DSH PSYCHOTROPIC MEDICATION
Operational Procedures
ZIPRASIDONE PROTOCOL

I. Indications:

A. At least 1 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 ziprasidone):

a. DSM diagnosis of schizophrenia, schizoaffective disorder or other psychotic disorder (e.g., major depression;

b. DSM diagnosis of bipolar mania (manic or mixed episodes or as an adjunct to a mood stabilizer);

c. 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.

2. For short-term intramuscular injections:

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

II. Contraindications:

A. Preexisting prolonged QT syndrome (with persistent findings of QTc interval >450 msec in men or 470 msec in women);

B. Recent history of cardiac arrhythmia;

C. Recent myocardial infarction;

D. Uncompensated heart failure;

E. Hypersensitivity to ziprasidone.

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

A. Concomitant use of drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (e.g. dofetilide, chlorpromazine, haloperidol, thioridazine, droperidol, pimozide, sparfloxacin, gatifloxacin, halofanttrine, meflozuine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus);

B. History of sudden death in the family;

C. Cardiovascular disease;

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

E. History of active (poorly controlled) seizure disorder requiring anticonvulsant medications, without neurological consultation;

F. Use of other drugs known to lower seizure threshold;

G. CNS depression or use of other drugs known to induce CNS depression (e.g. benzodiazepines);

H. Significant liver function impairment;

I. Signs (or history) of tardive dyskinesia;

J. Parkinson's disease, although ziprasidone is a less robust dopamine antagonist than risperidone;

K. History of neuroleptic malignant syndrome;

L. History of prolactin sensitive breast cancer;

M. Significant risk of electrolyte imbalances, especially hypokalemia (e.g. diarrhea, diuretic treatment);

N. Pregnancy or breast feeding. May cause neonatal dyskinesia;

O. Elderly patients with neurocognitive disorder-related psychosis;

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

IV. 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 history of high BMI;

5. Personal history of elevated triglycerides or hypercholesterolemia.

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 within 30 days;

5. AIMS rating within 1 year;

6. Serum potassium and magnesium levels (in individuals at significant risk for electrolyte imbalances) within 30 days;

7. Neurological consultation (for individuals with history of an active [poorly controlled] seizure disorder);

8. Vital signs within 30 days.

V. Monitoring:

A. Monthly monitoring includes weight;

B. Semi-annual monitoring includes:

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

2. Lipid panel or triglycerides and cholesterol;

3. Semi-annual monitoring includes ECG, if concurrent use of medications that prolong QT interval are 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 are present 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 is suggested 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.

Please see the appendix chapter of this policy regarding hyperprolactinemia. Prolactin-related adverse effects become increasingly likely at serum concentrations > 50 ng/mL;

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 is suggested if galactorrhea or gynecomastia persist despite the interventions cited above;

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

4. Waist circumference;

5. ECG;

6. AIMS rating should be done quarterly if positive until negative twice;

7. Fasting blood glucose levels of 100 mg/dl or higher or elevated Hgb A1c result in glucose tolerance test or 2-hour postprandial glucose measurement and medical consultation;

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

   a. Weight increase of 5% in 1 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 (less than 25 to higher than 25) or from overweight to obese (25 – 29.9 to 30 or higher).

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

VI. Dose initiation:

A. Typical initial dose is 40 – 60 mg twice daily *with food*;

B. If treatment is well tolerated and symptoms persist, dose is increased at intervals of 2 days or greater by increments of 20 – 40 mg daily;

C. Typical dose is up to 240 mg daily. Higher doses for >15 days require an MRC or TRC consultation or review;

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.

D. Dose is typically titrated more slowly in older individuals or if sedation or orthostatic changes develop;

E. Dose accounts for drug-drug interactions:

1. Approximately 1/3 higher dose may be needed if used with carbamazepine, phenytoin, phenobarbital or other CYP3A4 inducers;

2. Approximately 1/3 lower dose may be needed if used with strong CYP3A4 inhibitors including ketoconazole or erythromycin.

   Similarly, lower dose if used with other CYP3A4 inhibitors such as fluvoxamine or fluoxetine.

F. Pulse and blood pressure are monitored as clinically indicated (e.g., during titration or at doses above maximum) up to twice a day before giving ziprasidone doses, and signs of orthostatic changes are documented if the individual can verbalize.

Pulse and blood pressure are recorded first in the seated position after 3 minutes and then in the standing position after 2 minutes. If the individual cannot stand up, he/she is monitored closely until the dose is stable if they are 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 parameter, ziprasidone may be given. If still outside the parameter, a physician should be 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 greater than 120 beats/min or less than 60 beats/min.

If intramuscular use is necessary, dose is initiated at 10 – 20 mg as required up to a maximum daily dose of 40 mg. If needed, doses of 10 mg are administered no less than every 2 hours or doses of 20 mg are administered no less than every 4 hours up to a maximum daily dose of 40 mg. IM injections of ziprasidone arenot given more than 3 consecutive days. Oral ziprasidone replaces the IM administration as soon as possible.

VII. Possible adverse reactions:

A. Cardiovascular effects including QT interval prolongation, arrhythmia and orthostatic hypotension;

B. Sedation;

C. Seizure;

D. Tardive dyskinesia;

E. Akathisia;

F. Extrapyramidal signs;

G. Weight gain;

H. Hyperglycemia;

I. Diabetes mellitus;

J. Hyperprolactinemia;

K. Priapism.

VIII. Additional considerations.

It is not uncommon to see mild elevations of prolactin in patients taking antipsychotic medications. However, if there are no symptoms, this finding does not guide medication treatment. Furthermore, if symptoms are present (menstrual cycle changes, galactorrhea, gynecomastia, hirsutism), then medical consultation will be obtained, including breast examination.

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. *Diabetes Care,* 27**,** 596-601.

Aronow, W. S. & Shamliyan, T. A. 2018. Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders. *Ann Transl Med,* 6**,** 147.

Beach, S. R., Celano, C. M., Sugrue, A. M., Adams, C., Ackerman, M. J., Noseworthy, P. A. & Huffman, J. C. 2018. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update. *Psychosomatics,* 59**,** 105-122.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Backers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G. & Leucht, S.

2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet,* 394**,** 939-951.

Leucht, S., Crippa, A., Siafis, S., Patel, M. X., Orsini, N. & Davis, J. M. 2020. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. *Am J Psychiatry,* 177**,** 342-353.

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.

Pfizer INC 2020. Geodon Package Insert. New York, New York.

Pillinger, T., Mccutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A. & Howes, O. D. 2020. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry,* 7**,** 64-77.