

City and County of San Francisco

Gavin Newsom, Mayor



Department of Public Health

Community Behavioral Health Sciences
Community Health Network of San Francisco
San Francisco General Hospital

**GUIDELINES FOR THE USE OF
ATYPICAL ANTIPSYCHOTICS IN ADULTS**

Revised: October 2006

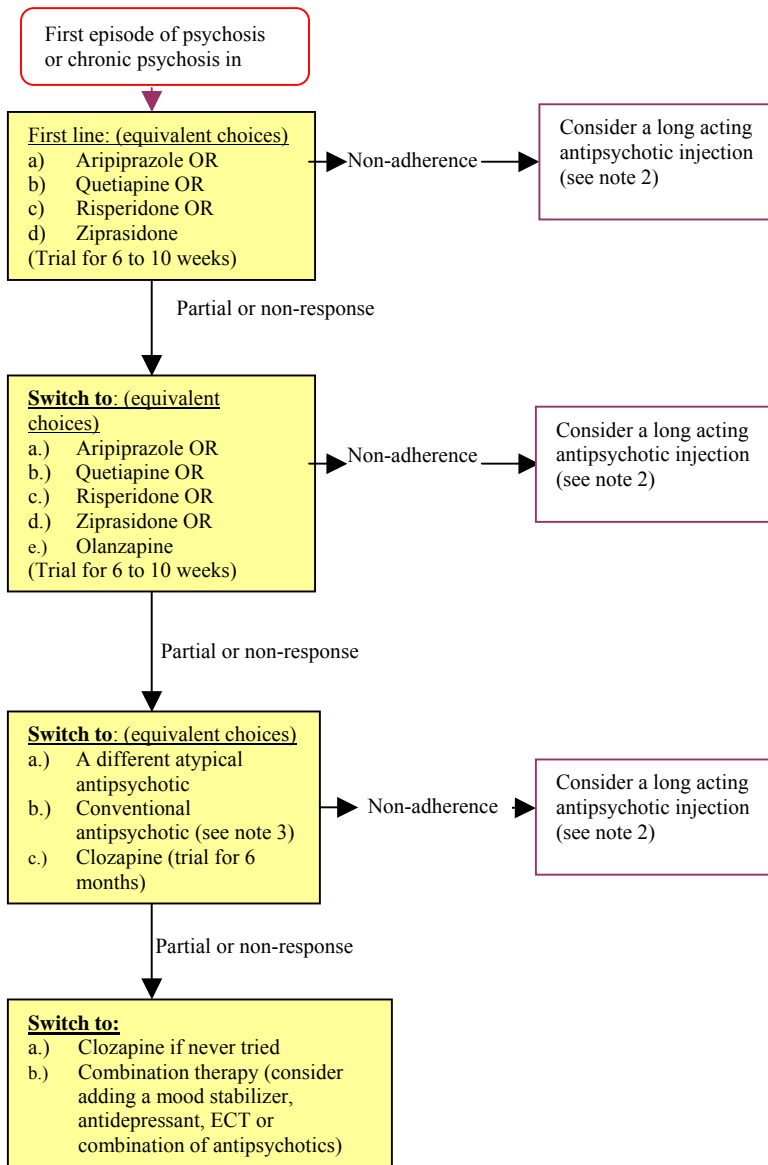
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Guidelines for Antipsychotic Use in Adults

Selection of therapy for individual patients is ultimately based on physicians' assessment of clinical circumstances and patient needs. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care. The following recommendations are dynamic and will be revised, as new clinical data become available.



Antipsychotic MONOtherapy is the goal (see note 1 below).

For use of ANY Atypical Antipsychotic in Diabetic Patients, refer to the Monitoring Guidelines posted on the CHN intranet.

For All Antipsychotics, Baseline ECG recommended if:

Heart rate <50 or
Hypokalemia or
Hypomagnesemia or
Significant cardiac history (ie. recent MI, arrhythmia, uncompensated heart failure) or Family history of sudden death
(Choose any atypical antipsychotic except ziprasidone)

Avoid ziprasidone, haloperidol, thioridazine, chlorpromazine, mesoridazine if:

- known history of QTc prolongation
- recent acute MI
- uncompensated heart failure
- taking other medications which prolong QT
- use caution in alcoholics or patients on diuretics which may alter electrolytes

Olanzapine (Non-formulary) exceptions SFGH only:

- OK to stay on it if patient is stabilized prior to admission
- Patient has failed or not tolerated one of the formulary agents (aripiprazole, quetiapine, risperidone, ziprasidone)

Risperidone Consta (Non-formulary) exceptions SFGH only:

- OK to stay on it if patient is stabilized prior to admission
- Must have an adequate trial with formulary agents: haloperidol decanoate or fluphenazine decanoate
- Outpatient MD should have already obtained the Prior Authorization from Medi-Cal or the third party insurance

Notes:

- 1) Antipsychotic monotherapy is the recognized standard for the treatment of schizophrenia; pharmacological justification for polypharmacy is weak. Combining medications adds to cost of treatment, increases potential for adverse effects, may make adherence more challenging, and increases possibility of unfavorable drug reactions. However, polypharmacy may be acceptable in the short term when one antipsychotic is being tapered/discontinued while the new antipsychotic is being initiated/titrated.
- 2) If patient is non-adherent to oral antipsychotic therapy, consider a long acting antipsychotic preparation such as haloperidol decanoate, fluphenazine decanoate, or risperidone consta (refer to text box for detailed information on obtaining risperidone consta).
- 3) Prioritize the use of newer generation antipsychotic medication for new antipsychotic medication starts and for patients not responding to or having problematic side effects on conventional antipsychotic medication. For patients with severe positive symptoms or violence/aggression, consider typical antipsychotic therapy; patients should not be subjected to numerous trials of newer generation antipsychotics before considering use of conventional antipsychotic such as haloperidol (or other conventional agents).
- 4) Patients eligible for clozapine trial: sub-optimal response or adverse events to 2 or more antipsychotics.
- 5) Utilize current approaches of clinical assessment to determine response to medication and whether medication changes are indicated. Such assessments should include the presence and severity of positive and negative symptoms (BPRS), tardive dyskinesia, EPS/tremor, weight gain, lipid status, glucose metabolism, and GAF.

GUIDELINES FOR THE USE OF NEWER GENERATION ANTIPSYCHOTICS

NOTE: THIS GUIDELINE IS AN EDUCATIONAL TOOL TO AID CLINICAL DECISION-MAKING. IT IS NOT THE STANDARD OF CARE. THE PHYSICIAN SHOULD ADAPT THIS GUIDELINE WHEN CLINICAL JUDGEMENT SO INDICATES.

Atypical antipsychotics are generally first line agents for the following patients:*

1. All patients with **new onset** of a chronic psychotic disorder, based on the tentative or working diagnosis, recognizing that in some patients there may be inadequate data to distinguish between a brief reactive psychosis or a drug-induced psychosis and first presentation of schizophrenia.
2. All patients with symptoms of **tardive dyskinesia**. While atypical antipsychotics may pose a lower risk of causing tardive dyskinesia than typical antipsychotics, long-term data with these newer agents are still limited. Therefore, the use of these agents should be limited to patients in whom the use of an antipsychotic is indicated.
3. Patients with **extrapyramidal symptoms** from conventional antipsychotic agents, unresponsive to an anti-parkinson agent at therapeutic doses and one other agent (benzodiazepine, propranolol, amantadine, etc.).
4. **Treatment refractory patients**, defined as patients who have negative or positive symptoms that significantly impair function despite an adequate trial with a typical antipsychotic (at least 7 mg/day of haloperidol equivalents for at least four weeks).
5. **Patients with co-occurring psychiatric and substance use disorders**. Atypical antipsychotics are preferred because they are less likely to cause movement disorders, dysphoria, and increased drug cravings that have been associated with typical antipsychotics.¹

***Clozapine** is the most effective agent in treatment-refractory psychotic patients. However, it should not be used as a first line agent because of the need for weekly* blood draws initially, the increased incidence of troubling side effects, including the risk of agranulocytosis and metabolic side effects. On the other hand, patients with significant symptoms and impairment should not be subjected to endless trials of other atypical agents. A reasonable standard is that a patient should have failed an adequate trial of one conventional antipsychotic agent and one newer generation antipsychotic agent or two newer generation antipsychotic agents. This can be modified depending on the severity of the symptoms. It is also the only newer generation antipsychotic agent which has been shown to reverse even severe tardive dyskinesia (TD) in controlled trials. It is also indicated in patients who cannot tolerate extrapyramidal side effects of standard antipsychotic treatment.

Note that weekly blood monitoring can be reduced to every other week monitoring if patient's WBC and ANC are stable and normal for 6 months of continuous clozapine treatment. For individuals with stable WBC and ANC for 12 months monitoring can be reduced to once every 4 weeks.

*Olanzapine is considered as second-line choice because of its increased rate of metabolic complications.

Newer generation antipsychotics do not appear to be effective for all patients who have responded to conventional antipsychotics, therefore the following issues need to be considered in switching a patient from a typical agent to an atypical agent:

1. The risk-benefit of the switch, given that some patients will not respond to the new agent.
2. The urgency of the switch: if the switch is not urgent then both agents should be cross-tapered over several weeks with close monitoring for the emergence of new symptoms.

Antipsychotic monotherapy is the recognized standard for the treatment of schizophrenia; pharmacological justification for polypharmacy is weak. Combining medications adds to cost of treatment, increases potential for adverse effects, may make adherence more challenging, and increases possibility of unfavorable drug reactions. However, polypharmacy may be acceptable in the short term when one antipsychotic is being tapered/discontinued while the new antipsychotic is being initiated/titrated.

Table 1: Pharmacology and Pharmacokinetics

	Aripiprazole (Abilify)	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)
Class	Quinolone derivative	Dibenzodiazepine	Thienbenzodiazepine	Dibenzothiazepine	Benzisoxazole	Benzothizolylpiperazine
Pharmacology	D ₂ and 5-HT _{1A} partial agonism, 5-HT _{2A} antagonism	5-HT ₂ , D ₁ , D ₂ , D ₃ , D ₄ , M ₁ , H ₁ , α ₁ - and α ₂ -antagonism	5-HT _{2A} , 5-HT _{2C} , D ₁ , D ₂ , D ₃ , D ₄ , M ₁ , 5, H ₁ , and α ₁ -antagonism	D ₁ , D ₂ , 5-HT _{2A} , 5-HT _{1A} , histamine H ₁ , and adrenergic alpha ₁ and alpha ₂ receptors	5-HT ₂ , D ₂ , H ₁ , α ₁ - and α ₂ -antagonism	D ₂ , D ₃ , 5-HT _{2A} , 5-HT _{2C} , 5-HT _{1D} and α ₁ - antagonism; moderate inhibition of 5-HT and NE reuptake; 5-HT _{1A} agonism
Absorption	Not affected by food	Not affected by food	Not affected by food	Not affected by food	Not affected by food	Doubled with food
Peak levels	3-5 hours	2.5 hours	6 hours	1.5 hours	1-2 hours	6 – 8 hours
Bioavailability	87%	50%	60%	100%	70%	60% with food
Protein Binding	99%	97%	93%	83%	90%	> 99%
Half-life (t_{1/2})	75 hours	12 hours	30 hours	6 hours	3 hours for risperidone; 20 hours for parent plus metabolite	6.6 hours
Metabolism	CYP 2D6, 3A4	CYP450 1A2, 2D6	CYP450 1A2 (major); CYP450 2D6 (minor)	CYP450 3A4	CYP450 2D6	CYP450 3A4 (1/3); aldehyde oxidase (2/3)
Therapeutic serum level	N/A	>350 ng/ml	N/A	N/A	N/A	N/A

Table 2: Relative Adverse Effects

	Aripiprazole (Abilify)	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)
Sedation	+	++++	++	++	+	++
Weight gain	±	++++	++++	++	++	±
Orthostatic hypotension	±	++++	++	++	++	+
Mean Change inQTc interval from baseline (msec)²	Similar to placebo	N/A	1.2	5.9	0.2	1.3
EPS	+	±	++	±	++	++
Hyperprolactinemia	±	±	+	±	++++	+
Others	Newest agent: least data and experience; most common adverse effects in pre- clinical trials: headache, anxiety, insomnia, nausea, akathisia, dizziness	Agranulocytosis (see monitoring guidelines), seizure, hypersalivation, severe constipation, tachycardia, rarely myocarditis or cardiomyopathy	Cases of hyperglycemia, diabetic ketoacidosis reported, weight gain severe in some patients	Dose titration required in order to minimize orthostasis and sedation	Dose titration to minimize orthostatis, tachycardia, nasal congestion, EPS and hyperprolactin- emia generally occur at doses >6 mg/d	Contraindicated in patients with a known history of QT prolongation, including congenital long QT syndrome, with recent acute myocardial infarction, or with uncompensated heart failure hypokalemia or hypomagnesemia; avoid/discontinue in patients with persistent QTc measurements > 500 msec

Table 3: Drug Interactions

	Aripiprazole (Abilify)	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)
Increased antipsychotic levels	azole antifungals* erythromycin fluoxetine nefazodone paroxetine protease inhibitors quinidine	azole antifungals* ciprofloxacin fluoxetine fluvoxamine citalopram	ciprofloxacin fluoxetine fluvoxamine	azole antifungals* erythromycin cimetidine fluvoxamine nefazodone protease inhibitors	azole antifungals* fluoxetine paroxetine quinidine ritonavir	azole antifungals*
Decreased antipsychotic levels	carbamazepine	omeprazole ritonavir smoking	omeprazole ritonavir smoking	carbamazepine nevirapine St. John's wort	carbamazepine	carbamazepine
Other		other agents which suppress bone marrow function (carbamazepine, chemotherapeutic agents)				other drugs which increase QT: quinidine, dofetilide, sotalol, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, moxifloxacin, sparfloxacin, gatifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus

*Azole antifungals- ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole

Table 4: Dosage forms, dosing

Drug	Available Dosage Forms	General Adult Dosing Recommendation (Elderly dosing)	Aggressive Dosing Titration for healthy adults (18-55 y/o) *Not intended for treatment-naïve pt
Aripiprazole (Abilify®)	2mg, 5mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets 1mg/ml oral solution; 10 mg, 15 mg ODT (non-formulary)	<i>Initial:</i> 10-15 mg qd <i>Titration:</i> may be increased to a maximum of 30 mg/d (Elderly initial dosing: 5-7.5 mg/d)	<i>Initial:</i> 30 mg qd, then adjust dose downward as needed ³ Low dose benzodiazepine, ie. clonazepam or lorazepam 1 mg bid is recommended for prevention of akathisia
Clozapine (Clozaril®)	12.5mg, 25 mg, 50mg, 100 mg, 200mg tablets; generics available 25 mg, 100mg ODT (non-formulary)	<i>Initial:</i> 25 mg qhs <i>Titration:</i> increased by 25–50 mg every 1-3 days as tolerated to 300-500 mg/d in bid dose <i>Max dose:</i> 900 mg/d (Elderly initial dosing: 12.5 mg qhs)	<i>Initial:</i> 25 mg qhs <i>Titration:</i> increased by 25-50 mg every day as tolerated to 300-500 mg/d in bid dose within 2-4 weeks
Olanzapine (Zyprexa®) Non-Formulary @SFGH PAR@ CBHS	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets 5 mg, 10 mg, 15 mg, and 20 mg ODT 10mg/vial IM	<i>Initial:</i> 10 mg qhs <i>Titration:</i> Increase by 5-10 mg/day at 1-week intervals <i>Max dose:</i> 20 mg/d (Elderly initial dosing: 2.5-5mg qhs) IM injection: 5-10mg IM then repeat q2-4hrs up to 30mg/day	<i>Initial:</i> 10-20 mg qhs ⁴ <i>Titration:</i> may increase by 10 mg/d every 3-4 days to 30-40 mg/d ¹⁰ *Monitor for sedation and orthostatic hypotension
Quetiapine (Seroquel®)	25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg tablets	<i>Initial:</i> 25mg bid <i>Titration:</i> increase by 25-50 mg bid every 1-2 days to target dose of 400-600 mg ⁵ <i>Max:</i> 800 mg/d (Elderly initial dosing: 12.5 mg bid or 25 mg qhs, target dose: 50-200 mg/d)	<i>Initial:</i> 50-100 mg bid <i>Titration:</i> Increase by 100-200 mg every day to target dose ^{6,7} * Monitor for sedation and orthostatic hypotension
Risperidone (Risperdal®)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets; 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg ODT; 1 mg/ml oral concentrate solution Consta® 25mg, 37.5mg, 50mg long acting injection (non-formulary)	<i>Initial:</i> 1 mg qd-bid <i>Titration:</i> Increase by 0.5 – 1 mg/d every 1-3 days <i>Target dose:</i> 4 –5 mg/d; can be given once daily if patient tolerates orthostasis (Elderly initial dosing: 0.5 mg qd) Long-acting injection: <i>Initial:</i> 25mg IM q2wks, continue po tabs x 3wks <i>Titration:</i> increase dose no more frequently than q4wks	<i>Initial:</i> 1-2 mg bid ^{8,9} <i>Titration:</i> Increase by 1-2 mg every day to 6-8 mg/d ¹⁰ Daily dosages >10 mg does not appear to confer any additional benefit *Monitor for orthostatic hypotension and EPS, ie. dystonia, akathisia, parkinsonism
Ziprasidone (Geodon®)	20 mg, 40 mg, 60 mg, 80 mg capsules; 20 mg/ml vials for IM injection	<i>Initial:</i> 40 mg bid with food; <i>Titration:</i> Increase by 20 mg bid every 2-3 days to 60-80 mg bid with food (Elderly initial dosing: 20mg bid with food) IM injection: 10mg q2hrs or 20mg q4hrs up to 40mg/day	<i>Initial:</i> 100-120 mg/d ¹¹ with food <i>Titration:</i> Increased to 160 mg/d by day 2 and up to 200 mg/d as tolerated ¹²

ODT = orally disintegrating tablet
PAR = prior authorization required

ATYPICAL ANTIPSYCHOTIC CLASS ISSUES

Metabolic Complications

Obesity: Weight gain is a prominent side effect of atypical antipsychotics. The onset can occur early in treatment and continue to increase even a year later. Patients that experience weight gain are more likely to be noncompliant and request discontinuation of the agent. The comparative risk profile suggests that weight gain is most profound with clozapine and olanzapine while aripiprazole and ziprasidone confer only limited liability. Quetiapine and risperidone likely are intermediate in their effects on weight.

Diabetes mellitus: Atypical antipsychotics can cause diabetic ketoacidosis, worsening of pre-existing diabetes, new onset diabetes, and hyperglycemia. The exact mechanism is unknown however it may be linked to a direct toxic effect on the pancreas, impairment of insulin receptors/glucose transporters, weight gain, 5-HT_{1A} antagonism, or hypothalamic dopamine antagonism. Analogous to weight gain the risk is highest with clozapine and olanzapine, lower with quetiapine and risperidone and minimal with ziprasidone and aripiprazole.

Dyslipidemia: The effect on serum lipids is less clearly elucidated, however it seems to occur in concert with weight gain, thus clozapine and olanzapine carry the highest risk, quetiapine and risperidone carry intermediate risk, and ziprasidone and aripiprazole carry the least risk. The primary effect is on increasing triglycerides with secondary effects on increasing total and LDL cholesterol while decreasing HDL cholesterol.

Treatment: The management of metabolic side effects and cardiovascular risk should involve lifestyle modifications (diet, exercise, smoking cessation), consideration of a switch to a lower risk atypical antipsychotic, and drug therapy targeting the metabolic side effect including antiglycemic and lipid lowering therapy.

Table 5: Metabolic Complications of Atypical Antipsychotics: Results from the CATIE Study*

Reference value compared to baseline	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Clozapine	Aripiprazole
Weight Change (lbs/month)	2	0.5	0.4	-0.3	0.5	–
HbA1c (%)	0.4	0.04	0.07	0.1	0.1	–
Blood Glucose (mg/dl)	13.7	7.5	6.6	2.9	13.2	0.90
Total Cholesterol (mg/dl)	9.4	6.6	-1.3	-8.2	7.3	-0.7
Triglycerides (mg/dl)	40.5	21.2	-2.4	-16.5	52.6	0.6

*Data for clozapine¹³ and aripiprazole¹⁴ are from separate sources

Table 6: Monitoring Criteria for Metabolic Complications¹⁵

	Baseline	4 wks	8 wks	12 wks	Quarterly	Annually	Every 5 yrs
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
BP	X			X		X	
Fasting glucose	X			X		X	
Fasting lipid	X			X			X

Prolactin Elevations: Clinical ConsequencesWomen

Menstrual disturbances
Galactorrhea
Breast engorgement
Sexual dysfunction
Infertility

Men

Loss of libido
Erectile dysfunction
Ejaculatory dysfunction
Reduced spermatogenesis

Risk of hyperprolactinemia: Risperidone >>> Olanzapine / Ziprasidone > Aripiprazole / Clozapine / Quetiapine

Tardive Dyskinesia:

The incidence of tardive dyskinesia (TD) with atypical antipsychotics in adults is approximately 0.8% per year compared to 5.4% annual incidence in adults treated with the conventional antipsychotic haloperidol.¹⁶ TD may be alleviated by antipsychotic discontinuation, dose reduction, or switching to an atypical antipsychotic. Clozapine lacks the capacity to cause TD and has been found to have a therapeutic effect on reducing TD symptoms, particularly dystonia.¹⁷

Use of Atypical Antipsychotics in the Elderly:

Atypical antipsychotics are often used off-label to treat behavioral disturbances or dementia-related psychosis in elderly patients. However, the use of atypical antipsychotics in elderly patients with dementia has been associated with increased mortality. Analyses of seventeen placebo controlled trials in these patients revealed a higher risk of death in the atypical antipsychotic-treated patients than seen in placebo-treated patients (4.5% vs 2.6%). Although the causes of death were varied, most of the death appeared to be either cardiovascular (eg., heart failure, sudden death) or infection (eg., pneumonia) in nature. Cerebrovascular adverse events (CAEs), including stroke and fatalities also have been reported in elderly patients with dementia-related psychosis taking risperidone, olanzapine or aripiprazole in clinical trials. The incidence of CAEs with these atypical agents was significantly higher than placebo. Conventional antipsychotics such as haloperidol were associated with a higher risk of death and CAEs than were with atypical antipsychotics in recent studies.¹⁸ These results suggest that antipsychotics should be regarded only as rescue medications for acute-onset or for severe chronic behavioral and psychiatric symptoms in elderly patients with dementia, or used in patients who are aggressive and/or represent a danger to themselves or others. If antipsychotics are prescribed, physicians should screen for

risk factors for both stroke and cardiovascular disease when initiating treatment and regular monitoring should be undertaken if patients with chronic behavioral problems receive antipsychotic maintenance therapy.

For aging of individuals with psychotic disorders, they may need lower doses of antipsychotic since older patients may develop adverse drug reactions more easily in later years.

Dosing Guidelines:

Patients should be tried on at least four to six weeks (outpatient) or two weeks (inpatient) of the usually effective dose of an atypical agent before the dose is increased, or a change of medication is considered. For patients currently on conventional antipsychotics, agents should be cross-tapered during the initiation of newer generation antipsychotic treatment.

OBRA maximum daily* dose for patients over 65 years and who reside in nursing facilities have been established for:

Clozapine	50 mg/day
Olanzapine	10 mg/day
Risperidone	2 mg/day
Quetiapine	200 mg/day

Such dosage guidelines have not yet been established for ziprasidone or aripiprazole. The clinician must consider that geriatric patients and those with hepatic or renal impairment will require lower dosages.

*these “maximum” daily doses are not absolute but above these doses, OBRA regulations require documentation that lower doses are not effective in the case in question

PRN Use:

Intramuscular Administration (SFGH)

Ziprasidone and olanzapine are the only intramuscular (IM) atypical antipsychotics available for the treatment of acute agitation. The onset of action occurs within 15-30 minutes. Ziprasidone IM may be administered concurrently with lorazepam IM for additional sedation. Ziprasidone IM should be reserved for second-line therapy after haloperidol IM for those patients where:

1. Extrapyramidal side effects (EPS) are a concern (past history of EPS to haloperidol or similar agents; young patients with high muscle mass; extremely paranoid patients)
2. Anticholinergic medications (e.g., diphenhydramine, benztropine) should be avoided, or
3. Patients with a history of neuroleptic malignant syndrome (NMS) as a result of conventional antipsychotic treatment.

IM olanzapine is non-formulary.

Oral Administration

Although conventional antipsychotics are used from time to time on an “as needed” or “PRN” basis there is only limited scientifically based evidence supporting such use of atypical antipsychotics. Because of the high cost of the newer generation antipsychotics and the lack of safety and efficacy data for the oral formulations, these agents should not be used on a PRN basis.

Polypharmacy:

- Antipsychotic monotherapy is the recognized standard for the treatment of schizophrenia
- Pharmacological justification for polypharmacy is weak.
- Polypharmacy has been associated with higher antipsychotic doses, longer hospitalizations, and higher risk of adverse effects when compared to symptom severity matched patients receiving monotherapy.¹⁹
- No data to determine whether any particular pattern of receptor blockade is useful for control of psychosis; assertion that a specific combination of medications will provide superior results cannot be substantiated
- Safety and efficacy of this practice are generally untested and unproven
- Combining medications adds to cost of treatment, may make adherence more challenging, and increases possibility of unfavorable drug reactions
- Note: polypharmacy may be acceptable in the short term when one antipsychotic is being tapered/discontinued while the new antipsychotic is being initiated/titrated

Augmentation strategies:

There are limited data suggesting augmentation of antipsychotic treatment in patients with schizophrenia may improve therapeutic outcome. Agents most often used in this manner include benzodiazepines, particularly in the setting of acute exacerbations, and mood stabilizers such as lithium, carbamazepine, lamotrigine and valproic acid. Use of mood stabilizers may be particularly effective in patients who have affective symptoms or violence/aggression.

APPENDIX A

ATYPICAL ANTIPSYCHOTIC ADVERSE EFFECT MANAGEMENT:

The following recommendations are for patients with a good response to an agent, but who have significant side effects.

Refractory EPS (bradykinesia or muscle rigidity): Treat with anticholinergic agent (e.g., benztropine, diphenhydramine). If ineffective, switch to a different anticholinergic agent or amantadine, or consider a switch to a different agent (quetiapine has the lowest risk of EPS).

Akathisia: Consider propranolol (or a benzodiazepine, or consider a switch to a different agent such as quetiapine which has the lowest risk of EPS).

Neuroleptic malignant syndrome: Wait and monitor for at least two weeks after recovery from NMS before rechallenging with any antipsychotic agent. Consider another newer generation antipsychotic; avoid depot formulations of antipsychotic.

Hyperprolactinemia/Sexual side effects: Consider quetiapine (alternative agents: olanzapine or ziprasidone or aripiprazole).

Insomnia/agitation: Eliminate stimulants (including caffeine), advise regarding sleep hygiene, consider benzodiazepine (also consider switch to olanzapine or quetiapine).

Weight gain, increased lipids, increased glucose: consider switch to ziprasidone or aripiprazole and treatment of metabolic side effect.

APPENDIX B

CLOZAPINE ADVERSE EFFECT MANAGEMENT:

Hematologic: See appendix E

Seizure: The occurrence of seizures appears dose-related in patients taking clozapine: 1-2% of patients on low doses (below 300 mg/day), 3-4% of patients on moderate doses (300-600 mg/day), and 5% of patients at high doses (600-900 mg/day). The majority of seizures are of the generalized tonic-clonic type and can usually be managed successfully without clozapine discontinuation. To minimize seizure risk, avoid concomitant use of other medications that lower the seizure threshold, avoid rapid dosage elevation of clozapine (e.g., increase dose by 12.5-25 mg every 2-3 days), minimize the clozapine dose and consider obtaining an EEG before raising clozapine dosage above 600 mg/day). If seizures are suspected or confirmed, obtain an EEG and neurology consult, reduce clozapine dosage by 50%, and consider adding a concomitant anticonvulsant agent such as divalproex sodium (avoid phenytoin and carbamazepine).

Hypersalivation: Encourage patients to sleep on their sides or alternatively with head slightly propped up and advise patients to cover pillows with towels. During the day, some patients find chewing sugar-free gum helpful, possibly by prompting them to swallow more often. If severe, cautiously consider an anticholinergic medication (benztropine or trihexyphenidyl) though efficacy with these agents is limited.

Constipation: Avoid concomitant anticholinergic agents, ensure adequate hydration, add psyllium, docusate sodium; encourage prune juice. Lastly, if still unrelieved, consider bisacodyl or other laxative.

Tachycardia: Generally occurs early in treatment and is transient. Usually is not a reason to stop clozapine but may pose a risk for individuals with compromised cardiovascular function. Rule out myocarditis or other cardiac disease through EKG and appropriate medical testing. Advise tachycardic patients to reduce caffeine intake and cigarette smoking. If persistent and symptomatic, tachycardia may require treatment with a peripheral beta blocker (choose atenolol).

Sedation: Very common side effect which occurs early on in treatment. Some patients may gain tolerance to this side effect while others will continue to experience it. Ways to manage it include dosing at bedtime, rather than bid and titrating dose more slowly so that tolerance develops. Also, decreasing dosage or discontinuing other sedating agents whenever possible may help.

APPENDIX C

San Francisco Community Behavioral Health Services Olanzapine (Zyprexa) Prior Authorization Criteria

Olanzapine will be provided as a plan benefit for patients meeting one of the following criteria:

1. Currently taking olanzapine with good response
2. Diagnosis of schizophrenia or schizoaffective disorder with treatment failure or adverse effect to ONE atypical antipsychotic (aripiprazole, risperidone, quetiapine, or ziprasidone)
3. Diagnosis of bipolar disorder with treatment failure or adverse effect to lithium, valproic acid, AND carbamazepine

APPENDIX D

Community Health Network

STAMP NAME AND HOSPITAL NUMBER

SAN FRANCISCO GENERAL HOSPITAL MEDICAL CENTER

Oral Atypical Antipsychotic Initiation Order Sheet

Directions: Use this form for initial hospital order for oral atypical antipsychotic and appropriate baseline labs. Document any changes or adjustments on regular Physician Order Sheet.

Adverse Drug Events (including allergies): _____

Non Drug Allergy: _____

PLEASE SELECT AGENT, PROVIDE DOSING AND DIRECTION:

- ARIPIPRAZOLE (ABILIFY)** _____
- QUETIAPINE (SEROQUEL)** _____
- RISPERIDONE (RISPERDAL)** _____
- ZIPRASIDONE (GEODON)** _____

*For clozapine order, please use clozapine order sheet

LABORATORY MONITORING (Please select appropriate labs)

****Please reorder labs until studies are completed****

- Weight on admission and every week on _____** (specify day)
- Glucose, fasting**
- Lipid panel, fasting (if not documented within the past 3 months)**
- Complete Metabolic panel**
- HbA1C (for diabetics and if not documented within the past 3 months)**

NON-FORMULARY (PLEASE PROVIDE JUSTIFICATION)

OLANZAPINE (ZYPREXA) _____

Documentation/Justification: _____

Olanzapine (Zyprexa) clinical exception criteria (circle one and provide documentation above):

1. Currently taking olanzapine with good response
2. Diagnosis of schizophrenia or schizoaffective disorder with treatment failure or adverse effect to ONE atypical antipsychotic (aripiprazole, risperidone, quetiapine, or ziprasidone)
3. Diagnosis of bipolar disorder with treatment failure or adverse effect to lithium, valproic acid, AND carbamazepine

• Order above may not be noted unless all sections are completed by physician.

Date _____ Time _____ Physician _____ / _____ ID# _____ BPR# _____

Date _____ Time _____ LVN/LPT/UC Signature _____ Title _____

Date _____ Time _____ RN Signature _____

APPENDIX E

CLOZAPINE MONITORING AND MANAGEMENT²⁰

Situation	Hematological Values for Monitoring	Frequency of WBC and ANC Monitoring
Initiation of Therapy	WBC \geq 3500/mm ³ ANC \geq 2000/mm ³ *Do not initiate in patients with 1) history of myeloproliferative disorder or 2) clozapine induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 months – 12 months of therapy	All results for WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³	Every 2 weeks for 6 months
12 months of therapy	All results for WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³	Every 4 weeks ad infinitum
Immature forms present	N/A	Repeat WBC and ANC
Discontinuation of Therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³
Substantial drop in WBC or ANC	Single drop or cumulative drop within 3 weeks of WBC \geq 3000/mm ³ ANC \geq 1500/mm ³	1. Repeat WBC and ANC 2. If repeat values are 3000/mm ³ \leq WBC \leq 3500/mm ³ and ANC $<$ 2000/mm ³ , then monitor twice weekly
Mild Leukopenia ----- Mild Granulocytopenia	3500/mm ³ $>$ WBC \geq 3000/mm ³ and/or 2000/mm ³ $>$ ANC \geq 1500/mm ³	Twice-weekly until WBC $>$ 3500/mm ³ and ANC $>$ 2000/mm ³ then return to previous monitoring frequency
Moderate Leukopenia ----- Moderate Granulocytopenia	3000/mm ³ $>$ WBC \geq 2000/mm ³ and/or 1500/mm ³ $>$ ANC \geq 1000/mm ³	1. Interrupt therapy 2. Daily until WBC $>$ 3000/mm ³ and ANC $>$ 1500/mm ³ 3. Twice weekly until WBC $>$ 3500/mm ³ and ANC $>$ 2000/mm ³ 4. May rechallenge when WBC $>$ 3500/mm ³ and ANC $>$ 2000/mm ³ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months then every 4 weeks ad infinitum
Severe Leukopenia ----- Severe Granulocytopenia	WBC $<$ 2000/mm ³ and/or ANC $<$ 1000/mm ³	1. Discontinue treatment and do not rechallenge 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: • Daily until WBC $>$ 3000/mm ³ and ANC $>$ 1500/mm ³ • Twice weekly until WBC $>$ 3500/mm ³ and ANC $>$ 2000/mm ³ • Weekly after WBC $>$ 3500/mm ³
Agranulocytosis	ANC \leq 500/mm ³	1. Discontinue treatment and do not rechallenge 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: • Daily until WBC $>$ 3000/mm ³ and ANC $>$ 1500/mm ³ • Twice weekly until WBC $>$ 3500/mm ³ and ANC $>$ 2000/mm ³ • Weekly after WBC $>$ 3500/mm ³

White Blood Cells include the neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Neutrophils are essential in killing invading microorganisms such as bacteria. The ANC is defined as the total number of neutrophils present in the entire system of WBC; the risk of infection increases as ANC drops below 1.5 K/UL. The ANC is calculated by the WBC count multiplied by the percentage of neutrophils. Example if WBC = 4.4 and the percentage of neutrophils in the WBC is 45.5%; $4.4 \times 0.455 = 2.002$; therefore the ANC is 2.0 K/UL.

References:

- ¹ Journal of Clinical Psychopharmacology 2003;23:384-8
- ² NEJM 2005;353:1209-1223
- ³ Psychopharmacology 2003;166:391-9
- ⁴ Journal of clinical psychopharmacology 2003;23:342-8
- ⁵ Archives of general psychiatry 1997;54:549-57
- ⁶ Journal of clinical psychopharmacology 2005;25:331-5
- ⁷ Journal of psychopharmacology 2006;20:119-24
- ⁸ The American journal of psychiatry 1999;156:869-75
- ⁹ The Journal of clinical psychiatry 2000;61:909-11
- ¹⁰ The Journal of clinical psychiatry 2005;66:887-93
- ¹¹ Schizophrenia research 2006;83:277-84
- ¹² American Psychiatric Association 2004. Practice Guideline for the Treatment of Patients with Schizophrenia.
- ¹³ Am J Psychiatry 2006;163:600-610
- ¹⁴ BMS and Otsuka Pharmaceutical Inc data on file 2004
- ¹⁵ Diabetes Care 2004;27:596-601
- ¹⁶ Am J Psychiatry 2004;161:414-425
- ¹⁷ British Journal of Psychiatry 1991;158:503-10
- ¹⁸ NEJM 2005; 353:2335-41
- ¹⁹ Am J Psychiatry 2004;161:700-6
- ²⁰ Clozaril® Package Insert. Rev. May 2005