DSH PSYCHOTROPIC MEDICATION Operational Procedures

Appendix -- Selected Treatment of Psychomotor Agitation (STOP-A)

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

I. PURPOSE:

Data collection regarding violent incidents at DSH-Atascadero and DSH-Patton indicated an increased incidence of violent events shortly after hospital admission, with a relatively small number of individuals suffering from schizophrenia or bipolar spectrum disorders prone to psychomotor agitation accounting for a disproportionately large number of aggressive or violent incidents.

The purpose of this proposal is to outline a pharmacological algorithm designed to hasten stabilization of targeted aggressive or violent agitated individuals.

II. BACKGROUND:

Historically, violence has been broadly divided into 2 categories: (a) predatory violence and (b) affective violence.

A. Predatory violence is exemplified by a cat stalking its prey. The cat in this circumstance is highly focused and motorically controlled, with the only overt evidence of increased sympathetic output typically being dilation of the pupils (an aid to hunting in low-light conditions).

B. In contrast, affective or psychomotorically agitated violence is exemplified by a cat suddenly startled by a large dog. In such circumstances, the cat shows hissing, raised fur, arched back, increased poorly focused motor activity, and a proneness to “strike out” in all directions.

In cats, the psychomotorically agitated state or “sham rage” can be induced by implantation and activation of electrodes in the medial portion of the amygdala complex in the anterior portion of the temporal lobe.

Imaging studies have indicated overactivity of the amygdala complex in persons exhibiting hypervigilance, paranoia, and proneness to psychomotorically agitated violence.

Brain injuries resulting in either irritative lesions in the anterior temporal lobe (e.g., temporal lobe epilepsy or loss of prefrontal cortical inhibition of the amygdala) have also pointed to the role of the amygdala in producing psychomotorically agitated violent behavior.

Electrophysiological and imaging studies have likewise reflected hypofrontality and increased temporal lobe/amygdala hyperactivity as common in the pathophysiology of schizophrenia spectrum disorders. Similar, but less pronounced, patterns of disturbed physiology have been described in bipolar spectrum disorders, as well as borderline personality disorder.

With respect to neuromodulator signal transduction, the above described pattern of frontal and temporal lobe pathophysiology has been associated with increased *dopamine* signaling (especially in the mesolimbic circuit), decreased *glutamate* signaling, decreased serotonin signaling, and increased *norepinephrine* signaling. Some studies also have found central *substance P* to be increased; however, the clinical relevance of this observation remains uncertain.

Pharmacologically, the initial goal is to perturb identified disturbances in neuromodulatory signaling toward homeostasis.

NOTE: Some animal models have suggested that judiciously applied interventions may assist overwhelmed homeostatic feedback mechanisms to regain control of neuronal signaling processes.

III. INDIVIDUAL SELECTION:

A. The algorithm described hereafter is targeted toward a relatively narrow population of individuals.

1. If too broadly applied, many of the measures indicated carry increased risks of adverse effects which are counterbalanced only by the increased risks of injury or death imposed by frequent, recurring violent behavior.

2. Moreover, the cited approaches best fit individuals suffering from schizophrenia or bipolar spectrum disorders.

B. Individuals selected for this algorithm should exhibit many, if not most, of the following features:

A. Overt psychomotor agitation (e.g., frequent pacing, yelling, screaming, shadow boxing, etc.)

B. Current or recent violent behavior toward objects

C. Verbalized ideas of being watched, followed, or harmed by others

D. Verbalized or gestured threats to harm others without apparent rational cause

E. Attempts to harm others without apparent rational cause

F. Battery of others without apparent rational cause

G. History of recurring violent behavior which appears to derive from persecutory perception, severe mood lability, or psychotic disorganization

H. Need for enhanced nursing observation due to severely impaired behavioral control

IV. ALGORITHM OVERVIEW:

The following algorithm is divided into 3 phases:

- Phase 1 – Acute Intervention
- Phase 2 – Stabilization
- Phase 3 – Maintenance

While duration estimates are included for each phase, the duration of each phase should be flexible and should be based on the response of the patient to treatment.

Although specific medications and doses are indicated, the prescriber should attend to relevant indications, contraindications, precautions, and monitoring requirements. For example, suggested doses for older or medically fragile individuals should typically be decreased by 30 – 50%. [Please see the relevant medication protocols from the DSH Psychotropic Medication Policy.]

Moreover, in selecting medications within this algorithm, the clinician should endeavor to determine the likely origins of the individual's psychomotor agitation and propensity toward violence. For example:

- Paranoid delusional ideation associated with schizophrenia
- Mood elevation and associated irritability in bipolar mood disorder

- Mood lability and impulsiveness associated with cluster B personality disorder, etc.

Development of a clinical hypothesis regarding the origins of observed psychomotor agitation and violence will be helpful in applying the psychopharmacological measures described in this algorithm or in choosing alternative treatment approaches (e.g., clonidine for impulsiveness related to head injury or attention deficit hyperactivity disorder).

The goal of Phase 1 is to control the individual's level of psychomotor agitation and acute risk of violence. Once these acute issues are adequately controlled, the focus of treatment shifts to stabilization of the underlying mental disorder(s) in the next phase.

Once the acute risk of injury has subsided, Phase 2 employs additional psychotherapeutic modalities which may help further reduce the risk of violence and promote normative socialization. One of the principal reasons for pursuing psychopharmacological treatment is to make the individual mentally available for further modalities of psychosocial treatment.

NOTE: The most common clinical errors by treating clinicians employing the STOP-A algorithm are: (1) staying in Phase 1 treatment too long, or (2) moving too quickly toward more typical medication doses and strategies (Phase 3).

Phase 3 is focused toward adjusting medications discovered to be effective toward the simplest and least risky configuration which is likely to continue to provide stabilization of the patient's mental disorder(s).

V. ALGORITHM:

A. Phase 1 (Acute Intervention)

For *psychotic disorders*, *bipolar disorders*, and *borderline personality disorder* afflicted individuals meeting the description of someone at elevated risk of violence due to psychomotor agitation, the initial cornerstone of pharmacological treatment is an antipsychotic (a.k.a., neuroleptic or major tranquilizer).

1. Based on the CATIE trial and subsequent meta-analyses, **olanzapine** (Zyprexa or Zyprexa Zydis) beginning at a dose of 20 mg PO BID to TID is recommended. Olanzapine 10 mg can be given intramuscularly (IM) if oral doses are refused (approximates 17 mg PO).

- Baker, et al., found that initiating olanzapine at a relatively high dose and then tapering to a lower dose to be an effective strategy in treating acute mania characterized by psychomotor agitation.

- Citron, et al., found that olanzapine exerted additional antipsychotic and anti-violence effects at doses greater than 20 mg per day with a moderate effect size of 0.35.

- Conversely, Kelly, et al., found increased anticholinergic adverse effects with little additional benefit at doses of 5 mg per day in a double-blind cross-over study of 13 individuals suffering from schizophrenia.

2. If little response is seen in psychotic signs and symptoms or related psychomotor agitation by the end of week 1:

    a. Add **risperidone** beginning at 2 mg QHS and increase by 2 mg every other day to a target of 6 mg QHS. Some data have suggested that the combination of olanzapine and risperidone may be more effective than either drug alone in the context of refractory psychosis. (Suzuki, et al.).

    b. Alternatively, **haloperidol** 5 mg can be substituted for risperidone 2 mg for those individuals in whom risperidone is contraindicated. NOTE: The first expected change in psychotic signs and symptoms is diminishment of the ability of the psychotic signs and symptoms to compel behavior, rather than a change in the frequency or content of the psychotic signs and symptoms themselves.

    c. If the individual is uncooperative with oral antipsychotic treatment, then choose treatment with **a long-acting injectable formulation** (e.g., fluphenazine decanoate, haloperidol decanoate, or paliperidone palmitate).

        i. **Fluphenazine decanoate** typically achieves a therapeutic plasma concentration (0.8 – 4.0 ng/mL) circa 20 hours post injection. Give fluphenazine decanoate 50 – 100 mg IM every 2 weeks. Fluphenazine plasma levels should be used to ensure optimal dosing. Blood draws for plasma concentrations should be obtained 2 – 72 hours before a maintenance dose.

ii. Because of the pharmacokinetics of **haloperidol decanoate**, a loading dose strategy is required to achieve effective plasma concentrations (5 – 20 ng/mL) in less than 2 to 3 months. Give loading doses of haloperidol decanoate 300 mg IM every week for 3 weeks. Maintenance dosing begins 14 days after the third loading dose and shifts to haloperidol decanoate 300 mg every 28 days. Haloperidol plasma levels should be used to ensure optimal dosing. Blood draws for plasma concentrations should be obtained 2 – 72 hours before a maintenance dose.

iii. For **paliperidone palmitate**, give 234 mg IM in the deltoid. Give a second dose of 234 mg one week later. Thereafter, shift to 156 mg every 28 days.

3. Mood stabilizers are an established adjunctive treatment among psychomotorically agitated individuals suffering from a primary psychotic disorder, as these tend to further decrease limbic firing rates and the activity level of the amygdaloid nuclei. Of course, as their name suggests, mood stabilizers are typically the primary treatment of bipolar mood disorders.

   a. If not contraindicated, give **valproic acid** at an initial dose of 20-30 mg/kg, divided into a TID to QID schedule. For example, for an 80 kg individual, give 1500 to 2500 mg per day (e.g., 500 mg TID to 500 mg TID and 1000 mg QHS). [NOTE: The calculated doses should be rounded to the nearest available dose form.]

      Obtain a valproic acid (VPA) level in 3-4 days. If valproic acid is not tolerated due to acid reflux, tremor, sedation, or ataxia, then switch to divalproex extended release (Depakote ER). Depakote ER provides a steady absorption across approximately 22 of 24 hours and has much less propensity to cause side-effects, probably due to lack of sharply increased peak plasma concentrations.

      When using valproic acid derivatives, the optimal VPA plasma concentration range is *100 – 120 mg/L for acutely manic or agitated states*. The *maintenance range is 80 – 120 mg/L*.

      Above 80 mg/L the proportion of free drug available to enter the CNS increases at a greater than linear rate due to saturation of plasma proteins. For example, at a VPA plasma concentration of 40 mg/L the free fraction is about 10% of the VPA level (4 mg/L),

while at 130 mg/L, the free fraction is about 18.5% of the VPA level (24 mg/L).

The beneficial effects and toxicities are mediated by free valproate levels with a Therapeutic Range from 7 – 23 mg/L (toxic: > 30 mg/L).

b. If valproic acid and divalproex are contraindicated, try **lithium**. Start lithium 600 mg QHS and increase by 300 mg every other day to a target of 900 – 1200 mg QHS.

The tissue (brain) half-life of lithium is around 28 hours, while the plasma half-life is shorter. Because of the shorter plasma half-life, once per day lithium dosing spares renal concentrating capacity by providing a maximum daily trough period.

When used as an adjunctive medication, lithium plasma concentrations do not correlate well with clinical effectiveness but should be at least 0.6 mEq/L. For bipolar mood disorder, optimal plasma concentrations are thought to be *0.8 – 1.2 mEq/L*. The maximum recommended plasma concentration during *acute mania is 1.4 mEq/L*.

c. Finally, if neither valproic acid/divalproex or lithium can be safely given, try **clonazepam** beginning at a dose of 1 mg TID to QID. Doses can then be adjusted to 0.5 – 2 mg TID to QID depending on clinical response.

NOTE: At very low doses, *disinhibition is a risk*. However, this risk tends to be overridden by limbic GABAergic inhibition at higher doses. Excessively high doses may carry a risk of inducing delirium.

d. **Hydroxyzine** can be a helpful option to clonazepam and could be administered 25 – 50 mg PO/IM BID to QID or, alternatively, given 100 mg PO/IM BID. This antihistamine is not anticholinergic. The maximum recommended daily dose is 200 mg.

4. *If hypomania or mania are driving psychomotor agitation and violence risk*, then promotion of sleep using **sedatives** is vital to avoiding the antidepressant and destabilizing effects of sleep deprivation.

   a. A trial of zolpidem at 10 mg HS is recommended.

b. If zolpidem does not maintain sleep due to its relatively short half-life (circa 3 hours), eszopiclone starting at 4 mg QHS. The dose range for eszopiclone is 1 – 8 mg QHS and provides a relatively broad dose range and treatment flexibility.

c. Diphenhydramine is an antihistamine with anticholinergic properties that often fragments sleep and may cause an idiosyncratic activation in some individuals. Also note that diphenhydramine IM doses >50 mg may induce seizures by lowering the seizure threshold abruptly.

5. Individuals *without* a bipolar component to their mental illness may benefit from the addition of an SSRI antidepressant because increased limbic serotonin has been associated with decreased irritability, impulsive violence, and impulsive suicide.

   NOTE: SSRI antidepressants have been reported to increase irritability and violent behavior in individuals suffering from autistic spectrum disorders, intellectual disability, and in some cases of brain injury.

   The most frequently used and studied medications have been:

   a. **Sertraline** starting at 50 mg per day with titration to 150-200 mg per day.

   b. **Citalopram** beginning at 20 mg per day and titrating to 40 mg per day. Note that the U.S. Food and Drug Administration has warned of possible QT interval prolongation and cardiac arrhythmia at citalopram doses >40 mg per day.

   c. **Fluoxetine** beginning at 20 mg per day and titrating to 40 – 60 mg per day.

   d. **Paroxetine** is less popular due to increased sedation and anticholinergic effects. [NOTE: Avoid the combination of fluvoxamine and olanzapine, as fluvoxamine potently inhibits the hepatic metabolism of olanzapine via cytochrome P450 isoenzyme 1A2 and may increase olanzapine plasma concentrations several fold, resulting in toxicity.]

6. Finally, Phase 1 treatment usually requires **PRN medications** to control breakthrough episodes of psychomotor agitation, especially in the first few days of treatment.

a. Recommended PRN antipsychotic medications *with lorazepam 1 – 2 mg PO/IM*:

   i. Haloperidol 5 mg

   ii. Fluphenazine 5 mg

   iii. Chlorpromazine 50 mg

   iv. Olanzapine 5 mg

   v. Ziprasidone 20 mg

b. Avoid using these oral medications as PRNs:

   i. Oral olanzapine should not be given orally for treatment of acute psychomotor agitation. Oral olanzapine requires 8 – 9 hours to reach peak plasma concentration due to very slow gastrointestinal absorption.

   ii. Chlorpromazine should be avoided if orthostatic hypotension is a substantial risk.

Regardless of the PRN agents chosen, the most common error is writing the PRN such that breakthrough psychomotor agitation recurs and increases substantially before the next PRN dose is available.

An important portion of the strategy of PRN use is to "get ahead" of the psychomotor agitation. Smaller doses at closer frequencies work better (e.g., haloperidol 5 mg with lorazepam 2 mg PO/IM Q-2 hours/PRN psychomotor agitation associated with threatening behavior, attempted violent behavior, or violent behavior, not to exceed 6 doses in 24 hours).

In general, an order for PRN medications to treat EPS also should be written. Do not automatically include the EPS PRN in the order for psychomotor agitation because this would introduce a risk of anticholinergic overdose.

Phase 1 measures are expected to be effective within 1 – 3 weeks, as measured against overall level of psychomotor agitation and frequency of threatened or completed violent behavior.

If substantial improvement is not seen by week 3, then re-evaluation of the initial diagnoses and medication choices should be actively pursued, including psychopharmacology consultation.

Once the individual exhibits a sustained decline in the level of psychomotor agitation and associated frequency of threatening or violent behavior, Phase 2 could begin.

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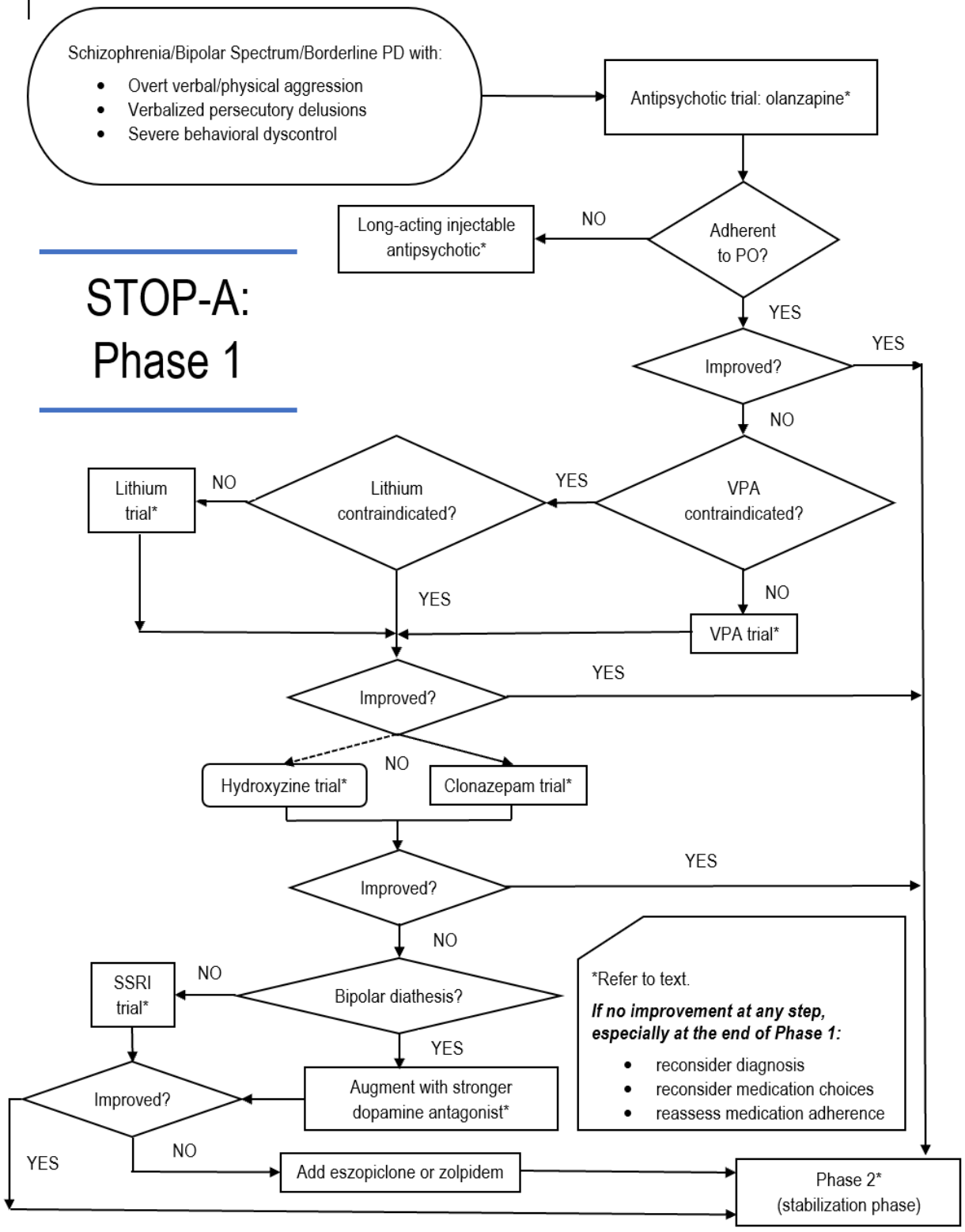

B. Phase 2 (Stabilization)

Phase 2 is a transitional phase, which should begin as soon as the individual exhibits a sustained decline in the level of psychomotor agitation and associated frequency of threatening or violent behavior.

Phase 2 is typically more flexible than phase 1 with respect to duration but should be expected to last from 12 to 26 weeks before transitioning into Phase 3.

One of the most common mistakes in using the STOP-A algorithm is persisting in Phase 1 too long. This likely exposes the treated individual to unnecessary medication side-effects and/or risks.

The second most common mistake in using the STOP-A algorithm is moving too quickly into Phase 3, where more typical (lower) medication doses and strategies are employed. When this occurs, relapse is commonly observed.

1. For oral antipsychotics, Step 1 of Phase 2 is to move toward a more consolidated dosing schedule.

    a. For example, if the individual was successfully treated in Phase 1 with **olanzapine** 20 mg TID, then the initial step of phase 2 would be to consolidate the dose to 20 mg QAM and 40 mg QHS.

        i. Before beginning a gradual taper, a measurement of plasma concentration is helpful to rule-out rapid metabolism. [Note: The olanzapine laboratory reference range 5 – 75 ng/mL is not a therapeutic range. It simply represents the mean concentration +/- 2 S.D. at a dose of 10 – 15 mg per day. Some data have suggested that refractory psychosis is more likely to respond at concentrations of > 120 ng/mL (i.e., at dopamine receptor occupancies > 80%).]

        ii. If stability was maintained over 4 weeks, the dose could be gradually reduced, beginning with the morning dose at a rate of 5 mg per week.

        iii. Risks of QT prolongation (taken from overdose case reports) does not appear to be a concern in the context of a healthy myocardium and normal plasma concentrations of potassium and magnesium until olanzapine plasma concentrations of circa 500 – 700 ng/mL are reached.

iv. Thus far, no cases of torsades de pointes have been reported with olanzapine.

b. While acute treatment of psychomotor agitation with **fluphenazine** may require plasma concentrations of up to 4.0 ng/mL. The more typical therapeutic plasma concentration range for fluphenazine is 0.8 – 2.0 ng/mL.

c. **Haloperidol** plasma concentrations may be very helpful in adjusting the dose of either oral or depot haloperidol.

i. Kamal, et al., identified an optimal plasma concentration range for haloperidol based on work by Van Putten (parent compound excluding reduced haloperidol) of 5 – 12 ng/mL. Higher and lower concentrations were typically less effectively antipsychotic, with any further benefit clearly trailing off by circa 30 ng/mL.

ii. Phase 2 of treatment should be approached via gradual change (e.g., a decrease in dose not faster than 10 – 15% per month).

d. **Paliperidone palmitate** modal dose is 117 mg Q-28 days. Available doses are 234 mg, 156 mg, 117 mg, 78 mg, and 39 mg. Depending on the robustness of clinical response, the eventual maintenance dose can vary across a fairly large range of doses. As before, dose should change gradually (i.e., not more than one dose level per 28 days).

2. For mood stabilizers successfully employed in Phase 1 should be consolidated into BID dosing in Phase 2.

a. Neither **valproic acid** or **divalproex** should be given once per day due to the risk of induction of seizures during trough plasma concentrations.

b. Conversely, divalproex extended release (**Depakote ER**) should be given only once per day from the beginning, as it provides constant absorption across about 22 of 24 hours.

c. **Lithium** should be given in a <u>single bedtime dose</u> from the beginning if tolerated to spare renal function.

d. If phase 1 employed **clonazepam** TID to QID, then the goal of phase 2 is to taper and consolidate the dose to a BID schedule with an eye toward eventual discontinuation in Phase 3.

i. For example, if phase 1 required clonazepam 1 mg QID, then the initial step of phase 2 would be to consolidate this to 2 mg BID and then to decrease by 0.5 mg at each dose point per month.

3. For an **SSRI antidepressant**, the usual decision is whether or not the SSRI should be continued. SSRI consolidation is unnecessary, as the SSRIs cited are typically given once per day from the beginning. If the SSRI is no longer needed, then it is best to taper it over 2-4 weeks to avoid a withdrawal syndrome. Fluoxetine can be discontinued without taper since its active metabolite, norfluoxetine, exhibits a typical half-life of 9 to 14 days.

4. **PRN medication** continuation in phase 2 depends on the clinical stability achieved. If occasional breakthrough psychomotor agitation continues, a simpler PRN order can be written, using effective medications from Phase 1.

a. For example, if haloperidol 5 mg with lorazepam 2 mg PO/IM every 2 hours PRN psychomotor agitation with threatening or violent behavior not to exceed 6 doses in 24 hours was effective in phase 1, this might be changed to: Haloperidol 5 mg with lorazepam 1 mg PO/IM PRN psychomotor agitation with threatening or violent behavior every 4 hours.

5. If applicable, consider whether a **sedative** is still needed depending on whether insomnia was acute, subacute or chronic. If needed for chronic insomnia, both zolpidem and eszopiclone have been so indicated.

C. Phase 3 (Maintenance)

Phase 3 of this algorithm represents establishment of a maintenance course of pharmacological treatment. The overriding goal is to identify those medications which have proven beneficial and to optimize their use, specifically (1) identifying the lowest effective dose and (2) to simplify the dosing schedule to interfere as little as possible with the individual's long-term psychosocial functioning.

1. The goals are to fine-tune medications to provide maximum long-term stability with the least risk exposure and to identify clinical

2. targets for which either other medications or additional treatment modalities may be beneficial.

3. In this context, adherence to treatment shows a strong inverse correlation with dosing frequency.

4. For oral medications, once per day dosing is optimal whenever the pharmacokinetics of the medication permit.

5. By this phase of treatment, psychotropic PRN medications not used in the previous 30 days should generally be discontinued.

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