

QUETIAPINE



"A Mad Woman", oil on canvas, 1822, Eugene Delacroix, Musée du Louvre

They reached the territory of the Gerasenes on the other side of the lake, and when he disembarked, a man with an unclean spirit at once came out from the tombs towards him. The man lived in the tombs and no one could secure him anymore, even with a chain, because he had often been secured with fetters and chains but had snapped the chains and broken the fetters, and no one had the strength to control him. All night and all day among the tombs, and in the mountains he would howl and gash himself with stones. Catching sight of Jesus from a distance, he ran up and fell at his feet and shouted at the top of his voice, "What do you want with me Jesus, son of the Most High God? In God's name do not torture me". For Jesus had been saying to him, "Come out of this man unclean spirit". Then he asked "What is your name". He answered, "My name is legion for we are many".

Mark 5:1-9

In the First century A.D exorcism was the definitive cure for madness. In the 21st century, a more secular age, medical science has taken the lead role in the treatment of the mentally ill. Whilst we are unable to match the marvels of First century definitive cures, our science at least provides us with the means for a temporary relief in the form of our second generation of antipsychotic agents.

QUETIAPINE

Introduction

Quetiapine (trade name in Australia, **Seroquel**), is a second generation (or "atypical") antipsychotic agent.

It is as effective as any of the newer antipsychotic agents and has far less (if any) extrapyramidal side effects that are characteristic of the older agents.

It is effective in the treatment of both the "**positive**" and "**negative**" symptoms of schizophrenia.

See also separate document on Quetiapine Overdose (in Toxicology folder).

History

Chlorpromazine was developed in 1950. It was the first drug developed with a specific antipsychotic action and served as the prototype of the phenothiazine class of antipsychotic drugs that followed it.

The introduction of chlorpromazine during the 1950s into clinical use for schizophrenia and acute psychoses represented a significant advance in the history of psychiatry.

The “atypical” or second generation antipsychotics were developed and introduced into clinical practice during the 1990s. Olanzapine, risperidone, and **quetiapine** were introduced initially while ziprasidone and aripiprazole came onto the market in the early 2000s.

Quetiapine was introduced into clinical practice in Australia in 1997.

An **extended release** preparation became available in 2008.

Classification

There is no formal classification of the antipsychotic agents, however by tradition they are loosely divided into two principal groups.

1. The older “**first generation**” or “**typical**” group.
2. The newer “**second generation**” or “**atypical**” group.

In general the second generation agents have significantly less adverse effects profiles such as sedation, extrapyramidal side effects, anticholinergic effects or the development of neuroleptic malignant syndrome. The risk of these particular adverse effects although small is not completely eliminated with the second generation agents.

It has also been claimed that the second generation agents are more effective against the “negative” symptoms of schizophrenia, but this has *not* been convincingly proven as a *class* effect.

It should be noted that designating antipsychotics as first generation and second generation may be of limited value as it probably exaggerates the differences between groups and overstates similarities between members within each group. On this basis some prefer not to use this classification; nonetheless the terminology remains widely used.

First Generation Antipsychotic Agents :

These fall into two major groups:

1. **Phenothiazines:**
 - *Lower potency:*
 - Chlorpromazine.
 - Pericyazine.
 - Thioridazine.

- *Higher potency:*
 - Fluphenazine.
 - Flupenthixol
 - Prochlorperazine
 - Trifluoperazine.
 - Zuclopenthixol

2. **Butyrophenones:**

- Droperidol.
- Haloperidol.

Second Generation Antipsychotic Agents :

These include:

1. Amisulpride
2. Aripiprazole
3. Asenapine
4. Clozapine
5. Olanzapine
6. Paliperidone
7. **Quetiapine**
8. Risperidone
9. Ziprasidone

Preparation

Quetiapine as:

Tablets, (as quetiapine fumarate) standard release:

- 25 mg, 100 mg, 200 mg, 300 mg

Tablets, MR (modified release i.e. slow release):

- 50 mg, 150 mg, 200 mg, 300 mg, 400 mg.

There is no current parenteral form available.

Mechanism of Action

Antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain (in particular the limbic system).

Evidence suggests:

- All effective antipsychotics block D₂ receptors
- Differential blockade of other dopamine receptors (e.g. D₁) may influence therapeutic and adverse effects.
- Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT₂ antagonism with some agents.

Quetiapine has no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

Pharmacokinetics

Absorption:

- Quetiapine is administered orally.

It is rapidly but incompletely absorbed.

Distribution:

- It has a large volume of distribution at 10 L/kg
- Protein binding is around 83%.
- It is highly lipid soluble
- Human placental transfer can occur.
- Very small amounts can be distributed into breast milk

Metabolism and excretion:

- Quetiapine is almost completely metabolized in the liver to an active metabolite, 7-hydroxyquetiapine

- It is metabolized by the CP450 (3A4) system
- Half-life s around 7 hours for quetiapine; and around 12 hours for the active metabolite.

Pharmacodynamics

Quetiapine is effective in the treatment of both the “**positive**” and “**negative**” symptoms of schizophrenia.

The symptoms of schizophrenia involve:

- 1 Positive symptoms:
 - Delusions:
 - Hallucinations:
 - Formal thought disorder
- 2 Negative symptoms:
 - Blunted affect (lack of emotional response)
 - Apathy (loss of volition
 - Social withdrawal
 - Paucity of speech

Indications

Indications for quetiapine include:

1. Acute and chronic psychoses (e.g. schizophrenia)
2. Bipolar disorder, including:
 - Maintenance therapy
 - Acute mania episodes
 - *Depressive* episodes
3. Adjunct in treatment-resistant major depression (failed adequate trials of 2 or more single antidepressants)

4. Generalized anxiety disorder

Off label:

Since its introduction, a number of “off-label” uses of quetiapine have become common including: ⁵

5. Insomnia
6. Behavioural disturbances in the elderly
7. Substance withdrawal syndromes

It has also been used as a “recreational drug” to reduce anxiety symptoms while using stimulants, such as amphetamines

Contraindications/ Precautions

These include:

1. Known hypersensitivity to quetiapine.
2. Caution with other CNS depressants, including alcohol, (synergistic sedation)
3. Caution with other agents of conditions that prolong the QT interval
4. Hypotension
5. Renal impairment
 - Dose should be reduced.
6. Parkinson’s disease:
 - Antipsychotics used in Parkinson’s disease may aggravate the condition and may oppose the action of the dopamine agonists used to treat it.

Quetiapine or clozapine may be more suitable.
7. Hepatic
 - Use with caution in severe hepatic impairment; consider dose reduction.

Pregnancy

Quetiapine is a category C drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

There is limited information available describing the use of quetiapine at conception and throughout pregnancy.

Maternal use of quetiapine has not been associated with an increased risk of congenital malformations.

Quetiapine is transferred via the placenta to the fetus.

Healthy outcomes in infants exposed to quetiapine in utero have been reported. However, consultation with a perinatal psychiatrist is recommended if the initiation or continuation of quetiapine therapy is required during pregnancy.

Maternal use of antipsychotic medicines during pregnancy has been associated with an increased risk of developing gestational diabetes.

Other adverse effects such as weight gain and lipid abnormalities have also been associated with the use of the atypical antipsychotic medicines.

These may possibly contribute to poor pregnancy outcomes.

If quetiapine is the medicine of choice, use the lowest effective dose and closely monitor maternal mental health, fetal development and possible pregnancy complications such as metabolic changes (e.g. excessive weight gain, increased serum triglyceride and cholesterol levels, glucose intolerance and/or gestational diabetes).

Quetiapine use during pregnancy may also be associated with neonatal withdrawal syndromes, which include physical and behavioural symptoms such as irritability, restlessness, excessive crying, hypertonia, tachycardia and seizures. Inform neonatal care providers about the use of quetiapine as adverse effects or withdrawal signs may be present in newborns.

Limited information is available regarding the long term effects of quetiapine on childhood development following in utero exposure.

Breastfeeding

Considered safe in breast feeding.

There is limited safety information available following the use of quetiapine during breastfeeding.

Very small amounts of quetiapine are excreted into breast milk, but use with caution in women breastfeeding pre-term infants.

Observe the infant closely for potential adverse effects such as excessive drowsiness, poor feeding and unusual sleeping pattern changes.

Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

Adverse Effects

1. Sedation
2. Orthostatic hypotension
3. Mild prolongation of QT_c interval
4. Extrapyramidal side effects:
 - As quetiapine is a second generation antipsychotic, extrapyramidal effects are minimal compared to the older generation agents when used in usual therapeutic doses.

See Chlorpromazine for a description of these effects.

5. Neuroleptic malignant syndrome (NMS)
 - Again this is much less seen compared to the older generation of antipsychotic agents.

Dosing

For a first psychotic episode:

For standard release preparations:

Initially:

- Quetiapine 50 mg orally, b.d on day 1

Then

- Quetiapine 100 mg b.d on day 2

Then increasing to:

- Quetiapine 200 mg twice daily.

Response is frequently not seen until higher doses of up to **400 mg twice daily** are achieved.

Maximum daily dose is 800 mg

For slow release preparations:

- **Controlled-release formulations of quetiapine are available that allow for once daily night-time dosing.**

See latest Therapeutic Guidelines for dosing regimens for other indications.

References

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2. Quetiapine in Australian Medicines Handbook Website, July 2019.
3. Quetiapine in MIMs Website 1 December 2018.
4. Quetiapine in RWH Pregnancy & Breastfeeding Guidelines, 7 May 2019.
5. Lucy Taylor, Andis Graudins, Extended-release quetiapine overdose is associated with delayed onset of toxicity compared to immediate-release quetiapine overdose. *Emergency Medicine Australasia* (2019) 31, 562 - 568.
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