variables and study sites (data not shown). All four secondary endpoints also showed significant differences between the treatment groups. Health outcome measures were similar between groups at baseline. Limitations of the study include substantial clinical response to placebo, although treatment group still showed greater benefits. Retention in the placebo group might have been reduced by recognition upon opioid use that one was on placebo or among patients in the placebo group who had relapsed to regular opioid use by reluctance to return to the clinic and face a withdrawal reaction from a naloxone challenge test. **The high retention rate might have been influenced by having someone supervise attendance, provision of individual counselling, and the absence of alternative treatments (ie methadone or buprenorphine use for opioid dependence is prohibited in Russia) and the promise of active extended-release naltrexone treatment for all patients after 6 months in the subsequent open-label extension safety study.**<sup>7</sup>

Kleber et al. concluded that tolerance does not develop for naltrexone's antagonist properties, even after many months of regular use.<sup>8</sup>

Analysis observing 6 months after initiation of pharmacotherapy found similar or lower costs compared to other oral agents and less substance-related inpatient utilization. However, statistical power may have been limited given the availability of only a single opioid dependence study and a relatively smaller number of patients treated with injectable extended-release naltrexone.<sup>6</sup>

## Safety:

There is limited experience with overdose of Vivitrol®. Single doses up to 784 mg were administered to 5 healthy subjects without serious or severe adverse events. The safety of Vivitrol® every 3 weeks in patients who may rapidly metabolize naltrexone has not been established.<sup>9</sup> On December 8, 2015, Alkermes, Inc. released an important drug warning concerning the risk of severe injection site reaction including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis.<sup>3</sup>

### Alcohol dependence

In a double-blind, placebo-controlled, multicenter randomized trial (details under Efficacy section), the most common adverse events were nausea, headache and fatigue. Nausea was mild or moderate in approximately 95% of cases; however, the large majority of these episodes occurred only during the first month of treatment. Nausea and decreased appetite occurred more frequently in patient treated with long-acting naltrexone 380 mg. **Most common injection site reaction was tenderness, 7 patients (~1%) discontinued injections due to site reactions: 4 in the 380 mg naltrexone and 2 in the 190 mg naltrexone groups and 1 in the placebo group. Study discontinuation secondary to adverse events occurred in 29 (14.1%) in the 380 mg naltrexone, 14 (6.7%) in the 190 mg naltrexone and 14 (6.7%) in the placebo groups (p = 0.01; 380 mg vs 190 mg and placebo (the group difference being accounted for by a greater number of adverse events of nausea, injection site reaction, and headache).** The percentage of patients who experienced SAEs during treatment was similar among the treatment group: 11 (5.4%) for 380 mg and 10 (4.8%) for 190 mg naltrexone and 15 (7.2%) for placebo. **The most common SAE was hospitalization for alcohol detoxification. Two SAEs (eosinophilic pneumonia and interstitial pneumonia) were judged by the investigator to be possibly related to study medication. Both events occurred in patients treated with naltrexone 380 mg and resolved with treatment.** Mean AST and ALT levels did not change significantly over the course of treatment or with medication.<sup>5</sup>

### Opioid dependence:

In a double-blind, placebo-controlled, multicenter randomized trial (details under Efficacy section), extended-release naltrexone was generally well tolerated. **Adverse reaction including nasopharyngitis, insomnia, hypertension, influenza, injection site pain, toothache and headache (incidence 3-7%) were summarized in a table but did not go into details.** Injection site pain was more prevalent in the extended-release naltrexone group compared with the placebo group, although no severe adverse reactions were reported. 2 patients in the 380 mg extended-release naltrexone and 2 patients in the placebo group discontinued owing to adverse events. **Study does not clarify which reactions were associated with discontinuation.** 103 of 250 patients experienced at least one adverse event. A higher proportion of patient in the extended-release naltrexone group than placebo group had at least one adverse event (p=0.005). All non-serious adverse events were deemed mild or moderate by investigators and most were judged to be unrelated to the study drug. No overdose events, suicide attempts or death, or other severe adverse events were reports. The mean increase from baseline of ALT was 6.9 IU/L in the extended-release naltrexone group and 5.6 IU/L in the placebo group, and for AST the mean increase from baseline was 3.8 IU/L in the extended-release group and 6.7 IU/L for placebo.<sup>7</sup>

Naltrexone has no abuse potential in contrast to opioids. Buprenorphine overcame potential for IV abuse by combining with naloxone. Patients transitioning from opioid agonist to extended-release injectable naltrexone may be vulnerable to precipitation of withdrawal symptoms for as long as 2 weeks.<sup>3</sup> If the patient would like to switch from naltrexone to methadone or buprenorphine, 30 days should be waited until last injection to ensure that significant amount of naltrexone is not in the

system. Patients who discontinue extended-release injectable naltrexone and resume opioid use have an increase risk in opioid overdose, which may include the risk of death. In an open-label, long-term safety study; adverse events of a suicidal nature (depressed mood, suicidal ideation, suicide attempt) were reported by 5% of opioid-dependent patients treated with extended-release injectable naltrexone vs 10% with oral naltrexone. The efficacy and safety of injectable extended-release naltrexone has been established for up to 1 year.<sup>10,11</sup>

### **Conclusion:**

Efficacy of Vivitrol® has only been established in trials that had psychosocial therapy support.<sup>5,7</sup> Vivitrol® has a higher chance of adherence compared to oral agents in the outpatient setting and lacks abuse potential. Side effects are very similar to that of oral naltrexone except Vivitrol® is associated with more injection site related reactions, which may be severe. Vivitrol® is contraindicated in patients who take opioid analgesics.<sup>1</sup>

### **Alcohol dependence:**

Vivitrol® is indicated for treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation.<sup>1</sup> In a meta-analysis observing 6 months after initiation of pharmacotherapy, extended-release naltrexone had as low or lower healthcare costs, with the longest medication persistence and the least inpatient utilization.<sup>6</sup> However, the analysis looks at outpatient use and in the inpatient setting, oral naltrexone adherence can be supported by staff. The study establishing efficacy and safety for Vivitrol® excluded patients with major depression with SI, psychosis, or bipolar disorders (although depression patients that are stable on pharmacotherapy for at least 8 weeks were not excluded). Thus, efficacy and safety for patients with psychiatric co-morbidities or psychiatric medication are unknown. Although Vivitrol® is associated with reduction in rate of heavy drinking, a significant association with abstinence was not established.<sup>3,5</sup>

### **Opioid dependence:**

Vivitrol® is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.<sup>1</sup> Naltrexone is a valuable option for patients that have failed opiate agonist therapy or do not wish to engage in agonist therapy. Cost-analysis observing 6 months after initiation of pharmacotherapy found similar or lower costs compared to other oral agents and less substance-related inpatient utilization for patients treated in the outpatient setting.<sup>9</sup> However, this finding is for the outpatient setting. The study establishing efficacy and safety for Vivitrol® excluded patients with psychosis, bipolar disorder, major depressive disorders with SI. Prohibited medications while on the study included antipsychotics, anticonvulsants, antidepressants and anxiolytics (only stable dosing anticonvulsants and short-acting insomnia drugs were allowed). Thus, efficacy and safety for patients with psychiatric co-morbidities or psychiatric medication are unknown.<sup>3,7</sup>

### **Recommendation:**

The advantage of Vivitrol® is higher patient adherence in the outpatient setting. However, in the inpatient setting, administration of oral naltrexone can be supported by staff. The studies establishing efficacy and safety of Vivitrol® in alcohol or opioid dependent patients excluded patients with many psychiatric co-morbidities and psychiatric medication so the safety and efficacy of Vivitrol® in the psychiatric patient population is not established. The studies also excluded patients that were dependent on both alcohol and opioids so efficacy and safety were not established in this mixed population.<sup>5,7</sup>

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**ATYPICAL ANTIPSYCHOTICS**

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

**INDICATIONS**

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

**PRECAUTIONS TO CONSIDER**Contraindications*Absolute:*

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

*Relative:*

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

## **ATYPICAL ANTIPSYCHOTICS** (continued)

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

## **PRECAUTIONS TO CONSIDER** (continued)

### Precautions

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

### Pregnancy and Breast-Feeding

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

### Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Concomitant use of agents that cause EPS (including droperidol, metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 3) Concomitant use of hypotension producing agents
- 4) levodopa
- 5) Antithyroid agents
- 6) Drugs that prolong the QT interval
- 7) Strong inhibitors or inducers of Cytochrome 450
- 8) The following are the major metabolic pathways for the atypical antipsychotics:
  - Risperidone: CYP 2D6
  - Olanzapine: CYP 1A2
  - Quetiapine: CYP 3A4
  - Aripiprazole: CYP 2D6 and 3A4
  - Ziprasidone; aldehyde oxidase
  - Paliperidone (non-hepatic, primarily renal elimination)
  - Asenapine: CYP 1A2 and UGT1A4 (direct glucuronidation)
  - Iloperidone: CYP 3A4 and 2D6
  - Lurasidone: CYP 3A4
  - Brexpiprazole: CYP3A4 and 2D6

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

### Age-Specific Considerations

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

## **ATYPICAL ANTIPSYCHOTICS** (continued)

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

## **PRECAUTIONS TO CONSIDER** (continued)

### **Side Effects Which Require Medical Attention**

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

## **PATIENT MONITORING**

### **Patient Monitoring Parameters**

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

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

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

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

## **ATYPICAL ANTIPSYCHOTICS** (continued)

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

## **PATIENT MONITORING** (continued)

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

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

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

### Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

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

Tier	Generic	Relative Cost *
<b>Tier 1:</b> No Prior Approval	Aripiprazole	\$
	Asenapine	\$\$\$\$\$\$
	Chlorpromazine	\$\$\$
	Fluphenazine	\$
	Fluphenazine Decanoate LAI	\$\$
	Haloperidol	¢
	Haloperidol Decanoate LAI	\$
	Loxapine	\$
	Lurasidone	\$\$\$\$\$\$\$\$\$\$
	Olanzapine	¢
	Perphenazine	\$\$
	Quetiapine <sup>3</sup>	¢
	Risperidone	¢
	Thiothixene	\$
	Trifluoperazine	\$
<b>Tier 2:</b> Requires Documentation for Reason for Use Instead of Tier 1 Option	Aripiprazole LAI (Aristada)	\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Aripiprazole LAI (Maintena)	\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Brexipiprazole	\$\$\$\$\$\$\$
	Clozapine <sup>1</sup> Tablets, Oral Disintegrating Tablets	\$\$ - \$\$\$\$\$\$\$\$\$
	Iloperidone <sup>1, 2</sup>	\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Paliperidone	\$\$\$\$\$\$
	Paliperidone Palmitate LAI <sup>1</sup>	\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Risperidone Microspheres LAI	\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Ziprasidone <sup>4</sup>	\$
Any combination of 2 antipsychotics for hospitals	—	
<b>Tier 3:</b> Requires Prospective Review by Clinical Director or Designee	Cariprazine	\$\$\$\$\$\$\$
	Clozapine <sup>1</sup> Suspension	\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Olanzapine Pamoate LAI	\$\$\$\$\$\$\$\$\$\$\$\$\$\$
	Quetiapine ER <sup>3</sup>	\$\$\$\$\$\$\$
	Thioridazine <sup>1,5</sup>	\$
	Any combination of 3 or more antipsychotics	—

\* For LAI (Long-Acting Injection), includes amortized cost of any loading dose or oral overlap over one year

**Specific Medication Notes**

- 1) DSHS Formulary Reserve Drug
- 2) Iloperidone Indication: "In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration." (Fanapt Product Label) DSHS Formulary Reserved Drug Criteria: (a) For use in patients that have failed on two antipsychotics given for a sufficient time; or (b) For patients who cannot tolerate other antipsychotics due to akathisia.
- 3) Caution advised for use in forensic or correctional environments due to potential for diversion and misuse.
- 4) Ziprasidone Indication: "GEODON is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the capacity of GEODON to prolong the QT interval and may consider the use of other drugs first." (Geodon Product Label)
- 5) Thioridazine Indication: "Thioridazine hydrochloride tablets are indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life threatening, proarrhythmic effects with thioridazine treatment, thioridazine hydrochloride tablets should be used only in patients who have failed to respond adequately to treatment with appropriate courses of other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Consequently, before initiating treatment with thioridazine hydrochloride tablets, it is strongly recommended that a patient be given at least two trials, each with a different antipsychotic drug product, at an adequate dose, and for an adequate duration" (Thioridazine Product Label)