TECHNICAL COMMENTARY

Quetiapine

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Introduction

Second generation antipsychotics (sometimes referred to as 'atypical' antipsychotics) are a newer class of antipsychotic medication than first generation 'typical' antipsychotics. Second generation antipsychotics are effective for the positive symptoms of schizophrenia. It is sometimes claimed that they are more effective than first generation antipsychotics in treating the negative symptoms of schizophrenia, although the evidence for this is weak. Negative symptoms include a lack of ordinary mental activities such as emotional expression, social engagement, thinking and motivation, whereas positive symptoms include the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions).

Second generation antipsychotics may also cause less extra-pyramidal side effects. These include dyskinesias such as repetitive, involuntary, and purposeless body or facial movements, Parkinsonism (cogwheel muscle rigidity, pill-rolling tremor and reduced or slowed movements), akathisia (motor restlessness, especially in the legs, and resembling agitation) and dystonias such as muscle contractions causing unusual twisting of parts of the body, most often in the neck. These effects are caused by the dopamine receptor antagonist action of these drugs. One explanation for differences in producing these side effects is that high potency first generation antipsychotics are usually selective dopamine receptor antagonists with a high affinity for the dopamine receptor and they induce extrapyramidal effects by the blockade of these dopamine receptors. In contrast, second generation antipsychotics generally have a lower affinity for the dopamine receptor and also block serotonin receptors, both of which mechanisms may play a role in mitigating the effects of dopamine blockade. Amisulpride is an exception to other second generation antipsychotics in that it is a pure dopamine receptor antagonist, however it tends to block dopamine receptors more selectively in the limbic system relative to the nigrostriatal system, which is the site responsible for inducing extrapyramidal symptoms. In addition to amisulpride, olanzapine and quetiapine also tend to selectively block dopamine receptors in the mesolimbic system but target serotonin receptors[1].

This table summarises overall group effectiveness of quetiapine from information gained from randomised controlled trials (RCTs), however individual treatment programs need to be tailored by trained clinicians as response - both in symptoms and adverse effects - can vary between individuals.

Method

Owing to the vast number of reviews on antipsychotics, we have prioritised information reported in the abstracts of Cochrane systematic reviews[2]. This is because the Cochrane internal review process ensures a high level of scientific rigor and meta-analyses are usually conducted, giving treatment effect sizes. Data from the abstracts were supplemented from the full text when clarification was required. When multiple copies of reviews were found and/or when findings conflict, we present the most recent version and the most recent conclusions. Where no Cochrane review exists, other reviews with pooled data are included.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from RCTs may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a

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dose dependent response or if results are reasonably consistent, precise and direct with low associated risks[3]. The resulting table represents an objective summary of the evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight reviews that met our inclusion criteria[4-11].

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Quetiapine

Compared to placebo

Efficacy: High quality evidence (consistent, precise, direct) suggests quetiapine increases study retention more than placebo.

Adverse effects: Moderate quality evidence (imprecise) suggests no differences in movement disorders between quetiapine and placebo.

Compared to first generation antipsychotics

Efficacy: High quality evidence (consistent, precise, direct) suggests no differences in study retention, global state or mental state between quetiapine and first generation antipsychotics.

Adverse effects: Moderate quality evidence (inconsistent) suggests quetiapine may be associated with fewer patients leaving the study due to adverse effects, fewer extrapyramidal effects, lower prolactin levels, and less weight gain than first generation antipsychotics.

Compared to second generation antipsychotic clozapine

Efficacy: Moderate to low quality evidence (1 small RCT) suggests no difference between quetiapine and clozapine for mental state.

Adverse effects: Moderate quality evidence (consistent, imprecise) suggests quetiapine may be associated with less hypersalivation, sedation, electrocardiogram alterations, and lower triglyceride levels than clozapine.

Compared to second generation antipsychotic risperidone

Efficacy: Moderate quality evidence (imprecise or inconsistent or unable to assess) suggests no differences in treatment retention between quetiapine and risperidone, but risperidone has higher efficacy than quetiapine for improving symptoms.

Adverse effects: Moderate to high quality evidence (imprecise or unable to assess) suggests quetiapine may be associated with fewer extrapyramidal effects, less sedation but more cholesterol than risperidone.

Compared to second generation antipsychotic paliperidone

Efficacy: Moderate quality evidence (imprecise) suggests quetiapine increased study attrition more than paliperidone.

Adverse effects: Moderate quality evidence (imprecise) suggests quetiapine had lower risk of hypertonia and tremor than paliperidone.

Compared to second generation antipsychotic olanzapine

Efficacy: Moderate to high quality evidence (unable to assess precision) suggests olanzapine improves general mental state more than quetiapine. High quality evidence suggests olanzapine results in fewer people leaving the study early due to higher efficacy and there are less hospital re-admissions.

Adverse effects: Moderate quality evidence (unable to assess precision, inconsistent) suggests quetiapine had less weight gain, and high quality evidence suggests less extrapyramidal effects with quetapine compared to olanzapine.

Compared to second generation antipsychotic ziprasidone

Efficacy: Moderate quality evidence suggests no differences in mental state between ziprasidone and quetiapine.

Adverse effects: Moderate quality evidence (imprecise) suggests quetiapine was associated with fewer extrapyramidal adverse effects than ziprasidone, but led to more weight gain.

See below for detailed results from six reviews.

Asenjo Lobos, C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 11: Art. No.: CD006633 DOI: 10.1002/14651858.CD006633.pub2.	
The review includes 27 blinded RCTs, N = 3099 – five comparing clozapine with quetiapine. No significant difference in mental state (BPRS total score) between quetiapine and clozapine (1 RCT, N = 72, MD = 0.89, 95%CI -1.33 to 3.11, $p = 0.43$)	
Risks	Compared to clozapine, quetiapine showed less hypersalivation (2 RCTs, N = 135, $p < 0.05$); sedation (2 RCTs, N = 135, $p < 0.05$); ECG alterations (1 RCT, N = 72, $p < 0.05$); triglyceride levels (1 RCT, N = 27, $p < 0.001$).
Consistency in results‡	Consistent for all measures. Unable to assess for 1 RCT.
Precision in results§	Imprecise for adverse effects. Unable to assess precision for mental states and triglyceride levels as standardised values not reported.
Directness of results‖	Direct
Bergman H, Rathbone J, Agarwal V, Soares-Weiser K. Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia. Cochrane Database of Systematic Reviews 2018; 2: CD000459.	
There was greater clinical improvement in tardive dyskinesia with switching to quetiapine than switching to haloperidol (1 RCT, N = 45, RR 0.45, 95%CI 0.21 to 0.96, $p < 0.05$).	
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W, Leucht S. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD006626. DOI: 10.1002/14651858.CD006626.pub2.	
Risperidone was more effective for symptom severity than quetiapine (PANSS total score: 9 RCTs, N = 1953, MD -3.09, 95%CI -5.16 to -1.01, I^2 = 24%, *p* = 0.23).	
Risks	Risperidone produced more extrapyramidal side effects (6 RCTs, N = 1715, RR 1.98, 95%CI 1.16 to 3.39, I^2 = 37%, *p* = 0.16), but less cholesterol increase (5 RCTs, N = 1433, MD -8.49, 95%CI -12. 23 to -4.75, I^2 = 6%, *p* = 0.37) and less sedation (8 RCTs, N = 2226, RR 0.82, 95%CI 0.69 to 0.97, I^2 = 26%, *p* = 0.22).
Consistency in results	Consistent
Precision in results	Precise for sedation, otherwise imprecise or unable to assess.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, Kissling W, Leucht S. Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD006654 DOI: 10.1002/14651858.CD006654.pub2.	
The review includes 50 RCTs (N = 9476) of olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone. Olanzapine had greater improvement of general mental state (measured by PANSS) compared to quetiapine (10 RCTs, N = 1449, WMD -3.66, 95%CI -5.39 to -1.93, I^2 = 0%, *p* = 0.69). Olanzapine had significantly fewer participants leave the study early due to inefficacy compared to quetiapine (8 RCTs, N = 1563, RR 0.56, 95%CI 0.44 to 0.70, NNT 11, I^2 = 7%, *p* = 0.38). Olanzapine had fewer hospital re-admissions compared to quetiapine (2 RCTs, N = 876, RR 0.56, 95%CI 0.41 to 0.77, NNT 11, I^2 = 0%, *p* = 0.98).	
Risks	Olanzapine induced more weight gain compared to quetiapine (7 RCTs, N = 1173, WMD2.68kg, 95%CI 1.10kg to 4.26kg, I^2 = 76, *p* = 0.00036). Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine. Olanzapine was associated with slightly more extrapyramidal side effects than quetiapine, measured as the use of antiparkinson medication (6 RCTs, N = 1090, RR 2.05, 95%CI 1.26 to 3.32, NNH 25, I^2 = 0%, *p* = 0.52). Olanzapine also increased prolactin more than quetiapine (5 RCTs, N

	= 1021, WMD 5.89, 95%CI 0.16 to 11.62, I^2 = 59%, p = 0.04).
Consistency in results	Consistent for all except weight gain compared to quetiapine.
Precision in results	Precise for dichotomous outcomes, unable to assess continuous measures.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, Kissling W, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006625 DOI: 10.1002/14651858.CD006625.pub2.	
This review includes 21 RCTs (N = 4101) compared quetiapine with clozapine, olanzapine, risperidone or ziprasidone. No significant difference in study attrition was reported between the interventions, all had high numbers of participants leaving the study early. Compared to olanzapine, quetiapine had lower efficacy for reducing symptom severity (10 RCTs, N = 1449, WMD 3.66, 95%CI 1.93 to 5.39, I^2 = 0%, p = 0.69). Compared to risperidone, quetiapine had lower efficacy for reducing symptom severity (9 RCTs, N = 1953, WMD 3.09, 95%CI 1.01 to 5.16, I^2 = 24%, p = 0.23). There were no significant differences in mental state when quetiapine was compared to ziprasidone (2 RCTs, N = 710, WMD -0.11, 95%CI -6.36 to 6.14, I^2 = 62%, p = 0.10).	
Risks	Compared to olanzapine, quetiapine produced fewer movement disorders (as measured by use of antiparkinson medication, 6 RCTs, N = 1090, RR 0.49, 95%CI 0.3 to 0.79, NNH 25, I^2 = 0%, p = 0.52) and less weight gain (7 RCTs, N = 1173, WMD -2.68, 95%CI -4.26 to -1.10, I^2 = 76%, p = 0.00036), but more QTc prolongation (3 RCTs, N = 643, WMD 4.81, 95%CI 0.34 to 9.28, I^2 = 0%, p = 0.68). Compared with risperidone, quetiapine induced fewer movement disorders (as measured by use of antiparkinson medication, 6 RCTs, N = 1715, RR 0.5, 95%CI 0.3 to 0.86, NNH 20, I^2 = 37%, p = 0.16), less prolactin increase (6 RCTs, N = 1731, WMD -35.28, 95%CI -44.36 to -26.19, I^2 = 9%, p < 0.00001), but more cholesterol increase (5 RCTs, N = 1433, WMD 8.61, 95%CI 4.66 to 12.56, I^2 = 5%, p = 0.38). Compared with ziprasidone, quetiapine induced fewer extrapyramidal adverse effects (as measured by use of antiparkinson medication, 1 RCT, N = 522, RR 0.43, 95%CI 0.2 to 0.93) but led to more weight gain (2 RCTs, N = 754, RR 2.22, 95%CI 1.35 to 3.63, NNH 13, I^2 = 0%, p = 0.95).
Consistency in results	Consistent for all except weight gain compared to olanzapine, and

	prolactin compared to risperidone.
Precision in results	Unable to assess continuous outcomes, imprecise for dichotomous outcomes.
Directness of results	Direct
Nussbaum AM, Stroup TS. Oral paliperidone for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006369. DOI: 10.1002/14651858.CD006369.pub2.	
One RCT (N = 314) compared paliperidone to quetiapine. Compared to quetiapine, paliperidone reduced study attrition (N = 314, 1 RCT, RR 0.64, 95%CI 0.44 to 0.93, NNT 9 CI 6 to 43). No significant difference was observed in the rate of psychotic relapse (N = 317, 1 RCT, RR 0.65, 95%CI 0.29 to 1.45, NNT 52).	
Risks	Compared to quetiapine, participants on paliperidone were more likely to experience hypertonia (N = 317, 1 RCT, RR 3.19, 95%CI 1.31 to 7.77, NNH 13 CI 4 to 86) and tremor (N = 317, 1 RCT, RR 2.60, 95%CI 1.39 to 4.88, NNH 9 CI 4 to 34).
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct
Srisurapanont M, Maneeton B, Maneeton N. Quetiapine for schizophrenia. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD000967 DOI: 10.1002/14651858.CD000967.pub2 **Suttajit S, Srisurapanont M, Xia J, Suttajit S, Maneeton B, Maneeton N. Quetiapine versus typical antipsychotic medications for schizophrenia. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD007815. DOI: 10.1002/14651858.CD007815.pub2**	
Comparing different doses of quetiapine, higher attrition was reported in the lower dose groups (58% in < 250 mg/day vs. 49% in >/= 250 mg/day; N = 1066, 3 RCTs, RR 0.84 CI 0.8 to 0.9, NNT 11 CI 7 to 29, I^2 = 0%, p = 0.94). Compared to placebo, higher attrition was reported in the placebo groups with, 53% of those on quetiapine lost to follow up compared to 61% on placebo (N = 716, 4 RCTs, RR 0.84 CI 0.7 to 0.9, NNT 11 CI 7 to 55, I^2 = 0%, p = 0.65). Quetiapine groups reported significantly improved global and mental state, although authors suggest that with such high attrition, the data is not interpretable. Compared to first generation antipsychotics there were no significant differences in leaving the study due to any reason (N = 3576, 23 RCTs, RR 0.91 CI 0.81 to 1.01, I^2 = 22%, p = 0.17). No difference was reported for average change in global state (N = 1607, 16 RCTs, RR 0.96 CI 0.75 to 1.23, I^2 = 0%, p = 0.58) or for mental state (PANSS general: N = 1569, 18 RCTs, MD -0.20 CI -0.83 to 0.42, I^2 = 0%, p = 0.98).	

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Compared to second generation antipsychotic risperidone, no significant differences were found in numbers lost to follow up (N = 728, 1 RCT, RR 0.94 CI 0.74 to 1.20). No difference was reported between the groups for mental state (N = 637, 1 RCT, WMD 1.2 CI -2.0 to 4.4).	
Risks	Compared to placebo, there was no significant difference in frequency of movement disorder (N = 395, 2 RCTs, RR 0.62 CI 0.34 to 1.15, I^2 = 0%, *p* = 0.48). Compared to first generation antipsychotics, quetiapine resulted in fewer patients leaving the study early due to adverse events (N = 3010, 15 RCTs, RR 0.48 CI 0.30 to 0.77, I^2 = 55%, *p* = 0.01), less extrapyramidal effects (N = 1095, 8 RCTs, RR 0.17 CI 0.09 to 0.32, I^2 = 67%, *p* = 0.004), lower prolactin level (4 RCTs, N = 1034, MD -16.20 CI -23.34 to -9.07, I^2 = 92%, *p* < 0.00001) and less weight gain (9 RCTs, N = 866, RR 0.52 CI 0.34 to 0.80, I^2 = 46%, *p* = 0.06). Compared to second generation antipsychotic, risperidone significantly fewer patients on quetiapine reported extrapyramidal symptoms (N = 712, 1 RCT, RR 0.27 CI 0.15 to 0.49, NNT 11 CI 10 to 16). Quetiapine caused more dizziness (N = 728, 1 RCT, RR 1.85 CI 1.0 to 3.3, NNH 18 CI 7 to 487), more dry mouth (N = 728, 1 RCT, RR 2.11 CI 1.2 to 3.8, NNH 14 CI 6 to 82) and more sleepiness (N = 728, 1 RCT, RR 2.03 CI 1.4 to 2.9, NNH 7 CI 4 to 17).
Consistency in results	Consistent where applicable apart from side effects in the comparison with first generation antipsychotics.
Precision in results	Precise for all reported dichotomous outcomes apart from movement disorder in the comparison with placebo, and dizziness, dry mouth and sedation in the comparison with risperidone. Unable to assess continuous outcomes, standardized values not reported.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, NNH = number of patients needed to treat for one to show one negative effect, NNT = number of patients needed to treat for one to show a positive effect, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), RR = relative risk, vs = versus, WMD = weighted mean difference

Explanation of technical terms

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[2].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[2];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

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§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either

direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[13].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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