DRUG REVIEW

A Brief Review of Quetiapine

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Quetiapine is a commonly prescribed second-generation antipsychotic (SGA) that was initially developed for the treatment of schizophrenia and received Food and Drug Administration approval in 1997. Subsequent research led to approval for use in both bipolar depression and mania and in the adjuvant treatment of major depressive disorder.

PHARMACOLOGY

Quetiapine has dose-dependent clinical efficacy, inspiring Dr. Stephen Stahl (1, 2) to question whether it was a different drug at different doses. At low doses (50 mg per day), quetiapine has well-demonstrated hypnotic and sedative effects attributable to histamine 1-receptor blockade. With midrange doses (300 mg per day), mood effects are secondary to both dopaminergic (D2 receptor) and serotonergic (5HT2A receptor) blockade. With higher doses (800 mg per day), for the purposes of true antipsychotic activity, clinical effects are mediated through serotonergic, muscarinic, alpha adrenergic, and histaminergic receptor blockade (1, 2).

The metabolism of quetiapine is mediated by the cytochrome P450 system, and CYP 3A4 and CYP 2D6 are the predominant enzymes involved in drug transformation (1). With respect to the pharmacokinetic characteristics of quetiapine, the half-life of the parent compound is 7 hours, and the oral bioavailability of the drug in tablet form is nearly 100% of the bioavailability in oral solution. The time to peak plasma concentration is 1–2 hours for the immediate-release formulation. Plasma protein binding is 83%, and the volume of distribution of quetiapine is 10±4 L per kg (3).

Norquetiapine, the active metabolite of quetiapine, is thought to be responsible for the anxiolytic and antidepressant effects of quetiapine through inhibition of the norepinephrine transporter (NET) and serotonin receptor agonism (2). The sedative effects of quetiapine are sometimes diminished at higher doses, a phenomenon potentially attributable to the high affinity of norquetiapine for NET and resulting elevated synaptic norepinephrine levels.

CLINICAL EFFICACY

Schizophrenia

In one seminal study, researchers found quetiapine to be statistically superior to placebo and comparable to haloperidol in the treatment of the positive and negative symptoms of schizophrenia (4). In another large study, discontinuation rates due to treatment failure were lower with high-dose quetiapine than low-dose quetiapine and placebo (5). The high-dose regimen exhibited a statistically significant advantage over placebo as measured by the Brief Psychiatric Rating Scale and Clinical Global Impression severity scores. Importantly, as demonstrated by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, compared with first-generation antipsychotics and other SGAs, quetiapine was associated with the highest rate of hospitalization due to exacerbation of schizophrenia and the highest discontinuation rate due to lack of efficacy (6).

Bipolar Depression

The landmark Bipolar Depression (BOLDER) trial assessed the efficacy of quetiapine monotherapy in bipolar depression at doses of 300 mg and 600 mg, compared with placebo (7, 8). Significant improvements in Montgomery–Åsberg Depression Rating Scale (MADRS) scores were observed with both doses, but discontinuation because of adverse effects was higher in the 600-mg group. In an 8-week trial involving patients with bipolar depression, quetiapine was statistically superior to placebo, whereas no statistical difference was found between lithium and placebo (9). In the treatment of acute depression in patients with either bipolar I or II, quetiapine was significantly more effective than placebo in improving MADRS scores, whereas paroxetine monotherapy and placebo showed no significant difference (10). Furthermore, the use of quetiapine monotherapy for acute bipolar depression has been supported by meta-analysis (11).

Bipolar Mania

A 12-week randomized controlled trial (RCT) evaluating quetiapine at doses up to 800 mg showed the drug to have a statistically significant benefit over placebo with respect to improvement from baseline in scores on the Young Mania Rating Scale (YMRS) (12). A second double-blind RCT established both quetiapine (up to 800 mg) and lithium to be statistically superior to placebo for improving YMRS scores (13).

Major Depressive Disorder

A 2009 study compared adjuvant quetiapine to adjuvant placebo in patients with major depressive disorder who had shown inadequate response to antidepressant therapy and found that daily doses of either 150 mg or 300 mg produced statistically significant improvements in MADRS scores after as early as 1 week (14).

Insomnia

One double-blind RCT assessing quetiapine in patients with primary insomnia showed some benefit with low-dose therapy, but the results were inconclusive and not statistically significant (15). Further, quetiapine has not been

approved for use in insomnia, and prescribers should be cognizant of its cost, side-effect profile, and abuse potential.

Generalized Anxiety Disorder

A 2016 meta-analysis highlighted the effectiveness of low-dose quetiapine (50–150 mg/day) in the treatment of adult generalized anxiety disorder (16). Quetiapine administration resulted in response rates (severity of anxiety) and remission rates similar to those observed with administration of selective serotonin reuptake inhibitors, and some participants experienced improved sleep.

Borderline Personality Disorder

Emerging data has supported off-label use of quetiapine in borderline personality disorder (BPD). A 2014 randomized placebo-controlled trial found that 150 mg of quetiapine per day significantly decreased overall BPD symptom severity (as measured by the Zanarini Rating Scale for Borderline Personality Disorder), as well as irritability and verbal and physical aggression (17). These findings are consistent with other findings demonstrating improvements in impulsivity and aggression. Further investigation is necessary, and future studies should consider a longer duration of therapy, inclusion of those with comorbid psychopathology, and treatment arms that incorporate other psychotropic agents.

PREGNANCY

Data related to use of quetiapine in pregnancy are extremely limited, although clear evidence of teratogenic effects is lacking. Risks to the newborn associated with third-trimester antipsychotic use include abnormal muscle movements and withdrawal symptoms (1). However, uncontrolled psychiatric conditions may also be associated with fetal harm; thus, the decision to initiate or discontinue antipsychotic therapy in pregnant patients should be made on a case-by-case basis.

USE IN CHILD AND ADOLESCENT POPULATIONS

One randomized placebo-controlled trial showed statistically significant improvements in Positive and Negative Syndrome Scale scores in youths ages 13–17 who had a diagnosis of schizophrenia (18). Although some evidence suggests a role for quetiapine in the treatment of bipolar mania, data related to its use in bipolar depression are limited (11). Additionally, there is limited evidence for the use of quetiapine in children with autism.

ABUSE POTENTIAL

A less well-known consequence of quetiapine prescription is related to its potential for abuse. Quetiapine is the most abused drug among the SGAs and carries considerable street value (19). Street names for the drug include "Susie-Q," "baby heroin," and "quell," and the combination of quetiapine with either heroin or cocaine is referred to as a "Q-ball". Importantly, quetiapine can enhance the euphoric effects of recreational drugs, such as cocaine and heroin, but it can also be used to counter the effects of stimulants and mitigate withdrawal symptoms. Of note, quetiapine misuse is relevant in correctional settings, where clinicians may be more hesitant or unable to prescribe the medication, potentially leading to disruptions in care.

ADVERSE EFFECTS

Histamine 1-receptor blockade leads to sedative effects and is also believed to be responsible for dose-dependent weight gain. Dizziness, hypotension, and syncope result from blockade of the alpha 1-adrenergic receptor (1). Anticholinergic side effects, particularly at high doses, are a consequence of muscarinic cholinergic receptor blockade. Classic adverse effects include blurred vision, dry mouth, urinary retention, constipation, and paralytic ileus (1, 2). Temperature dysregulation is a dose-independent adverse effect hypothesized to result from D2 and 5HT2A receptor antagonism. Importantly, compared with first-generation antipsychotics, quetiapine, an SGA, exhibits more transient D2 receptor activity and is therefore associated with a decreased incidence of extrapyramidal symptoms (EPS). Nevertheless, EPS and tardive dyskinesia are risks of quetiapine therapy (2). Quetiapine also has the potential to produce neuroleptic malignant syndrome because of its dopamine receptor blockade, although this side effect is rare. Metabolic side effects include triglyceride elevation, insulin resistance, and hypothyroidism at midrange and higher doses. Secondary to insulin resistance, quetiapine is associated with an increased risk of type 2 diabetes.

Lethal overdose is rare when quetiapine is taken alone. Quetiapine-related toxicity is typically associated with central nervous system (CNS) depression, leading to slurred speech, sedation, and hypotension. Notably, quetiapine has a black box warning associated with death in older adults with dementia, and higher doses are believed to exacerbate this risk (1).

DRUG INTERACTIONS

Rifampin, carbamazepine, phenytoin, and phenobarbital all decrease quetiapine levels via CYP 3A4 enzymatic induction (1). Phenytoin has the potential to reduce quetiapine levels by up to five times. Conversely, ketoconazole and other medications of the same antifungal class are potent CYP 3A4 inhibitors, potentially leading to increased drug levels. Many antiviral medications used in the

KEY POINTS/CLINICAL PEARLS

- Quetiapine has hypnotic effects at low doses, mood effects at midrange doses, and antipsychotic effects at higher doses.
- Quetiapine is approved as a first-line therapy for bipolar mania and depression and as an adjuvant for major depressive disorder.
- There is limited evidence for quetiapine use in insomnia, and prescribers should be aware of its marked abuse potential.
- Quetiapine has a black box warning indicating an increased risk of death when used by older adults with dementia-related psychosis.

treatment of HIV, AIDS, and hepatitis C are also strong 3A4 inhibitors (20).

Quetiapine is a QT-prolonging medication, and concomitant use with amiodarone, sotalol, methadone, or fluoroquinolones comes with the risk of prolonged QT and Torsades de Pointes (20).

Medications used in the treatment of Parkinson's disease (such as levodopa, ropinirole, or pramipexole) will interact with quetiapine, and combined use with dopamine antagonists (such as metoclopramide) is associated with the development of EPS (1, 20).

Antihypertensive medications and alpha adrenergic blockers, such as tamsulosin, can enhance the hypotensive effects of quetiapine. Other synergistic interactions include those with anticholinergic medications (tricyclic antidepressants, cholinesterase inhibitors, and antihistamines), antidiabetic agents, stimulants, and CNS depressants, such as opioids, benzodiazepines, and alcohol (1, 20). Quetiapine should be used cautiously in patients taking warfarin because an increased international normalized ratio has been observed with this combination. Additionally, an 11-fold increase in quetiapine levels has been reported when the drug is taken in combination with the antiemetic aprepitant (20).

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