DSH PSYCHOTROPIC MEDICATION
Operational Procedures
XANOMELINE/TROSPIUM PROTOCOL

I. Indications:

A. At least 1 of the following clinical indications is present and documented in the chart:

1. DSM diagnosis of schizophrenia or schizoaffective disorder.

2. Neurocognitive disorder with or without psychotic features or Parkinson's disease with psychotic features.

3. Severe persistent aggression or self-injurious behavior with evidence that a behavioral treatment, as part of a formal treatment program, was adequately implemented and found to be ineffective.

B. Contraindications:

1. Hypersensitivity to xanomeline, trospium, or any of the components of the formulation.

2. Category C child-Pugh liver failure. Xanomeline/trospium is substantially dependent on metabolism by cytochrome P-450 2D6.

3. **Concurrent use of M_1 or M_4 muscarinic receptor antagonists that cross the blood-brain barrier** e.g., clozapine, chlorpromazine, olanzapine, quetiapine, benztropine, diphenhydramine, trihexyphenidyl, paroxetine, oxybutynin, tolterodine, darifenacin, solifenacin, amitriptyline, nortriptyline, clomipramine, imipramine, desipramine. **Such medications will negate the cognitive and antipsychotic effects of xanomeline/trospium, respectively.**

Xanomeline provides its clinical benefits by acting as a partial agonist at M_1 and M_4 muscarinic receptors in the central nervous system. Trospium is a muscarinic antagonist that does not cross the blood-brain barrier. It is present to prevent xanomeline-induced peripheral cholinergic adverse effects, e.g., nausea, vomiting, cramping, diarrhea, etc.

II. Precautions (risk/benefit analysis supports use):

A. Impaired hepatic synthetic capacity, i.e., Child-Pugh category.

B. Conditions likely to be sensitive to the anticholinergic effects of trospium, e.g. history of narrow angle glaucoma, constipation, bowel impaction, bowel obstruction, urinary retention (benign prostatic hypertrophy, atonic bladder, etc.

C. History of nausea, dyspepsia, or gastrointestinal reflux disease (GERD) which are not well-controlled.

D. Poorly controlled hypertension. Xanomeline/trospium may cause transient elevation of blood pressure.

E. Poorly controlled tachycardia. Persisting tachycardia (> 100 BPM) is a long-term risk factor for dilated cardiomyopathy.

F. Biliary disease, e.g., symptomatic gallstones. Xanomeline/trospium may cause contraction of the bile ducts.

G. Moderate to severe renal disease.

H. Pregnancy or breast feeding. Risks are currently not known. The manufacturer has established a registry to screen for potential risks.

III. The following initial workup should be completed:

A. There is informed consent or alternate legal authorization.

B. There is chart documentation of:

1. Weight/BMI.

2. Waist circumference

3. Personal or family history of narrow angle glaucoma, cardiac disease, hypertension, gastrointestinal disease, renal disease or urinary tract disease.

4. Personal history of diabetes mellitus.

5. Personal history of biliary or liver disease

C. Initial workup includes:

1. ECG within 1 year or 30 days if cardiac history is positive.

2. Fasting blood glucose and/or Hgb A1c (optional) within 30 days.

3. Lipid panel or cholesterol and triglycerides within 30 days.

4. Electrolytes and liver function tests (including bilirubin) within 30 days.

5. BUN, creatinine, and estimated glomerular filtration rate (eGFR) within 30 days.

6. AIMS within one year.

IV. Monitoring:

A. Monthly monitoring includes weight.

B. Annual monitoring includes:

1. Hepatic functions (including bilirubin).

2. BUN, creatinine, and eGFR.

3. ECG.

4. AIMS.

V. Dose initiation:

A. Xanomeline/trospium (Cobenfy®) is supplied in capsules containing 50/20 mg, 100/20 mg, and 125/30 mg. Typical initial dosing is 50/20 mg b.i.d. for two days to assure tolerability, then 100/20 mg b.i.d. for one week, and then 125/30 mg b.i.d. as the maintenance dose. Doses > 125/30 mg b.i.d. for more than 15 days require TRC or MRC consultation or review.

B. If cholinergic or anticholinergic adverse effects occur during titration, they may be mitigated by returning to the last tolerated dose and titrating more slowly.

C. Dose is typically titrated more slowly in older individuals or medically fragile individuals.

D. Dose accounts for drug-drug interactions:

1. Higher dose may be needed if used with carbamazepine, phenytoin, phenobarbital or other CYP2D6 inducers.

2. Lower dose may be needed if used with strong CYP2D6 inhibitors including fluoxetine, paroxetine, bupropion, etc.

3. Pulse and blood pressure are monitored as clinically indicated (e.g., during titration or at doses above the typical maximum of 125/30 mg of xanomeline/trospium BID.

a) The patient is monitored frequently during the first month of treatment for emergence of cholinergic or anticholinergic adverse effects, with institution of an effective bowel regimen as needed (Please see the appendix chapter in these operational procedures regarding Treatment of Medication-induced Constipation).

VI. Possible adverse reactions:

A. Cardiovascular effects including tachycardia and hypertension.

B. Anticholinergic effects including acute narrow angle glaucoma, constipation, bowel impaction, bowel obstruction, urinary retention, etc.

C. Biliary constriction with elevation of bilirubin.

D. Nausea, dyspepsia, vomiting, and gastrointestinal reflux disease (GERD).

E. Cramping and diarrhea.

F. Angioedema (rare).

References:

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