



Clinical Review: Atypical Antipsychotics and Adverse Metabolic Effects

Learning Objectives:

- Review the risk of adverse metabolic effects with the use of atypical antipsychotics.
- List monitoring parameters recommended in consensus guidelines for patients starting and continuing on atypical antipsychotics.
- Describe strategies to reduce the risk of adverse metabolic effects among patients who use atypical antipsychotics.

Key Points:

- Atypical antipsychotics have been associated with potentially serious adverse metabolic effects, including weight gain, hyperlipidemia, and glucose intolerance.
- Antipsychotic medications should be prescribed for a specific clinical indication only when the scientific evidence supports the likelihood that benefits will exceed harms.
- In general, the use of antipsychotic medication for United States Food and Drug Administration (FDA)-approved indications implies more certainty that benefits will exceed risks when compared with off-label use.
- Modifiable risk factors for cardiovascular disease are common in patients with major mental illness and should be addressed even in the absence of metabolic changes.
- Consensus guidelines for screening and monitoring of adverse metabolic effects should be used to guide patient management.

Background

Antipsychotic medications are an important component in the medical management of a variety of psychiatric disorders and severe behavioral disturbances. Since the introduction of atypical antipsychotics, or second-generation antipsychotics, the use of these medications has soared for both on-label and off-label uses. Although the atypical antipsychotics have many notable benefits compared with their earlier counterparts, their use has been associated with potentially serious adverse metabolic effects, including weight gain, hyperlipidemia, and glucose intolerance.¹⁻⁶ Studies suggest these antipsychotic-induced metabolic side effects can increase both the 10-year risk of cardiovascular disease and mortality from cardiovascular disease.^{7,8}

As seen in Table 1, there is variation among atypical antipsychotic medications in both the FDA-approved indications for adults and the propensity of these medications to induce adverse metabolic effects.⁹⁻¹² The Agency for Health Research and Quality (AHRQ) states that, with few exceptions, there is insufficient evidence to support the efficacy of off-label uses of atypical antipsychotic medications, especially in light of the potential adverse effects.⁹

Table 1. Comparison of Atypical Antipsychotics⁹⁻¹²

	FDA-Approved Indications for Adults	Adverse Metabolic Effects		
		Weight gain	Risk for diabetes	Dyslipidemia
aripiprazole*	A,D,I,M,S,T	Low to none	None	None
asenapine*	M,S	Low to none	Low to none	Low to none
brexpiprazole	D,S	(Newer drugs with limited long-term data)		
cariprazine	M,S			
clozapine*	S,SA,SU	High	High	High
iloperidone*	S	Moderate	Low	Low
lurasidone*	M,S	Low	Low	Low to none
olanzapine*	D,M,S	High	High	High
paliperidone	S,SA	Low	Low	None
quetiapine*	D,M,S	Moderate	Moderate	Moderate
risperidone*	I,M,S	Moderate	Moderate	Low
ziprasidone*	A,B,M,S,T	Low to none	None	None

* As of the date of publication of this article, these drugs appear on the Medi-Cal List of Contract Drugs, although some medications have restrictions on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available on the [Formulary File](#) Web page of the DHCS website.

Key

A	Agitation associated with schizophrenia or bipolar mania
B	Severe behavioral disturbances associated with dementia
D	Adjunctive therapy to antidepressants for the treatment of Major Depressive Disorder
I	Irritability associated with Autistic Disorder
M	Acute treatment of manic and mixed episodes associated with Bipolar I
S	Schizophrenia
SA	Schizoaffective disorder
SU	Suicidal behavior in schizophrenia or schizoaffective disorder
T	Treatment of Tourette's disorder

Modifiable risk factors for cardiovascular disease such as smoking, obesity, unhealthy diet, and lack of physical activity are common in patients with major mental illness.¹² Even in the absence of therapy with atypical antipsychotics, cardiovascular disease is the single largest cause of death in patients with schizophrenia. Therefore, modifiable risk factors should be addressed even in the absence of adverse metabolic effects due to atypical antipsychotics. As needed, providers should address smoking cessation, exercise, and weight management with patients. Behavioral weight loss interventions have been shown to decrease the amount of weight gained when atypical antipsychotic therapy is initiated and may be associated with weight loss in patients receiving continued therapy with antipsychotics.¹³

Finally, given the serious health risks, patients taking atypical antipsychotics should receive appropriate baseline screening and ongoing monitoring.¹⁻¹¹ Baseline monitoring is recommended at the start of a new medication and when there is a switch in medication. A recommended monitoring protocol is shown in Table 2, although more frequent assessments may be warranted based on clinical status to mitigate the likelihood of developing cardiovascular disease, diabetes, or other metabolic complications.¹¹

Table 2. American Diabetes Association and American Psychiatric Association Consensus Guidelines for Baseline Assessment and Monitoring of Patients on Atypical Antipsychotics¹¹

	Baseline	4 weeks	8 weeks	12 weeks	Annually
Personal and family history	X				X
Weight (BMI)	X	X	X	X	
Waist circumference	X				X
Blood pressure	X			X	X
Fasting plasma glucose	X			X	X
Fasting lipid profile	X			X	

Atypical Antipsychotic Use in the Medi-Cal Fee-for-Service Population

A retrospective cohort study was conducted to assess the use of atypical antipsychotics, potential adverse metabolic effects, and rates of metabolic monitoring in the Medi-Cal fee-for-service population using pharmacy and medical claims data. The initial study population included all continuously-eligible Medi-Cal fee-for-service beneficiaries between 18 and 64 years of age with at least one paid claim for an atypical antipsychotic medication during every four-month period between November 1, 2013, and February 29, 2016. These parameters were established to ensure the study population consisted of beneficiaries with at least two years of continuous atypical antipsychotic use.

Beneficiaries were excluded from the study population if they were not on the same atypical antipsychotic for at least 180 days during the measurement year (between March 1, 2015, and February 29, 2016). Beneficiaries were classified as being on two or more atypical antipsychotics if there was an overlap of two or more atypical antipsychotic medications for greater than 90 consecutive days during the measurement year. Medical claims were reviewed for any documented FDA-approved indication for each atypical antipsychotic.

In order to determine the prevalence of any co-morbid metabolic medical conditions, medical claims data between November 1, 2013, and February 29, 2016, were reviewed for the following ICD-9-CM codes:

- Overweight/obesity/weight gain (278.00, 278.01, 278.02, 783.1, V85.30 – V85.39, or V85.41 – V85.45)
- Diabetes (250, 357.2, 362.0, 366.41 or 648.0)
- Dyslipidemia (272.0 or 272.4)
- Hypertension (401)
- Other cardiovascular disease, including acute myocardial infarction, congestive heart failure, stroke, angina, and/or transient ischemic attack (410, 414.8, 412, 411.1, 428, 434.91, 434.11, 434.01, 413.9, 435.1, 435.9, 437.1 or 414.9)

In addition, paid pharmacy claims between March 1, 2015, and February 29, 2016, (the measurement year) were reviewed for the study population to determine the prevalence of concomitant use of statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB) drugs, and metformin. Concomitant use was defined as ≥ 2 paid claims during the measurement year.

Metabolic monitoring rates were calculated by reviewing medical claims data from the same timeframe as the initial inclusion criteria (November 1, 2013, through February 29, 2016). This expanded timeframe was used to capture any metabolic monitoring within at least a two-year period (two months were added on either end of the 2014 – 2015 calendar years to allow an additional window). The following CPT codes were used to determine metabolic monitoring:

- LDL-C or cholesterol: 80061, 82465, 83700, 83701, 83704, 83718, 83721 or 84478
- Glucose or hemoglobin A1c (HbA1c): 80047, 80048, 80050, 80053, 80069, 82947, 82950, 82951, 83036 or 83037

Results

A total of 6,561 Medi-Cal fee-for-service beneficiaries met the inclusion/exclusion criteria. Demographic and clinical characteristics of the beneficiaries are listed in Table 3, stratified by whether or not beneficiaries had an FDA-approved indication for an atypical antipsychotic documented in their medical claims data.

Table 3. Demographic and Clinical Characteristics of the Medi-Cal Fee-for-Service Study Population

	FDA-Approved Indication	
	Documented in medical claims n (%)	Not documented in medical claims n (%)
Overall Population (n = 6,561)	4,237 (65%)	2,324 (35%)
Gender		
• Male (n = 3,476; 53%)	2,252 (65%)	1,224 (35%)
• Female (n = 3,085; 47%)	1,985 (64%)	1,100 (36%)
Race/Ethnicity		
• White/Caucasian, non-Hispanic (n = 3,195; 49%)	2,082 (65%)	1,113 (35%)
• All other races/ethnicities (n = 3,366; 51%)	2,155 (64%)	1,211 (36%)
Age		
• 18 – 39 years (n = 2,358; 36%)	1,405 (60%)	953 (40%)
• 40 – 64 years (n = 4,203; 64%)	2,832 (67%)	1,371 (33%)
Atypical Antipsychotic		
• Aripiprazole (n = 923; 14%)	539 (58%)	384 (42%)
• Asenapine (n = 27; <1%)	*	*
• Clozapine (n = 199; 3%)	173 (87%)	26 (13%)
• Iloperidone (n = 30; <1%)	*	*
• Lurasidone (n = 159; 2%)	99 (62%)	60 (38%)
• Olanzapine (n = 951; 15%)	628 (66%)	323 (34%)
• Paliperidone (n = 126; 2%)	91 (72%)	35 (28%)
• Quetiapine (n = 1,262; 19%)	769 (61%)	493 (39%)
• Risperidone (n = 1,283; 20%)	694 (54%)	589 (46%)
• Ziprasidone (n = 243; 4%)	144 (59%)	99 (41%)
• Two or more concurrently for ≥90 days (n = 1,358; 21%)	1,059 (78%)	299 (22%)

* Data are not stratified due to the small number of beneficiaries in the study population taking these drugs.

Approximately one-third of beneficiaries in the study population did not have an FDA-approved indication documented in their medical claims. Higher rates of FDA-approved indications were seen among those beneficiaries taking clozapine (87%) or two or more atypical antipsychotics concurrently (78%).

A summary of the prevalence of metabolic-related comorbidities and medications is provided in Table 4, stratified by whether the beneficiary had paid claims for one atypical antipsychotic medication or multiple concurrent atypical antipsychotic medications during the measurement year.

Table 4. Use of Atypical Antipsychotics in the Medi-Cal Fee-for-Service Study Population

	Atypical antipsychotic monotherapy n (%)	Multiple concurrent atypical antipsychotics n (%)
Overall population (n = 6,561)	5,203 (79%)	1,358 (21%)
Prevalence of any of the following co-morbid medical conditions:		
• Overweight/obesity/weight gain (n = 1,265; 19%)	949 (18%)	315 (23%)
• Diabetes (n = 1,893; 29%)	1,522 (29%)	371 (27%)
• Dyslipidemia (n = 2,374; 36%)	1,852 (36%)	519 (38%)
• Hypertension (n = 2,759; 42%)	2,163 (42%)	596 (44%)
• Other cardiovascular disease (n = 739; 11%)	612 (12%)	127 (9%)
Prevalence of any concomitant use of:		
• Statins (n = 975; 15%)	781 (15%)	194 (14%)
• ACE inhibitors/ARBs (n = 725; 11%)	580 (11%)	145 (11%)
• Metformin (n = 527; 8%)	412 (8%)	115 (9%)

The majority of beneficiaries (67%) had at least one co-morbid metabolic condition, with the most common comorbidity being hypertension (42%). A total of 1,358 beneficiaries (21%) were taking two or more atypical antipsychotics concurrently. When compared to beneficiaries on monotherapy with an atypical antipsychotic, those taking more than one concurrent atypical antipsychotic medication had a higher prevalence of being overweight, obese, or having abnormal weight gain (23% vs. 18%). Use of concomitant statins, ACE inhibitors/ARBs and metformin were no different among those beneficiaries taking more than one atypical antipsychotic medication.

Metabolic monitoring rates for the study population are shown in Table 5. Overall rates are shown as well as rates for beneficiaries with documented co-morbid conditions and/or concomitant medications due to clinical guidelines recommending more frequent assessment when there is a known comorbidity or increased risk of a potential adverse metabolic event.

Table 5. Metabolic Monitoring Rates in the Medi-Cal Fee-for-Service Study Population

	Metabolic Monitoring Rates		
	LDL-C/ cholesterol n (%)	Glucose/ HbA1c n (%)	Both tests n (%)
Overall population (n = 6,561)	4,534 (69%)	5,524 (84%)	4,507 (69%)
Prevalence of any of the following co-morbid medical conditions:			
• Overweight/obesity/weight gain (n = 1,265)	1,058 (84%)	1,197 (95%)	1,054 (83%)
• Diabetes (n = 1,893)	1,613 (85%)	1,836 (97%)	1,613 (85%)
• Dyslipidemia (n = 2,374)	2,171 (91%)	2,295 (97%)	2,157 (91%)
• Hypertension (n = 2,759)	2,266 (82%)	2,639 (96%)	2,260 (82%)
• Other cardiovascular disease (n = 739)	607 (82%)	727 (98%)	605 (82%)
Prevalence of any concomitant use of:			
• Statins (n = 975)	897 (92%)	930 (95%)	893 (92%)
• ACE inhibitors/ARBs (n = 725)	623 (86%)	655 (90%)	619 (85%)
• Metformin (n = 527)	447 (85%)	483 (92%)	446 (85%)

A total of 4,507 beneficiaries (69%) had both monitoring tests (blood glucose or HbA1c and LDL-C or cholesterol) completed within the past two years. The rates were much higher for blood glucose or HbA1c (84%) when compared to LDL-C or cholesterol (69%). Importantly, monitoring rates were greater among those beneficiaries with a co-morbid metabolic condition and among those taking concomitant statins, ACE inhibitors/ARBs and/or metformin.

Conclusion/Discussion

Adverse metabolic effects remain a concern among patients who take atypical antipsychotic medication. Although it is difficult to determine causality using claims data, the high prevalence of co-morbid metabolic conditions among the study population highlights the importance of following recommended assessment and monitoring schedules in order to help mitigate risks to patients.

Clinical Recommendations

- Prescribe atypical antipsychotics for FDA-approved indications.
- Address modifiable risk factors (smoking, obesity, lack of physical activity, unhealthy diet) in patients with mental illness even in the absence of metabolic changes.
 - Active tobacco users should be encouraged to quit at every patient encounter, as multiple attempts are often required to treat tobacco dependence.
 - ❖ Recommend both counseling and medication to patients for best results unless contraindicated or not indicated, such as with light smokers (individuals smoking less than 10 cigarettes daily).
 - ❖ A medication regimen that includes combination nicotine replacement therapy (NRT) (nicotine patch once daily plus short-acting NRT as needed) has been shown to be more effective at improving smoking cessation rates than NRT monotherapy.
 - As needed, suggest caloric restriction, increased exercise, a food intake diary (for weight gain >10 lbs), consultation with a nutritionist, group exercise/diet programs, and evaluate weight at 1 – 4 week intervals.
- Follow ADA and APA consensus guidelines for baseline assessment and monitoring, including measuring waist circumference three and six months after starting treatment and annually thereafter.

- For patients with a worsening metabolic profile, especially weight gain, consider switching from an agent with a high risk of metabolic side effects to an agent with low risk.
- Primary care and mental health providers should communicate frequently for early detection of adverse metabolic effects and to minimize duplicate laboratory monitoring/workup.

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