DSH PSYCHOTROPIC MEDICATION Operational Procedures

ILOPERIDONE PROTOCOL:

I. Indications:

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

1. DSM diagnosis of schizophrenia, schizoaffective disorder or other acute and/or chronic psychoses;

2. DSM diagnosis of bipolar disorder, current episode manic or mixed;

3. DSM diagnosis of a major depressive episode with current psychotic features. Adjunctive treatment also may benefit depressive features;

4. Severe persistent agitation, aggressive, self-injurious, stereotypic, or impulsive behaviors with evidence that a behavioral treatment, as part of a formal treatment program, was adequately implemented and found to be ineffective.

B. Contraindications:

Hypersensitivity to iloperidone or any component of its formulation.

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

1. Diabetes mellitus, glucose intolerance, hyperglycemia, personal history of high BMI, family history of diabetes, drug exposure to alpha or beta blockers, hypertension, and obesity (especially abdominal);

2. Concomitant use of medications known to cause elevated blood glucose (e.g., steroids, niacin, thiazide diuretics, atypical antipsychotics);

3. Hypertriglyceridemia or hypercholesterolemia (current or history of);

4. Cerebrovascular disease and conditions that would predispose individuals to hypotension (e.g., dehydration, hypovolemia and treatment with antihypertensive medications);

5. Severe cardiovascular disease;

6. Liver disease, history of hepatitis or treatment with potentially hepatotoxic drugs;

7. History of active (or, poorly controlled) seizure disorder requiring anticonvulsant treatment or use of other drugs known to lower seizure threshold without neurological consultation;

8. Signs (or, history) of tardive dyskinesia;

9. Pregnancy or breast feeding. (may cause neonatal dyskinesia);

10. History of prolactin sensitive or dependent tumors (e.g., breast cancer), or other conditions or drugs known to elevate prolactin (e.g., metoclopramide, pituitary adenoma);

11. Parkinson's Disease;

12. Renal impairment;

13. Elderly neurocognitively disordered individuals with psychosis;

14. History of leukopenia or severe neutropenia. The risk is low; however, the U.S. Food and Drug Administration has mandated a class warning for the second-generation antipsychotics.

II. 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 diabetes.

4. Personal past history of high BMI.

5. Personal history of hyperlipidemia or hypercholesterolemia.

C. Initial work up includes:

1. Fasting blood glucose or Hgb A1c (optional) within 30 days;

2. Lipid panel or cholesterol and triglycerides within 30 days;

3. Electrolytes and liver function tests within 30 days;

4. Serum prolactin within 30 days;

5. AIMS rating within one year;

6. Neurology consultation (for individuals with history of an active or poorly controlled seizure disorder);

7. ECG within one year;

8. Vital signs within 30 days.

III. Monitoring:

A. Monthly monitoring includes weight.

B. Semi-annual monitoring includes:

1. Lipid panel or triglycerides and cholesterol;

2. Fasting glucose and/or Hgb A1c (optional);

3. Semi-annual monitoring includes ECG if concurrent use of medications which prolong QT interval is present, as indicated by boxed warning in the package insert.

C. Annual monitoring includes:

1. Serum prolactin level. Prolactin measurement should be obtained sooner if prolactin-related symptoms, such as menstrual cycle changes, galactorrhea, gynecomastia and/or hirsutism, occur. Medical consultation and consideration of brain imaging with focus on the pituitary/sella turcica should be considered if symptoms persist despite interventions such as changing to a less robust dopamine antagonist medication or partial dopamine agonist medication, lowering the dose of the medication, or treating with a dopamine agonist medication. Prolactin-related adverse effects become increasingly likely at serum concentrations exceeding 50ng/mL. [Please see the appendix chapter of this policy regarding hyperprolactinemia.]

   Persisting prolactin level above 100ng/mL, despite the aforementioned interventions, results in medical consultation and consideration of obtaining brain imaging with focus on the pituitary/sella turcica.

2. Breast examination in men and women (including a note regarding presence or absence of galactorrhea or gynecomastia). Medical consultation and consideration of brain imaging with focus on the pituitary/sella turcica should be considered if galactorrhea or gynecomastia persist despite the interventions cited above.

3. Waist circumference;

4. ECG;

5. AIMS rating. (Done quarterly if positive until twice negative);

6. Fasting serum glucose is 100 mg/dL or higher or elevated Hgb A1c results in glucose tolerance test or 2-hour postprandial glucose measurement and medical consultation.

7. Nutritional consultation and appropriate dietary and exercise interventions if any of the following weight gain indicators occurs:

   a. Weight increase of 5% in one month, 7.5% in three months, or 10% in six months

   b. Waist circumference increase from below 35in. to > 35in. for females and from below 40in. to > 40in. for males

   c. BMI increase from normal to overweight (from <25 to >25) or from overweight to obese (from 25 – 29.9 to 30 or higher)

8. Abnormal or rising triglyceride and cholesterol levels result in medical consultation and appropriate interventions.

IV. Dose initiation and titration:

A. Typical initial dose is 1 – 2 mg BID. If treatment is well tolerated and symptoms persist, dose can be increased slowly. Doses range from 4 – 24 mg/day, with typical daily doses ranging from 12 – 24 mg BID.

In general, oral antipsychotics should be titrated upward every two weeks until one of four endpoints is reached, i.e., the desired clinical result is achieved, intolerable unmanageable adverse effects are encountered, the point of futility for the antipsychotic is reached, or an upper dose limit established by law or regulation is reached.

B. Lower dose is typically started in the elderly and in those with renal or hepatic impairment (1 mg BID). Dose is titrated slowly with careful monitoring for EPS, orthostatic blood pressure abnormality, and sedation.

C. There is documented explanation if dose higher than 24 mg/day is used (see next section). Doses > 24 mg/day for > 15 days require MRC or TRC consultation or review.

D. Dosage accounts for drug-drug interactions:

1. Approximately two-fold increase in dose may be needed if used with carbamazepine, a metabolic inducer. Similar changes may be needed for other metabolic inducers (e.g., phenytoin, phenobarbital, rifampin, and possibly oxcarbazepine).

2. Lower doses may be needed if used with CYP2D6 and/or CYP3A inhibitors (e.g., fluoxetine, paroxetine, bupropion, sertraline, fluvoxamine, ketoconazole, erythromycin, clarithromycin, and diltiazem.). Avoid combining iloperidone with cimetidine, grapefruit juice and protease inhibitors.

E. Pulse and blood pressure are monitored prior to dose administration as clinically indicated (e.g., during titration or at doses above maximum) for one week after starting or increasing dose. Signs of orthostatic hypotension are documented if individual can verbalize. Pulse and blood pressure are recorded first in the seated position after three minutes and then in the standing position after two minutes. If individual cannot stand up, he/she is monitored closely until the dose is stable if he/she is known to try to get up and not follow recommendations.

If any recorded item lies outside the following parameters, the measure is repeated after 15 minutes. If the item is then within the parameters, iloperidone may be given. If still outside the parameter, the physician is called to assess before dose administration.

1. The parameters are:

a. Systolic blood pressure <90 mm or >150 mm.

b. Diastolic blood pressure <60 mm or >100 mm.

c. Drop >20 mm in systolic or diastolic pressure between sitting and standing.

d. Pulse >120/min or <60/min.

V. Possible adverse reactions:

A. Headache;

B. Sedation;

C. Insomnia;

D. Agitation and anxiety;

E. Reversible extrapyramidal symptoms (parkinsonian side effects, akathisia and acute dystonic reactions);

F. Tardive Dyskinesia, especially with the demented elderly;

G. Orthostatic Hypotension;

H. Weight gain;

I. Hyperglycemia, ranging from mild glucose intolerance to diabetic ketoacidosis and nonketotic hyperosmolar coma;

J. Hyperlipidemia;

K. Hyperprolactinemia with associated decreased libido, galactorrhea, menstrual disturbances (including amenorrhea), infertility, decreased bone density (long-term), gynecomastia, and erectile and ejaculatory dysfunction;

L. Dyspepsia and other upper gastrointestinal symptoms.

M. Rare severe adverse reactions include:

1. Transient ischemic attack and stroke especially with the demented elderly

2. Neuroleptic Malignant Syndrome

3. QT interval prolongation

VI. Additional Considerations:

Risk is increased if the individual has cardiac arrhythmias; history of sudden death in the family; significant risk of electrolyte imbalances (e.g., diarrhea, diuretic treatment); or concomitant use of drugs that have demonstrated QT prolongation as one of their pharmacological effects. This effect is described in the full prescribing information as a contraindication or a boxed or bolded warning (e.g., mefloquine, pimozide).

References:

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists & North American Association for the Study of Obesity 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Obes Res,* 12**,** 362-8.

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Meyer, J. M. 2001. Effects of atypical antipsychotics on weight and serum lipid levels. *J Clin Psychiatry,* 62 Suppl 27**,** 27-34; discussion 40-1.

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