North Dakota Medicaid

Drug Utilization Review Board

Drug Class Review

Antipsychotic Agents

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Pharmacotherapy Review
Antipsychotic Medications
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Introduction

Antipsychotics are used to treat the symptoms of schizophrenia and bipolar disorder. This class of medication is usually referred to as 'typical' or 'atypical' antipsychotics. In general, atypical antipsychotics produce antipsychotic responses with fewer acute extrapyramidal side effects (EPS) than 'typical' antipsychotic drugs. rief introductions of the disease states most commonly treated with these medications.

Disease States Most Commonly Treated with Antipsychotics

Schizophrenia

Schizophrenia is a chronic, severe, and disabling brain disorder. Recent statistics report that schizophrenia affects about one percent of people all over the world.

Diagnosis of Schizophrenia

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM IV-TR) lists the following criteria for diagnosing schizophrenia:

Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a one-month period (or less, if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (e.g., frequent derailment or incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms (i.e., affective flattening, alogia, or avolition)

Note: Only one of the above symptoms is required if delusions are bizarre or if hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or of two or more voices conversing with each other.

Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset, or when the onset is in childhood or adolescence, or there is a failure to achieve the expected level of interpersonal, academic, or occupational achievement.

Duration: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if successfully treated) that meet the characteristic symptom criterion (i.e., active-phase symptoms), and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms, or by two or more

active-phase symptoms present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) mood episodes have occurred during active-phase symptoms, and their total duration has been brief relative to the duration of the active and residual periods.

Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., drug abuse; a medication) or a general medical condition.

Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less, if successfully treated).

Classification of Longitudinal Course *(can be applied only after at least one year has elapsed since the initial onset of active-phase symptoms)*

Episodic with inter-episode residual symptoms (episodes are defined by the re-emergence of prominent psychotic symptoms); *also specify if:* **with prominent negative symptoms**

Episodic with no inter-episode residual symptoms

Continuous (prominent psychotic symptoms are present throughout the period of observation); *also specify if:* **with prominent negative symptoms**

Single episode in partial remission; *also specify if:* **with prominent negative symptoms**

Single episode in full remission

Other or unspecified pattern

Categories of Symptoms

Generally, there are three categories of symptoms associated with schizophrenia:

Positive symptoms, as a rule, are easier to notice. These symptoms include hallucinations, delusions, thought disorders, and disorders of movement.

Negative symptoms often refer to symptoms that involve emotional and behavioral states. Common negative symptoms include flat affect, lack of pleasure in everyday life, reduced ability to initiate and sustain planned activity, and speaking infrequently.

Cognitive symptoms include poor executive functioning, inability to sustain attention, and problems with working memory.

Bipolar Disorder

Simply defined, bipolar disorder is a disorder in which a person can experience recurrent attacks of depression and mania or hypomania. Bipolar disorder is also known as manic depression.

There are two types of bipolar disorder: Type I and Type II. Type I is the classic cyclic, recurrent, and relapsing mood disorder which is characterized by cycles of depression and mania.

Type II does not have a history of full manic episodes. It is characterized by a history of major depressive episodes and at least one hypomanic episode.

Common symptoms associated with Type I bipolar disorder include insomnia, anxiety, confusion, euphoria, depression, and anhedonia (failure to enjoy positive emotional experiences).

Other symptoms might include impulsiveness, irritability, hallucinations, and delusions.

Most Type I cases often begin with mild hypomanic symptoms that progress toward a full manic episode. Patients may seek constant enthusiastic interaction from others and display pressured speech, flight of ideas, and disorganization. Commonly, reckless behavior with negative consequences appears, as well as a severe inability to sleep.

Patients may present with hypomania or a mixed state. In this case, hypomania is distinguished from mania by the lack of social and/or occupational impairment. A mixed state may occur when manic and depressive symptoms are present but neither predominates. Type II shares common symptoms with Type I. In Type II patients, however, hypomanic episodes tend to happen in close proximity to depressive episodes, which increase in frequency with advancing age. In some cases, patients may have four or more episodes in a given year. These patients are referred to as "rapid cyclers."

The following table lists the agents included in this drug class review by chemical group:

Generic Name	Brand Name	Dosage Forms	Generic Available	Manufacturer
Atypicals				
Aripiprazole	Abilify®	Solution, Tablet, ODT, IM	No	Otsuka/Bristol-Myers Squibb
Clozapine	Clozaril®	Tablet, ODT	Yes (not ODT)	Novartis
Olanzapine	Zyprexa®/ Symbyax® (combo with fluoxetine)	Tablet, ODT, Capsule (combo)	No No	Lilly
Quetiapine	Seroquel®, Seoquel XR®	Tablet	No	AstraZeneca
Risperidone	Risperdal®, Risperdal Consta®	Tablet, ODT, IM	No	Janssen
Paliperidone	Invega®	Tablet	No	Janssen
Ziprasidone	Geodon®	Capsule, IM	No	Pfizer
Butyrophenones				
Haloperidol	Haldol®	Tablet, solution, injection, IM	Yes	Ortho McNeil/Scios
Phenothiazines				
Chlorpromazine	Thorazine®	Suppository, solution, tablet	Yes	GSK/Scios
Fluphenazine	Prolixin®	Elixir, solution, tablet, IM	Yes	Sandoz
Perphenazine	N/A	Solution, tablet	Yes	N/A
Prochlorperazine	Compazine®	Suppository, solution, tablet, capsule	Yes	GSK
Thioridazine	Mellaril®	Solution, tablet	Yes	Novartis
Trifluoperazine	Stelazine®	Tablet	Yes	GSK
Thiothixenes				

Generic Name	Brand Name	Dosage Forms	Generic Available	Manufacturer
Thiothixene	Navane®	Capsule, solution	Yes	Pfizer
Miscellaneous				
Loxapine	Loxitane®	Capsule	Yes	Watson
Molindone	Moban®	Tablet	No	Endo
Pimozide	Orap®	Tablet	No	Gate

*(ODT=Oral Dissolving Tablet; IM=Intramuscular)

Treatment Guidelines

Schizophrenia[1]

Practice guidelines for the treatment of patients with schizophrenia suggest pharmacological intervention in conjunction with other therapies for the effective treatment of this chronic illness. For the sake of brevity, however, only pharmacological recommendations will be mentioned in this section. The omission of the other recommended interventions should not be construed as devaluing their importance in the total management plan for patients diagnosed with schizophrenia.

The most recent guidelines published in 2004 by the American Psychiatric Association make several recommendations regarding the pharmacological treatment of schizophrenic patients. The following are summary recommendations from this publication:

1. **Acute Phase**

   The determination of which antipsychotic to use for treatment during the acute phase should be guided by the patient's previous experience with antipsychotics, degree of symptom response, side effect profile, and the patient's preference.

   The second-generation agents, or atypicals, should be considered first-line treatment in the acute phase because of a lower risk of extrapyramidal side effects (EPS) and tardive dyskinesia. If a patient has been treated successfully in the past with a first-generation agent or prefers one of the first generation agents, these agents are clinically useful and may be the appropriate.

   Those patients with recurrent relapses due to partial or full non-adherence are candidates for a long-acting injectable medication. If a long-acting injectable is indicated, the oral form of the same medication should be considered the choice for initial treatment during the acute phase. Because long-acting injectable agents may take months to reach a stable steady state, these preparations are not usually prescribed for acute psychotic episodes. If a patient experiences an acute psychotic episode while on a long-acting injectable, it may be useful to continue that medication and supplement it temporarily with oral medication. The determination of the target dose should be made with consideration of the patient's history of response, clinical condition, and severity of symptoms. Titration should occur rapidly, as tolerated, to the target therapeutic dose using sedation, orthostatic hypotension, and tachycardia side effects that limit the rate of increase. The patient's clinical status should be monitored for two to four weeks before increasing the dose or switching the medication.

   If the patient is adherent to treatment and plasma concentrations are adequate but the patient is not responding, alternative treatments may be considered or a higher dose (depending on

tolerability) may be tried. The incremental efficacy of higher doses, however, has not been well established.

2. **Stabilization Phase**

   Stabilization is important in preventing or reducing the risk of relapse. Deciding on the dose during stabilization is complicated due to the lack of a reliable strategy to identify the minimum effective dose to prevent relapse. Higher doses may be more effective at preventing relapse, but they often are responsible for causing greater side effects and may lessen tolerability, which then results in non-adherence and a possible patient relapse.

   For first-generation agents, it is recommended that doses be made around the "EPS threshold." Higher doses of these agents are usually not more effective and increase intolerable side effects.

   Second-generation agents can generally be administered at doses that are therapeutic but will not cause EPS effects.

3. **Clozapine**

   Generally, clozapine should be considered for patients with an inadequate response to other antipsychotic treatment or for patients with suicidal ideation or behavior.

Bipolar[2]

Practice guidelines for the treatment of patients with bipolar disorder suggest pharmacological intervention in conjunction with other therapies for the effective treatment of this chronic illness. For the sake of brevity, however, only pharmacological recommendations will be mentioned in this section. The omission of the other recommended interventions should not be construed as devaluing their importance in the total management plan for patients diagnosed with bipolar disorder. In keeping with the purposes, this summary will focus only on the recommended role of antipsychotics in this illness.

Atypical antipsychotics are considered first-line agents for adjunctive treatment of mania, as are benzodiazepines in non-psychotic cases. Additionally, atypicals are considered first-line agents for combined treatment of psychotic depression. These agents are strongly preferred when an antipsychotic is needed for long-term maintenance, and are considered "backups" in any phase of rapid cycling. The first-generation agents are considered first-line for psychotic mania or for those patients with mania unresponsive to one or two atypicals. The depot preparations of first-generation agents are considered second-line for the treatment of non-adherent patients.

Although there is strong support for atypical adjunctive use, they are not recommended over traditional mood stabilizers for monotherapy in mania. In cases of hypomania, benzodiazepines are recommended over atypicals. Atypicals and benzodiazepines are equally recommended, however, in more severe manic episodes with psychosis. Atypicals are recommended in cases of psychotic mania.

Clozapine is reserved for treatment-resistant illness or for rapid cycling.

Ziprasidone is a good alternative, if weight gain is a concern, or for those who have gained weight on other therapy.

Product Specific Information[3]

The first-generation products are available generically. No advantage is to be gained by further discussion of these agents considering the current operational environment in which there is no prior authorization requirement on most generically available preparations. Therefore, this review will focus on the atypical antipsychotic agents, as well as the miscellaneous agents, Moban® and Orap®.

Indications

Agent	FDA Approved Indication(s)
Aripiprazole	Acute manic and/ or mixed episodes associated with bipolar disorder Schizophrenia Treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed (IM only)
Clozapine	Recurrent suicidal behavior Schizophrenia
Molindone	Schizophrenia
Olanzapine	Schizophrenia Acute manic and/or mixed episodes associated with bipolar I disorder as acute, maintenance, or combination therapy Acute agitation associated with bipolar I mania (IM only) Acute agitation in schizophrenia (IM only)
Pimozide	Tourette's disorder
Quetiapine	Acute manic and/or mixed episodes associated with bipolar disorder Depressive episodes associated with bipolar disorder Schizophrenia
Risperidone	Acute manic and/or mixed episodes associated with bipolar I disorder alone or in combination in adults and alone in children and adolescents 10-17 years Schizophrenia in adults and adolescents 13-17 years Irritability associated with autistic disorder in children and adolescents 5-16 years
Paliperidone	Schizophrenia
Ziprasidone	Acute manic and/or mixed episodes associated with bipolar disorder with or without psychotic features Schizophrenia Acute agitation in schizophrenia (IM only)

Pharmacology

The exact mechanism of action of the antipsychotic agents is unknown. It is thought, however, to be a result of their antagonistic actions on the receptors of several neurotransmitters. The following table provides information on antipsychotic receptor affinity. All produce antagonistic effects on the receptors unless otherwise specified.

Agent	Receptor Affinity
Aripiprazole	High — dopamine D2 b, D3, serotonin 5-HT1A b, 5-HT2A Moderate — dopamine D4, 5-HT2C, 5-HT7, alpha1-adrenergic, histamine H1

Agent	Receptor Affinity
Clozapine	High — dopamine D4 Other receptors — dopamine D1, D2, D3, D5, adrenergic, cholinergic, histaminergic, serotonergic
Olanzapine	High — serotonin 5-HT2A, 5-HT2C, dopamine D1, D2, D3, D4, muscarinic M1, M2, M3, M4, M5, histamine H1, alpha1-adrenergic Weak —GABAA, benzodiazepine receptor, beta-adrenergic
Quetiapine, (XR)	Serotonin 5-HT1A, 5-HT2, dopamine D1, D2, alpha1 and 2-adrenergic, histamine H1
Risperidone	High — dopamine D2, serotonin 5-HT2 Low to moderate — 5-HT1C, 5-HT1D, 5-HT1A, histamine H1, Alpha1-adrenergic Weak —D1, haloperidol-sensitive sigma site
Palperidone	High — dopamine D2, serotonin 5HT2A Low to moderate — alpha 1&2 adrenergic, histamine H1
Ziprasidone	High — dopamine D2, D3, 5-HT2A, 5-HT2C, 5-HT1A1, 5-HT1D, alpha1-adrenergic Moderate — histamine H1
Pimozide	Dopamine D2, alpha-adrenergic, serotonin 5-HT2
Molindone	Low — dopamine D2, alpha-adrenergic, serotonin 5-HT2

Key: b=partial agonist activity

The atypical antipsychotics can be structurally classified as dibenzepines, benzisoxazoles, or quinolinones. They have diverse pharmacodynamic profiles, differing considerably from the typical antipsychotics, but in general have an increased affinity for 5-HT2 receptors compared with D 2 receptors. They act upon several neurotransmitter systems, including antagonism at one or more types of dopamine receptors (e.g., D1, D2, D4, D5); selectivity for limbic dopamine receptors; antagonism at one or more types of serotonin receptors (e.g., 5-HT1, 5-HT2); antagonism at alpha1-adrenergic receptors; and activity at muscarinic or histamine H1 receptors. They are considered atypical because of their decreased ability or inability to induce EPS. Newer agents also have a decreased propensity to induce agranulocytosis compared with clozapine. Studies indicate that some atypical agents are effective in patients resistant to conventional antipsychotic therapy and may be more effective in relieving negative symptoms than conventional agents.

The following table summarizes the pharmacological effects of the reviewed agents:

Agent	Sedation	EPS	Anticholinergic Effects	Orthostatic hypotension	Weight gain
Aripiprazole	+	0	0-+	+	+
Clozapine	+++	0	+++	+++	++++
Olanzapine	++	+	++	++	++++
Quetiapine, (XR)	++	0	0-+	++	+++
Risperidone	+	++	0-+	++	+++
Paliperidone	+	+	0-+	+	++
Ziprasidone	++	++	+	++	+

Agent	Sedation	EPS	Anticholinergic Effects	Orthostatic hypotension	Weight gain
Pimozide	+	+++	++	+	
Molindone	+	++	+	+	

+ = low incidence
++ = moderate incidence
+++ = high incidence
++++ = very high incidence

Pharmacokinetics

Agent	Bio-availability	Mean Cmax	Tmax (hours)	Protein bound	Routes of metabolism	Active metabolite	T1/2 (hours)	Excretion
Molindone			1.5				12	Urine, feces
Pimozide	> 50%	≈ 10ng/mL	4-12	99%	N-dealkylation by CYP3A and CYP1A2 to a lesser extent		≈55	Urine
Aripiprazole	87%		3-5	> 99%	Dehydrogenation, hydroxylation, and N-dealkylation by CYP3A4 and CYP2D6	Dehydro-aripiprazole	75 -146	Feces (≈55%), urine (≈25%)
Clozapine	27%-47%	319ng/mL	2.5	≈97%	Demethylation, hydroxylation, and N-oxidation	Desmethyl metabolite has limited activity	8; 12	Urine (≈50%), feces (≈30%)
Olanzapine	≈60%	≈12.9ng/mL	≈6	93% over a concentration range of 7-1100ng/mL	Glucuronidation and oxidation by CYP1A2 and CYP2D6		21-54	Urine (≈57%), feces (≈30%)
Quetiapine	≥73%	778-1080mcg/L	1.5	83%	Sulfoxidation and oxidation by CYP3A4		≈6	Urine (≈73%), feces (≈20%)
Risperidone	70%	10ng/mL	≈1	90%	Hydroxylation by CYP2D6 and N-dealkylation	9-hydroxy-Risperidone	3-20	Feces (≈66%), urine (≈20%)
Paliperidone	28%		24	74%	Dehydrogenation, Benzisoxazolescission, Dealkylation, Hydroxylation		23	Urine (80%) Feces (11%)
Ziprasidone	≈60% (oral); 100% (IM)	44.6-139.4mcg/L	6-8 (oral); ≈60 min (IM)	> 99%	Reduction by aldehyde oxidase, methylation, and oxidation by CYP3A4 and CYP1A2 to a lesser extent		≈7 (oral); 2-5 (IM)	Feces (≈66%), urine (≈20%)

Adverse Effects

Rates of incidence are expressed as percentages.

Adverse Reaction	Molin-done	Pimo-zide	Aripipra-zole	Cloza-pine	Olanza-pine	Queti-apine	Quetia pine XR	Risper-idone	Paliperid one	Ziprasi-done, oral (IM)
Hypertension		√	2	4	2	√		0.1-1	<1	> 1 (≤ 2)
Hypotension	Rare	√	>1	9	3-5	7	7	0.1-1		1 (≤5)
Tachycardia	√	√	>1	25	3	7		3-5	12	2
Twitch			0.1-1	√		0.1-1				
Vasodilation			0.1-1		0.1-1	0.1-1				(≤1)
QTc interval prolongation		√	0.1-1			0.1-1			4	√
Accommodation abnormality					0.1-1	0.1-1		0.1-1		
Agitation			25	4				22-26		>1 (≤2)
Akathisia	√	40	15-17	3	3				3	8 (≤2)
Akinesia	√	40	0.1-1	4	<0.1					>1
Anxiety			20	1				12-20	7	(≤2)
Asthenia		45	8		10-15	4			<1	5 (≤2)
Confusion			>1	3		0.1-1		0.1-1		>1
Convulsions (Especially with sudden marked increase in dosage)		√		3						
Depression	√	10	>1	1				0.1-1		
Dizziness		√		19	11-18	10	10	4-7	5	8 (3-10)
Dreams, abnormal/ bizarre/ increased		3	≥1	√	>1	0.1-1		≥1		
Drowsiness/ sedation/ Somnolence	√	25-70	7.5-15.3	39-46	29-35	18	12-13	3-8	9	14 (8-20)
Dyskinesia		√	0.1-1		≤2	0.1-1				>1
Dystonia	√	√	0.1-1		2-3				1	4
Extrapyramidal symptoms	√	Frequent	6			√		17-34	2	5 (≤2)
Fatigue				2				>1	1	
Abnormal gait			>1		6	0.1-1				>1
Headache		5-22	31	7		19		12-14	12	(3-13)
Hyperkinesias		6	0.1-1	1		0.1-1				>1
Hypokinesia			0.1-1	4	0.1-1					>1
Insomnia		10								
Decrease/loss of libido		√	0.1-1	√		<0.1		≥5		
Lightheadedness			11							
Restlessness				4						
Syncope				6						
Tardive dyskinesia	√	√	0.1-1		0.1-1	0.1-1				>1
Tremor	√	1	2-3	6	4-6	√			3	>1
Vertigo			0.1-1	19	0.1-1	0.1-1		0.1-1		>1
Ecchymosis			>1	√	5	0.1-1				0.1-1

Adverse Reaction	Molindone	Pimozide	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Quetiapine XR	Risperidone	Paliperidone	Ziprasidone, oral (IM)
Eczema			0.1-1	√	0.1-1	0.1-1		2-4		0.1-1
Rash	√	8	6	2		4		2-5		4
Abdominal discomfort/pain			√	4		3		1-4	3	>1 (≤2)
Anorexia		√	>1	1		>1		>1		2 (≤2)
Appetite increased		5	0.1-1	√	3-6	0.1-1		0.1-1		
Constipation	√	20	10	14	9-11	9	6	7-13		9 (≤2)
Diarrhea		5	√	2		√		≥5		5 (≤3)
Dry mouth	√	25	√	6	9-22	7	12	≥5	3	4(≤1)
Dyspepsia			√	14	7-11	6	5	5-10	3	8 (1-3)
GERD			0.1-1	4		0.1-1		<0.1		
Nausea	√	√	14	5	0.1-1	√		4-6	4	10 (4-12)
Polydipsia		5	0.1-1		>1	0.1-1		>1		0.1-1 (≤2)
Rectal hemorrhage			0.1-1	√	0.1-1	0.1-1				<2
Salivation	√	14	>1	31	>1	0.1-1		≤2	<1	√
Altered taste		5	0.1-1			0.1-1				
Vomiting		√	12	3	4	√		5-7		>1(<3)
Weight gain	√	√	8	4	5-6	2		18		10
Dysmenorrhea			√	√		0.1-1		0.1-1		(≤2)
Ejaculation disorders			0.1-1	1	0.1-1	0.1-1		≥5		0.1-1
Impotence		15	0.1-1	√	0.1-1	0.1-1		≥5		0.1-1
Urinary incontinence			>1		2	0.1-1		0.1-1		
Manorrhagia	√		0.1-1		0.1-1			≥5		0.1-1
Leukopenia	Rare		0.1-1	3	>1	>1		<0.1		0.1-1
Peripheral edema			2		3	>1				0.1-1
Arthralgia/ joint pain			0.1-1	√	5	0.1-1		2-3		√
Muscle rigidity	√	15		√						
Myalgia		3	4	1		√		0.1-1		1
Rigidity		10		5				0.1-1		
Torticollis		3						<0.1		<0.1
Increased cough			3	√	6	>1		3		3
Pharyngitis			4		4	>1		2-3		
Rhinitis			4		7	3		8-10		4 (≤1)
Abnormal vision						0.1-1		2		3
Blurred vision	√	√	3						<1	
Visual disturbances				5						
Accidental injury			6		12	√				4
Back pain			√	1	5	2		≤2	1	(≤1)
Chest pain		√	>1	1	3	√		2-3		
Diaphoresis		√	>1	6	>1	>1		0.1-1		(≤2)
Fever			≥1	5	6	2		2-3		>1
Hypertonia			√		3	>1				3

√=incidence unknown

In addition to the adverse events included in the table above, the following adverse events have been reported:

1. **Molindone—**menses resumption, alterations in blood glucose, BUN alterations, RBC alterations, and thyroid function alterations.

2. **Clozapine—**arrhythmias, cardiomyopathy, DVT, ST-depression, aphasia, altered EEG tracings, GI distress, hypothermia, periorbital edema, delusions, amentia, bitter taste, bronchitis, mild cataplexy, chills with fever, cholestasis, poor coordination, ear disorders, epileptiform movements, erythema multiforme, increased erythrocyte sedimentation rate (ESR), eyelid disorders, bloodshot eyes, gastric ulcer, granulocytopenia, elevated hematocrit, elevated hemoglobin, histrionic movements, hot flashes, acute interstitial nephritis, involuntary movements, irritability, ischemic changes, laryngitis, impaired memory, numbness, overdose, acute pancreatitis, pericardial effusions, pericarditis, petechiae, pleural effusion, pneumonia-like symptoms, premature ventricular contraction, rhabdomyolysis, rhinorrhea, sepsis, shakiness, sneezing, status epilepticus, Stevens-Johnson syndrome, stuttering, abnormal stools, dry throat, throat pain/discomfort, tics, tongue numb/sore, vaginal infections/itch, vasculitis, ventricular fibrillation, wheezing, nightmares, sleep disturbance (4%), neutropenia, WBC decreased (3%), urinary abnormalities (2%), incontinence, cardiac abnormality, leg pain (1%).

3. **Olanzapine—**personality disorders (8%), extremity pain (not joint) (5%), amblyopia (3%), articulation impaired, UTI (2%), angioedema, dental pain, intentional injury (at least 1%), antisocial reaction, CNS stimulation, arthrosis, voice alteration, laryngitis, obsessive compulsive symptoms, phobias, tobacco misuse (0.1% to 1%),s normocytic anemia, arthritis, fatty liver deposits, keratoconjunctivitis, nystagmus, ketosis, hangover effect, encephalopathy, hiccough, hyperventilation, hypoxia, lung edema, stridor, breast pain, cystitis, uterine fibroids (less than 0.1%), aphthous stomatitis, enteritis, periodontal abscess, acidosis, bilirubinemia, atelectasis, alcohol misuse, coma (rare).

4. **Quetiapine—**UTI, infection, pain, ear pain, dry skin, increased triglycerides (1%), bundle branch block, paranoid reaction, cystitis, vulvovaginitis, leg cramps, increased gamma-glutamyl transpeptidase (GGT), alcohol intolerance, bruxism, cerebral ischemia, delusions, depersonalization, diabetes mellitus, dysuria, eye pain, hemiplegia, involuntary movements, leukorrhea, manic reaction, orchitis, pathological fracture, irregular pulse, QRS duration, skin ulcer, abnormal thinking, vaginitis (0.1% to 1%), aphasia, emotional lability, deafness, hand edema, hemolysis, hiccough, neuralgia, neutropenia, skin discoloration, ST abnormality, ST elevated, stuttering, subdural hematoma, T-wave abnormality, water intoxication (less than 0.1%).

5. **Risperidone—**lymphedema (8%), upper respiratory infection (3%), angioedema, cerebral vascular disorder, aggressive reaction (1% to 3%), toothache, sinusitis (2% or less), hyperpigmentation (at least 1%), concentration impaired, hyperkeratosis, nonthrombocytopenic purpura, skin exfoliation, bronchospasm, stridor, xerophthalmia (0.1% to 1%), myocarditis, ST-depression, cholinergic syndrome, emotional lability, nightmares, bullous eruption, furunculosis, hypertrichosis, skin ulceration, verruca, feces discoloration, GI hemorrhage, tongue paralysis, genital pruritus, normocytic anemia, ascites, yawning, eye pain, abnormal lacrimation, photopsia, arthrosis, leg cramps, cachexia, coma, increased sputum, sarcoidosis (less than 0.1%).

6. **Paliperdone —**tachycardia (12%), bundle branch block (2%), sinus arrhythmia (1%), asthenia, fatigue, pyrexia, blood insulin increased, EKG T wave abnormality, back pain, pain in extremity, hypertonia, cough, orthostatic hypotension, tremor, Parkinsonism, hyperkinesia,

thrombocytopenia, palpitations, bradycardia, edema, coordination abnormal, confusional state, pulmonary embolus, ischemia, venous thrombosis.

7. **Ziprasidone—**injection site pain (7% to 9%), respiratory disorder (8%), personality disorder, speech disorder, furunculosis (2% or less), hypotonia, buccoglossal syndrome, accidental fall, hypothermia, motor vehicle accident, flank pain, hypertonia (at least 1%), tooth disorder (less than 1%); cerebral infarct, polycythemia, anorgasmia, male sex dysfunction, tenosynovitis, increased lactic dehydrogenase (0.1% to 1%), bundle branch block, cardiomegaly, myocarditis, keratitis, leukoplakia of the mouth, female sex dysfunction, uterine hemorrhage, basophilia, hypocalcemia, hypochloremia, hypocholesterolemia, lymphedema, lymphocytosis, monocytosis, fatty liver deposits, hepatomegaly, laryngismus, respiratory alkalosis, keratoconjunctivitis, nystagmus, visual field defect, increased BUN, increased GGT, decreased glucose tolerance, ketosis, cerebral infarct, hyperchloremia, oliguria (less than 0.1%).

8. **Pimozide—**adverse behavior effect (5% to 10%), sensitivity of eyes to light (5%), accommodation decrease (4%), speech disorder, stooped posture (2%); gingival hyperplasia, handwriting change (1%), skin irritation, GI distress, tonic spasm, transient dyskinetic signs, periorbital edema, T-wave notching, U-wave appearance.

Drug Interactions

Precipitant drug	Object Drug	Effect	Description
Caffeine	Clozapine	↑	Plasma levels of clozapine may be increased, resulting in increased adverse effects. Caffeine should be avoided if interaction is suspected.
Carbamazepine	Aripiprazole Olanzapine Risperidone Ziprasidone	↓	The antipsychotic plasma concentrations may be decreased, resulting in decreased therapeutic effect. Adjust antipsychotic dose as needed. When carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled.
Charcoal	Antipsychotics	↓	Charcoal can decrease the absorption of antipsychotics, reducing their effectiveness or toxicity.
Cimetidine	Quetiapine	↑	Cimetidine decreased quetiapine oral clearance by 20%.
Citalopram Fluoxetine Fluvoxamine Sertraline	Clozapine	↑	Plasma levels of clozapine may be increased, resulting in increased pharmacologic and toxic effects. Adjust clozapine dose as needed when starting or stopping certain SSRIs.
Clozapine	Benzodiazepines	↑	Cases of orthostatic hypotension, collapse, respiratory arrest, and cardiac arrest have been reported with concomitant use of certain benzodiazepines. Co-administer with caution.
Clozapine	Risperidone	↑	Chronic administration of clozapine with risperidone may decrease risperidone clearance.
CYP1A2 inducers (e.g., carbamazepine, omeprazole, rifampin)	Clozapine Olanzapine	↓	May decrease clozapine or olanzapine serum concentrations. May need dosage increase for olanzapine. Carbamazepine increased olanzapine clearance by 50%.
CYP1A2 inhibitors (e.g., fluvoxamine)	Clozapine Olanzapine	↑	May increase clozapine or olanzapine serum concentrations. Dose reduction may be needed. Fluvoxamine decreased olanzapine clearance, resulting in a

Precipitant drug	Object Drug	Effect	Description
			mean increase in Cmax of 54% in female nonsmokers and 77% in male smokers; AUC increased 52% and 108%, respectively.
CYP3A4 inhibitors (e.g., ketoconazole)	Aripiprazole Clozapine Quetiapine Ziprasidone	↑	The plasma concentrations of the antipsychotic may be increased. Reduce aripiprazole dose 50% with co-administration of ketoconazole. Increase the aripiprazole dose when the CYP3A4 inhibitor is withdrawn.
Famotidine	Aripiprazole	↓	Co-administration of a single dose of aripiprazole and famotidine resulted in decreased aripiprazole solubility and, therefore, decreased its rate of absorption, Cmax, and AUC.
Fluoxetine	Olanzapine	↑	Co-administration resulted in a small (approximately 16%) increase in Cmax, and a decrease in olanzapine clearance.
Fluoxetine Paroxetine	Risperidone	↑	Risperidone concentrations may be elevated, increasing the risk of adverse effects. Fluoxetine increased risperidone plasma levels 2.5 to 2.8 fold. Adjust risperidone dose as needed.
Olanzapine Quetiapine Risperidone Ziprasidone Paliperidone	Levodopa and dopamine agonists	↓	May antagonize the effects of levodopa and dopamine agonists.
Phenobarbital	Clozapine	↓	Plasma levels of clozapine may be decreased, resulting in decreased pharmacologic effects.
Quetiapine	Lorazepam	↑	Lorazepam mean oral clearance was reduced 20% with co-administration.
Paliperidone	Antihypertensive agents	↑	Paliperidone may enhance the effects of antihypertensive agents. Because of paliperidone's alpha-blocking activity, orthostatic hypotension and syncope may be induced.
Paliperidone	CNS depressants, alcohol	↑	Coadministration may lead to enhanced CNS depression. Use with caution.
Phenytoin	Quetiapine	↓	Quetiapine plasma levels may be decreased, resulting in decreased pharmacologic effects. Adjust quetiapine dose as needed.
Risperidone	Clozapine	↑	Pharmacologic and adverse effects of clozapine may be increased. Adjust dose as needed.
Risperidone	Valproate	↑	Co-administration resulted in a 20% increase in valproate Cmax. Adjust therapy as needed.
Ritonavir	Clozapine Risperidone	↑	Increases in serum antipsychotic concentrations may occur, increasing risk of toxicity.
Thioridazine	Quetiapine	↓	Thioridazine increased quetiapine oral clearance 65%.
Valproate	Aripiprazole	↓	Aripiprazole Cmax and AUC were decreased 25% with co-administration.

Key: ↑ = object drug increased, ↓ = object drug decreased.

Contraindications

1. **Clozapine**

   Clozapine is contraindicated with drugs having a well-known potential to cause agranulocytosis or to suppress bone marrow function. Clozapine is contraindicated for use in the following instances: myeloproliferative disorders, uncontrolled epilepsy, history of clozapine-induced agranulocytosis, or severe granulocytopenia.

2. **Ziprasidone**

   Ziprasidone is contraindicated with drugs that prolong the QT interval and in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure. The following drugs may prolong the QT interval and increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes: antiarrhythmic agents (e.g., amiodarone, bretylium, disopyramide, dofetilide, procainamide, quinidine, sotalol), arsenic trioxide, chlorpromazine, cisapride, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, sparfloxacin, tacrolimus, thioridazine, ziprasidone.

3. **Pimozide**

   This agent is contraindicated with drugs that prolong the QT interval, as well as CYP3A inhibitors (e.g., clarithromycin, dirithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, protease inhibitors, sertraline, telithromycin, troleandomycin, voriconazole). Additionally, pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette’s disorder and in combination with drugs that may cause motor or phonic tics (e.g., pemoline, methylphenidate, amphetamines) until it is determined that the drugs, rather than Tourette’s disorder, are responsible for the tics.

Warnings and Precautions

Black Box Warning

All antipsychotics carry the following Black Box warning:

> **INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS. Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.**

In addition, clozapine carries additional Black Box warnings as follows:

> **Agranulocytosis: Because of a significant risk of agranulocytosis, a potentially life-threatening adverse event, clozapine use should be reserved for 1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or 2) reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for re-experiencing suicidal behavior. Patients being treated with clozapine must have a baseline white blood cell (WBC) and differential count before initiation of treatment, as well as regular WBC counts during treatment and for four weeks after discontinuation of treatment. Clozapine is available only through a distribution system that ensures monitoring of WBC counts according to the schedule described below prior to delivery of the next supply of medication. Seizures: Seizures have been associated with the use of clozapine. Dose appears to be an important seizure predictor, with a greater likelihood at higher clozapine doses. Caution should be used when administering clozapine to patients with a history of seizures or other predisposing factors. Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others[3]. Myocarditis: Analyses of post marketing safety databases suggest clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, discontinue clozapine treatment promptly.[3] Other adverse cardiovascular and respiratory effects: Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. In rare cases collapse can be profound and accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine (two or more days since the last dose), start treatment with 12.5mg once or twice daily. Because collapse, respiratory arrest, and cardiac arrest during initial treatment have occurred in patients receiving benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.[3]**

Quetiapine carries the following additional Black Box warnings:

Suicidality in children and adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of quetiapine or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Closely observe patients who are started on therapy for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescriber. Quetiapine is not approved for use in children. Pooled analyses of short-term (4- to 16-week), placebo-controlled trials of nine antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving more than 4,400 patients) have revealed a greater risk of adverse reactions representing suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such reactions in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Tardive dyskinesia (TD): TD, a syndrome consisting of potentially irreversible, involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although prevalence of TD appears highest among the elderly, especially women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drugs differ in their potential to cause TD is unknown.[4] Atypical antipsychotics, however, appear to have a lower risk of TD.[5] Both the risk of developing TD and the likelihood that it will become irreversible are increased as the duration of treatment and total cumulative dose administered increase. The syndrome can develop, however, after relatively brief treatment periods at low doses, although this happens much less frequently.

Neuroleptic malignant syndrome (NMS): A potentially fatal symptom complex, sometimes referred to as NMS, has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS (2/2387 [0.1%]) have been reported in clinical trials with quetiapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or BP, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The onset may be after hours to months of treatment or may occur after discontinuation of therapy. Once begun, NMS proceeds rapidly over 24 to 72 hours.[4]

The risk of NMS is higher in patients receiving high-potency, injectable, or depot antipsychotics. NMS may occur with atypical antipsychotics, but the risk is lower.[4] There have been several reported cases of NMS in patients receiving clozapine alone or in combination with lithium or other CNS-active agents.[3]

ECG changes: A minority of clozapine patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, all of which normalize after discontinuation of clozapine. The clinical significance is unclear. Several patients, however, have experienced significant cardiac events, including ischemic changes, MI, arrhythmias, and

sudden death. In addition, there have been post marketing reports of CHF, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious pre-existing cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.[3]

Ziprasidone and pimozide have been shown to prolong the QT interval, and drugs with this potential have been associated with torsades de pointes-type arrhythmias and sudden death. Certain circumstances may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QT interval, including the following: 1) bradycardia, 2) hypokalemia or hypomagnesemia, 3) concomitant use of other drugs that prolong the QT interval, and 4) presence of congenital prolongation of the QT interval. A baseline ECG should be performed and serum potassium and magnesium measured before initiation of treatment, as well as periodically during treatment—especially during periods of dose adjustment. Ziprasidone should be avoided in patients with histories of significant cardiovascular illness (e.g., QT prolongation, recent acute MI, uncompensated heart failure, cardiac arrhythmia). Prolongations of the QT interval and torsades de pointes have been reported with risperidone overdoses.[6]

Myocarditis: Post-marketing clozapine surveillance data from four countries revealed cases of myocarditis, some fatal. The rate of myocarditis in clozapine-treated patients appears to be 17 to 322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14 to 161 times greater than the general population. Therefore, consider the possibility of myocarditis in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or ECG findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with clozapine treatment, also has been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis. Prompt discontinuation of clozapine treatment is warranted upon suspicion of myocarditis. Patients with clozapine related myocarditis should not be rechallenged with clozapine. [3]

Cardiomyopathy: Cases of cardiomyopathy have been reported in patients treated with clozapine. Approximately 80 percent of clozapine treated patients in whom cardiomyopathy was reported were younger than 50 years of age. The duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but was more than six months in 65 percent of the reports. Dilated cardiomyopathy was most frequently reported. Signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, discontinue clozapine unless the benefit to the patient clearly outweighs the risk.[3]

Pulmonary embolism: Consider the possibility of pulmonary embolism in patients receiving clozapine who present with deep vein thrombosis, acute dyspnea, chest pain, or with other respiratory signs and symptoms. Deep vein thrombosis also has been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to

clozapine or to some characteristics of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.[3]

Hypotension: Orthostatic hypotension with or without syncope can occur, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients.

Cerebrovascular effects: Cerebrovascular adverse events (e.g., stroke, transient ischemic attack) including fatalities, were reported in trials of risperidone in elderly patients (mean age, 85 years; age range, 73 to 97 years) with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone and olanzapine compared with patients treated with placebo.[5] Risperidone increases the risk of stroke for elderly people with dementia:

43 strokes per 1,000 elderly people taking risperidone while 11 strokes per 1,000 elderly people taking placebo. Olanzapine increases the risk of stroke for elderly people with dementia - 13 strokes per 1,000 elderly people taking olanzapine compared to four () strokes per 1,000 elderly people taking a placebo.

Hyperprolactinemia: Antipsychotic drugs elevate prolactin levels, with elevation persisting during chronic administration. In contrast to more typical antipsychotic drugs, however, clozapine therapy produces little or no prolactin elevation.[3] Drugs that antagonize dopamine D 2 receptors elevate prolactin levels. Experiments indicate that approximately 33 percent of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously-detected breast cancer.[7, 5]

Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients.[8]

Risperidone, ziprasidone, and olanzapine elevate prolactin levels. As is common with compounds that increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia or neoplasia was observed in risperidone carcinogenicity studies conducted in mice and rats. An increase in mammary gland neoplasia was observed in the olanzapine and ziprasidone carcinogenicity studies conducted in mice and in the olanzapine studies in rats.[6,5,9]

Elevated prolactin levels were not demonstrated in clinical trials with quetiapine. Increased prolactin levels were, however, observed in rats studied with this compound.[7]

Hyperglycemia and diabetes mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Epidemiological studies, however, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose

levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100 – 126 mg/dL, non-fasting 140 – 200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening glucose control.[3]

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be regularly monitored for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic is discontinued, while some patients have required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.[10]

Hyperlipidemia: Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.[3]

Weight gain: Potential consequences of weight gain should be considered prior to starting olanzapine. Patients should receive regular monitoring of weight.[3]

Agranulocytosis: Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500/mm^3, occurs in association with clozapine use at a cumulative incidence at one year of approximately 1.3 percent, based on 15 cases out of 1743 patients exposed to clozapine during clinical testing. All of these cases occurred when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and if therapy is interrupted.

Patients must have a blood sample drawn for a WBC count before initiation of treatment with clozapine, and must have subsequent WBC counts done at least weekly for the first six months of treatment, as well as for four weeks after discontinuation. The distribution of clozapine is contingent upon performance of the required blood tests.

Except for evidence of significant bone marrow suppression during initial clozapine therapy, there are no established risk factors for the development of agranulocytosis. A disproportionate number of the U.S. cases of agranulocytosis, however, occurred in patients of Jewish background, compared with the overall proportion of such patients exposed during clozapine's domestic development. Most of the U.S. cases occurred within four to 10 weeks of exposure, but neither dose nor duration was a reliable predictor. No patient characteristics have been clearly linked to the development of agranulocytosis in association with clozapine use, but agranulocytosis associated with other antipsychotic drugs occurred with a greater frequency in women, the elderly, and in

patients who are cachetic or have serious underlying medical illness. Such patients may also be at particular risk with clozapine.[3]

Seizure disorders: Some antipsychotics can lower the convulsive threshold and may precipitate seizures. Grand mal seizures have occurred, particularly in patients with EEG abnormalities or a history of such disorders. These drugs should be used cautiously in patients with a history of epilepsy or those in a state of alcohol withdrawal. These drugs may be used concomitantly with anticonvulsants. An adequate anticonvulsant dosage should be maintained.[3]

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at one year of approximately 5 percent, based on the occurrence of one or more seizures during its clinical testing prior to domestic marketing. Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher clozapine doses used. Caution should be exercised in administering clozapine to patients with a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others.[3]

GI dysmotility: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer dementia. Quetiapine, ziprasidone, risperidone, olanzapine, aripiprazole, and others should be used cautiously in patients at risk for aspiration pneumonia.[6,7,5,8]

Hepatic effects: Caution is advised in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in patients with normal liver function as well as in those with pre-existing liver function abnormalities. Liver function tests should be immediately performed in patients who develop nausea, vomiting, and/or anorexia during clozapine treatment. If the elevation of these values is clinically relevant, or if symptoms of jaundice occur, discontinue clozapine treatment.

Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect.[5]

Six percent of quetiapine and two percent of olanzapine patients had transaminase elevations over three times the upper limit of normal. Hepatic enzyme elevations usually occurred within the first three weeks of quetiapine treatment and promptly returned to pre-study levels with ongoing treatment. Because quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population and dosage adjustment may be needed.[6,7]

Anticholinergic effects: The anticholinergic effects of clozapine are very potent. Caution should be used in patients with clinically-significant prostatic hypertrophy, narrow-angle glaucoma, or a history of paralytic ileus.[6] Clozapine use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus. On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration and with the use of ancillary therapy such as bulk laxatives. Olanzapine exhibits in vitro muscarinic receptor affinity and was associated with constipation, dry mouth, and tachycardia.[6] Risperidone, aripiprazole, ziprasidone, and quetiapine have no affinity for cholinergic muscarinic receptors.[10, 7, 5, 8]

Cholesterol: Quetiapine-treated patients had increases from baseline in cholesterol and triglyceride of 11 percent and 17 percent, respectively.[7]

Concomitant conditions: Use with caution in patients on atropine or related drugs because of additive anticholinergic effects. Risperidone has not been evaluated or used to any appreciable extent in patients with a recent history of MI or unstable heart disease; use with caution.[5]

Hematologic: Various blood dyscrasias have occurred (see Adverse Reactions). In clinical trials, one percent of clozapine patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4000/mm 3, clozapine therapy should be interrupted until eosinophil count falls below 3000/mm 3. If sore throat or other sign of infection occurs, or if white cell and differential counts indicate cellular depression, stop treatment and institute an antibiotic and other suitable therapy.

Thrombotic thrombocytopenic purpura (TTP): A single case of TTP was reported in a 28-year-old female patient receiving risperidone. She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to therapy is unknown.[5]

Hypothyroidism: Quetiapine demonstrated a dose-related decrease in total and free thyroxine (T 4) of approximately 20 percent at the higher end of the therapeutic dose range. This change was maximal in the first two to four weeks of treatment and was maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH and TBG were unchanged in most patients. Approximately 0.4 percent of quetiapine patients, however, did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.[7]

Hyperpyrexia: A significant, not otherwise explained, rise in body temperature may indicate intolerance to antipsychotics. Discontinue in this case.[6] Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised for patients who will be experiencing conditions that may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, being subject to dehydration).

During clozapine therapy, patients may experience transient temperature elevations above 100.4^{o}F (38^{o}C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Carefully evaluate patients with fever to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of NMS must be considered.[3]

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer’s disease. Antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.[3]

Suicide: The possibility of suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Elderly: Dosages in the lower range are sufficient for most elderly patients. Because these patients appear more susceptible to various cardiovascular, neuromuscular, and anticholinergic reactions, observe patients closely. The prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women. Response should be monitored and dosage adjusted accordingly. Increases in dosage should be made gradually in elderly patients.

Pregnancy: Category C, Category B (clozapine[3]). Safety for use during pregnancy has not been established. Use only when clearly needed and when potential benefits outweigh potential hazards to the fetus.

Pediatrics: Recently risperidone received indications for acute manic and/or mixed episodes associated with bipolar I disorder alone in children and adolescents 10-17 years and schizophrenia in adults and adolescents 13-17 years and irritability associated with autistic disorder in children and adolescents 5-16 years. The safety and effectiveness of clozapine, olanzapine, aripiprazole, quetiapine, and ziprasidone in pediatric patients have not yet been established.[3, 5, 11, 7, 8]

Abrupt withdrawal: These drugs are not known to cause psychic dependence. Following abrupt withdrawal of high-dose therapy, however, symptoms such as gastritis, nausea, vomiting, dizziness, headache, restlessness, sweating, increased salivation, and insomnia have occurred. To lessen the likelihood of adverse reactions related to cumulative drug effects, periodically determine whether the maintenance dosage should be lowered or drug therapy discontinued. These symptoms can be reduced by gradual reduction of the dosage or by continuing anti-Parkinson agents for several weeks after the antipsychotic is withdrawn.[3, 4]

Dosing and Administration

Agent	Recommended doses by indication
Aripiprazole[10]	**Bipolar mania** *Usual dose:* In clinical trials, the starting dose was 30mg given once a day. A dose of 30mg/day was found to be effective. Approximately 15% of patients had their dose decreased to 15mg based on assessment of tolerability. The safety of doses above 30mg/day has not been evaluated in clinical trials. *Maintenance:* There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with aripiprazole. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable for maintenance of the initial response and prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole in such longer-term treatment (i.e., beyond six weeks). **Schizophrenia** *Usual dose:* The recommended starting and target dose is 10 or 15mg/day administered on a once-daily schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10 to 30mg/day; however, doses higher than 10

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	or 15mg/day (the lowest doses in these trials) were not more effective than 10 or 15mg/day. Dosage increases should not be made before two weeks, the time needed to achieve steady state. *Maintenance:* There is no body of evidence available to determine how long a patient should continue treatment; however, systematic evaluation of patients with schizophrenia, who had been symptomatically stable on other antipsychotic medications for periods of three months or longer, who were discontinued from those medications and then were administered 15mg/day aripiprazole and observed for relapse during a period of up to 26 weeks demonstrated a benefit of such maintenance treatment. Patients should be periodically reassessed to determine the need for maintenance treatment. *Concomitant use with potential CYP3A4 inhibitors:* When co-administration of ketoconazole with aripiprazole occurs, the aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from combination therapy, the aripiprazole dose should be increased. *Concomitant use with potential CYP2D6 inhibitors:* When co-administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, the aripiprazole dose should be reduced to at least one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from combination therapy, the aripiprazole dose should be increased. *Concomitant use with potential CYP3A4 inducers:* When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled to 20 to 30mg. Base additional dose increases on clinical evaluation. When carbamazepine is withdrawn from combination therapy, the aripiprazole dose should be reduced to 10 to 15mg. *Switching from other antipsychotics:* There are no systemically-collected data to specifically address switching patients with schizophrenia from other antipsychotics to aripiprazole or concerning co-administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, gradual discontinuation may be more appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. *Oral solution:* The oral solution can be given on a mg-per-mg basis in place of the 5, 10, 15, or 20mg tablet strengths. Solution doses can be substituted for the tablet doses on a mg-per-mg basis up to 25mg of the tablet. Patients receiving 30mg tablets should receive 25mg of the solution.
Clozapine[3]	Clozapine is available only through a distribution system that ensures monitoring of WBC counts according to the schedule described below prior to delivery of the next supply of medication. Upon initiation of clozapine therapy, up to a one-week supply of additional tablets may be provided to the patient to be held for emergencies (e.g., weather, holidays). Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for WBC testing every other week, then a two-week supply can be dispensed. Dispensing should be contingent on the results of a WBC count. *Monitoring*: Patients must have a blood sample drawn for a WBC count before initiation of treatment with clozapine and must have subsequent WBC counts done at least weekly for the first six months of continuous treatment. If WBC counts remain acceptable (WBC at least 3,000/mm 3, ANC at least 1,500/mm 3) during this period, WBC counts may be monitored every other week thereafter. After the discontinuation of clozapine, continue weekly WBC counts for an additional four weeks. *Initial:* 12.5mg once or twice daily then continue with daily dosage increments of 25 to 50mg/day, if well tolerated, to achieve a target dose of 300 to 450mg/day by the end of two weeks. Make subsequent dosage increments no more than once or twice weekly, in increments not to exceed 100mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation. *Dose adjustment:* Continue daily dosing on a divided basis to an effective and tolerable dose level. While many patients may respond adequately at doses between 300 to 600mg/day, it may be necessary to raise the dose to the 600 to 900mg/day range. Do not exceed 900mg/day.

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	The mean and median clozapine doses are approximately 600mg/day for schizophrenia and 300mg/day for reducing recurrent suicidal behavior. Because of the possibility of increased adverse reactions at higher doses, particularly seizures, give patients adequate time to respond to a given dose level before escalation to a higher dose. Because of the significant risk of agranulocytosis and seizure (events which both present a continuing risk over time), avoid extended treatment of patients failing to show an acceptable level of clinical response. *Maintenance:* Continue clozapine at the lowest level needed to maintain remission. Periodically reassess patients to determine the need for maintenance treatment. *Discontinuation:* In the event of planned termination of clozapine therapy, gradual reduction in dose is recommended over a one to two week period. Should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound (e.g., headache, nausea, vomiting, and diarrhea). After the discontinuation of clozapine, continue weekly WBC counts for an additional four weeks. *Re-initiation of treatment:* When restarting patients who have had even a brief interval off clozapine (i.e., two days or more since the last dose), it is recommended that treatment be re-initiated with one-half of a 25mg tablet (12.5mg) once or twice daily. If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. Any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after even 24 hours of discontinuation.
Molindone	**Schizophrenia** *Initial dosage:* 50 to 75mg/day, increase to 100mg/day in three or four days. Based on severity of symptomatology, dosage may be titrated up or down depending on individual patient response. An increase to 225mg/day may be required. Elderly and debilitated patients should be started on lower dosage. *Maintenance therapy:* Mild - 5 to 15mg three or four times/day. Moderate - 10 to 25mg three or four times/day. Severe - 225mg/day may be required.
Olanzapine[6]	**Bipolar disorder (oral)** *Monotherapy:* Initial dose is 10 to 15mg orally, once daily without regard to meals. Adjust dosage, if indicated, at 5mg/day increments or decrements in intervals of not less than 24 hours. When dosage adjustments are necessary, dose increments/decrements of 5mg QD are recommended. Short-term (three to four weeks) anti-manic efficacy was demonstrated in a dose range of 5 to 20mg/day in clinical trials. The safety of doses above 20mg/day has not been evaluated. *Maintenance monotherapy:* The benefit of maintaining bipolar patients on monotherapy with olanzapine at a dose of 5 to 20mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial. Periodically reevaluate olanzapine use in patients taking the drug for extended periods. *Combination therapy:* When co-administered with lithium or valproate, olanzapine dosing should generally begin with 10mg orally, once daily without regard to meals. Short-term (six weeks) anti-manic efficacy was demonstrated in a dose range of 5 to 20mg/day in clinical trials. The safety of doses above 20mg/day has not been evaluated in clinical trials. **Schizophrenia (oral)** *Initial dosage:* 5 to 10mg orally, once daily without regard to meals, with a target dose of 10mg/day within several days of initiation. Adjust dosage, if indicated, at 5mg/day increments or decrements in intervals not less than one week. Efficacy was demonstrated in a dose range of 10 to 15mg/day in clinical trials. Increases in efficacy were not demonstrated in doses above 10mg/day. Doses above 10mg/day are recommended only after clinical assessment. The safety of doses above 20mg/day has not been evaluated in clinical trials. *Maintenance treatment:* Patients should be periodically reassessed to determine the need for maintenance treatment.

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	Agitation associated with schizophrenia and bipolar I mania (IM) *Usual dose:* The efficacy of IM olanzapine injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 to 10mg. The recommended dose is 10mg. A lower dose of 5 or 7.5mg may be considered when clinical factors warrant. If agitation warranting additional IM doses persists following the initial dose, subsequent doses up to 10mg may be given. The efficacy of repeated doses in agitated patients, however, has not been systematically evaluated in controlled clinical trials. Also the safety of total daily doses greater than 30mg, or 10mg injections given more frequently than two hours after the initial dose, and four hours after the second dose have not been evaluated in clinical trials. Maximal dosing of IM olanzapine (e.g., three doses of 10mg given two to four hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension. Thus, it is recommended that patients requiring subsequent IM injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of IM olanzapine. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended. If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5 to 20mg/day as soon as clinically appropriate. **Special populations** *Oral:* The recommended starting dose is 5mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking women 65 years of age and older), or who may be more pharmacodynamically sensitive to olanzapine. When indicated, use caution with dose escalation. *Injection:* Consider a dose of 5mg per injection for geriatric patients or when other clinical factors warrant. Consider a lower dose of 2.5mg per injection for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine.
Pimozide	The suppression of tics by pimozide requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug. ECG should be performed at baseline and periodically thereafter, especially during dosage adjustment. **Tourette's Disorder** Adults- *Initial dose:* 1 to 2mg/day in divided doses. Thereafter, increase dose every other day. *Maintenance dose:* Less than 0.2mg/kg/day or 10mg/day, whichever is less. Doses greater than 0.2mg/kg/day or 10mg/day are not recommended. Children- Although Tourette's disorder most often has its onset between two and 15 years of age, information on the use and efficacy of pimozide in patients less than 12 years of age is limited. A 24-week, open-label study in 36 children between two and 12 years of age demonstrated that pimozide has a similar safety profile in this age group as in older patients and there were no safety findings that would preclude its use in this age group. **Pimozide is not recommended for any childhood condition other than Tourette's disorder**. *Initial dosage:* 0.05mg/kg, preferably taken once at bedtime; dose may be increased every third day to a maximum of 0.2mg/kg, not to exceed 10mg/day. *Gradual withdrawal:* Attempts should be made periodically to reduce dosage to see if tics persist. Increases of tic intensity and frequency may represent a transient, withdrawal-related phenomenon rather than a return of symptoms. Allow one or two weeks to elapse before concluding that an increase in tic manifestations is due to the underlying disease rather than drug withdrawal. A gradual withdrawal is recommended in any case.
Quetiapine[7]	**Schizophrenia**: *Usual dose:* Initial dose of 25mg twice daily, with increases in increments of 25 to 50mg two or three times/day on the second and third day, as tolerated, to a target dose range of 300 to 400mg/day by the fourth day, given two or three times/day. Further dosage adjustments, if

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	indicated, should generally occur at intervals of at least two days. Dose increments/decrements of 25 to 50mg twice daily are recommended. Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750mg/day. The safety of doses greater than 800mg/day has not been evaluated in clinical trials. The effectiveness of quetiapine for more than six weeks has not been systematically evaluated. Periodically reevaluate the long-term usefulness of the drug for the individual patient. *Maintenance:* The effectiveness of maintenance treatment is well established for many other antipsychotic drugs. Quetiapine should be continued in responding patients at the lowest dose needed to maintain remission. Patients should be periodically reassessed. *Hepatic function impairment:* Patients with hepatic impairment should be started on 25mg/day. The dose should be increased daily in increments of 25 to 50mg/day to an effective dose, depending on the clinical response and tolerability of the patient. *Re-initiation of treatment in patients previously discontinued:* When restarting patients who have had an interval of less than one week off of quetiapine, titration of quetiapine is not required; the maintenance dose may be reinitiated. For patients who have been off of quetiapine for more than one week, follow the initial titration schedule. *Switching from other antipsychotics:* The period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate quetiapine therapy in place of the next scheduled injection. Periodically reevaluate the need for continuing existing EPS medication. **Bipolar mania**: *Mania* *Usual dose:* When used as monotherapy or adjunct therapy (with lithium or divalproex), initiate quetiapine in twice-daily doses totaling 100mg/day on day one, increased to 400mg/day on day four, in increments of up to 100mg/day in twice daily divided doses. Further dosage adjustments up to 800mg/day by day six should be in increments of no more than 200mg/day. Data indicate that the majority of patients responded between 400 and 800mg/day. The safety of doses above 800mg/day has not been evaluated in clinical trials. *Depression* *Usual dose*: Should be given once daily at bedtime to reach 300mg/day by day 4. In the clinical trials supporting effectiveness, the dosing schedule was 50mg, 100mg, 200mg, and 300mg/day for days 1-4 respectively. Antidepressant efficacy was demonstrated at both 300mg and 600mg however, no additional benefit was seen in the 600mg group. **Special populations**: Consider a slower rate of dose titration and a lower target dose in the elderly, debilitated patients, or those who have a predisposition to hypotensive reactions. Perform dose escalation with caution. Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.
Risperidone[5]	**Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)** The safety and effectiveness in pediatric patients with autistic disorder less than five years of age have not been established. The dosage should be individualized according to the response and tolerability of the patient. The total daily dose can be administered once daily, or half the total daily dose can be administered twice daily. Dosing should be initiated at 0.25 mg per day for patients < 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weigh less than 15 kg. In clinical trials, 90% of patients who showed a response (based on at least 25% improvement on ABC-I) received doses between 0.5 mg and 2.5 mg per day. The maximum daily dose in one of the pivotal trials, when the therapeutic effect reached plateau, was 1 mg in patients < 20 kg, 2.5 mg in patients ≥ 20 kg,

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	or 3 mg in patients > 45 kg. No dosing data is available for children who weighed less than 15 kg. Once sufficient clinical response has been achieved and maintained, consideration should be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. The physician who elects to use risperidone for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Bipolar mania (oral only**) ***Adults*** *Usual dose:* Administer on a once daily schedule, starting with 2 to 3mg/day. If indicated, adjust dosage at intervals of not less than 24 hours and in dosage increments/decrements of 1mg/day as studied in the short-term, placebo-controlled trials. In these trials, short-term (three week) anti-manic efficacy was demonstrated in a flexible dosage range of 1 to 6mg/day. Risperidone doses higher than 6mg/day were not studied. *Maintenance therapy:* There is no evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically-obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond three weeks). ***Pediatrics*** The dosage should be initiated at 0.5mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and 6 mg/day, no additional benefit was seen above 2.5 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied. Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily. **Schizophrenia (oral)** ***Adults*** *Initial dose:* Risperidone can be administered once or twice daily. Initial dosing is generally 2 mg/day. Dose increases should then occur at intervals not less than 24 hours, in increments of 1-2 mg/day, as tolerated, to a recommended dose of 4-8 mg/day. In some patients, slower titration may be appropriate. Efficacy has been demonstrated in a range of 4-16 mg/day. However, doses above 6 mg/day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. In a single study supporting once-daily dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials. *Maintenance therapy:* The effectiveness of risperidone 2 to 8mg/day at delaying relapse was demonstrated in controlled trials in patients who had been clinically stable for at least four weeks and then were followed for a period of one to two years. Periodically, patients should be reassessed to determine the need for maintenance treatment with appropriate dose. *Re-initiation of treatment:* When restarting patients who have had an interval off risperidone, the initial titration schedule should be followed. *Switching from other antipsychotic agents:* When switching from other antipsychotic agents to risperidone, immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients; gradual discontinuation may be more appropriate for other patients. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from a depot antipsychotic, risperidone therapy should be initiated in place of the next scheduled injection. Reevaluate the need for continuing existing medications that treat extrapyramidal symptoms. ***Adolescents*** The dosage of risperidone should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at

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	intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg/day, no additional benefit was seen above 3 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied. Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily. There are no controlled data to support the longer term use beyond 8 weeks in adolescents with schizophrenia. The physician who elects to use for extended periods in adolescents with schizophrenia should periodically re-evaluate the long-term usefulness of the drug for the individual patient. **Long acting IM injection** For patients who have never taken oral risperidone, tolerability should be established with oral risperidone prior to initiating treatment with injectable risperidone. The recommended dose is 25mg IM every two weeks. Although dose response for effectiveness has not been established for risperidone injection, some patients not responding to 25mg may benefit from a higher dose of 37.5 or 50mg. The maximum dose should not exceed 50mg risperidone injection every two weeks. Oral risperidone, or another antipsychotic medication, should be given with the first risperidone injection and continued for three weeks (then discontinued) to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site. *Dose adjustments:* Do not make upward dosage adjustments more frequently than every four weeks. The clinical effects of this dose adjustment should not be anticipated earlier than three weeks after the first injection with the higher dose. *Maintenance therapy:* Responding patients should be continued on treatment with risperidone injection at the lowest dose needed. Patients should be reassessed periodically to determine the need for continued treatment. *Renal/hepatic impairment:* Patients with renal/hepatic impairment should be treated with titrated doses of oral risperidone prior to initiating treatment with risperidone injection. The recommended starting dose is 0.5mg oral risperidone twice daily during the first week, which can be increased to 1mg twice daily or 2mg once daily during the second week. If a dose of at least 2mg oral risperidone is well tolerated, an injection of 25mg risperidone can be administered every two weeks. Oral supplementation should be continued for three weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate. *Re-initiation of treatment:* When restarting patients who have had an interval off treatment with risperidone injection, supplementation with oral risperidone or another antipsychotic medication is recommended. *Switching from other antipsychotic agents:* Continue previous antipsychotic agents for three weeks after the first risperidone injection to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun. For schizophrenic patients who have never taken oral risperidone, establish tolerability with oral risperidone prior to initiating treatment with risperidone injection. As recommended with other antipsychotic medications, periodically reevaluate the need for continuing existing extrapyramidal symptom medication. *Concomitant therapy:* When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of risperidone between two to four weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25mg), it is recommended to continue treatment with the 25mg dose unless clinical judgment necessitates interruption of treatment with risperidone. *Administration:* Administer risperidone injection every two weeks by deep IM gluteal injection. A health care professional should administer each injection using the enclosed safety needle. Injections should be alternated between the two buttocks. Injections should not be administered IV. Two different dosage strengths of a risperidone injection should not be combined in a single administration. The dose pack from refrigerator should be allowed to

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	reach room temperature before reconstitution. It is recommended that the risperidone injection be used immediately upon suspension in the diluent. It must be used within six hours of suspension. Re-suspension of a risperidone injection is necessary prior to administration because settling occurs over time once the product is in suspension. Keeping the vial upright, the vial should be shaken vigorously back and forth for as long as it takes to re-suspend the microspheres. **Special populations (oral)** *Initial dosage:* The recommended initial dose is 0.5mg twice daily in patients who are elderly, debilitated, have severe renal or hepatic impairment, are predisposed to hypotension, or in whom hypotension would pose a risk. Adjust dose at increments of no more than 0.5mg twice daily. Give increases to dosages above 1.5mg twice daily at intervals of at least one week. In some patients, slower titration may be medically appropriate. Once-daily dosing in the elderly or debilitated may occur after the patient has been titrated on a twice-daily regimen for two to three days at the target dose. *Oral solution administration:* The oral solution can be mixed with water, coffee, orange juice, or low-fat milk. It is not compatible with cola or tea. *Orally disintegrating tablet administration:* Blister should not be opened until ready to administer. For single tablet removal, one of the four blister units should be separated by tearing apart at the perforation. The corner can then be bent back as indicated, and the foil peeled back to expose the tablet. The tablet should not be pushed through the foil because this could damage the tablet. The tablet should then be, removed from the blister unit with dry hands, and immediately placed whole on the tongue. The tablet should be consumed immediately, as it cannot be stored once removed from the blister unit. Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should be advised not to split or chew the tablet.
Ziprasidone[10]	**Acute agitation in Schizophrenia** *Reconstitution:* Ziprasidone should be administered by IM injection only. Single-dose vials require reconstitution prior to administration. Any unused portion should be discarded. Add 1.2mL sterile water for injection to the vial and shaken vigorously until the drug is completely dissolved. Each mL of reconstituted solution contains 20mg ziprasidone. It must not be mixed with other medicinal products or solvents other than sterile water for injection. *Usual dose:* The recommended dose is 10 to 20mg IM administered as required up to a maximum dose of 40mg/day. Doses of 10mg IM may be administered every two hours; doses of 20mg IM may be administered every four hours up to a maximum of 40mg/day. IM administration of ziprasidone for more than three consecutive days has not been studied. If long-term therapy is indicated, IM administration should be replaced with oral ziprasidone hydrochloride capsules as soon as possible. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already taking oral ziprasidone, co-administration is not recommended. **Bipolar mania** *Initial treatment:* Oral ziprasidone should be administered at an initial daily dose of 40mg twice daily with food. The dose should then be increased to 60 or 80mg twice/day on the second day of treatment, and subsequently adjusted on the basis of toleration and efficacy within the range of 40 to 80mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120mg. *Maintenance treatment:* There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of mania with ziprasidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable for maintenance of the initial response and prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone in such longer-term treatment (i.e., beyond three weeks). **Schizophrenia** When deciding among the alternative treatments available for schizophrenia, consider ziprasidone's greater capacity to prolong the QT/QTc interval compared with other

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	antipsychotic drugs. *Initial treatment:* Ziprasidone capsules should be administered at an initial daily dose of 20mg twice daily with food. In some patients, daily dosage subsequently may be adjusted on the basis of individual clinical status up to 80mg twice daily. If indicated, dosage adjustments generally should occur at intervals of two days or more, as steady state is achieved within one to three days. In order to ensure use of the lowest effective dose, observe patients for improvement for several weeks before upward dosage adjustment. Efficacy in schizophrenia was demonstrated in a dose range of 20 to 100mg twice daily in short-term, placebo-controlled, clinical trials. There were trends toward dose response within the range of 20 to 80mg twice daily, but results were not consistent. Generally, an increase to a dose greater than 80mg twice daily is not recommended. The safety of doses above 100mg twice daily has not been systematically evaluated in clinical trials. *Maintenance treatment:* While there is no body of evidence available to answer the question of how long to treat a patient with ziprasidone, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80mg twice daily. No additional benefit was demonstrated for doses above 20mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment.
Paliperidone	**Schizophrenia** *Initial treatment:* The recommended dose is 6 mg once daily, administered in the morning. Initial dose titration is not required. Although it has not been systematically established that doses above 6 mg have additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse reactions. Thus, some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment, and generally should occur at intervals of more than five days. When dose increases are indicated, small increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day. Paliperidone can be taken with or without food. Paliperidone must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a non-absorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool. *Concomitant medications:* Concomitant use of paliperidone with risperidone has not been studied. Because paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is co-administered with paliperidone. **Special populations** *Hepatic function impairment:* For patients with mild to moderate hepatic function impairment (Child-Pugh class A and B), no dose adjustment is recommended. *Renal function impairment*: Dosing must be individualized according to the patient's renal function status. For patients with mild renal function impairment (creatinine clearance [Ccr] = 50 to less than 80 mL/min), the maximum recommended dose is 6 mg once daily. For patients with moderate to severe renal function impairment (Ccr = 10 to less than 50 mL/min), the maximum recommended dose of paliperidone is 3 mg once daily. *Elderly*: Because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status. In general, recommended dosing for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. For patients with moderate to severe renal function impairment (Ccr = 10 to less than 50 mL/min), the maximum recommended dose of paliperidone is 3 mg once daily.
Quetiapine XR	**Schizophrenia** Should be administered once daily, preferably in the evening. The recommended initial dose

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	is 300mg/day. Patients should be titrated within a dose range of 400-800mg/day depending on the response and tolerance. Dose increases can be made at intervals as short as one day and in increments of up to 300mg/day. The safety of doses above 800mg/day has not been evaluated in clinical trials. Tablets should be swallowed whole and not split, chewed or crushed. It is recommended to take without food or only with a light meal ~300 calories. *Special Populations:* Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions. For patients who require less than 200mg per dose during the initial titration, use the immediate release formulation. Elderly patients should be started on the immediate release formulation 25mg/day, depending on the response and tolerance of the individual. When an effective dose has been reached, the patient may be switched to the extended release formulation at an equivalent total daily dose. Patients with hepatic impairment should be started on immediate release formulation 25mg/day. The dose can be increased daily in increments of 25-50mg/day to an effective dose, depending on the clinical response and tolerance of the patient. When an effective dose has been reached, the patient may be switched to an equivalent total daily dosage in the extended release formulation. If a patient has been off of therapy for more than a week, the initial dosing schedule should be followed. Schizophrenic patients who are currently being treated with divided doses of the immediate release formulation 2-3 times daily may be switched to the extended release formulation at the equivalent total daily dose taken once daily.

Efficacy

The efficacy of the atypical agents in respect to their approved indications has been proven, as reflected in the treatment guidelines and recommendations. Therefore, there is little benefit in addressing studies stating clinical efficacy in placebo-controlled studies or head-to-head studies comparing atypical antipsychotics with the first-generation agents. The following table summarizes those studies which look at adverse effects, efficacy in unlabeled uses, or other physiological effects, such as effects on glycemic control, dyslipidemias, hypertension, etc.

Agent(s)	Study Type and Size	Method/Results/Conclusions
Olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone[12]	Randomized, double-blind study 1,493 patients with schizophrenia at 57 U.S. sites	**Method:** Patients were randomized to olanzapine (7.5-30mg/day); perphenazine (8-32mg/day); quetiapine (200-800mg/day); or risperidone (1.5-6.0mg/day) for up to 18 months. Ziprasidone (40-160mg/day) was included after its FDA approval. Patients were randomly assigned to receive olanzapine, perphenazine, risperidone, or quetiapine under double-blind conditions and followed for up to 18 months or until treatment was discontinued for any reason (phase I). Ziprasidone was approved after the study began and was added to the study in Jan. 2002. Patients whose assigned treatment was discontinued could receive other treatments in phases II and III. Current reported data reflects phase I data only. **Results:** Overall, 74% of patients discontinued the study medication before 18 months (64% in olanzapine group, 75% in perphenazine group, 82% in quetiapine group, 74% in risperidone group, and 79% in ziprasidone group). The time to discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine or risperidone group, but not in the perphenazine or ziprasidone group. The times to discontinuation because of intolerable side effects were similar among the groups. Olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for extrapyramidal effects.

Agent(s)	Study Type and Size	Method/Results/Conclusions
		Conclusions: The majority of patients in each group discontinued their assigned treatment due to inefficacy or intolerable side effects or for other reasons. Olanzapine was the most effective in terms of the rates of discontinuation, and the efficacy of perphenazine seemed similar to quetiapine, risperidone, and ziprasidone. Olanzapine, however, was associated with greater weight gain and increases in measures of glucose and lipid metabolism.
Ziprasidone, risperidone, and olanzapine[13]	Medical and pharmacy claims data analysis 1,810 patients	**Method:** Medical and pharmacy claims data were used to compare persistence, compliance, and treatment costs in patients who were initiated on atypical antipsychotics. Medical and pharmacy claims were obtained for the time period of September 1, 2000 to November 30, 2003. All patients at least 18 years old with one or more paid pharmacy claims for risperidone, olanzapine, quetiapine, or ziprasidone between March 1, 2001, and August 31, 2003 were first selected for inclusion. Only patients with a schizophrenia or schizoaffective diagnosis in the claims history were included. Persistence was calculated as the duration of index therapy in days, from the first to last observed prescription date. The results were stratified by index therapy. The data was presented as descriptive statistics for each treatment group. **Results:** Persistence was nearly 30 days longer for those receiving ziprasidone (228 days) than risperidone (193 days) or olanzapine (201 days). Compliance was significantly higher among ziprasidone patients (87%) compared with other treatments (78-80%). **Conclusion:** Patients initiated on ziprasidone had longer persistence and better compliance. **Limitations:** Compliance and persistence were assessed using administrative claims data. Prescription claims data can not verify administration or that patients took the drug, but can verify drug availability at the time of dispensing. Although quetiapine was initially included in this study, upon review of the distribution of the daily doses, the majority were using a daily dose below that recommended for schizophrenia treatment. This suggested that the majority of quetiapine users were using the agent not as a primary antipsychotic agent.
Clozapine, olanzapine, risperidone on glucose and lipid metabolism in first-episode schizophrenia[14]	Randomized 112 schizophrenic patients	**Method:** Patients were randomly assigned to receive clozapine, olanzapine, risperidone, or sulpiride for eight weeks. Planned assessments included BMI, waist-to-hip ration, fasting glucose, insulin, C-peptide, insulin resistance index, cholesterol and triglyceride. All measures were collected at baseline and at the end of the eight weeks of treatment. **Results:** After treatment, insulin, C-peptide, and insulin resistance index (IRI) were significantly higher in the four groups, but not fasting glucose levels. Cholesterol and triglyceride levels were significantly increased in the clozapine and olanzapine groups. Patients treated with clozapine and olanzapine had higher fasting insulin, C-peptide, and IRI levels than those treated with risperidone and sulpiride. Among all the agents, increases in BMI (high to lowest) were as follows: clozapine, olanzapine, sulpiride, and risperidone. **Conclusions:** All agents were associated with an increase in insulin, C-peptide, and IRI. Clozapine and olanzapine were associated with an increase in cholesterol and triglyceride levels. The effects of clozapine and olanzapine on the glucose and lipid metabolism outweighed those of risperidone and sulpiride.

Agent(s)	Study Type and Size	Method/Results/Conclusions
Olanzapine and risperidone[15]	Crossover 15 schizophrenic patients	**Method:** Fifteen patients were shifted from olanzapine and risperidone or from risperidone and olanzapine due to poor treatment response. The body weights, lipid profiles and fasting glucose levels were assessed before medication switch and three months after crossover. **Results:** Seven patients taking risperidone at the time of inclusion (risperidone first group), after shifting to olanzapine, showed a significant increase in triglyceride level and body weight. In the other eight patients (olanzapine-first group), after shift to risperidone, there was a decrease in triglyceride level, body weight, and BMI. When comparing the metabolic profiles in all patients after olanzapine and risperidone (irrespective of the order of treatment), mean triglycerides, body weight, and BMI were significantly higher in patients receiving olanzapine than those on risperidone. Additionally, there was a small and insignificant increase in total cholesterol level and small decrease in HDL in the olanzapine group. There were no significant differences found in fasting glucose and LDL between olanzapine and risperidone. **Conclusion:** Elevations in triglycerides and body weight could be associated with olanzapine use as compared with risperidone.
Ziprasidone versus olanzapine[16]	Retrospective cohort chart review 191 randomly selected patients	**Results:** There were no significant differences on QTc interval observed. A significant weight gain was observed in olanzapine treated patients but not in the ziprasidone-treated cohort. Additionally, adverse metabolic changes associated with olanzapine administration were significant with respect to effects on total cholesterol, triglycerides, and hemoglobin A1C; whereas significant favorable metabolic effects were observed in ziprasidone patients with regard to total cholesterol, LDL, HDL and HbA1C. **Conclusion:** Both agents are safe and well tolerated from a cardiovascular standpoint, with no differences in QTc interval prolongation being observed. Olanzapine patients exhibited significant weight increases, whereas ziprasidone patients exhibited weight loss. Olanzapine treatment was also associated with significant adverse effects on lipid profile and HbA1c. These adverse metabolic effects were not observed in ziprasidone patients, although favorable effects were observed with regard to total cholesterol, LDL, HDL, and HbA1c.
Olanzapine and aripiprazole[17]	26-week, multi-center, randomized, double-blind, active controlled trial 317 patients with DSM-IV schizophrenia in acute relapse and requiring hospitalization	**Method:** Significant weight gain was defined as $\geq$ 7% increase in body weight from baseline. Body weight, Positive and Negative Syndrome Scale, and Clinical Global Impressions-Improvement Scale (CGI-I) assessments were performed at baseline and at regular intervals. The study period was from April 200 through June 2001. **Results:** A greater proportion of olanzapine treated patients exhibited clinically significant weight gain during the trial compared with those treated with aripiprazole. By week 26, 37% of patients treated with olanzapine had experienced significant weight gain compared with 14% of those on aripiprazole. Statistically significant differences in mean weight change were observed between treatments at week one and sustained throughout the study. At week 26, there was a mean weight loss of 1.37kg with aripiprazole, compared with a mean increase of 4.23kg with olanzapine, among patients who remained on therapy. Changes in fasting plasma levels of total cholesterol, HDL-c and triglycerides were significantly different in the two treatment groups, with worsening of the lipid profile among patients treated with olanzapine. There was a consistent and sustained improvement in symptoms in patients who remained on therapy with either olanzapine

Agent(s)	Study Type and Size	Method/Results/Conclusions
		or aripiprazole as assessed by CGI-I scores and responder rates throughout the study. **Conclusion:** Olanzapine had a greater impact on patients' weight than aripiprazole. Significant differences in favor of aripiprazole were also observed in the effects of therapy on plasma lipid profile. Both arms achieved comparable clinically meaningful improvements on efficacy measures. The observed effects on weight and lipids indicate a potentially lower metabolic and cardiovascular risk in patients treated with aripiprazole compared with those treated with olanzapine.
Olanzapine, quetiapine, risperidone, and ziprasidone[18]	Randomized, double-blind study 444 schizophrenic patients	**Method:** Patients who had discontinued the atypical antipsychotic randomly assigned during phase I of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) were randomly reassigned to double-blind treatment with a different antipsychotic (olanzapine, 7.5-30mg/day; quetiapine, 200-800mg/day; risperidone, 1.5-6mg/day; or ziprasidone, 40-160mg/day). The primary goal was to determine if there were differences between these four agents in effectiveness measured by time until discontinuation for any reason. **Results:** The time to treatment discontinuation was longer for patients treated with risperidone (7.0 months median) and olanzapine (6.3 months median) than with quetiapine (4.0 months median) and ziprasidone (2.8 months median). Among patients who discontinued their previous antipsychotic because of inefficacy, olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among those who discontinued their previous treatment because of intolerability. **Conclusions:** Risperidone and olanzapine were found to be more effective than quetiapine and ziprasidone among patients with chronic schizophrenia who had just discontinued treatment with an atypical antipsychotic, as reflected by longer time until discontinuation for any reason.
Ziprasidone and olanzapine[19]	Six-week, multi-center, double-blind, parallel-design, flexible dose trial 273 patients	**Method:** Patients were randomly assigned to receive ziprasidone or olanzapine. Primary efficacy measures were improvement in Brief Psychiatric Rating Scale and Clinical Global Impression Severity Scale scores. Secondary measures were scores on the CGI improvement Scale, Positive and Negative Syndrome Scale (PANSS), and Calgary Depression Scale for Schizophrenia. Tolerability assessments included fasting lipid profiles, fasting glucose and insulin measurements, electrocardiography, and monitoring of vital signs and body weight. **Results:** The overall mean daily doses were 129.9mg for ziprasidone and 11.3mg for olanzapine. Both antipsychotics were efficacious in improving symptoms and global illness severity. The two treatment groups did not differ significantly in primary or secondary efficacy measures at endpoint or in by-visit analysis. Both agents were well tolerated. Body weight, total cholesterol, triglycerides, and LDL-c significantly increased with olanzapine but not with ziprasidone; all between-group comparisons of these variables were significant and favored ziprasidone. Olanzapine, but not ziprasidone, was associated with significant increases in fasting insulin level. No patient in either group exhibited a corrected QT interval $\geq$ 500msec. **Conclusions:** During six weeks' treatment, ziprasidone and olanzapine demonstrated comparable antipsychotic efficacy. Differences favoring ziprasidone were observed in metabolic parameters.

Agent(s)	Study Type and Size	Method/Results/Conclusions
Ziprasidone and clozapine in treatment refractory schizophrenic patients[20]	18-week, double-blind, parallel group 146 patients	**Method:** Patients who met criteria for treatment resistance were enrolled. Treatment resistance was defined as a non-response in ≥ 3 adequate trials in past five years and/or inability to tolerate antipsychotic treatment; and who had a PANSS score of ≥ 80. Patients completed a three to seven day screening period prior to randomization to ziprasidone 80-160mg/day or clozapine 250-600mg/day. **Results:** On the primary intent-to-treat (last observation carried forward) analysis, the baseline to endpoint decrease in PANSS total score was similar for both agents (ziprasidone -25.0 ± 22.0 and clozapine -24.5 ± 22.5). A progressive and significant reduction from baseline in the PANSS total score was seen from day 11 on both agents. The mean baseline to endpoint improvement was also similar on the Calgary Depression Scale, the CGI-I, and the Global Assessment of Functioning Scale. Ziprasidone was associated with fewer treatment related adverse effects than clozapine, and a more favorable metabolic profile in terms of absence of weight gain, and significant reduction in median cholesterol (-5 vs. +2), LDL cholesterol (-6 vs. +4mg/dL), triglycerides (15 vs. +10mg/dL). No QTc interval prolongation was reported with either drug. **Conclusions:** Treatment with ziprasidone and clozapine resulted in equivalent improvement in the PANSS total score. Both drugs produced statistically significant baseline-to-endpoint improvement in the PANSS. Ziprasidone exhibited a significantly more favorable metabolic profile compared to clozapine. No QTc interval prolongation was reported with either drug.
Quetiapine in the treatment of bipolar I or II depression[21]	Eight-week, randomized, double-blind, placebo controlled 542 outpatients with bipolar I or II disorder experiencing a major depressive episode	**Method:** Patients were randomly assigned to eight weeks of quetiapine (300 or 600mg/d) or placebo. The primary efficacy measure was mean change from baseline to week eight in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Additional assessments included the Hamilton Depression Rating Scale, Clinical Global Impression of Severity and Improvement, Hamilton Anxiety Rating Scale, Pittsburg Sleep Quality Index, and Quality of Life Enjoyment and Satisfaction Questionnaire. **Results:** Both doses of quetiapine showed statistically significant improvement in the primary endpoint total scores compared with placebo from week one forward. 58.2% of those on quetiapine 600mg/day and 57.6% of those on 300mg/day met response criteria (≥ 50% Montgomery-Asberg Depression Rating scale score improvement). The proportions of patients meeting the remission criteria were 52.9% in the quetiapine groups and 28.4% in the placebo group. Treatment emergent mania rates were low and similar for both arms (3.2% and 3.9% respectively). **Conclusions:** This study demonstrates that quetiapine monotherapy for bipolar depression in patients with bipolar I or II disorder is efficacious.

Symbyax® (olanzapine/fluoxetine combination)

This combination agent has not been addressed in the body of work up to this point. For information regarding pharmacology, pharmacokinetics, adverse effects, precautions/warnings, etc., please refer to the individual agents previously covered in this review or in the antidepressant review.

According to the manufacturer label, the efficacy of this product was established in two eight-week, randomized, double-blind, controlled studies of patients diagnosed with bipolar I disorder, depressed (DSM-IV) using a flexible dosing of Symbyax® 6/25, 6/50, or 12/50; olanzapine 5-20mg/day, and placebo. The mean change from baseline to endpoint demonstrated that in both studies the combination the agent significantly improved MADRS scores over olanzapine and placebo.

Symbyax® should dosed once daily in the evening starting with the 6/25mg strength. The target dose should is recommended at 6-12mg olanzapine and 25-50mg fluoxetine.

Conclusion

The APA guidelines are clear in the treatment recommendations. Atypical agents are recommended as first-line agents in the treatment of schizophrenia. First-generation agents, however, may still be useful, although their status in treatment has diminished.

The agents Orap® and Moban® are limited by either indications or side effect profiles. Moban® most closely aligns with the first-generation agents. Additionally, its adverse effect profile is similar to that of the first-generation agents. The majority of agents classified as first-generation antipsychotics are available generically.

The atypical agents provide effective response on positive and negative symptoms of schizophrenia with less capability of reproducing the sometimes debilitating adverse effects attributable to the first-generation agents. The atypical agents, however, are not completely “clean” in respect to the metabolic and/or cardiovascular effects. Generally, the data available on these agents show comparative effectiveness among all the agents but with varying degree of metabolic effects among them.

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Health Information
Designs, Inc.

North Dakota Medicaid
Market Share

Antipsychotics

	200401	200402	200403	200404	200405	200406	200407	200408	200409	200410	200411	200412
ABILIFY	3.3	3.7	3.94	4.35	4.74	4.85	4.73	4.71	4.86	5.31	5.05	5.65
ABILIFY DISCMELT	0	0	0	0	0	0	0	0	0	0	0	0
CLOZAPINE	6.41	6.44	6.57	7.05	6.62	7.37	6.71	6.96	7.22	6.71	7.47	7.05
CLOZARIL	5.81	5.52	5.22	5.35	5.39	6.02	5.08	5.39	5.16	5.33	6.19	4.97
FAZACLO	0	0	0	0	0	0	0	0	0	0	0	0
GEODON	5.1	5.78	5.56	5.91	6.54	6.52	6.34	7.04	7.37	7.38	7.37	7.8
INVEGA	0	0	0	0	0	0	0	0	0	0	0	0
RISPERDAL	33.92	34.15	33.08	32.32	31.98	31.34	32.26	31.66	31.17	30.41	29.77	30.66
RISPERDAL CONSTA	0.32	0.43	0.87	0.63	0.47	0.39	0.4	0.29	0.2	0.18	0.16	0.16
RISPERDAL M-TAB	0	0	0	0	0	0	0	0	0	0	0	0
SEROQUEL	20.87	20.98	20.46	21.64	21.97	21.14	21.99	21.37	22.35	22.4	23.19	23
SEROQUEL XR	0	0	0	0	0	0	0	0	0	0	0	0
ZYPREXA	23.03	21.79	23.17	21.53	20.92	20.84	21.09	21.06	20.39	20.78	19.58	19.15
ZYPREXA ZYDIS	1.24	1.22	1.12	1.21	1.37	1.53	1.41	1.53	1.28	1.5	1.23	1.56

	200501	200502	200503	200504	200505	200506	200507	200508	200509	200510	200511	200512
ABILIFY	5.52	5.74	5.74	6.03	5.92	5.64	5.89	5.61	6.2	5.86	6.13	6.28
ABILIFY DISCMELT	0	0	0	0	0	0	0	0	0	0	0	0
CLOZAPINE	7.77	7.71	8.34	9.08	10.28	9.85	9.47	8.55	8.17	7.53	7.23	7.18
CLOZARIL	5.07	5.17	4.72	3.56	3.23	2.21	1.88	1.74	1.97	2.08	1.78	1.4
FAZACLO	0	0	0.07	0	0	0	0	0	0	0	0.05	0.05
GEODON	7.21	7.44	7.35	7.56	7.49	7.83	7.7	7.95	8.41	8.18	8.34	8.76
INVEGA	0	0	0	0	0	0	0	0	0	0	0	0
RISPERDAL	29.47	29.72	29.91	29.75	29.65	30.28	29.83	29.9	30.19	30.22	30.04	30.33
RISPERDAL CONSTA	0.23	0.27	0.22	0.24	0.25	0.3	0.29	0.39	0.39	0.36	0.49	0.52
RISPERDAL M-TAB	0	0	0	0	0	0	0	0	0	0	0	0
SEROQUEL	23.95	23.63	23.29	23.33	23.18	23.38	24.87	25.32	25.22	26.37	26.51	27.16
SEROQUEL XR	0	0	0	0	0	0	0	0	0	0	0	0
ZYPREXA	19.18	18.89	18.82	18.87	18.27	18.86	18.53	18.81	17.77	17.67	17.85	16.98
ZYPREXA ZYDIS	1.6	1.42	1.54	1.57	1.73	1.66	1.53	1.74	1.67	1.72	1.57	1.35

Health Information
Designs, Inc.

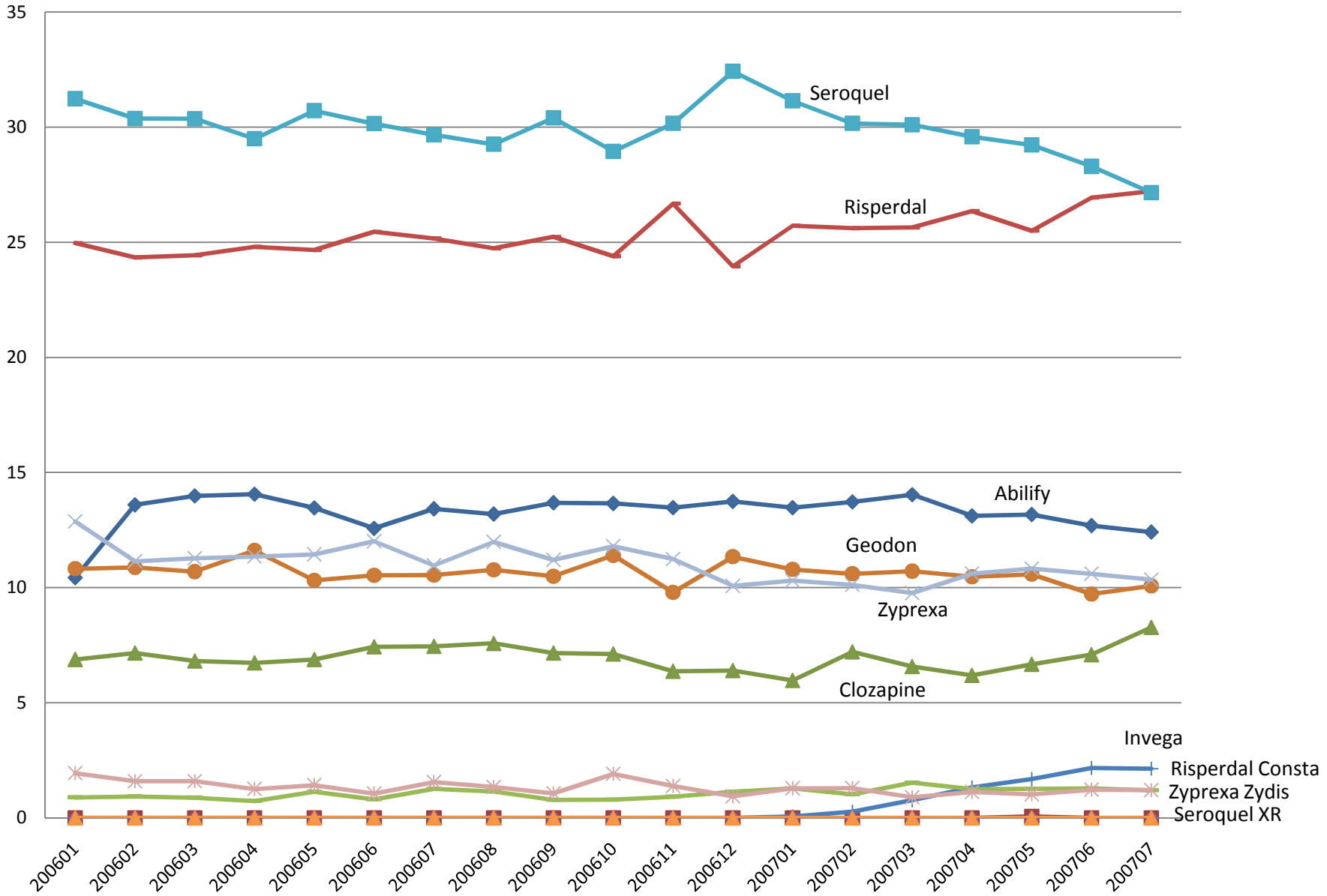
North Dakota Medicaid
Market Share

Antipsychotics

	200601	200602	200603	200604	200605	200606	200607	200608	200609	200610	200611	200612
ABILIFY	10.43	13.59	13.98	14.05	13.46	12.57	13.42	13.19	13.68	13.65	13.47	13.74
ABILIFY DISCMELT	0	0	0	0	0	0	0	0	0	0	0	0
CLOZAPINE	6.27	6.23	5.99	6.6	6.64	7.31	7.45	7.33	7.02	7.12	6.11	6.4
CLOZARIL	0.61	0.93	0.82	0.13	0.24	0.12	0	0.25	0.14	0	0.26	0
FAZACLO	0	0	0	0	0	0	0	0	0	0	0	0
GEODON	10.82	10.88	10.69	11.61	10.31	10.53	10.54	10.77	10.49	11.4	9.79	11.34
INVEGA	0	0	0	0	0	0	0	0	0	0	0	0
RISPERDAL	24.96	24.34	24.43	24.8	24.66	25.45	25.16	24.73	25.23	24.39	26.68	23.95
RISPERDAL CONSTA	0.89	0.93	0.88	0.73	1.13	0.8	1.26	1.15	0.78	0.79	0.92	1.13
RISPERDAL M-TAB	0	0	0	0	0	0	0	0	0	0	0	0
SEROQUEL	31.23	30.37	30.36	29.49	30.71	30.15	29.66	29.25	30.4	28.94	30.16	32.42
SEROQUEL XR	0	0	0	0	0	0	0	0	0	0	0	0
ZYPREXA	12.87	11.14	11.27	11.35	11.44	12.01	10.96	11.98	11.2	11.8	11.24	10.07
ZYPREXA ZYDIS	1.94	1.59	1.59	1.25	1.42	1.05	1.55	1.34	1.06	1.91	1.38	0.93

	200701	200702	200703	200704	200705	200706	200707
ABILIFY	13.47	13.72	14.03	13.11	13.17	12.69	12.41
ABILIFY DISCMELT	0	0	0	0	0.06	0	0
CLOZAPINE	5.85	7.07	6.44	6.06	6.55	6.95	8.14
CLOZARIL	0.12	0.14	0.13	0.13	0.12	0.14	0.13
FAZACLO	0	0	0	0	0	0	0
GEODON	10.79	10.6	10.71	10.47	10.58	9.72	10.07
INVEGA	0.06	0.27	0.77	1.32	1.68	2.16	2.13
RISPERDAL	25.72	25.61	25.64	26.35	25.5	26.94	27.22
RISPERDAL CONSTA	1.28	1.02	1.53	1.25	1.26	1.28	1.2
RISPERDAL M-TAB	0	0	0	0	0	0	0
SEROQUEL	31.14	30.16	30.1	29.58	29.22	28.29	27.15
SEROQUEL XR	0	0	0	0	0	0	0
ZYPREXA	10.3	10.12	9.76	10.61	10.82	10.6	10.34
ZYPREXA ZYDIS	1.28	1.29	0.89	1.12	1.02	1.22	1.2

Percent Market Share by Drug January 2006 - July 2007



North Dakota Medicaid

Antipsychotics

DRUG USAGE from 07/01/06 to 06/30/07			
Generic Name	**Rx Num**	**Total Reimb Amt**	**Average Cost per Script**
QUETIAPINE FUMARATE	5413	$1,113,741.17	$205.75
OLANZAPINE	2121	$867,839.65	$409.17
RISPERIDONE	4621	$849,810.72	$183.90
ARIPIPRAZOLE	2423	$724,870.70	$299.16
ZIPRASIDONE HCL	1886	$435,667.42	$231.00
CLOZAPINE	1240	$122,829.29	$99.06
RISPERIDONE MICROSPHERES	208	$110,603.60	$531.75
PALIPERIDONE	96	$33,285.25	$346.72
OLANZAPINE/FLUOXETINE HCL	57	$18,643.17	$327.07
TOTAL	18065	$4,277,290.97	

HEALTH INFORMATION DESIGNS

North Dakota Medicaid

Antipsychotics

NDC USAGE from 07/01/06 to 06/30/07			
Label Name	**Rx Num**	**Total Reimb Amt**	**Average Cost Per Script**
SEROQUEL 300 MG TABLET	764	$322,159.22	$421.67
SEROQUEL 200 MG TABLET	1038	$321,828.44	$310.05
ZYPREXA 20 MG TABLET	371	$291,242.31	$785.02
GEODON 80 MG CAPSULE	776	$215,508.00	$277.72
ABILIFY 10 MG TABLET	754	$204,885.61	$271.73
SEROQUEL 100 MG TABLET	1550	$196,881.27	$127.02
RISPERDAL 1 MG TABLET	1320	$192,766.13	$146.03
RISPERDAL 2 MG TABLET	776	$179,469.10	$231.27
ZYPREXA 15 MG TABLET	301	$179,296.07	$595.67
ZYPREXA 10 MG TABLET	502	$172,146.18	$342.92
ABILIFY 20 MG TABLET	359	$153,273.18	$426.94
ABILIFY 5 MG TABLET	581	$152,114.17	$261.81
RISPERDAL 4 MG TABLET	391	$150,921.95	$385.99
RISPERDAL 0.5 MG TABLET	1108	$138,332.37	$124.85
SEROQUEL 25 MG TABLET	1211	$112,674.03	$93.04
RISPERDAL 3 MG TABLET	427	$111,578.83	$261.31
ABILIFY 15 MG TABLET	447	$109,885.64	$245.83
ABILIFY 30 MG TABLET	265	$102,082.69	$385.22
SEROQUEL 50 MG TABLET	729	$99,114.99	$135.96
GEODON 40 MG CAPSULE	527	$98,296.02	$186.52
CLOZAPINE 100 MG TABLET	825	$97,691.81	$118.41
ZYPREXA 5 MG TABLET	399	$82,773.49	$207.45
GEODON 60 MG CAPSULE	327	$80,074.12	$244.87

Label Name	Rx Num	Total Reimb Amt	Average Cost Per Script
SEROQUEL 400 MG TABLET	121	$61,083.22	$504.82
RISPERDAL CONSTA 50 MG SYR	71	$46,147.78	$649.97
GEODON 20 MG CAPSULE	245	$41,476.68	$169.29
RISPERDAL 0.25 MG TABLET	357	$40,266.63	$112.79
RISPERDAL CONSTA 37.5 MG SYR	73	$40,208.17	$550.80
ZYPREXA 2.5 MG TABLET	234	$38,299.66	$163.67
ZYPREXA ZYDIS 20 MG TAB	41	$27,698.74	$675.58
ZYPREXA ZYDIS 10 MG TABLET	93	$25,975.83	$279.31
RISPERDAL CONSTA 25 MG SYR	64	$24,247.65	$378.87
ZYPREXA ZYDIS 15 MG TAB	40	$21,934.14	$548.35
RISPERDAL 1 MG/ML SOLUTION	110	$20,799.44	$189.09
ZYPREXA 7.5 MG TABLET	72	$19,171.74	$266.27
INVEGA 9 MG ER TABLET	30	$13,390.38	$446.35
INVEGA 6 MG ER TABLET	41	$12,732.44	$310.55
CLOZARIL 100 MG TABLET	22	$11,233.68	$510.62
CLOZAPINE 25 MG TABLET	327	$10,195.86	$31.18
ZYPREXA ZYDIS 5 MG TABLET	46	$8,685.98	$188.83
SYMBYAX 12-50 MG CAPSULE	20	$8,097.15	$404.86
RISPERDAL 0.5 M-TAB	68	$7,416.16	$109.06
INVEGA 3 MG ER TABLET	25	$7,162.43	$286.50
RISPERDAL 1 MG M-TAB	58	$7,001.19	$120.71
SYMBYAX 12-25 MG CAPSULE	17	$5,331.84	$313.64
CLOZAPINE 50 MG TABLET	66	$3,707.94	$56.18
SYMBYAX 6-50 MG CAPSULE	10	$2,704.62	$270.46
SYMBYAX 6-25 MG CAPSULE	10	$2,509.56	$250.96
ABILIFY 2 MG TABLET	7	$2,048.19	$292.60
RISPERDAL 2 MG M-TAB	6	$1,258.92	$209.82

Label Name	Rx Num	Total Reimb Amt	Average Cost Per Script
ZYPREXA 10 MG VIAL	22	$615.51	$27.98
ABILIFY 1 MG/ML SOLUTION	3	$482.16	$160.72
GEODON 20 MG VIAL	11	$312.60	$28.42
ABILIFY 9.7 MG/1.3 ML VIAL	6	$79.84	$13.31
ABILIFY DISCMELT 10 MG TABLET	1	$19.22	$19.22
TOTAL	18065	$4,277,290.97	

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 0-5

Rx Num	Total Reimb Amt	Label Name
1	$373.02	ABILIFY 15 MG TABLET
2	$565.70	SEROQUEL 50 MG TABLET
2	$608.28	RISPERDAL 2 MG TABLET
12	$752.47	SEROQUEL 25 MG TABLET
11	$927.19	RISPERDAL 0.25 MG TABLET
7	$1,359.63	SEROQUEL 200 MG TABLET
18	$2,711.62	RISPERDAL 1 MG TABLET
23	$3,612.24	RISPERDAL 1 MG/ML SOLUTION
48	$8,397.03	RISPERDAL 0.5 MG TABLET
124	$19,307.18	22 recipients

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 6-10

Rx Num	Total Reimb Amt	Label Name
3	$482.16	ABILIFY 1 MG/ML SOLUTION
1	$510.04	ZYPREXA ZYDIS 5 MG TABLET
2	$668.00	INVEGA 3 MG ER TABLET
4	$1,144.06	ABILIFY 2 MG TABLET
4	$1,336.00	INVEGA 6 MG ER TABLET
12	$1,357.83	RISPERDAL 1 MG/ML SOLUTION
14	$2,150.20	RISPERDAL 1 MG M-TAB
14	$1,991.56	SEROQUEL 200 MG TABLET
3	$2,929.80	ZYPREXA 15 MG TABLET
9	$2,016.78	RISPERDAL 3 MG TABLET
21	$2,578.49	GEODON 80 MG CAPSULE
23	$3,048.51	RISPERDAL 0.5 M-TAB

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 6-10

Rx Num	Total Reimb Amt	Label Name
7	$3,112.51	ABILIFY 20 MG TABLET
9	$3,224.87	ZYPREXA 10 MG TABLET
27	$3,502.62	GEODON 20 MG CAPSULE
22	$4,508.16	SEROQUEL 300 MG TABLET
21	$5,847.22	GEODON 60 MG CAPSULE
55	$7,515.46	ABILIFY 15 MG TABLET
44	$7,547.41	GEODON 40 MG CAPSULE
41	$7,701.67	ZYPREXA 2.5 MG TABLET
38	$8,755.63	ZYPREXA 5 MG TABLET
72	$11,581.00	SEROQUEL 50 MG TABLET
93	$11,848.61	RISPERDAL 0.25 MG TABLET
24	$11,908.79	ABILIFY 30 MG TABLET
123	$13,184.56	SEROQUEL 100 MG TABLET
53	$13,975.57	RISPERDAL 2 MG TABLET
57	$14,839.28	ABILIFY 10 MG TABLET
167	$18,258.86	SEROQUEL 25 MG TABLET
74	$18,379.86	ABILIFY 5 MG TABLET
183	$26,642.64	RISPERDAL 1 MG TABLET
284	$39,122.62	RISPERDAL 0.5 MG TABLET
1504	$251,670.77	191 Recipients

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 11-20

Rx Num	Total Reimb Amt	Label Name
1	$19.22	ABILIFY DISCMELT 10 MG TABLET
6	$79.84	ABILIFY 9.7 MG/1.3 ML VIAL
1	$186.57	ABILIFY 2 MG TABLET
10	$197.75	GEODON 20 MG VIAL
3	$280.00	SYMBYAX 12-25 MG CAPSULE
1	$533.80	ZYPREXA ZYDIS 15 MG TAB
21	$587.55	ZYPREXA 10 MG VIAL
14	$740.73	CLOZAPINE 50 MG TABLET
1	$1,067.68	RISPERDAL CONSTA 50 MG SYR
35	$1,462.27	ZYPREXA ZYDIS 10 MG TABLET
68	$1,625.56	CLOZAPINE 25 MG TABLET
4	$1,625.85	SYMBYAX 12-50 MG CAPSULE
9	$1,672.53	INVEGA 3 MG ER TABLET
6	$1,975.68	INVEGA 9 MG ER TABLET
40	$2,024.68	RISPERDAL 1 MG/ML SOLUTION
5	$2,160.50	RISPERDAL CONSTA 25 MG SYR
3	$2,194.74	ZYPREXA ZYDIS 20 MG TAB
9	$2,283.12	INVEGA 6 MG ER TABLET
10	$2,438.96	ZYPREXA 7.5 MG TABLET
20	$3,079.05	ZYPREXA ZYDIS 5 MG TABLET
43	$4,132.98	ZYPREXA 2.5 MG TABLET
40	$4,231.88	RISPERDAL 1 MG M-TAB
47	$4,551.04	RISPERDAL 0.5 M-TAB
13	$7,516.30	SEROQUEL 400 MG TABLET
120	$9,199.05	CLOZAPINE 100 MG TABLET

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 11-20

Rx Num	Total Reimb Amt	Label Name
116	$15,439.27	GEODON 20 MG CAPSULE
87	$15,546.36	GEODON 60 MG CAPSULE
164	$16,334.95	RISPERDAL 0.25 MG TABLET
65	$16,966.66	RISPERDAL 4 MG TABLET
96	$19,067.69	RISPERDAL 3 MG TABLET
107	$21,179.02	ZYPREXA 5 MG TABLET
31	$25,244.98	ZYPREXA 20 MG TABLET
179	$26,788.75	GEODON 40 MG CAPSULE
57	$29,624.73	ZYPREXA 15 MG TABLET
111	$31,908.11	ZYPREXA 10 MG TABLET
163	$33,695.28	GEODON 80 MG CAPSULE
287	$34,081.83	SEROQUEL 50 MG TABLET
448	$35,947.57	SEROQUEL 25 MG TABLET
171	$41,625.24	SEROQUEL 300 MG TABLET
140	$42,971.22	ABILIFY 30 MG TABLET
214	$43,382.61	RISPERDAL 2 MG TABLET
485	$55,080.18	RISPERDAL 0.5 MG TABLET
271	$57,592.47	SEROQUEL 200 MG TABLET
260	$58,786.02	ABILIFY 15 MG TABLET
537	$61,437.82	SEROQUEL 100 MG TABLET
184	$69,927.33	ABILIFY 20 MG TABLET
590	$82,297.89	RISPERDAL 1 MG TABLET
392	$95,407.63	ABILIFY 5 MG TABLET
490	$121,888.20	ABILIFY 10 MG TABLET
6175	$1,108,089.14	721 recipients

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 21-49

Rx Num	Total Reimb Amt	Label Name
5	$694.20	RISPERDAL 1 MG M-TAB
2	$717.56	ABILIFY 2 MG TABLET
6	$1,258.92	RISPERDAL 2 MG M-TAB
9	$2,244.37	SYMBYAX 6-25 MG CAPSULE
40	$2,271.84	CLOZAPINE 50 MG TABLET
11	$3,710.88	CLOZARIL 100 MG TABLET
144	$3,811.20	CLOZAPINE 25 MG TABLET
14	$4,637.00	INVEGA 3 MG ER TABLET
23	$4,839.57	ZYPREXA ZYDIS 5 MG TABLET
12	$4,881.25	SYMBYAX 12-25 MG CAPSULE
16	$6,471.30	SYMBYAX 12-50 MG CAPSULE
25	$8,120.32	INVEGA 6 MG ER TABLET
68	$8,943.08	RISPERDAL 0.25 MG TABLET
32	$10,651.55	RISPERDAL CONSTA 25 MG SYR
24	$11,414.70	INVEGA 9 MG ER TABLET
69	$11,886.12	ZYPREXA 2.5 MG TABLET
50	$13,541.41	ZYPREXA 7.5 MG TABLET
35	$13,804.69	RISPERDAL 1 MG/ML SOLUTION
92	$20,868.80	GEODON 20 MG CAPSULE
36	$21,079.95	RISPERDAL CONSTA 37.5 MG SYR
39	$21,400.34	ZYPREXA ZYDIS 15 MG TAB
54	$23,226.35	ZYPREXA ZYDIS 10 MG TABLET
36	$24,483.08	ZYPREXA ZYDIS 20 MG TAB
195	$25,412.76	RISPERDAL 0.5 MG TABLET
85	$27,747.16	ABILIFY 5 MG TABLET

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 21-49

Rx Num	Total Reimb Amt	Label Name
77	$27,889.45	SEROQUEL 400 MG TABLET
156	$33,121.37	ZYPREXA 5 MG TABLET
104	$33,557.80	ABILIFY 15 MG TABLET
52	$35,038.48	RISPERDAL CONSTA 50 MG SYR
262	$36,380.71	SEROQUEL 50 MG TABLET
139	$36,569.91	GEODON 60 MG CAPSULE
292	$39,263.49	CLOZAPINE 100 MG TABLET
441	$41,610.57	SEROQUEL 25 MG TABLET
96	$45,256.79	ABILIFY 30 MG TABLET
237	$48,683.50	GEODON 40 MG CAPSULE
316	$52,848.49	RISPERDAL 1 MG TABLET
165	$54,389.50	ABILIFY 10 MG TABLET
210	$57,797.47	RISPERDAL 3 MG TABLET
165	$58,534.46	RISPERDAL 4 MG TABLET
183	$63,646.51	ZYPREXA 10 MG TABLET
143	$67,689.66	ABILIFY 20 MG TABLET
307	$76,530.15	RISPERDAL 2 MG TABLET
667	$93,160.96	SEROQUEL 100 MG TABLET
174	$96,160.22	ZYPREXA 15 MG TABLET
471	$145,695.03	GEODON 80 MG CAPSULE
197	$154,635.09	ZYPREXA 20 MG TABLET
526	$178,454.91	SEROQUEL 200 MG TABLET
432	$222,188.38	SEROQUEL 300 MG TABLET
6934	$1,977,221.30	773 Recipients

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 50-64

Rx Num	Total Reimb Amt	Label Name
1	$27.96	ZYPREXA 10 MG VIAL
1	$114.85	GEODON 20 MG VIAL
2	$170.59	SYMBYAX 12-25 MG CAPSULE
2	$257.32	ZYPREXA ZYDIS 5 MG TABLET
1	$265.19	SYMBYAX 6-25 MG CAPSULE
1	$331.00	INVEGA 3 MG ER TABLET
12	$695.37	CLOZAPINE 50 MG TABLET
3	$993.00	INVEGA 6 MG ER TABLET
2	$1,020.92	ZYPREXA ZYDIS 20 MG TAB
4	$1,287.21	ZYPREXA ZYDIS 10 MG TABLET
10	$1,665.99	GEODON 20 MG CAPSULE
19	$2,146.75	RISPERDAL 0.25 MG TABLET
6	$2,471.50	ABILIFY 30 MG TABLET
10	$2,704.62	SYMBYAX 6-50 MG CAPSULE
12	$3,191.37	ZYPREXA 7.5 MG TABLET
103	$4,322.30	CLOZAPINE 25 MG TABLET
11	$7,522.80	CLOZARIL 100 MG TABLET
21	$9,592.54	RISPERDAL CONSTA 25 MG SYR
27	$9,653.34	ABILIFY 15 MG TABLET
18	$10,041.62	RISPERDAL CONSTA 50 MG SYR
94	$10,087.39	RISPERDAL 0.5 MG TABLET
31	$10,775.19	ABILIFY 5 MG TABLET
24	$12,018.07	ABILIFY 20 MG TABLET
94	$12,469.90	SEROQUEL 50 MG TABLET
39	$12,661.57	ABILIFY 10 MG TABLET

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 50-64

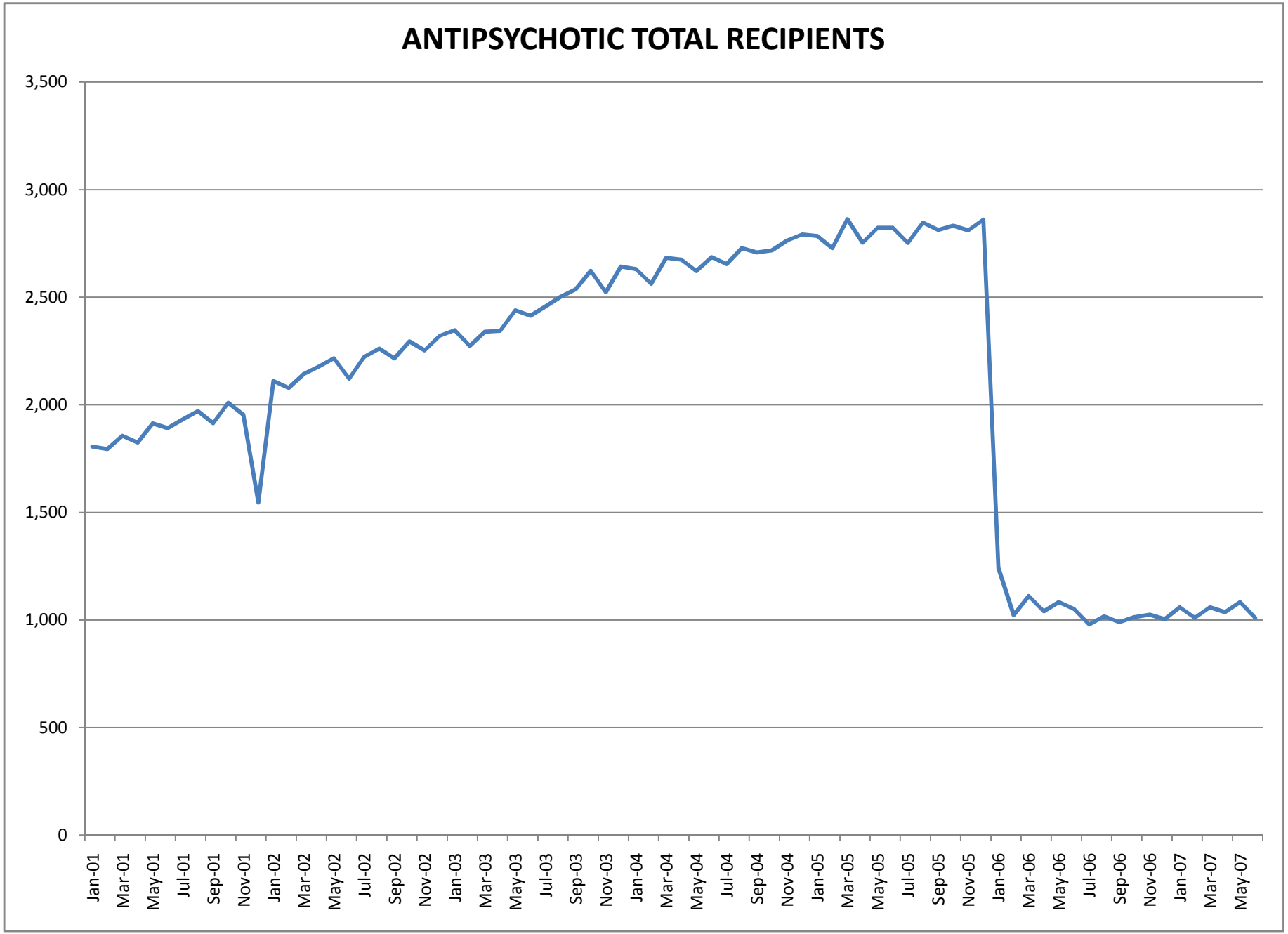
Rx Num	Total Reimb Amt	Label Name
71	$12,850.02	ZYPREXA 2.5 MG TABLET
65	$14,977.86	GEODON 40 MG CAPSULE
133	$16,069.21	SEROQUEL 25 MG TABLET
37	$19,128.22	RISPERDAL CONSTA 37.5 MG SYR
99	$19,932.10	ZYPREXA 5 MG TABLET
77	$21,690.30	GEODON 60 MG CAPSULE
191	$24,742.11	SEROQUEL 100 MG TABLET
31	$25,677.47	SEROQUEL 400 MG TABLET
208	$27,669.94	RISPERDAL 1 MG TABLET
104	$30,935.78	RISPERDAL 3 MG TABLET
115	$32,728.65	GEODON 80 MG CAPSULE
199	$44,416.32	RISPERDAL 2 MG TABLET
405	$48,309.47	CLOZAPINE 100 MG TABLET
67	$50,581.32	ZYPREXA 15 MG TABLET
131	$51,762.13	SEROQUEL 300 MG TABLET
200	$73,903.80	ZYPREXA 10 MG TABLET
156	$74,001.16	RISPERDAL 4 MG TABLET
210	$80,277.50	SEROQUEL 200 MG TABLET
137	$103,488.89	ZYPREXA 20 MG TABLET
3184	$889,630.61	273 Recipients

HEALTH INFORMATION DESIGNS

NDC USAGE for Antipsychotics 07/01/06 to 06/30/07

Claims Type: Medicaid ages 65+

Rx Num	Total Reimb Amt	Label Name
11	$167.96	SEROQUEL 25 MG TABLET
2	$298.50	GEODON 40 MG CAPSULE
5	$428.12	RISPERDAL 0.25 MG TABLET
12	$436.80	CLOZAPINE 25 MG TABLET
6	$484.91	RISPERDAL 0.5 MG TABLET
2	$757.46	RISPERDAL 2 MG TABLET
7	$837.73	RISPERDAL 1 MG TABLET
12	$1,024.80	CLOZAPINE 100 MG TABLET
6	$1,295.92	GEODON 60 MG CAPSULE
8	$1,344.48	GEODON 80 MG CAPSULE
5	$1,419.67	RISPERDAL 4 MG TABLET
4	$1,480.08	ABILIFY 10 MG TABLET
10	$1,728.87	ZYPREXA 2.5 MG TABLET
8	$1,761.11	RISPERDAL 3 MG TABLET
6	$1,843.06	RISPERDAL CONSTA 25 MG SYR
11	$2,336.55	SEROQUEL 200 MG TABLET
12	$2,842.18	SEROQUEL 300 MG TABLET
21	$4,841.85	SEROQUEL 50 MG TABLET
34	$5,353.97	SEROQUEL 100 MG TABLET
7	$9,262.75	ZYPREXA 20 MG TABLET
200	$41,270.34	24 Recipients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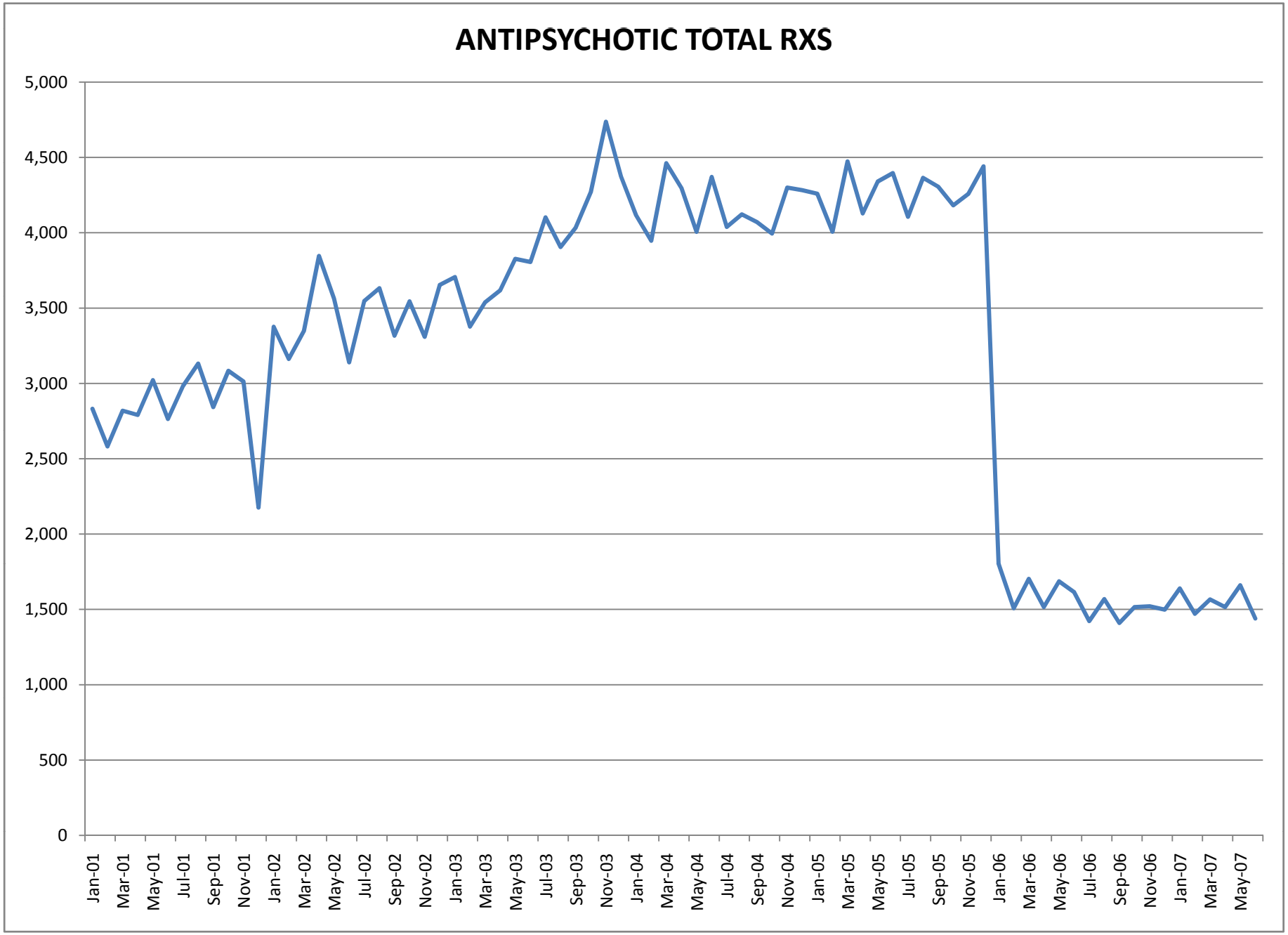
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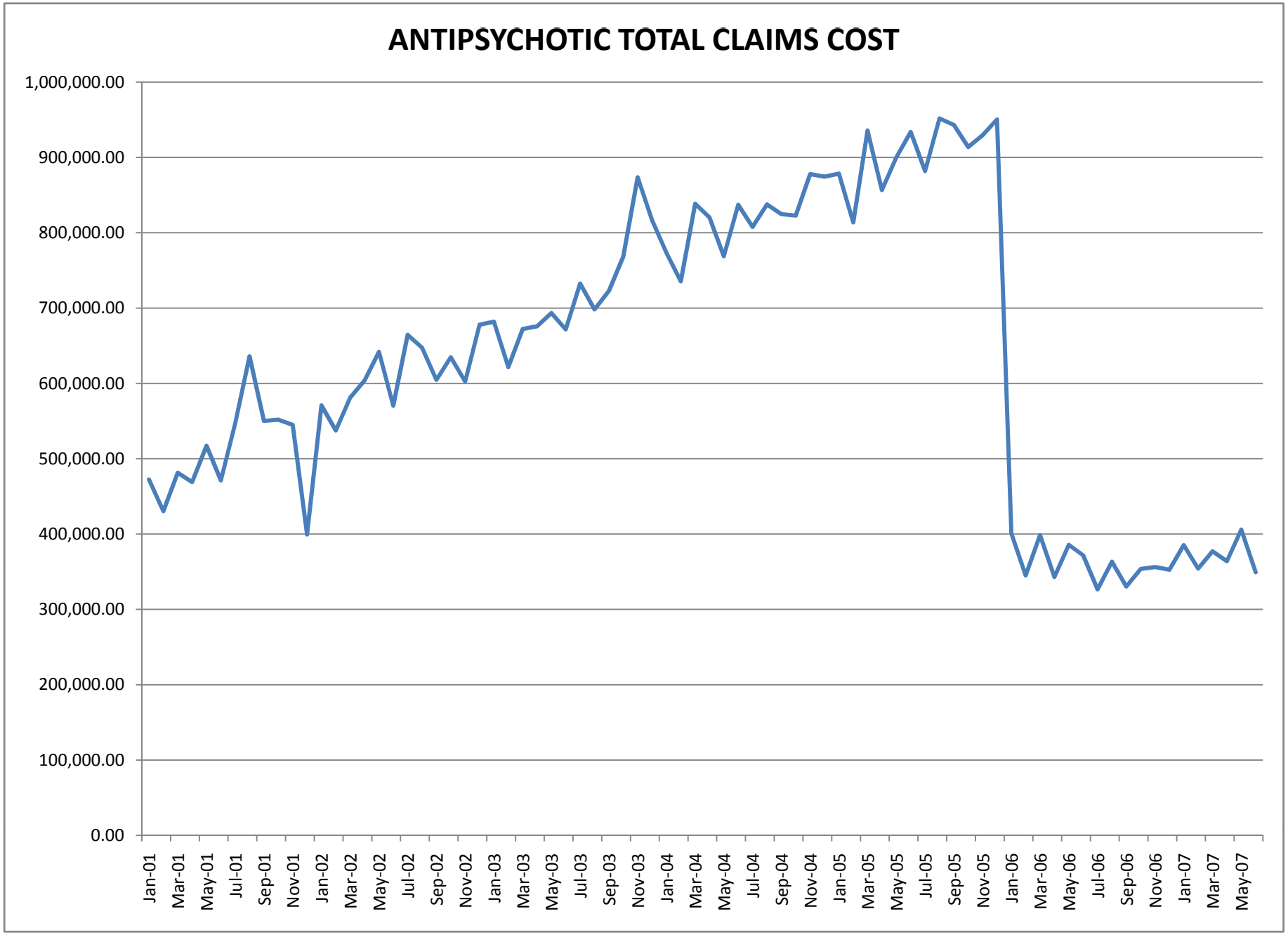
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Jul-06
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North Dakota Medicaid
02/01/07 - 07/31/07
Geodon

Scan for patients receiving low dose antipsychotics at least twice during a 6 month period of time who are not taking any other antipsychotics.

Timeframe of 6 months

Low dose antipsychotics will make up at least 2 scripts during the 6 month period of time

Low dose antipsychotics are Abilify 2mg, Zyprexa 2.5mg, Risperdal 0.25mg, Geodon 20mg, and Seroquel 25mg

Quantities should be 34 or less

6 recipients

Number Of Geodon Low Dose Scripts	Age	Specialty
6	17	N/A
6	16	Psychiatrist
6	13	Psychiatrist
6	10	FNP
5	17	N/A
6	18	Psychiatrist

North Dakota Medicaid
02/01/07 - 07/31/07
Risperdal

Scan for patients receiving low dose antipsychotics at least twice during a 6 month period of time who are not taking any other antipsychotics.

Timeframe of 6 months

Low dose antipsychotics will make up at least 2 scripts during the 6 month period of time

Low dose antipsychotics are Abilify 2mg, Zyprexa 2.5mg, Risperdal 0.25mg, Geodon 20mg, and Seroquel 25mg

Quantities should be 34 or less

8 recipients

Number Of Risperdal Low Dose Scripts	Age	Specialty
6	41	Psychiatrist
6	17	Psychiatrist
2	14	N/A
4	75	Psychiatrist
2	5	Psychiatrist
3	6	Pediatrics
2	21	Family Practice
2	7	Psychiatrist

North Dakota Medicaid
02/01/07 - 07/31/07
Seroquel

Scan for patients receiving low dose antipsychotics at least twice during a 6 month period of time who are not taking any other antipsychotics.

Timeframe of 6 months

Low dose antipsychotics will make up at least 2 scripts during the 6 month period of time

Low dose antipsychotics are Abilify 2mg, Zyprexa 2.5mg, Risperdal 0.25mg, Geodon 20mg, and Seroquel 25mg

Quantities should be 34 or less

36 Recipients

Number Of Seroquel Low Dose Scripts	Age	Specialty
3	42	Psychiatrist
4	52	Psychiatrist
2	42	Family Practice
8	40	N/A
2	21	Psychiatrist
5	24	Psychiatrist
3	20	N/A
6	41	Psychiatrist
6	19	Family Practice
2	36	Family Practice
2	18	N/A
4	18	Psychiatrist
4	17	Psychiatrist
4	17	Psychiatrist
2	18	Psychiatrist
3	13	Psychiatrist
4	48	N/A
4	12	Psychiatrist
5	15	Pediatrics
3	9	Psychiatrist
6	9	Psychiatrist
3	8	Psychiatrist
3	15	Psychiatrist
2	15	Psychiatrist
2	13	Psychiatrist
6	49	Psychiatrist
4	5	Psychiatrist
2	22	Family Practice
2	99	Family Practice
2	5	Psychiatrist
5	17	Psychiatrist
2	26	Psychiatrist
6	17	Psychiatrist
4	14	Psychiatrist

Number Of Seroquel Low Dose Scripts	Age	Specialty
2	21	Family Practice
2	56	Family Practice

North Dakota Medicaid
02/01/07 - 07/31/07
Zyprexa

Scan for patients receiving low dose antipsychotics at least twice during a 6 month period of time who are not taking any other antipsychotics.

Timeframe of 6 months

Low dose antipsychotics will make up at least 2 scripts during the 6 month period of time

Low dose antipsychotics are Abilify 2mg, Zyprexa 2.5mg, Risperdal 0.25mg, Geodon 20mg, and Seroquel 25mg

Quantities should be 34 or less

3 recipients

Number Of Zyprexa Low Dose Scripts	Age	Specialty
3	53	Psychiatrist
5	63	Psychiatrist
5	10	FNP