DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX—IST Treatment Guidelines:

NOTE: Directive statements and procedures described in this chapter are informational and advisory in nature.

"The test must be whether he has sufficient present ability to consult with his lawyer with a reasonable degree of rational understanding-and whether he has a rational as well as factual understanding of the proceedings against him." (emphasis added) ~Dusky v. U.S. 362 U.S. 402 1960

Introduction: In community settings, the most common barriers to independent living, employment, and stable interpersonal relationships for patients suffering from schizophrenia-spectrum disorders or other psychotic disorders are negative symptoms and cognitive deficits.[1] In contrast, severely mentally ill individuals often entangled in the criminal justice system more frequently experience substantial barriers to trial competency or return to the community related to positive psychotic symptoms.[2] This is not to say that among the severely mentally ill population that positive psychotic symptoms are the only source of trial incompetency. Studies have indicated that incompetency to stand trial may arise from a variety of sources, e.g. cognitive, cultural, or language limitations, as well as impulsivity.[3-5] Nevertheless, amelioration or control of positive psychotic symptoms commonly forms the initial treatment focus among the severely mentally ill determined to be incompetent to stand trial.[6,7]

Dopamine and positive symptoms: Elevated dopamine signal transduction in the dopamine pathway from ventral tegmentum to the associative striatum (mesolimbic circuit) and/or inadequate top-down glutamate modulation of dopamine signaling to the associative striatum by frontal lobe structures is thought to underlie the expression of such positive psychotic signs and symptoms as illusions, hallucinations, delusions., and psychomotor agitation. Respectively, these views of the roles of dopamine and glutamate have been termed the dopamine and glutamate hypotheses of psychosis.[8,9]

Evaluation of psychosis: As in all of medicine, the initial step in treatment is evaluation. Table 1 on page 2 outlines the initial evaluation of patients in whom preliminary data point to positive psychotic signs and symptoms as a principal source of incompetency to stand trial.

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Table 1: Initial Review and Treatment of Severely Ill Psychotic Patients [10-14]

Decisions	Assessments	Brief Comments
Trial incompetency arises from psychosis? • Yes, continue • No, alternate treatment approaches	Review prior history and assessments • Frequency of psychotic symptoms • Severity of psychosis • Patient factors associated with incompetency • Environmental factors associated with incompetency • Cause of latest decompensation • Comorbid violence factor - Substance abuse - Impulse dyscontrol - Predatory violence	
Patient poses an immediate risk? • Yes, decide level of control • No, repeat risk assessment as clinically indicated	Evaluate need for segregation or restraint • Clinical observation • Clinical interview • Use of rating scale, e.g. DASA	Be familiar with relevant regulations/procedures governing seclusion or use of physical restraints
Physical conditions contribute to incompetency? • No, continue • Yes, treat physical condition	Physical evaluations • Psychomotor agitation • Evaluate for the following: • akathisia • pain or physical discomfort • delirium • intoxication or withdrawal • complex partial seizures • Evaluate sleep	
Abnormal labs contribute to incompetency? • Yes, correct underlying abnormality • No, continue	Evaluation of laboratory data • Plasma glucose and calcium • WBC to rule out sepsis • Infectious disease screens as clinically indicated • Plasma sodium to rule out hyponatremia or hypernatremia • Oxygen saturation if suspect • Serum ammonia if suspect • Thyroid status • Sedimentation rate and C-reactive protein if history of inflammatory disease	Serum ammonia useful only if elements of delirium clinically present

A second important element in approaching the treatment of positive psychotic symptoms is evaluation of past treatment responses and of elements that may affect medication responses such as nonadherence to oral medications, altered medication kinetics, or past pharmacodynamic issues. A systematic approach is described below in Table 2.

Table 2: Evaluation of Psychopharmacology for Severe Psychosis [6,15,16]

Decisions	Assessments	Brief Comments
Inadequate treatment contributes • Yes, adjust treatment • No, observe treatment response	Evaluate adequacy of current treatment • Duration (4-6 weeks) • Dose (at least standard) • Dosing (e.g. with food if needed) • Adherence • Plasma concentrations • Hepatic inducers, e.g. carbamazepine or phenytoin	See appendix regarding use of plasma concentrations
Adverse medication effects present • Yes, adjust treatment or treat adverse effect • No, continue	Presence of adverse antipsychotic effects • Neurological ➢ Akathisia ➢ Dystonia ➢ Parkinsonism • Sedation • Orthostasis Presence of adverse anticonvulsant effects • Ataxia • Tremor • Cognitive impairment Presence of adverse lithium effects • Polyuria • Nausea, vomiting, diarrhea • Tremor • Cognitive impairment Presence of adverse beta blocker effects • Hypotension • Bronchospasm • Bradycardia	• Many adverse effects respond to time or gradual dose reduction.
Patient is responding to treatment • Yes, optimize and continue • No, alter treatment approach	Evaluate response to current treatment • Partial response • No response	• A partial response (< 20% to 30% improvement on the PANSS or BPRS) with minimal or no adverse effects argues for a higher-dose trial of the present antipsychotic. • Failure of ≥ 2 adequate trials with at least one

		being a second-generation antipsychotic, argues for a clozapine trial. • A partial response (small decline in BIS-11) with adequate anticonvulsant plasma concentrations argues for the addition of an anticonvulsant or other medication with distinct mechanism of action.

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Treatment of psychosis: After evaluation of the patient and of the patient's pharmacotherapy, the next step is to design the primary pharmacological approach to the patient's illness. In this context, it should be remembered that all medication trials have one of three end points: (1) the patient's illness improves; (2) intolerable adverse effects occur which cannot be adequately addressed to permit continuation of the medication trial; or (3) a point of futility is reached for the plasma antipsychotic level. An example of reaching a point of futility would be a patient whose olanzapine plasma concentration has reached circa 150 ng/ml without improvement over two to four weeks. By a plasma concentration of circa 150 ng/ml, olanzapine's receptor occupancy curve for dopamine D2 receptors has become very flat, such that doubling the drug's plasma concentration would increase receptor occupancy by only an additional 2% to 3%. Importantly, absence of improvement after medication initiation or dose adjustment should prompt dose titration until progress toward trial competency, intolerable adverse effects, or a point of futility is reached. Dosing should be informed by measurements of plasma concentrations. An approach to a choice of a principal medication trial is outlined below in Table 3.

Table 3: Principal Medication Choice (Excluding Elderly Demented) [6,17,18]

Decisions	Assessments	Brief Comments
Patient responding to optimal treatment? • Yes, continue • No, adjust treatment	Patient's frequency and severity of psychosis, as well as progress toward trial competency are improving with adequate dose and plasma concentration, then continue present treatment	Note that although no response by weeks 2 to 4 of adequate to high-dose treatment portends a poor outcome, many patients show ongoing improvement for many weeks following a favorable, albeit partial, response to early treatment.
Patient response absent? • Yes, check adherence • No, consider alternate treatment	Patient has demonstrated an inadequate response to present antipsychotic treatment. • Adherent to oral medications • Not adherent to oral medications	• Preferred oral agents: olanzapine; fluphenazine; haloperidol • Preferred long-acting injectable agents: fluphenazine; haloperidol; paliperidone
Plasma concentrations are adequate? • Yes, continue • No, adjust dosing or switch to depot	Dosing and plasma concentrations (oral medications)	• Olanzapine: 40-60 mg/d with plasma concentration–120-150 ng/mL • Fluphenazine: 20-60 mg/d with plasma concentration of 1.0–2.0 ng/mL • Haloperidol: 20 - 80 mg/d with plasma concentration of 2- 15 ng/mL

Plasma concentrations are adequate? • Yes, continue • No, adjust dosing	Dosing and plasma concentrations (depot medications)	• Fluphenazine: 25-100 mg/14d after loading at 25 to 75 mg q. week times three with plasma concentration of 1.0–2.0 ng/mL • Haloperidol: 200-300 mg/28d after loading with 200-300 mg weekly times 3 with steady state plasma concentrations 2 - 15 ng/mL. • Paliperidone: 234 mg followed one week by 156 mg then continuing at 117-234 mg every 28d with plasma level of 20 to 90 ng/ml.

- Note that some patients may require higher than cited antipsychotic plasma concentrations to achieve stabilization, e.g. haloperidol up to 18 ng/mL or fluphenazine up to 4.0 ng/mL.

Geriatric patients: Due to risks of increased mortality among elderly patients suffering from neurocognitive disorders on antipsychotic exposure, starting with less dangerous alternatives and progressing toward antipsychotic treatment only as forced by failure of safer treatments is prudent.[19] It should be noted that the majority of patients suffering from a major neurocognitive disorder are unlikely to achieve trial competency and that a no substantial likelihood of restoration to competency status should be considered early in hospitalization. An approach to the elderly demented patient who develops problematic behaviors and/or psychotic symptoms related to positive psychotic symptoms is shown below in Table 4.

Table 4: Principal Medication Choice in Major Neurocognitive Disorder with Severe Psychosis [6]

Decisions	Assessments	Brief Comments
Antipsychotic precautions • Yes, consider alternatives • No, treatment with antipsychotic	Patient has increased risk with antipsychotics • Elderly • Vascular disease • Dementia with Lewy bodies • Parkinson's disease • Huntington's disease	
Increased risk with antipsychotics? • Yes, select alternative • No, continue	Pharmacological alternatives to antipsychotics in patients with major cognitive disorders • Lithium • Valproic acid • Clonidine • Guanfacine • Memantine • Cholinesterase inhibitor • Pimavanserin • SSRI antidepressant • Trazodone	
Alternative effective • Yes, continue • No, choose recommended antipsychotic	Evidence-based antipsychotics • Aripiprazole • Lumateperone • Clozapine • Olanzapine • Quetiapine • Risperidone	• Antipsychotics increase mortality risk by 1.5 to 2.0-fold among elderly demented patients but may be worthwhile if alternative choices to control problem behaviors or violence are ineffective. • For major cognitive disorder with Lewy bodies or Parkinson's disease, aripiprazole, clozapine, and quetiapine appeared to be the

		best tolerated antipsychotics if pimavanserin is ineffective.

Some authors have suggested tapering and discontinuing antipsychotic medications after major neurocognitive disorders have stabilized or progressed and/or to periodically test whether the prior antipsychotic dose is required to maintain stability. Given mortality risks in elderly demented patients, begin with the least dangerous options and progress to more dangerous options only as forced by treatment failure.

Adjunctive medications: In many cases of severe psychotic illness even optimal antipsychotic treatment may not adequately address all of the patient's target symptoms. In this context, while the effect sizes of adjunctive treatments are modest, they may exert important effects on specific illness domains.[20] An outline of the approach to the use of adjunctive medications is given below in Table 5.

Table 5: Adjunctive Medications [17,21]

Decisions	Assessments	Brief Comments
Mood stabilizers	• Irritability • Mood lability • Suicidality (lithium)	• VPA can be loaded at 20 - 30 mg/Kg, reaching steady state at circa three days. • Lithium can be initiated at 600 mg once per day and titrated by 300 mg every other day to 900 - 1200 mg once per day. Lithium also can be loaded at 30 mg/Kg up to 3000 mg by giving three ER doses at 1600, 1800, and 2000 hours on day one and then measuring a plasma concentration the following morning. If the plasma concentration is < 1.0 meq/L, then give 1200 mg IR q. bedtime. If the plasma concentration is > 1.0 meq/L, then give 900 mg IR q. bedtime. Once per day dosing spares renal function. Plasma concentrations should be 0.6-1.0 mEq/L. • Lamotrigine may be helpful for dysphoric or negative symptoms but may promote hypomania or mania.
Clonazepam	• Agitation or anxiety incompletely responsive to primary treatment	Dose at 0.5-2.0 mg TID and then taper as the patient stabilizes. Avoid use in major neurocognitive disorders.
SSRI antidepressants	• Residual negative symptoms • Impulsive behavior or suicidality	Avoid use in patients in whom bipolarity may be present. May increase irritability in brain injured or autism patients. Avoid use of fluvoxamine with clozapine or olanzapine, as fluvoxamine may increase clozapine or olanzapine plasma concentrations 5 to 10-fold.
Sedatives	• Insomnia worsens irritability, dysphoria, agitation, and mood lability in many patients. • Consider trials of zolpidem 5 mg to 10 mg at bedtime, eszopiclone 1 mg to 8 mg at bedtime, hydroxyzine 100 mg at bedtime, diphenhydramine 25 - 50 mg at bedtime, or trazodone 25 - 100 mg at bedtime until the	Note that antihistamines may cause idiosyncratic excitation and agitation and that diphenhydramine, but not hydroxyzine, will add to anticholinergic burden.

	patient stabilizes.	
Beta blockers	• Propranolol has excellent CNS penetration and the most evidence for response	Propranolol contraindicated in those with asthma. Monitor blood pressure to avoid hypotension.
	• ECT	If adjunctive medications fail, then ECT should be considered. This is especially true if the patient is taking clozapine and continues to have inadequate response.

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Pro re nata (PRN) Medications: While a patient's routine treatment regimen is expected to be the mainstay of pharmacological treatment, fluctuations in symptom severity or behavior may require as needed or prn medications. This is especially true early in treatment prior to achieving an optimal response from the patient's routine psychopharmacological treatment. Principles and practice in using prn or stat medications is described below in Table 6.

Table 6: PRN and STAT Medications [22]

Decisions	Assessments	Brief Comments
Patient unstable? • No, continue • Yes, provide frequent PRN or STAT treatment	Estimate severity of agitation • Mild • Moderate • Severe	• For mild agitation, give lorazepam 1-2 mg or hydroxyzine 25-50 mg PO or IM every two hours not to exceed four doses per 24 hours. Titrate against agitation based on observation, not patient complaint. • For moderate to severe agitation, give antipsychotic ± lorazepam 2 mg ± diphenhydramine 25-50 mg or hydroxyzine 25-50 mg PO or IM not to exceed four doses per 24 hours. (See caveats following table.)
Stability improved? • No, continue frequent PRN or STAT medications and adjust primary treatment • Yes, simplify PRN and STAT treatment and eventually discontinue.	Estimate frequency of breakthrough agitation • Seldom • Moderately frequent • Very frequent	As determined by frequency and severity of breakthrough psychomotor agitation, gradually increase PRN dose interval and reduce the number of medications or doses prescribed. Once agitation is controlled, discontinue PRN orders for agitation.

• Caveats: Whenever possible choose an antipsychotic that also is being used as part of the primary treatment. Available dose forms may limit this option.

• The most commonly prescribed PRN and STAT antipsychotics are haloperidol, fluphenazine, chlorpromazine, olanzapine, and risperidone. Of these, haloperidol, fluphenazine, chlorpromazine, olanzapine, and ziprasidone are available in oral and injectable formulations.

• Haloperidol and fluphenazine carry the highest risks of acute neurological adverse effects, especially given parenterally. Chlorpromazine carries a risk of orthostasis. Olanzapine is not effective orally due to an absorption time to peak plasma concentration of 6 to 9 hours. Olanzapine, especially at higher parenteral doses, is prone to cause severe orthostasis if combined with a benzodiazepine, usually lorazepam. Intramuscular ziprasidone should be limited to two doses of 10 mg per 24 hours, especially if given in

addition to oral ziprasidone.

- Diphenhydramine, but not hydroxyzine, adds to anticholinergic burden.
- Limit doses of potent dopamine antagonists in Parkinson's disease and major cognitive disorder with Lewy bodies. Limit benzodiazepine and anticholinergic use in all major neurocognitive disorders.

Treatment resistance: An important issue among individuals suffering from psychotic severe mental illness is that a substantial portion, circa 30%, of such patients are treatment resistant.[23] John Kane, et al., defined treatment resistant schizophrenia according to very stringent criteria. These included failures of three antipsychotic trials of at least six weeks duration at doses of at least 1000 mg chlorpromazine equivalents, absence of any period of good functioning during the prior five years, and failure of a prospective high-dose (haloperidol 60 mg per day or greater) trial to produce a significant reduction in psychotic signs and symptoms.[24] Because the criteria created by Kane, et al., are difficult to complete outside a research setting, treatment resistance has more recently been redefined as failure of two six-week trials of antipsychotic medications from two different classes at least 600 mg. chlorpromazine equivalents. If one of the antipsychotics was a long-acting injectable formulation, then the trial duration should have been four months. One check of plasma concentration, as well as two other measures of medication adherence was defined as a minimal requirement. Optimal assurance of medication adherence was held to include two measurements of plasma concentration separated by at least two weeks without informing the patient prior to laboratory sampling.[9]

The development of treatment resistance is of critical importance because the vast majority of antipsychotic medications become largely ineffective in this context. That is, response rates to almost all antipsychotic medications are 0% to 5% in treatment resistant psychosis. High plasma concentration olanzapine, possibly due to modest glutamate modulation, does slightly better at 7%. Fortunately, in treatment resistant psychotic patients clozapine at plasma concentrations of 350 ng/ml to circa 1000 ng/ml produces a decrease in psychotic signs and symptoms of at least 20% to 30% in up to 60% of such patients.[24,25] Even clozapine, however, begins to show a decline in efficacy after resistant psychosis has been ongoing for > 2.8 years, arguing strongly for not delaying clozapine treatment among patients determined to be treatment resistant.[26]

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Summary Points:

- Positive psychotic symptoms are frequently the cause of institutionalization or incarceration for complex severely mentally ill psychotic patients and are a common, but not sole source of trial incompetence.
- Positive psychotic symptoms are driven by dopaminergic overactivity in the meso-limbic circuit, making dopamine antagonist antipsychotics the first step in treatment.
- Failure to respond to two adequate dopamine antagonist antipsychotic trials should strongly prompt consideration of treatment with clozapine.
- Even clozapine's superior antipsychotic efficacy begins to fade after about 2.8 years of treatment-resistant status, indicating that use of clozapine should not be delayed in such cases

Appendix: Optimal Antipsychotic Plasma Concentration Ranges [17,27-29]

MEDICATION	MINIMUM RESPONSE THRESHOLD	POINT OF FUTILITY
Aripiprazole expected level = 11 x oral dose (mg/d)	110 ng/mL	500 ng/mL
Clozapine male nonsmoker – expected level = 1.08 x oral dose (mg/d) female nonsmoker – expected level = 1.32 x oral dose (mg/d)	350 ng/mL	1000 ng/mL
Fluphenazine nonsmoker – expected level = 0.08 x oral dose (mg/d)	1.0 ng/mL	4.0 ng/mL
Haloperidol expected level = 0.78 x oral dose (mg/d)	2 ng/mL	18 ng/mL
Olanzapine nonsmoker – expected level = 2.0 x oral dose (mg/d)	23 ng/mL	150 ng/mL
Paliperidone expected level = 4.7 x oral dose (mg/d)	20 ng/mL	90 ng/mL
Risperidone + 9-OH Risperidone expected level = 7.0 x oral dose (mg/d)	28 ng/mL	112 ng/mL
Perphenazine expected level = 0.04 x oral dose (mg/d)	0.8 ng/mL	4.0 ng/mL

Optimal Mood Stabilizer Plasma Concentration Ranges [30,31]

	ACUTE MANIA	MAINTENANCE

MOOD STABILIZER		
lithium	1.0 – 1.4mEq/L	0.8 – 1.2mEq/L (See #2 under Mood Stabilizers.)
divalproex valproic acid	100 – 120mcg/L	80 – 120mcg/L
carbamazepine	9 – 12mcg/mL	6 – 12mcg/L

- **IMPORTANTLY,** chronic exposure to maintenance lithium plasma concentrations > 1.0 meq/L may increase the long-term risk of renal insufficiency.

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