DSH PSYCHOTROPIC MEDICATION Operational Procedures

ARIPIPRAZOLE 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 psychotic disorder (e.g., major depression with psychotic features); also, may adjunctively assist in depression treatment.

2. DSM diagnosis of bipolar I disorder for acute treatment during a current episode, manic or mixed (if used beyond three weeks, long-term usefulness is reevaluated). Also, has efficacy for prophylaxis of mood cycling.

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 aripiprazole or any component of its formulation.

2. PKU individual taking orally disintegrating tablets (ODT), which contain phenylalanine.

3. The depot formulations (Abilify Maintena® and Aristada®) were not approved by the U.S. Food & Drug Administration for treatment of the elderly suffering from major neurocognitive disorders.

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

A. Signs or history of tardive dyskinesia.

B. Pregnancy (no evidence of teratogenicity but human data are lacking) or breast feeding. May cause neonatal dyskinesia.

C. Elderly patient with neurocognitive disorder-related psychosis. See under contraindications regarding the depot formulations.

D. History of leukopenia or severe neutropenia. The risk is low for aripiprazole. However, the U.S. Food and Drug Administration has mandated a class warning for the second/third-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. Personal or family history of diabetes.
3. Personal history of high BMI (>25).
4. Personal history of elevated triglycerides or hypercholesterolemia.

C. Initial workup includes:

1. Fasting blood glucose and/or Hgb A1c (optional within 30 days).
2. Lipid panel or total cholesterol and triglycerides within 30 days.
3. AIMS rating within one year.
4. ECG within one year.

IV. Monitoring:

A. Monthly monitoring includes weight/BMI.

B. Semi-annual monitoring includes:

1. Fasting serum glucose and/or Hgb A1c (optional).
2. Lipid panel and/or triglycerides and cholesterol.

C. Annual monitoring includes waist circumference, ECG, and AIMS.

D. Positive AIMS results in quarterly monitoring, until negative twice.

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

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

1. Weight increase of 5% in one month, 7.5% in three months, or 10% in six months.
2. Waist circumference increase from below 35in. to > 35in. for females and from below 40in. to > 40in. for males.
3. BMI increase from normal to overweight (from <25 to >25) or from overweight to obese (from 25 – 29.9 to 30 or higher).

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

V. Dose initiation and titration:

A. Typical oral dose is 5 to 30 mg daily. For the oral formulations, it is suggested that, if treatment is well tolerated and symptoms persist, dose is increased by increments of 5 to 15 mg every two weeks to a typical dose of 15 to 30 mg daily. Clinically relevant receptor saturation usually occurs at 20 – 30 mg per day. Essentially all D2 dopamine receptors are occupied in a typical metabolizer by doses of 45 mg per day. The maximum oral recommended dose in the absence of drug-drug interactions is 30 mg/day. Higher doses for > 15 days require 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.

B. The depot formulations must be reserved for those patients who have demonstrated a positive response to aripiprazole and for whom oral aripiprazole is contraindicated, e.g. due to non-adherence or inability to swallow oral medications. Data regarding tolerance and effectiveness of oral aripiprazole must be reliable (i.e., not based on questionable or unreliable history).

The Otsuka-USA depot formulation (Abilify Maintena®) is usually initiated at 400 mg intramuscularly (gluteal or deltoid) every 28 days with continuation of oral aripiprazole 10 mg to 20 mg for the first 14 days of treatment. If an oral cross-over is not feasible, a second dose of 300 mg to 400 mg of depot aripiprazole (Maintena®) one week after the initial injection may be used as a loading strategy. Note that 400 mg of depot aripiprazole (Maintena®) every 28 days is approximately equivalent to 20 mg of the oral preparation per day, while 300 mg every 28 days produces plasma concentrations comparable to 15 mg of oral aripiprazole per day.

Aripiprazole lauroxil (Aristada®) is initiated at 441 mg, 662 mg, 882 mg, or 1064 mg with the three higher doses requiring gluteal injection. Oral aripiprazole must be continued for 21 days after the first injection unless a single dose of Aristada Initio® is given. The two lower doses of aripiprazole lauroxil have intended dose intervals of 28 days, while the 882 mg dose has a dose interval of up to 42 days, and the 1064 mg formulation has a dose interval of up to 56 days.

Doses of depot aripiprazole (Maintena®) higher than 400 mg every 28 days or depot aripiprazole (Aristada®) greater than 662 mg every 28 days, 882 mg every 42 days, or 1064 mg every 56 days require MRC or TRC consultation or review.

DEPOT FORMULATION	DAILY PO ABILIFY® EQUIVALENT
Maintena® 400 mg Q28-days (deltoid/gluteal)	20 – 30 mg
Aristada® 441 mg Q-28days (deltoid/gluteal)	10 mg
Aristada® 662 mg Q-28days (gluteal)	15 mg
Aristada® 882 mg Q-42days (gluteal)	20 mg
Aristada® 1064 mg Q-56days (gluteal)	20 mg

C. Dose accounts for drug-drug interactions:

1. Dose may require up to doubling if used with carbamazepine, a CYP3A inducer.
2. Dose may require increase if used with other CYP3A inducers (e.g., phenytoin, phenobarbital, primidone, oxcarbazepine or some glucocorticoids).
3. Dose may need to be up to halved if used with ketoconazole, a CYP3A and 2D6 inhibitor. Use of the depot formulation with strong 2D6 or 3A4 inhibitors is not recommended.
4. Dose may require decrease if used with other CYP2D6 inhibitors (e.g., paroxetine or bupropion) or with CYP3A inhibitors (e.g., erythromycin, cimetidine or fluvoxamine).
5. Lowest possible dose is prescribed if used with fluoxetine, a CYP2D6 and CYP3A inhibitor.

VI. Possible Adverse Reactions:

A. Headache.
B. Anxiety.
C. Insomnia.
D. Agitation.
E. Esophageal dysmotility.
F. Dyspepsia.
G. Nausea.
H. Vomiting.
I. Anorexia.
J. Constipation.

K. Light headedness.
L. Dizziness.
M. Seizures (one of lowest risks among antipsychotics).
N. Blurred vision.
O. Somnolence (one of lowest risks among antipsychotics).
P. Akathisia.
Q. Extrapyramidal signs.
R. Tardive dyskinesia.
S. Neuroleptic malignant syndrome.
T. Orthostatic hypotension (one of lowest risks among antipsychotics).
U. Weight gain or loss.
V. Hyperglycemia and diabetes mellitus.

References:

Alkermes Inc. 2020. Aristada Package Insert. Wilmington, Ohio.

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.

Bollu, P. C. & Kaur, H. 2019. Sleep Medicine: Insomnia and Sleep. *Mo Med,* 116**,** 68-75.

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.

Marder, S. R., Essock, S. M., Miller, A. L., Buchanan, R. W., Casey, D. E., Davis, J. M., Kane, J. M., Lieberman, J. A., Schooler, N. R., Covell, N., Stroup, S., Weissman, E. M., Wirshing, D. A., Hall, C. S., Pogach, L., Pi-Sunyer, X., Bigger, J. T., Jr., Friedman, A., Kleinberg, D., Yevich, S. J., Davis, B. & Shon, S. 2004. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry,* 161**,** 1334-49.

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.

Otsuka USA Pharmaceutical Inc. 2020. Abilify MyCite Package Insert. Rockville, Maryland.

Otsuka USA Pharmacuetical Inc. 2017. Abilify Maintena Package Insert. Rockville, Maryland.

Otsuka USA Pharmaceutical Inc. 2020. Abilify Package Insert. Rockville, Maryland.

Romeo, B., Blecha, L., Locatelli, K., Benyamina, A. & Martelli, C. 2018. Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: Efficacy and safety. *J Psychopharmacol,* 32**,** 385-396.