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Drug Use Evaluation: Low-Dose Quetiapine (Seroquel®,Seroquel XR®)

Quetiapine is a dibenzothiazepine antipsychotic agent that is FDA-approved in adults for Schizophrenia, Bipolar disorder, Bipolar Mania, Bipolar I Disorder maintenance adjunct therapy, and Bipolar Depression. Additionally, Seroquel XR® is also FDA-approved in adults for Major Depressive Disorder, as adjunctive therapy with antidepressants. Table 1 lists FDA approved doses for adults. Seroquel® is only FDA-approved in adolescents 13-17 years of age for Schizophrenia and in children 10-17 years of age for Bipolar Mania. Table 2 lists FDA approved doses for children and adolescents. Clinical studies indicate that the antipsychotic effect of quetiapine usually occurs in the range of 600-800 mg/day. An exception is use in the elderly (65 years of age or older) or debilitated patients where lower doses (25-50 mg/day) are recommended due to decreased drug clearance. FDA labeling specifically outlines a titration schedule with initial doses generally starting at 25 mg twice a day for Seroquel® and 50 to 300 mg once daily for Seroquel XR® titrated up over the range of course of up to 5 days depending on the condition being treated.[1,2]

Table1 - FDA-approved adult indications and dosages for quetiapine[1,2]

FDA-Approved Indications and Dosages in Adults		
Indication	**Recommended Dose / Dose Range**	**Maximum Recommended Daily Dose**
Schizophrenia	**150-800 mg/day**	**800 mg**
Bipolar Mania	**400– 800 mg/day**	
Bipolar I Disorder Maintenance Therapy as Adjunct Therapy	**400-800 mg/day**	
Bipolar Depression-*Adults*	**300 mg/day**	**300 mg**
Major Depressive Disorder, Adjunctive Therapy with Antidepressants for Seroquel XR only	**150-300 mg/day**	

Table 2 - FDA-approved pediatric indications and dosages for quetiapine[1]

FDA-Approved Indications and Dosages in Children and/or Adolescents		
Indication	**Recommended Dose / Dose Range**	**Maximum Recommended Daily Dose**
Schizophrenia – Adolescents (13-17 years)	**400-800 mg/day**	**800 mg**
Bipolar Mania – Children and Adolescents (10 to 17 years), Monotherapy	**400-600 mg/day**	**600 mg**

Recently a growing national trend has emerged with increased use of quetiapine at doses well below FDA recommended dosage ranges.[3] Anectdotal reports from OSU-DURM academic detailing sessions indicate that some clinicians are turning to quetiapine to avoid sedative quantity limits and prior authorization requirements from Medicaid managed care plans and the fee-for-service program. Quetiapine's sedative properties are thought to be due to antagonism at H1 and 5-HT2 receptors.[4, 5] Although use of quetiapine for insomnia in patients with comorbid psychiatric disorders has been documented in several journals, a 2005 NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in adults discusses off-label use of quetiapine noting that studies indicating usefulness are lacking and carry significant risks. It does not recommend quetiapine as treatment for chronic insomnia.[6-8]

Just last month, the federal government reached a $520 million dollar settlement with AstraZeneca for alleged promotion of off-label use of quetiapine to psychiatrists and other physicians for uses other than FDA approved indications.[5] During a recent press release, the Department of Justice reported that off-label uses promoted included Alzheimer's disease, anger management, anxiety, attention deficit hyperactivity disorder, bipolar maintenance, dementia, depression, mood disorder, post-traumatic stress disorder, and sleeplessness.[12]

During the Fourth Quarter of 2009 quetiapine ranked third on the list of top 40 brand name drugs utilized by OHP FFS clients. Not only is off-label use of this medication costly but also clearly not supported by the literature. An AHRQ comparative effectiveness review on off-label use of atypical antipsychotics encompassing over 100 systematic reviews concluded that off-label use of atypical antipsychotics, including quetiapine, carries unknown risks that are not clearly defined by the literature.[13]

Quetiapine is not an innocuous medication and use has been associated with QTc prolongation, hypotension and metabolic abnormalities such as weight gain (incidence 3-23%), serum cholesterol and triglyceride elevations (incidence 7-18% and 8-22%, respectively) along with glycemic abnormalities.[1,14-19] Weight gain and metabolic effects do not appear to be dose dependent and can occur at low doses.[20] These adverse effects are variable in occurrence and their prevalence is hard to predict due to individual risk factors.[19,24]

Additionally, there have been reports of quetiapine abuse, often referred to as "quell", "baby heroin", "Susie-Q" or "Q-ball when used with cocaine, in patients with a history of substance abuse and by inmates in correctional facilities. According to case reports, the rationale given by users for abuse was production of a calming effect or hallucinations. Abuse of quetiapine is a real concern, not only because of the risk of dangerous side effects but because those with psychiatric disorders often are afflicted with either a history of or co morbid substance abuse.[22,23]

DUE Questions:

1. What is the prevalence of use of low-dose quetiapine, defined as <150 mg for >60 days?
2. What is the distribution of FDA-approved and off-label insomnia indications of quetiapine in Oregon FFS Medicaid clients?
3. What are the demographic characteristics of clients using quetiapine at a dose <150 mg for >60 days and what are the safety implications for use?

Methods:

Analysis period:

Pharmacy claims analysis: 11/1/2008 – 10/31/2009

Diagnosis analysis: 11/1/2007-10/31/2009

Data: All paid fee-for service (FFS) pharmacy claims. Member months and medical data obtained from either FFS or Managed Care Database.

Inclusion Criteria:

1. All patients on quetiapine from 11/1/2008 - 10/31/2009
2. Clients with > 75% eligibility in same time period
3. Prescription claim(s) for <150mg per day for >60 days

Exclusion Criteria:

1. Claims with days supply ≤ 5

Results:

Table 3. Quetiapine Drug Use Summary per Patient

Average Claim Count	**11**
Average Total Days Supply	**300**
Average Daily Dose	**111**

Table 4 - Patient Demographics

	N=	%
Mean Age (range)	36 (4-89)	
≤9	57	3
10-18	354	18
19-64	1531	78
≥65	12	1
Gender		
F	1257	64
M	697	36

Table 5. Diagnosis distribution (not mutually exclusive)

Diagnosis	Patient Count	%	Comments
None of diagnoses queried	1090	56	Number of clients with no diagnosis available.
Bipolar Disorder (296.0, 296.4, 296.6-296.8, 296.89)	502	26	
Major Depressive Disorder (296.2, 296.24, 296.3, 296.23, 296.33, 296.34, 296.5, 296.53, 296.54)	247	13	Includes only clients concurrently on an antidepressant and quetiapine.
Insomnia (327.01, 327.02, 780.51, 780.52, 780.5, 780.50,780.59)	153	8	
Schizophrenia (295, 295.4, 295.44, 295.45, 295.6, 295.62, 295.64, 295.85, 295.95, 295.80-295.82,295.40-295.42, 295.90-295.92)	111	6	
Bipolar Mania (296.1, 296.3, 296.4, 296.43, 296.44)	48	2	
Senile Dementia (290.0,290.1 ,290.11, 290.12, 290.13, 290.2,290.20,290.21, 290.3,290.4, 290.41, 290.42 ,290.43, 290.8, 290.9)	14	1	
Bipolar Depression (296.5)	0	0	
Total	2165		

Discussion:

1. Demographics
    a. 12 (1%) of client's are ≥65 years of age are receiving quetiapine despite the FDA black box warning on increased risk of mortality when used in elderly patients with dementia-related psychosis. Use in this population is generally a concern.[1]
    b. 354(18%) of clients age 10 to 18 are receiving low-dose quetiapine despite the FDA black box warning of suicidal thinking and behavior in children, adolescents, young adults with Major Depressive Disorder, and other psychiatric disorders.[1]
    c. 57(3%) of clients on low-dose Seroquel were under the age of 10 where there is no FDA approved use, virtually no literature supporting use and despite the FDA black box warning of suicidal thinking and behavior in children, adolescents, young adults with Major Depressive Disorder, and other psychiatric disorders.[1, 24]
2. Insomnia was a recorded diagnosis for 153 (8%) of clients. Of the 2,251 patients found, 56% of clients did not have an FDA approved diagnosis available suggesting the potential for considerable off-label use.

Questions for the Board:

1. Is 60 days an appropriate length of time to account for dosage titration (upwards and downwards)?
2. Should quetiapine be approved for children under 10 years old for any indication?
3. Should quetiapine be approved for clients > 65 years old in light of the FDA's black box warning?

Recommendations:

1. Require prior authorization for quetiapine <150 mg/day for > 60 days. Deny for insomnia indications and for clients < 10 and > 65.
2. Begin RetroDur intervention for quetiapine <150mg/day to recommend alternative to quetiapine for insomnia.

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