

Low-Dose Quetiapine Usage in Older Adults

Michael S. Awadalla, PharmD
Director, Clinical Pharmacy Operations

In April 2005, the Food and Drug Administration (FDA) issued a public health advisory regarding the usage of atypical antipsychotic medications¹. A review of 17 placebo-controlled clinical trials that enrolled 5106 elderly patients showed there was an approximate 1.6 – 1.7 rate of increase in patient mortality. Based on these findings, a black box warning was required to alert clinicians that older adults with dementia-related psychosis treated with atypical antipsychotic medications have an increased mortality risk compared to those who took a placebo.

The precise mechanism of patient mortality is unknown. Patients may experience QT-interval prolongation that makes them more prone to arrhythmias and sudden cardiac death. Sedation and accelerated cognitive decline may increase the risk for aspiration syndromes and choking. Venous thromboembolism and other cerebrovascular events may occur. Also, patients may experience a fall leading to fractures and other consequences that may develop into a sequence of decline².

The Office of the Inspector General (OIG) of the Department of Health and Human Services (HHS) released a report in 2011 evaluating the high use of atypical antipsychotic medications in the nursing home setting for off-label indications³. This report found that 14% of nursing home residents had Medicare claims for atypical antipsychotics, of which half of the claims were not used for approved indications. These claims failed to comply with Federal nursing home quality and safety standards. These standards refer to the OBRA regulation provision that residents' drug therapy must be free from unnecessary medications and medications given in excessive

doses, in excessive duration, or without adequate monitoring and indications. The OIG report compelled the Centers for Medicare and Medicaid (CMS) to establish the National Partnership to Improve Dementia Care⁴, an initiative to ensure appropriate care and use of antipsychotic medications in the nursing home setting. Since the Partnership began, usage of antipsychotics had reduced in the nursing home setting. CMS has established a national goal to reduce use of antipsychotic medications by 25% in 2015 and 30% by 2016.

Quetiapine is an atypical antipsychotic that has several mechanisms of action for efficacy. It antagonizes serotonin (5-HT_{1A} & 5-HT₂), dopamine (D₁ & D₂), and histamine (H₁), as well as alpha₁ and alpha₂ receptors. It is metabolized by CYP 3A4 to norquetiapine, an active metabolite which has a higher affinity for muscarinic₁ receptors. The theory behind its efficacy as an antipsychotic is linked to D₂ and 5-HT₂ antagonism⁵.

Recently, an article by Blaszczyk and colleagues called into question some of the current practices used for treating behavioral and sleep problems with low doses of quetiapine ($\leq 25\text{mg/day}$). They examined studies of quetiapine doses and found that much higher doses were used for treating schizophrenia and agitation. Based on the pharmacokinetic profile, they concluded that at these low doses, quetiapine was only acting on alpha₁, H₁, and 5-HT₂. Due to the adverse effect profile, the authors have proposed consideration for the use of other psychotropic agents that act through similar mechanisms. Possible medication alternatives include trazodone, mirtazapine, and melatonin⁶.

A small study used positron emission tomography to study various doses of quetiapine from 150-600mg/day. This demonstrated that, at lower doses, dopamine is not being bound and that it is likely a different mechanism, such as histamine or serotonin binding, that leads to efficacy for acute agitation.

Table 1 (below) shows that appreciable occupancy of dopamine does not occur until dosing is closer to 600mg/day. Since this study examined only 12 patients, it was a starting point to support the notion that quetiapine only acts on dopamine at higher dosages, and it is difficult to make larger conclusions⁷.

A second dosing study provided further insight into the relationship between the dosing of quetiapine, its impact on dopamine receptors, and its therapeutic efficacy. The graph below demonstrates changes in the Brief Psychiatric Rating Scale (BPRS) at various

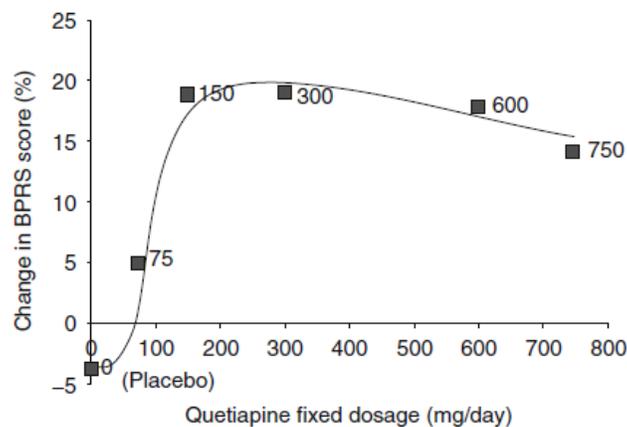
daily quetiapine dosages. The graph demonstrates a threshold-type relationship that is common with other antipsychotics. At doses of 150-750mg, a very similar change in BPRS score was seen.

At lower doses, such as 75mg/day, a much smaller effect was seen. The authors' analysis of dopamine occupancy showed a range of 2% at 150mg/day to 62% at 750mg/day. The theorized threshold for antipsychotic response is usually near 65%, but this information varies, and it is thought that quetiapine rapidly dissociates from dopamine receptors and may be difficult to measure accurately.

Dosage for optimal efficacy ranges from 150-800mg, which is aligned with FDA-approved recommended dosing of 150-750mg/day. Case reports have even used higher doses (>1000mg/day) for resistant patients⁸.

Table 1.

Daily Quetiapine Dosage (mg/day)	D ₂ Occupancy (%)
150mg	-2 ± 2
300mg	5 ± 7
450mg	14 ± 11
600mg	19 ± 1



A study by Schneider et al. looked at olanzapine, quetiapine, and risperidone compared to placebo for the treatment of psychosis and agitation in patients with Alzheimer's disease. This study used very low doses of quetiapine, with a mean dose of 56.5mg/day by the end of the 12-week study. The primary outcome looked at time to discontinuation of treatment due to lack of efficacy. The quetiapine and placebo had very similar time periods (9.1 and 9 weeks respectively). While quetiapine did demonstrate fewer adverse events, it was found to be inferior to olanzapine and risperidone⁹. Based on the FDA-recommended dosage and pharmacodynamic properties of quetiapine, it is not surprising to see that this low-dose quetiapine was ineffective.

A case report looked into the potential for low-dose quetiapine worsening episodes of hypomania. The patient received 6 weeks of quetiapine, with 25mg in the morning and 50mg at bedtime (75mg/day). The patient eventually experienced psychosis. It is theorized that the low quetiapine dose precipitated his worsening condition. For this patient with acute mania, the FDA-approved recommended dosage would have been 600mg/day.

At the doses of 25-50mg, the therapeutic effect was only via histamine and α_1 antagonism¹⁰.

Low-dose (25mg) and as-needed (PRN) quetiapine is not recommended for the treatment of acute mania. At these low doses of quetiapine (< 150mg/day), multiple studies have demonstrated that clinical improvement does not occur and surrogate markers of dopamine binding are not reached. Due to the substantial adverse effect profile that includes cardiovascular risk, sedation, and anticholinergic effects, quetiapine is not considered a benign medication to be used at subtherapeutic doses. It is likely that sedation is the only potential outcome when used at these low doses. Adverse effects can be minimized by initiating therapy at the lowest dose possible and beginning a slow titration. Additionally, an association between dosage and the risk of mortality or stroke is still uncertain¹¹.

Considering that the cost for 56 tablets (25mg BID x 28 days) is approximately more than \$200, there are more cost-effective agents with safer profiles that have sedative effects.

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