the medicine cabinet: Quetiapine

Quetiapine – a weak antipsychotic that is a great anxiolytic (anti- anxiety medication) and excellent for acute agitation

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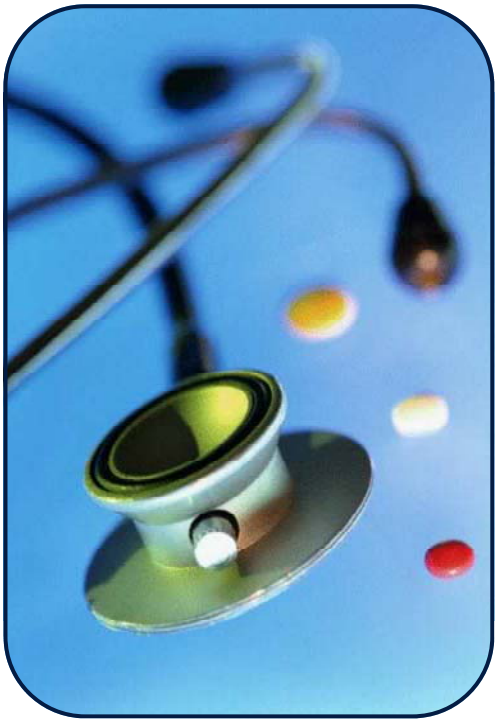
What are we treating?

In psychiatry, when treating patients, medication is often used to promote general safety rather than specific treatment, relieve symptoms rather than cure the disease. This is even more true for child and adolescent mental health where diagnostic uncertainty is present even where the young person may be very ill impaired. Most medications have been validated against symptom counts, not simply whether they have, or do not have, a given diagnosis. Arousal, agitation, aggression, anguish, restlessness, out-of-control behaviour and self-harm, are often more important, acutely, than whether or not someone has a particular diagnostic syndrome. This leads to uses both *licensed* (ie what the parent drug company applied to the Therapeutic Goods Association (TGA) to be marketed for use) and *off-label* (ie all the other indications for which the drug might be used). We treat the young person first and the specific diagnosis second.



The importance of sleep in psychiatric disorder

One very important symptom is sleep disturbance. Sleep disturbance is often the first sign of an impending episode of illness or of relapse. Severe sleep disorder is such a common accompaniment of mental illness, especially acute mental illness, that "sedation or no sedation?" is a key part of any medication decision tree. Quetiapine is a sedating second generation antipsychotic. Although it is called an *anti-psychotic* it has a much wider spectrum of symptom relief. It may be used for psychosis, mood disorder, bipolar disorder, depression, PTSD or anxiety. It may also be used for aggression where there is a willingness to take oral medication. All of these conditions have increased, often extreme, physiological arousal and motor activation in common.

Dealing with old problems in a new way

Quetiapine is a clozapine /olanzapine (brand names Clozaril® / Zyprexa®) like medication that is a *dibenzothiazepine.* This means that it is a cousin medication of diazepam (Valium®), but stronger and less addictive. Quetiapine will reduce the *positive symptoms* of psychosis, such as hallucinations and delusions. It will improve the *cognitive symptoms* (poor concentration and planning) as well as *negative symptoms* (inability to relate in groups, difficulty talking about feelings, difficulty experiencing pleasure or finding interest, and loss of motivation). Quetiapine does this without causing the traditional problems that were associated with the original first generation antipsychotics that were in use 20-30 years ago. Old style, first generation antipsychotics, like chlorpromazine and haloperidol, caused Parkinson Disease-like symptoms that slowed people up in their thoughts, their movements and even in the expression of their feelings. Some of them would also cause the hormone prolactin to rise, which reduced libido and would sometimes cause fullness of breasts and milk production. It was sometimes a big cost to pay to stop the anguish and impairment of psychosis.

How long does it take to work?

Quetiapine immediate release preparations reach maximum plasma concentration around 1.5 hours after ingestion. Quetiapine generally has an estimated half -life (time taken time for the drug to lose half its level in the blood) of 6 -7 hours. Quetiapine XR (extended release) peak at 5-6 hours. These times are adult times and in small studies to verify the times in adolescents they are slightly shorter times so dosing may need in some cases to be more frequent.

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What are the side effects of quetiapine?

The most common side effects are:-

- Sedation (short term)
- Postural hypotension (short term), a drop in blood pressure upon standing
- Dry mouth (medium term)
- Constipation (medium term)
- Weight gain (long term)
- High cholesterol, high triglycerides and high blood fats (all long term) are generally associated with weight gain and these lead to ongoing health issues such as diabetes that need to be monitored regularly (long term).
- Abuse potential (special setting side effect) – quetiapine has an emerging abuse and medication diversion (ie giving it to others) profile in forensic populations such as prisons and juvenile detention centres.

Quetiapine is extensively metabolised in the liver. While there is potential for drug interactions the vast majority of young people tolerate quetiapine well. They may be over sedated if put on the medicine regularly but this reduces rapidly after 3-5 days.

What happens if a patient overdoses on quetiapine?

In patients who regularly take quetiapine the lethal dose is far higher than those who have never taken the drug. Even so the tolerance for overdose is extremely high and few deaths have been recorded as a result of overdose. Toxic effects include sleepiness, unconsciousness, increased heart rate and low blood pressure.

What happens when the patient is pregnant, or breast feeding?

When used in pregnancy, quetiapine has a low rate of placental transfer but with use of medication during pregnancy and lactation the use needs to be weighed against the harm from the untreated mother. Currently there is an ongoing Australian psychotropic database that collects the records of mother and babies prescribed antipsychotics during pregnancy. This database can be accessed through Mothersafe 1800 647 848.

Conclusion

Quetiapine is a good sedative when a traditional benzodiazepine is to be avoided and a good acute treatment when physiological arousal and motor agitation must be lowered. Except for acute sedation, we generally avoid benzodiazepines (like diazepam: Valium®) in children and adolescents as they cause behavioural and emotional disinhibition and paradoxical over excitement in some. Quetiapine causes much fewer problems than traditional antipsychotics with Parkinson-like symptoms, but remains a metabolic challenge long term by causing weight gain. In general, if a medication sedates it puts on weight. For this reason we may switch from quetiapine as we move from acute to longterm medication management and if weight emerges as a problem. The extended release formulation offers once day dosing (or more subtle twice daily dosing) and potentially less daytime somnolence. Quetiapine generally requires a cooperative patient because intramuscular and intravenous formulations are not available. Its lack of sustained dopamine receptor blocking (so called D_2 occupancy) is thought by many clinicians to be the reason it is not as good at reducing longer term, or intractable, positive symptoms of psychosis as other newer antipsychotics.

References

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Practical information in relation to the public funding of quetiapine

Quetiapine was, and still is, marketed by Astra Zeneca and has recently come off patent in Australia. This means there are now generic equivalents available, which can mean the cost of the medication to the Australian government through claims via the PBS has also reduced. So instead of one brand name there are now 18 different brands of immediate release tablets. Extended release tablets (4-6 hours to work and continue to work for longer) are still patented to Astra Zeneca.

In Australia, quetiapine is reimbursed for treatment of schizophrenia and bipolar disorder, both as single therapy during the acute manic phase and maintenance and thus subsided by Pharmaceutical Benefits Advisory Committee (PBAC). Quetiapine is licensed ie what is recorded on the product information and applied for through TGA is listed below

TGA Indications Bipolar disorder.

Children/ adolescents aged 10 to 17 years. Monotherapy treatment of acute mania associated with bipolar I disorder.Schizophrenia.

Adults and adolescents aged 13 to 17 years. Treatment of schizophrenia.

Specialist information for medical practitioners and pharmacists

Quetiapine is metabolized mostly by CYP 3A4 in the liver and this means it is much less likely to be affected by the commonly reduced enzyme activity of CYP 2D6 (ie poor or intermediate metabolizer status).

Quetiapine has stronger $5HT_2$ receptor blocking capacity to D_2 blocking capacity. ($5HT_2$: D_2 affinity ratio) than first generation antipsychotics. $5HT_{2A}$ antagonism leads to reduction in glutamate release, which in turn reduces mesolimbic dopamine release, thus reducing positive symptoms.

Partial blockade of $5HT_{1A}$ can increase dopamine release in the frontal cortex (so called mesocortical dopamine system), which could improve affective, cognitive and negative symptoms while also reducing the risk of the debilitating EPS and prolactin elevation. $5HT_{1A}$ agonism can also decrease glutamate release, which could indirectly reduce positive symptoms of psychosis.

As for adverse effects quetiapine as, already mentioned, has lower EPS (parkinsonism) tendency due to the agonism of $5HT_{1A}$ receptors. But quetiapine also has agonist effects on many other receptors , listed below:

- $Alpha_1$ adrenergic receptors - postural hypotension
- $Alpha_2$ adrenergic receptors – postural hypotension, sedation
- M_1 Muscarinic receptors – dry mouth, constipation
- Histaminergic receptors – weight gain, sedation
- $5HT_{2C}$ receptors – weight gain.

Compared to the other antipsychotics there are less extra-pyramidal side effects (EPS), meaning less muscle stiffness, Parkinson –like symptoms or tendency to suffer from an oculogyric crisis ("the look ups"). There is less prolactin elevation and therefore less effect on libido and less galactorrhoea. Daytime somnolence, unwanted sedation and lethargy are all common. Sometimes this can be managed with dose adjustments (eg loading towards evening) as well as use of the XR. Steady state levels are reached within 48 hours on regular doses and over sedation usually attenuates after a further 48 hours, with histamine receptor desensitization.

Regular weight assessment can help as can some regular exercise. Rhinitis and nasal congestion and mild elevation of QTc have all been noted but with little consequence. XR formulation has a similar profile but the single daily dose may be associated with less daytime sedation. Cataracts, at much higher doses than used in humans, have been found in dogs. Tardive dyskinesia and neuroleptic malignant syndrome are thought to have occurred, although quetiapine is sometimes used to treat tardive dyskinesia, as is clozapine. There are limited studies and most are anecdotal. Tardive dyskinesia is much less frequent than typical or first-generation antipsychotics, such as haloperidol. Raised liver transaminases that return to normal with continued use occur in 6% of those on longer-term treatment.