# DSH PSYCHOTROPIC MEDICATION Operational Procedures

## OLANZAPINE PROTOCOL:

I. Indications:

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

1. For long-term oral treatment (and intramuscular injection with intent to switch to oral or depot olanzapine);

a. DSM diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder (e.g., major depression with psychotic features). Also, may adjunctively assist in depression treatment.

b. DSM diagnosis of bipolar disorder. In monotherapy or combined with mood stabilizers for acute treatment during a current episode (manic or mixed). For maintenance after achieving responder status for two weeks. The long-term usefulness of olanzapine for the individual should be reassessed. Olanzapine has shown efficacy in prophylaxis of mood cycling.

c. Severe persistent self-injurious behavior, especially stereotypic subtype with evidence that a behavioral treatment, as part of a formal treatment program, was adequately implemented and found to be ineffective.

2. For short-term immediate release intramuscular injections:

a. Agitation particularly in patients with DSM diagnosis of bipolar mania, schizophrenia, schizoaffective disorder, or other psychotic disorder.

B. Contraindications:

1. History of hypersensitivity to olanzapine or any component of its formulation.

2. CNS depression (coma).

3. Individuals with PKU (if orally dissolvable olanzapine is prescribed, as it contains aspartate).

4. Narrow-angle glaucoma.

5. Myasthenia gravis.

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

A. 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).

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

C. Hyperlipidemia or hypercholesterolemia (currently or by history).

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

E. Severe cardiovascular disease.

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

G. History of active (or, poorly controlled) seizure disorder requiring anticonvulsant treatment without neurological consultation.

H. Use of drugs known to lower seizure threshold.

I. CNS depression or use of other drugs known to induce CNS depression.

J. Prostatic hypertrophy or paralytic ileus.

K. History of neuroleptic malignant syndrome.

L. Dysphagia.

M. Elderly individuals with neurocognitive disorder-related psychosis.

N. Signs (or, history) of tardive dyskinesia. May actually benefit extant tardive dyskinesia.

O. History of prolactin sensitive breast cancer.

P. Pregnancy or breast feeding. May be associated with decreased birth weights and, rarely, craniosynostosis. May cause neonatal dyskinesia.

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

III. The following initial workup should be completed:

A. There is informed consent or alternate legal authorization.

B. There is chart documentation of:

1. Waist circumference;

2. BMI;

3. Personal or family history of diabetes;

4. Personal history of high BMI;

5. Personal history of elevated triglycerides or hypercholesterolemia.

C. Initial work up includes:

1. Fasting blood glucose and/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. AIMS rating within one year.

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

6. ECG within one year.

7. Vital signs within 30 days.

IV. Monitoring:

A. Monthly monitoring includes:

1. Weight/BMI.

2. Fasting serum glucose and/or Hgb A1c (optional) for the first three months.

B. Quarterly monitoring includes:

1. Lipid panel or triglycerides and cholesterol.

2. Fasting glucose and or optional Hgb A1c (after first three months).

C. Semi-annual monitoring includes ECG (if concomitant medication that prolongs QT interval is present, as indicated by a boxed warning in the package insert).

D. 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 50 ng/mL. [Please see the appendix chapter of this policy regarding hyperprolactinemia.]

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 if galactorrhea or gynecomastia persist despite the above cited interventions.

3. Waist circumference.

4. AIMS (unless positive, then quarterly) until negative twice.

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

6. Nutritional consultation and appropriate dietary and exercise interventions if any of the following weight gain indicators occurs, as well as consideration of treatment with GLP-1/GIP medications:

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

   b. Waist circumference increase from below 35 to higher than 35 in females and below 40 to higher than 40 in males.

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

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

8. ECG.

V. Dose initiation and titration:

A. Typical oral initial dose is 10 – 20 mg once daily and is titrated as clinically indicated and tolerated. In acute agitated states, Baker, et al.., have described

beginning at a dose of 40 mg per day and tapering to a lower dose as agitation abates. Some anecdotal data have suggested even higher initial doses in the context of acute psychomotor agitation (e.g., 60 mg per day). A more gradual titration is used if hypotension, sedation, or other transient symptoms occur.

In general, oral antipsychotics should be titrated upward every two weeks until one of four end-points 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. If well tolerated and symptoms persist, the dose is increased to a maximum of 60 mg/day. Higher doses for >15 days require MRC or TRC consultation or review unless higher initial doses are being used as part of a hospital-approved treatment algorithm or protocol.

C. There is documented explanation if dose higher than 60 mg/day is used.

D. Depot olanzapine (not approved for use in DSH facilities—see below) does not require oral cross-over or a loading dose. Available doses are 150 mg, 210 mg, 300 mg, and 405 mg. The lower two doses may be given every two weeks; however, the medication is designed for a 4-week dose interval.

IMPORTANTLY, each injection of depot olanzapine is associated with a 0.1 – 0.2% risk of rapid drug-vehicle dissociation with subsequent delirium, obtundation, or coma. These altered mental states have typically required circa 72 hours to resolve. Overall risk for treated individuals is approximately 2%. Direct nursing observation is required following each injection for a minimum of three hours. If delirium, obtundation, or coma occur, transfer to an acute care facility should be strongly considered. Doses greater than 405 mg. every four weeks would require MRC or TRC consultation or review if this formulation were available.

*[NOTE: Per decision of the Medical Directors Council, DSH facilities have not been registered with the U.S. Food and Drug Administration for dispensing of depot olanzapine (Zyprexa Relprevv). Thus,* ***depot olanzapine cannot be prescribed in DSH facilities****.]*

E. Dosage accounts for drug-drug interactions and infections:

1. Approximately two-fold increase in dose may be required if used with carbamazepine, a metabolic inducer. Similar changes may be needed for other metabolic inducers (e.g., phenytoin, omeprazole, phenobarbital, or rifampin). Higher doses may be required in heavy smokers.

2. Lower doses may be needed if used with CYP1A2 inhibitors (e.g., fluvoxamine, high dose caffeine, ciprofloxacin, or cimetidine). Lower doses may be required if an individual stops smoking. Lower dose may be needed if used during pneumonias and other respiratory infections with fever.

3. If immediate-release intramuscular injections are necessary, the dose is started with 2.5 – 10 mg. Initial intramuscular doses of 2.5 – 5 mg should generally be used in elderly, small, or medically fragile individuals. The dose range is 2.5 – 10 mg. If necessary, the dose is repeated *no more frequently than two hours after the initial dose and four hours after the second dose for a maximum of three 10 mg injections per day* (i.e., 30 mg total dose per day).

F. An effort is made to monitor pulse and blood pressure before giving olanzapine IM doses and 30 minutes afterwards. If the individual refuses them due to agitation, orthostatic changes are measured when calmer as clinically indicated (e.g., during titration or at doses above maximum).

Signs of orthostatic changes are documented if the 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 following parameters, the measure is repeated after 15 minutes. If the item is then within the parameter, olanzapine IM may be given. If still outside the parameter, the physician is called to assess before dose administration.

The parameters are:

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

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

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

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

VI. Possible adverse reactions:

A. Weight gain.

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

C. Hyperlipidemia.

D. Peripheral edema.

E. Akathisia.

F. Somnolence.

G. Obtundation, confusion, delirium, and/or coma.

H. Extrapyramidal side effects.

I. Neuroleptic malignant syndrome.

J. Seizure.

K. Lightheadedness.

L. Pancreatitis.

M. Hyperamylasemia.

N. Nausea.

O. Dyspepsia.

P. Constipation.

Q. Dry mouth.

R. Increased salivation.

S. Postural hypotension, particularly for IM administration.

T. Tachycardia.

U. Prolonged QTc interval (very rare).

V. Cerebrovascular events in demented elderly.

W. Elevated liver enzymes.

X. Hyperprolactinemia.

VII. Additional Considerations:

A. Chronically elevated prolactin levels may increase risk of breast cancer or overt prolactin-related symptoms.

B. Average half-life in young, healthy persons is circa 37 hours. For oral administration, time to peak plasma concentration is 8 – 9 hours. Lower doses are usually used in geriatric individuals, as olanzapine half-life is 1.5 times that of non-geriatric individuals.

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