

Generalised anxiety disorder: quetiapine

Evidence summary

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[nice.org.uk/guidance/esuom12](https://www.nice.org.uk/guidance/esuom12)

Key points from the evidence

The content of this evidence summary was up-to-date in May 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

There is some evidence that quetiapine monotherapy improves the symptoms of generalised anxiety disorder (GAD) compared with placebo, and limited evidence suggests that it is not more effective than antidepressants. Other limited evidence suggests that adding quetiapine to an antidepressant does not improve symptoms in GAD that has not responded to the antidepressant alone. People taking quetiapine are more likely to discontinue treatment because of adverse effects compared with placebo or active treatment.

Licencing status: off-label.

<p>Effectiveness</p> <ul style="list-style-type: none"> • Moderate evidence suggests that quetiapine monotherapy at most doses statistically significantly improved rates of GAD response or remission compared with placebo (4 RCTs lasting 8–9 weeks) but not compared with escitalopram or paroxetine (2 RCTs lasting 8 weeks). • Adding quetiapine to an antidepressant did not statistically significantly improve symptoms in GAD that had not responded to the antidepressant alone (3 RCTs lasting 8 weeks). 	<p>Safety</p> <ul style="list-style-type: none"> • The most commonly reported adverse effects are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia. • SPC warns about the potential for several other important adverse effects, e.g. suicidal ideation, tardive dyskinesia, neuroleptic malignant syndrome, severe neutropenia (see the SPC for full details). • Acute withdrawal symptoms have been described after abrupt cessation of quetiapine.
<p>Patient factors</p> <ul style="list-style-type: none"> • Once-daily dosage regimen. • Discontinuation due to adverse effects statistically significantly more likely with quetiapine compared with placebo or active treatment. 	<p>Cost</p> <ul style="list-style-type: none"> • Up to around £80 per 28 days, depending on dose and formulation. • Prolonged-release formulation is considerably more costly than the immediate-release formulation.

Key points

Quetiapine is an atypical antipsychotic. It does not have UK marketing authorisation for treating GAD and so this is an off-label use of quetiapine.

NICE has published a clinical guideline on [generalised anxiety disorder and panic disorder \(with or without agoraphobia\) in adults](#). Evidence relating to quetiapine in GAD was not assessed as part of the guideline development because it was expected that this would be a subject of a NICE technology appraisal. The technology appraisal was suspended indefinitely after withdrawal of the licensing application by the manufacturer.

Evidence for quetiapine monotherapy in GAD comes from 4 randomised controlled trials (RCTs: [Bandelow et al. 2010](#), n=873; [Khan et al. 2011a](#), n=951; [Meredith et al. 2012](#), n=854; [Mezhebovsky et al. 2012](#), n=450). All were short term: 3 lasted 8 weeks and 1 lasted 9 weeks. They found that at most doses, prolonged-release quetiapine monotherapy was statistically significantly more effective in GAD compared with placebo, but was statistically significantly more likely to cause people to discontinue treatment because of adverse events. The studies found no statistically significant difference in efficacy between prolonged-release quetiapine and paroxetine or escitalopram, although they may not have had sufficient statistical power to detect such a difference. Again, at most doses quetiapine was statistically significantly more likely to cause people to discontinue treatment because of adverse events.

Three RCTs have investigated the efficacy of quetiapine as augmentation of antidepressant therapy for GAD that has not responded to other treatments (refractory GAD). The largest of these included 409 people with refractory GAD ([Khan et al. 2011b](#)) and lasted 8 weeks. This double-blind study was adequately powered for its primary outcome (improvement of [Hamilton Anxiety Rating Scale](#) [HAM-A] score from baseline) but did not detect a statistically significant difference between prolonged-release quetiapine and placebo for this outcome, or rates of response or remission. Quetiapine appeared to have been less well tolerated than placebo, although statistical analysis of rates of adverse events and withdrawals because of adverse events was not reported.

Two other RCTs ([Simon et al. 2008](#) and [Altamura et al. 2011](#)) did not find a statistically significant benefit from quetiapine in addition to antidepressants in people with refractory GAD. These also lasted 8 weeks and were small (22 and 20 participants, respectively). These trials are likely to have been statistically underpowered.

The [summary of product characteristics](#) states that the most commonly reported adverse effects of quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia. It also warns about the potential for several other important adverse effects, including suicidal ideation, tardive dyskinesia, neuroleptic malignant syndrome and neutropenia. Acute withdrawal symptoms have also been described after abrupt cessation of quetiapine (see the summary of product characteristics for full details).

The [NICE clinical guideline on GAD](#) assessed the evidence for augmentation of antidepressant therapy with antipsychotics other than quetiapine. The Guideline Development Group concluded that antipsychotic augmentation should not be routinely used and should be provided only in specialist settings. The guideline recommends that antipsychotics should not be offered for GAD in primary care.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Regulatory status of quetiapine

Quetiapine does not have UK marketing authorisation for treating generalised anxiety disorder (GAD) and therefore this use is off-label.

Quetiapine is available in generic formulations. The originator products are Seroquel standard-release tablets and Seroquel XL prolonged-release tablets, manufactured by AstraZeneca UK Ltd. Quetiapine (Seroquel) is licensed for treating schizophrenia and bipolar disorder, and the prolonged-release formulation is also licensed as an add-on treatment for major depressive disorder in people whose condition has not responded optimally to antidepressant monotherapy.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using quetiapine outside its authorised indications.

Evidence statements

- Monotherapy with prolonged-release quetiapine at different doses was compared with placebo and antidepressants in 4 short-term (8–9 week) randomised controlled trials (RCTs) including 3128 people with GAD. Pooled analysis showed a beneficial effect of quetiapine at most doses on rates of GAD response or remission compared with placebo, measured by the Hamilton Anxiety Rating Scale (HAM-A). However, the RCTs found no statistically significant

difference in rates of response or remission between prolonged-release quetiapine and either paroxetine or escitalopram, although they may not have had sufficient statistical power to detect such a difference.

- Adding prolonged-release quetiapine to antidepressants was compared with antidepressants plus placebo in 1 double-blind, adequately powered, 8-week RCT in 409 people with GAD that had not responded to antidepressant monotherapy (refractory GAD). It did not detect a statistically significant difference in improvement of HAM-A score from baseline, or in rates of response or remission as measured by HAM-A.
- Two smaller (n=20 and n=22) similar placebo-controlled RCTs of quetiapine in refractory GAD also found no statistically significant benefit from adding quetiapine to an antidepressant in terms of improvement of HAM-A score from baseline, or in rates of response or remission after 8 weeks of treatment.
- The [summary of product characteristics](#) for quetiapine states that the most commonly reported adverse effects of quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia. It also warns about the potential for several other important adverse effects including suicidal ideation, tardive dyskinesia, neuroleptic malignant syndrome, severe neutropenia. Acute withdrawal symptoms have also been described after abrupt cessation of quetiapine (see the summary of product characteristics for full details).
- Pooled analysis of the studies of quetiapine monotherapy in GAD found that at most doses it was associated with a statistically significantly greater risk of treatment discontinuation because of adverse events compared with placebo, paroxetine and escitalopram.
- In the larger study of quetiapine in refractory GAD, rates of adverse events and discontinuations because of adverse events were numerically greater in the antidepressant plus quetiapine group than in the antidepressant plus placebo group, although statistical analysis was not reported.

Summary of the evidence

Efficacy

The [HAM-A scale](#) was used in all the studies of quetiapine treatment in GAD. This is a 14-item clinician-rated scale, with each item rated 0–4. The total score range is 0–56, with less than 17 indicating mild anxiety, 18–24 indicating mild-to-moderate anxiety, and 25–30 indicating moderate-to-severe anxiety. The first 2 items relate to anxious mood and tension.

The [NICE full guideline on generalised anxiety disorder in adults](#) summarised data from 4 RCTs, which compared prolonged-release quetiapine monotherapy (50–300 mg per day) with placebo or antidepressants in people with GAD (total HAM-A score 20 or more with the score for the first 2 items of 2 or more, and Montgomery–Åsberg Depression Rating Scale [MADRS] score 16 or less). These were unpublished data supplied by the manufacturer, but the studies have subsequently been published in full ([Bandelow et al. 2010](#); [Khan et al. 2011a](#); [Meredith et al. 2012](#); [Mezhebovsky et al. 2012](#)). Pooled analysis in the [full NICE guideline](#) found a statistically significant beneficial effect of quetiapine monotherapy in GAD on rates of response (50% or greater reduction in HAM-A score) or remission (HAM-A score of 7 or less) compared with placebo. However, the trials found no statistically significant difference in efficacy between prolonged-release quetiapine and either paroxetine or escitalopram, although they may not have had sufficient statistical power to detect such a difference. The pooled analyses from the [full NICE guideline](#) are summarised in tables 1 and 2.

Table 1 Pooled analysis of quetiapine monotherapy compared with placebo in generalised anxiety disorder

	Quetiapine	Placebo	Analysis
Quetiapine 50 mg versus placebo (2 RCTs)			
Non-response ^a	n=455	n=452	Risk ratio 0.82 (95% CI 0.71 to 0.95), p=0.008
Non-remission ^b	n=455	n=452	Risk ratio 0.92 (95% CI 0.84 to 1.00), p=0.04
Discontinuation because of adverse events ^c	n=455	n=452	Risk ratio 2.62 (95% CI 1.68 to 4.07), p<0.0001
Quetiapine 150 mg versus placebo (3 RCTs)			
Non-response ^a	n=678	n=667	Risk ratio 0.73 (95% CI 0.62 to 0.85), p<0.0001
Non-remission ^b	n=678	n=667	Risk ratio 0.86 (95% CI 0.79 to 0.92), p<0.0001
Discontinuation because of adverse events ^c	n=678	n=667	Risk ratio 2.97 (95% CI 2.11 to 4.18), p<0.00001
Quetiapine 300 mg versus placebo (2 RCTs)			

Non-response ^a	n=448	n=450	Risk ratio 0.92 (95% CI 0.81 to 1.05), p=0.23
Non-remission ^b	n=448	n=450	Risk ratio 1.00 (95% CI 0.92 to 1.08), p=0.91
Discontinuation because of adverse events ^c	n=448	n=450	Risk ratio 3.69 (95% CI 2.54 to 5.37), p<0.00001
Quetiapine flexible dose 50–300 mg versus placebo (1 RCT)			
Non-response ^a	n=223	n=227	Risk ratio 0.42 (95% CI 0.34 to 0.51), p<0.00001
Non-remission ^b	n=223	n=227	Risk ratio 0.69 (95% CI 0.61 to 0.78), p<0.00001
Discontinuation because of adverse events ^c	n=223	n=227	Risk ratio 4.07 (95% CI 1.16 to 14.23), p=0.03
Abbreviations: CI, confidence interval; RCT, randomised controlled trial.			
^a Non-response was defined as a reduction in Hamilton Anxiety Rating Scale (HAM-A) score of <50% compared with baseline. A risk ratio <1 favours quetiapine.			
^b Non-remission was defined as a HAM-A score of >7. A risk ratio <1 favours quetiapine.			
^c A risk ratio >1 favours placebo.			

Table 2 Pooled analysis of antidepressant monotherapy compared with quetiapine monotherapy in generalised anxiety disorder

	Antidepressant	Quetiapine	Analysis
Paroxetine 20 mg versus quetiapine 50 mg (1 RCT)			
Non-response ^a	n=217	n=221	Risk ratio 0.92 (95% CI 0.72 to 1.18), p=0.52
Non-remission ^b	n=218	n=221	Risk ratio 0.91 (95% CI 0.79 to 1.04), p=0.16
Discontinuation because of adverse events ^c	n=217	n=221	Risk ratio 0.67 (95% CI 0.37 to 1.19), p=0.17
Paroxetine 20 mg versus quetiapine 150 mg (1 RCT)			

Non-response ^a	n=217	n=218	Risk ratio 1.17 (95% CI 0.89 to 1.54), p=0.25
Non-remission ^b	n=218	n=221	Risk ratio 0.91 (95% CI 0.79 to 1.04), p=0.16
Discontinuation because of adverse events ^c	n=217	n=218	Risk ratio 0.49 (95% CI 0.28 to 0.84), p=0.01
Escitalopram 10 mg versus quetiapine 150 mg (1 RCT)			
Non-response ^a	n=203	n=219	Risk ratio 1.18 (95% CI 0.94 to 1.47), p=0.14
Non-remission ^b	n=213	n=219	Risk ratio 1.09 (95% CI 0.96 to 1.25), p=0.18
Discontinuation because of adverse events ^c	n=213	n=219	Risk ratio 0.55 (95% CI 0.34 to 0.91), p=0.02
Escitalopram 10 mg versus quetiapine 300 mg (1 RCT)			
Non-response ^a	n=203	n=207	Risk ratio 0.95 (95% CI 0.77 to 1.16), p=0.61
Non-remission ^b	n=213	n=207	Risk ratio 0.97 (95% CI 0.85 to 1.09), p=0.18
Discontinuation because of adverse events ^c	n=213	n=206	Risk ratio 0.39 (95% CI 0.24 to 0.62), p=0.0001
Abbreviations: CI, confidence interval; RCT, randomised controlled trial.			
^a Non-response was defined as a reduction in Hamilton Anxiety Rating Scale (HAM-A) score of <50% compared with baseline. A risk ratio <1 favours the antidepressant.			
^b Non-remission was defined as a HAM-A score of >7. A risk ratio <1 favours the antidepressant.			
^c A risk ratio <1 favours the antidepressant.			

Three 8-week, placebo-controlled RCTs of augmentation of antidepressant therapy with quetiapine in people with GAD that had not responded to standard treatment were identified for this evidence summary ([Altamura et al. 2011](#); [Khan et al. 2011b](#); [Simon et al. 2008](#)). Results of these studies are summarised in table 3.

The RCT by [Altamura et al. \(2011\)](#) included 20 people with GAD that had not responded or only partly responded to at least 8 weeks' treatment with a selective serotonin reuptake inhibitor (SSRI). The study excluded people treated with benzodiazepines. Current SSRI treatment was maintained, and people were randomised to receive placebo (n=10) or immediate-release quetiapine 25–150 mg per day, mean dose 50 mg per day (n=10), for 8 weeks. The study did not report whether participants or investigators were blinded to treatment allocation or whether allocation was concealed. At 8 weeks, quetiapine produced an improvement from baseline in HAM-A score and the 7-point Clinical Global Impression of Severity (CGI-S) score, but there was no statistically significant difference between the groups in HAM-A score, HAM-A response rate, HAM-A remission rate or CGI-S score.

The double-blind RCT by [Khan et al. \(2011b\)](#) has been published in full; however, only a portion of the journal abstract is available at the time of publication of this evidence summary (AstraZeneca UK Ltd, personal communication March 2013). This summary is based on the poster presentation of the study (AstraZeneca UK Ltd, personal communication March 2013) and the report on the manufacturer's website ([AstraZeneca Clinical Trials 2009](#)). The study included 409 adults with GAD (HAM-A score of 20 or greater and a score for the first 2 items of 2 or more and CGI-S score of 4 or more). Participants' current anxious episode had either not responded or only partly responded to at least 8 weeks' treatment with duloxetine, escitalopram, paroxetine or venlafaxine. People were randomised to receive placebo or quetiapine prolonged-release tablets 150–300 mg per day, mean dose 174 mg per day (each in combination with the antidepressant therapy, with or without a benzodiazepine). It is unclear if allocation was concealed.

The primary outcome was the change in HAM-A score from baseline at week 8, and the study had 90% power based on an anticipated difference from placebo of 2.5 points. After 8 weeks' treatment there was a reduction in HAM-A score from baseline in both groups, but no statistically significant difference in reduction between quetiapine and placebo, or in rate of HAM-A response or remission. There was a statistically significantly greater reduction from baseline in the 7-point CGI-S score in the quetiapine group compared with placebo, but the difference was small (–1.13 from baseline in the placebo group compared with –1.36 in the quetiapine group. $P < 0.05$).

In the double-blind RCT by [Simon et al. \(2008\)](#), 22 people whose GAD had not shown HAM-A remission from 10 weeks' treatment with paroxetine (flexible dose, mean 47 mg per day) continued with paroxetine at the same dose and were randomised to receive double-blind augmentation with placebo (n=11) or quetiapine 25–200 mg per day (mean dose 120 mg per day, formulation not stated, n=11) for an additional 8 weeks. No power calculation was reported. It is unclear if allocation was concealed. Quetiapine did not produce a statistically significant decrease in HAM-A

score compared with placebo at week 8. There were also no statistically significant differences in rates of HAM-A remission or clinical global impression of response.

Table 3 Summary of the trials of quetiapine augmentation of antidepressant therapy in generalised anxiety disorder

	Quetiapine	Placebo	Analysis
<u>Altamura et al. (2011)</u>			
	n=10	n=10	
HAM-A change from baseline to week 8	Score change not reported	Score change not reported	No significant difference in HAM-A at 8 weeks (p=0.72)
CGI-S change from baseline to week 8	Score change not reported	Score change not reported	No significant difference in CGI-S at 8 weeks (p=1.00)
HAM-A response rate at week 8 ^a	6/10	3/10	p=0.37
HAM-A remission rate at week 8 ^b	4/10	2/10	p=0.63
Safety	1 person with sedation		
<u>Khan et al. (2011b)</u>			
Randomised	n=209	n=200	
Efficacy, mITT ^c	n=204	n=198	
Primary outcome			
LSM change in HAM-A from baseline at week 8	-10.74	-9.61	Difference - 1.13 points, p=0.079
Secondary outcomes			
HAM-A response rate at week 8 ^a	41.2%	36.4%	Difference 4.8%, p=0.342
HAM-A remission rate at week 8 ^b	23.5%	17.2%	Difference 6.3%, p=0.134

LSM in CGI-S score at week 8	-1.36	-1.13	Difference -0.23, p<0.05
Safety	n=209	n=200	
People with at least 1 treatment-related adverse event	62% (130/209)	36% (72/200)	No statistical analysis reported
Discontinuations because of adverse events	12% (24/209)	2% (4/200)	No statistical analysis reported
<u>Simon et al. (2008)</u>			
Randomised	n=11	n=11	
Primary outcome			
Mean change in HAM-A from baseline at week 8	-2.63	-0.27	p>0.3
Secondary outcomes			
HAM-A remission rate at week 8 ^b	36.4% (4/11)	18.2% (2/11)	p=0.635
Clinical response at week 8 ^d	54% (6/11)	45% (5/11)	p=1.0
Discontinuations because of adverse events	45.5% (5/11)	9.1% (1/11)	
Abbreviations: CGI-S, Clinical Global Impression of Severity Scale; HAM-A, Hamilton Anxiety Rating Scale; LSM, least squares mean.			
^a HAM-A response was defined as a reduction in HAM-A score of $\geq 50\%$ compared with baseline.			
^b HAM-A remission was defined as a HAM-A score of ≤ 7 .			
^c mITT: modified intention to treat population: all randomised participants who took study treatment and who had a HAM-A total score assessment at randomisation and at least 1 post-randomisation HAM-A total score.			
^d Clinical response was defined as a Clinical Global Impression of Improvement score of 1 or 2 ('very much improved' or 'much improved').			

Safety

The summaries of product characteristics (SPCs) for [Seroquel](#) and [Seroquel XL](#) state that the most commonly reported adverse effects of quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia. They also warn about the potential for several other important adverse effects, e.g. suicidal ideation, tardive dyskinesia, neuroleptic malignant syndrome, severe neutropenia. Acute withdrawal symptoms have also been described after abrupt cessation of quetiapine (see the SPCs for full details).

Pooled analysis in the [full NICE guideline](#) of the studies of quetiapine monotherapy in GAD found that at most doses it was associated with a statistically significantly greater risk of treatment discontinuation because of adverse events compared with placebo, paroxetine and escitalopram.

The 2 small RCTs of quetiapine ([Altamura et al. 2011](#) and [Simon et al. 2008](#)) do not provide reliable evidence on the risk of adverse effects with quetiapine in refractory GAD. However, in the larger study by [Khan et al. \(2011b\)](#), rates of adverse events – including those assessed as treatment-related – and rates of discontinuations because of adverse events were numerically greater in the antidepressant plus quetiapine group than in the antidepressant plus placebo group, although statistical analysis was not reported.

Cost effectiveness and cost

The costs of quetiapine are given in the table below (taken from the [Drug Tariff](#) April 2013, excluding VAT).

Quetiapine preparation and strength	Cost for 60 tablets
Immediate-release tablets	
25 mg	£2.25
100 mg	£4.83
150 mg	£5.18
200 mg	£5.54
300 mg	£7.65
Prolonged-release tablets	
50 mg	£67.66

150 mg	£113.10
200 mg	£113.10
300 mg	£170.00
400 mg	£226.20

Relevance to NICE guidance programmes

Quetiapine (Seroquel XL) for the treatment of generalised anxiety disorder was referred for a [NICE technology appraisal](#) in June 2010 but was suspended indefinitely after withdrawal of the licensing application by the manufacturer. It is not currently planned into any other work programme.

NICE has published a clinical guideline on [generalised anxiety disorder \(GAD\) and panic disorder \(with or without agoraphobia\) in adults](#). The [full NICE guideline](#) included evidence relating to quetiapine as monotherapy in GAD and as augmentation therapy in addition to an antidepressant. However, this evidence was not assessed during guideline development because it was expected that quetiapine in GAD would be the subject of a NICE technology appraisal.

NICE guidance also exists for quetiapine in its licensed indications:

- [Depression in adults: the treatment and management of depression in adults](#) (NICE clinical guideline 90)
- [Antenatal and postnatal mental health: clinical management and service guidance](#) (NICE clinical guideline 45)
- [Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care](#) (NICE clinical guideline 38).

Intervention and alternatives

Quetiapine is an atypical antipsychotic. It is available in generic formulations but the originator products are [Seroquel standard-release tablets](#) and [Seroquel XL prolonged-release tablets](#), manufactured by AstraZeneca UK Ltd. Quetiapine (Seroquel) is licensed for treating schizophrenia and bipolar disorder, and the prolonged-release formulation is also licensed as an add-on treatment for major depressive disorder in people whose condition has not responded optimally to antidepressant monotherapy. Quetiapine is not licensed for generalised anxiety disorder (GAD) in

Europe or the USA, but it is licensed for GAD in some other countries, e.g. Australia (AstraZeneca UK Ltd, personal communication March 2013).

Condition

The [NICE clinical guideline on GAD](#) describes the condition. The main features of GAD are excessive worry and tension. For a formal diagnosis using the [Diagnostic and statistical manual of mental disorders, fourth edition](#) (DSM-IV) classification system, 2 major symptoms are needed (excessive anxiety and worry about a number of events and activities, and difficulty controlling the worry) plus 3 or more additional symptoms from a list of 6. For the purpose of diagnosis, symptoms should be present for at least 6 months and cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

GAD may exist in isolation, but more commonly coexists with other anxiety disorders (including panic disorder, social phobia, specific phobias, obsessive compulsive disorder) or depression. The estimated proportion of people in England with GAD is 4.4%, with rates of 3.4% for men and 5.3% for women ([McManus et al. 2009](#)).

The [Hamilton Anxiety Rating Scale \(HAM-A\)](#) is often used in studies of treatment in GAD. This is a 14-item clinician-rated scale, with each item rated 0–4. The total score range is 0–56, with less than 17 indicating mild anxiety, 18–24 mild-to-moderate anxiety, and 25–30 moderate-to-severe anxiety. The first 2 items relate to anxious mood and tension.

Alternative treatment options

The [NICE clinical guideline on GAD](#) recommends a stepped-care model for managing GAD, offering the least intrusive, most effective intervention first. This is summarised in table 4.

Table 4 Stepped-care approach to treating generalised anxiety disorder

Focus of the intervention	Nature of the intervention
Step 1: All known and suspected presentations of GAD	Identification and assessment; education about GAD and treatment options; active monitoring
Step 2: Diagnosed GAD that has not improved after education and active monitoring in primary care	Low-intensity psychological interventions: individual non-facilitated self-help ^a , individual guided self-help and psychoeducational groups

Step 3: GAD with an inadequate response to step 2 interventions or marked functional impairment	Choice of a high-intensity psychological intervention (CBT/applied relaxation) or a drug treatment
Step 4: Complex treatment-refractory GAD and very marked functional impairment, such as self-neglect or a high risk of self-harm	Highly specialist treatment, such as complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care
^a A self-administered intervention intended to treat GAD involving written or electronic self-help materials (usually a book or workbook). It is similar to individual guided self-help but usually with minimal therapist contact, for example an occasional short telephone call of no more than 5 minutes.	

If drug treatment is selected, the [NICE clinical guideline](#) recommends a selective serotonin reuptake inhibitor (SSRI) as the first-line treatment option. Sertraline should be considered first because it is the most cost-effective drug, although it does not have a licence for use in GAD. If sertraline is ineffective, an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI) is recommended. If the person cannot tolerate SSRIs or SNRIs, pregabalin is recommended as an option. Benzodiazepines are not recommended in either primary or secondary care, except in the short-term management of crises.

The [full NICE guideline](#) included evidence relating to quetiapine as monotherapy in GAD and as augmentation therapy in addition to an antidepressant. However, this evidence was not assessed during guideline development because it was expected that quetiapine in GAD would be the subject of a NICE technology appraisal (see Relevance to NICE guidance programmes). Evidence for augmentation of antidepressant therapy with other antipsychotics (olanzapine, risperidone and ziprasidone) was assessed. The Guideline Development Group concluded that there was no evidence that these antipsychotics were effective as an augmentation treatment for reducing anxiety. In addition, there was evidence of an increase in treatment discontinuation due to adverse events. The Guideline Development Group therefore judged that such treatment should not be routinely used and should be provided only in specialist settings, and that antipsychotics should not be offered in primary care as stand-alone or augmentation treatment because this would need specialist expertise.

Evidence review: efficacy

The NICE guideline on [generalised anxiety disorder \(GAD\)](#) included evidence relating to quetiapine as monotherapy in GAD (4 randomised controlled trials [RCTs]: [Bandelow et al. 2010](#); [Khan et al.](#)

2011a; Meredith et al. 2012; Mezhebovsky et al. 2012) and as augmentation therapy in addition to an antidepressant (1 RCT: Simon et al. 2008). However, this evidence was not assessed during guideline development because it was expected that the use of quetiapine in GAD would be the subject of a NICE technology appraisal (see [Relevance to NICE guidance programmes](#)). Since the guideline was published, 2 additional RCTs have been published relating to use of quetiapine as augmentation to antidepressant therapy ([Altamura et al. 2011](#) and [Khan et al. 2011b](#)).

The key efficacy outcomes reported in all studies and summarised in the NICE guideline related to response (50% or greater reduction in [Hamilton Anxiety Rating Scale \[HAM-A\]](#) score) and remission (score of 7 or less on the HAM-A score).

Monotherapy: evidence summarised in the NICE full guideline

The [NICE full guideline on generalised anxiety disorder in adults](#) summarised 4 short-term RCTs, which compared prolonged-release quetiapine with placebo or antidepressants, and produced a pooled analysis of the data from them. At the time the full guideline was produced these were unpublished data supplied by the manufacturer, but the studies have subsequently been published in full ([Bandelow et al. 2010](#); [Khan et al. 2011a](#); [Meredith et al. 2012](#); [Mezhebovsky et al. 2012](#)). All 4 studies included people with GAD diagnosed according to [DSM-IV criteria](#) and a total HAM-A score of 20 or more, a score for the first 2 items of 2 or more, and a Montgomery–Åsberg Depression Rating Scale (MADRS) score of 16 or less. However, success or failure of previous treatment was not an inclusion criterion in any study.

In a pooled analysis of 2 RCTs lasting 8 weeks, prolonged-release quetiapine 50 mg per day (n=455) was compared with placebo (n=452). The pooled risk ratio for non-response was 0.82 (95% confidence interval [CI] 0.71 to 0.95); a statistically significant difference in favour of quetiapine (p=0.008). The pooled risk ratio for non-remission was 0.92 (95% CI 0.84 to 1.00), also favouring quetiapine (p=0.04).

In a pooled analysis of 3 RCTs lasting 8 weeks, prolonged-release quetiapine 150 mg per day (n=678) was compared with placebo (n=667). The pooled risk ratio for non-response was 0.73 (95% CI 0.62 to 0.85). The pooled risk ratio for non-remission was 0.86 (95% CI 0.79 to 0.92). Both results were statistically significant in favour of quetiapine (p<0.0001 for both).

In a pooled analysis of 2 RCTs lasting 8 weeks, prolonged-release quetiapine 300 mg per day (n=448) was compared with placebo (n=450). The pooled risk ratio for non-response was 0.92 (95%CI 0.81 to 1.05; p=0.23). The pooled risk ratio for non-remission was 1.00 (95% CI 0.92 to 1.08; p=0.91). Neither result was statistically significant.

In 1 RCT lasting 9 weeks, prolonged-release quetiapine in a flexible dose of 50–300 mg per day (n=223) was compared with placebo (n=227). The risk ratio for non-response was 0.42 (95% CI 0.34 to 0.51). The risk ratio for non-remission was 0.69 (95% CI 0.61 to 0.78). Both results were statistically significant in favour of quetiapine ($p < 0.00001$ for both).

Escitalopram and prolonged-release quetiapine were compared in 1 RCT lasting 8 weeks. Compared with prolonged-release quetiapine 150 mg per day, the risk ratio for non-response with escitalopram 10 mg per day was 1.18 (95% CI 0.94 to 1.47; $p = 0.14$). The risk ratio for non-remission was 1.09 (95% CI 0.96 to 1.25; $p = 0.18$). Compared with prolonged-release quetiapine 300 mg per day, the risk ratio for non-response with escitalopram 10 mg per day was 0.95 (95% CI 0.77 to 1.16; $p = 0.61$). The risk ratio for non-remission was 0.97 (95% CI 0.85 to 1.09; $p = 0.57$). None of these results was statistically significant, although the RCT may not have had sufficient statistical power to detect such a difference.

Paroxetine and prolonged-release quetiapine were compared in 1 RCT lasting 8 weeks. Compared with prolonged-release quetiapine 50 mg per day, the risk ratio for non-response with paroxetine 20 mg per day was 0.92 (95% CI 0.72 to 1.18; $p = 0.52$). The risk ratio for non-remission was 0.91 (95% CI 0.79 to 1.04; $p = 0.16$). Compared with prolonged-release quetiapine 150 mg per day, the risk ratio for non-response with paroxetine 20 mg per day was 1.17 (95% CI 0.89 to 1.54; $p = 0.25$). The risk ratio for non-remission was 0.91 (95% CI 0.79 to 1.04; $p = 0.16$). None of these results was statistically significant, although the RCT may not have had sufficient statistical power to detect such a difference.

Augmentation: Altamura et al. (2011)

The RCT by [Altamura et al. \(2011\)](#) included 20 people (5 male, 15 female) with GAD diagnosed according to DSM-IV criteria, in whom GAD was the primary mental health disorder needing treatment. In all people, GAD had not responded or only partly responded to at least 8 weeks' treatment with a selective serotonin reuptake inhibitor (SSRI) – escitalopram, citalopram, paroxetine or sertraline. People taking benzodiazepines were excluded. The baseline HAM-A score was 17, the mean age was 53 years and mean duration of illness was 8 years.

People stayed on their current SSRI treatment and were randomised to receive daily immediate-release quetiapine (n=10) or placebo (n=10) for 8 weeks. Quetiapine was started at 25 mg per day and could be increased by 25 mg per day per week up to a maximum 150 mg per day, depending on response and tolerability (mean dose during treatment: 50 mg per day). The study did not report whether participants or investigators were blinded to treatment allocation or whether allocation was concealed. No power calculation was reported and the primary outcome was not specified.

Quetiapine produced an improvement from baseline at 8 weeks in HAM-A score and the 7-point Clinical Global Impression of Severity (CGI-S) score (actual scores not reported). However, at week 8 there was no statistically significant difference between the groups in HAM-A score ($p=0.72$), HAM-A response rate (6 people in the quetiapine group compared with 3 people in the placebo group; $p=0.37$), HAM-A remission rate (4 people compared with 2 people respectively; $p=0.63$) or CGI-S score ($p=1.00$).

Augmentation: Khan et al. (2011b)

This double-blind RCT by [Khan et al. \(2011b\)](#) has been published in full; however, only a portion of the journal abstract is available at the time of publication of this evidence review (AstraZeneca UK Ltd, personal communication March 2013). This summary is based on the poster presentation of the study (AstraZeneca UK Ltd, personal communication March 2013) and the report on the manufacturer's website ([AstraZeneca Clinical Trials 2009](#)).

The study included 409 adults with GAD diagnosed according to DSM-IV criteria with a HAM-A score of 20 or greater with a score for the first 2 items of 2 or more, a CGI-S score of 4 or more. Participants' current anxious episode had either not responded or only partly responded to at least 8 weeks' treatment with duloxetine, escitalopram, paroxetine or venlafaxine, at or above the minimum effective dose (unless this was not tolerated). People were randomised to receive placebo or quetiapine prolonged-release tablets (each in combination with the antidepressant therapy, with or without a benzodiazepine). It is unclear if allocation was concealed.

All people randomised to quetiapine started on 50 mg per day, and increased to 150 mg per day on day 3. The dose was increased to 300 mg per day at week 3 (day 22) or week 4 (day 29) in people whose condition had shown no or limited improvement in the clinical global impression of illness. Those who were unable to tolerate the higher dose were returned to the 150 mg dose at the discretion of the investigator. The mean prescribed dose was 174 mg per day. The primary outcome was the change in HAM-A from baseline at week 8, and the study had 90% power based on an anticipated difference of 2.5 points from placebo and a standard deviation of 7.5. Secondary outcomes included response and remission measured by HAM-A, and changes in CGI-S.

The efficacy analyses were based on the modified intention-to-treat (mITT) analysis set; this included all randomised participants who took study treatment, and who had a HAM-A total score assessment at randomisation and at least 1 post-randomisation HAM-A total score (198 people randomised to placebo and 204 randomised to quetiapine). The mean age was 44 years and 74% of the mITT group were female.

After 8 weeks' treatment there was a reduction in HAM-A score from baseline in both groups but no statistically significant difference in reduction between quetiapine and placebo (mean reduction 10.74 points compared with 9.61 points respectively, difference 1.13 points, $p=0.079$). There was also no statistically significant difference in rate of in rate of HAM-A response (41.2% compared with 36.4% respectively, $p=0.342$) or rate of HAM-A remission (23.5% compared with 17.2% respectively, $p=0.134$). There was a mean reduction in CGI-S score of 1.36 in the quetiapine group and 1.13 in the placebo group at week 8 ($p<0.05$).

Augmentation: Simon et al. (2008)

This double-blind RCT by [Simon et al. \(2008\)](#) consisted of 2 phases. In the first phase, 54 adults with a primary diagnosis of GAD (according to DSM-IV criteria) and a HAM-A score of 18 or greater were treated with open-label controlled-release paroxetine (flexible dose, mean 47 mg per day) for 10 weeks. People taking concurrent psychotropic medication were excluded. In the second phase, the 22 people (50% female, mean age 42 years) who did not obtain remission (measured by HAM-A) at the end of this period continued with paroxetine at the same dose and were randomised to receive double-blind augmentation with quetiapine (formulation not stated, $n=11$) or placebo ($n=11$) for an additional 8 weeks. Quetiapine was started at 25 mg once daily for the first week and then increased according to response and tolerability to a maximum of 200 mg twice daily (mean dose 120 mg per day).

The primary outcome assessed was HAM-A score at the end of the second phase, but no power calculation was reported. Secondary outcomes included rates of remission measured by HAM-A, and response defined as a clinical global impression of 'very much improved' or 'much improved'. The trial was completed by 54.5% of the quetiapine group (6/11) and 90.9% of the placebo group (10/11). Analysis was by intention to treat. It is unclear if allocation was concealed.

Quetiapine did not produce a statistically significant decrease in HAM-A score compared with placebo (mean reduction from 16.27 points to 13.64 points in the quetiapine group, compared with a mean reduction from 15.82 points to 15.55 points in the placebo group, $p>0.3$). There was also no statistically significant difference in rates of HAM-A remission: 36.4% in the quetiapine group (4/11) compared with 18.2% (2/11) in the placebo group ($p=0.635$), or clinical global impression of response (54% compared with 45%, $p=1.0$).

Evidence review: safety

The summaries of product characteristics for [Seroquel tablets](#) and [Seroquel XL prolonged-release tablets](#) state that the most commonly reported adverse effects of quetiapine are somnolence,

dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia. They also warn about the potential for several additional adverse effects. These include suicidal thoughts, abnormal dreams and nightmares; tardive dyskinesia and extrapyramidal symptoms (including akathisia); weight gain, hyperglycaemia and lipid changes; hyperprolactinaemia and hypothyroidism; prolonged QT interval; venous thromboembolism; pancreatitis, hepatic effects, dysphagia and aspiration; seizures; neuroleptic malignant syndrome; severe neutropenia and other blood dyscrasias; and hypersensitivity reactions (see the summaries of product characteristics for full details). In addition, acute withdrawal symptoms (including insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) have been described after abrupt cessation of quetiapine.

Evidence summarised in the NICE full guideline on anxiety

The [NICE full guideline on generalised anxiety disorder in adults](#) summarised the outcome of treatment discontinuation because of adverse events, compared with placebo or antidepressants, from the 4 short-term RCTs of prolonged-release quetiapine in monotherapy (see [Evidence review: efficacy](#)). Compared with placebo, for a dose of 50 mg per day the pooled risk ratio for discontinuation because of adverse events was 2.62 (95% CI 1.68 to 4.07; $p < 0.0001$). For a dose of 150 mg per day it was 2.97 (95% CI 2.11 to 4.18; $p < 0.00001$). For a dose of 300 mg per day it was 3.69 (95% CI 2.54 to 5.37; $p < 0.00001$) and at a flexible dose of 50–300 mg per day it was 4.07 (95% CI 1.16 to 14.23; $p = 0.03$).

Compared with prolonged-release quetiapine 150 mg per day, the pooled risk ratio for discontinuation because of adverse events for escitalopram 10 mg per day was 0.55 (95% CI 0.34 to 0.91; $p = 0.02$). Compared with prolonged-release quetiapine 300 mg per day the pooled risk ratio for discontinuation because of adverse events for escitalopram 10 mg per day was 0.39 (95% CI 0.24 to 0.62; $p < 0.0001$). Both results were statistically significant in favour of escitalopram.

Compared with prolonged-release quetiapine 50 mg per day, the pooled risk ratio for discontinuation because of adverse events for paroxetine 20 mg per day was 0.67 (95% CI 0.37 to 1.19; $p = 0.17$; not statistically significant). Compared with prolonged-release quetiapine 150 mg per day, the pooled risk ratio for discontinuation because of adverse events for paroxetine 20 mg per day was 0.49 (95% CI 0.28 to 0.84; $p = 0.01$; a statistically significant result in favour of paroxetine).

Adverse events reported in randomised controlled trials

[Altamura et al. \(2011\)](#) reported that 1 person in the quetiapine group experienced sedation during the first week of treatment. No one was reported to have discontinued treatment because of adverse events.

In the trial by [Khan et al. \(2011b\)](#), safety analyses were performed on data from all randomised participants who took at least 1 dose of study medication. Of the people randomised to quetiapine, 154 out of 209 (74%) experienced at least 1 adverse event and 130 people (62%) experienced at least 1 adverse event judged to be drug-related. Although 24 people (12%) discontinued treatment because of adverse events, no assessment of whether or not these were treatment-related was reported. In comparison, 120 out of 200 (60%) people randomised to placebo experienced at least 1 adverse event, 72 people (36%) experienced at least 1 adverse event judged to be drug-related, and 4 people (2%) discontinued treatment because of adverse events. No statistical analysis of rates of adverse events was reported. No participants died or experienced serious adverse events.

In the trial by [Simon et al. \(2008\)](#), 45.5% of the quetiapine group (5/11) and 9.1% of the placebo group (1/11) withdrew from the study because of adverse events. No assessment of whether or not these were treatment-related was reported. Reasons for withdrawal were reported as 1 case each of weight gain, sedation, sleep fragmentation and akathisia, dry mouth, and unrelated medical illness in the quetiapine group, and 1 case of increased anxiety symptoms in the placebo group.

Evidence review: economic issues

Cost effectiveness

No cost effectiveness studies of quetiapine for use in generalised anxiety disorder (GAD) were identified.

Cost

The costs of quetiapine are given in the table below (taken from the [Drug Tariff April 2013](#), excluding VAT).

Quetiapine preparation and strength	Cost for 60 tablets
Immediate-release tablets	
25 mg	£2.25

100 mg	£4.83
150 mg	£5.18
200 mg	£5.54
300 mg	£7.65
Prolonged-release tablets	
50 mg	£67.66
150 mg	£113.10
200 mg	£113.10
300 mg	£170.00
400 mg	£226.20

Current drug usage

From the available prescribing data it is not possible to determine the indications for which quetiapine is prescribed. Therefore no information on prescribing rates of quetiapine for GAD is available.

Evidence strengths and limitations

The 4 randomised controlled trials (RCTs) that investigated prolonged-release quetiapine for monotherapy in generalised anxiety disorder (GAD) were short term (3 lasted 8 weeks and 1 lasted 9 weeks). They were assessed as providing moderate- to high-quality evidence in the [NICE full guideline](#). They provide evidence of a beneficial effect of prolonged-release quetiapine monotherapy in GAD compared with placebo. There was no statistically significant difference between quetiapine and paroxetine or escitalopram, although the RCTs may not have had sufficient statistical power to detect such a difference.

Three RCTs that investigated the safety and efficacy of quetiapine augmentation to antidepressant therapy in people with GAD have been identified. These were also short-term studies, lasting only 8 weeks. The quality of 2 of these ([Altamura et al. 2011](#) and [Simon et al. 2008](#)) is low; the small numbers of participants (20 and 22 people respectively) mean that they were unlikely to be adequately powered to detect differences between the quetiapine and placebo groups reliably (no power calculations were reported in either study), the trial by [Simon et al. \(2008\)](#) was double blind but blinding was not reported in the trial by [Altamura et al. \(2011\)](#), allocation concealment was

unclear in both trials, and the formulation of quetiapine was stated to be immediate release in the trial by [Altamura et al. \(2011\)](#), but was not stated in the trial by [Simon et al. \(2008\)](#).

The available information relating to the largest study of quetiapine augmentation to antidepressant therapy in people with GAD ([Khan et al. 2011b](#)) suggests that this double-blind study was adequately powered for its primary outcome (difference in improvement of HAM-A score from baseline): the study size ensured 90% power to detect a difference of 2.5 points or more. It is therefore important to note that this study did not detect a statistically significant difference between prolonged-release quetiapine and placebo for this outcome, or for rates of response or remission. Prolonged-release quetiapine appeared to be less well tolerated than placebo, although statistical analysis of rates of adverse events was not reported.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

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AstraZeneca UK Limited (2012) [Seroquel XL 50 mg, 150mg, 200 mg, 300 mg, 400 mg prolonged-release tablets summary of product characteristics](#) [online; accessed 2 April 2013]

Bandelow B, Chouinard G, Bobes J et al. (2010) Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study. *The International Journal of Neuropsychopharmacology* 13: 305–20

Khan A, Joyce M, Atkinson S et al. (2011a) A randomized, double-blind study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder. *Journal of Clinical Psychopharmacology* 31: 418–28

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Mezhebovsky I, Mägi K, She F et al. (2012) Double-blind, randomized study of extended release quetiapine fumarate (quetiapine XR) monotherapy in older patients with generalized anxiety disorder. *International Journal of Geriatric Psychiatry* doi: 10.1002/gps.3867

National Collaborating Centre for Mental Health (2011) Generalised anxiety disorder in adults: management in primary, secondary and community care. NICE clinical guideline 113. Leicester and London (UK): The British Psychological Society and The Royal College of Psychiatrists

National Institute for Health and Clinical Excellence (2011) Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. NICE clinical guideline 113

Simon NM, Connor KM, LeBeau RT et al. (2008) Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. *Psychopharmacology* 197: 675–81

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [interim process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Project team

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AstraZeneca UK Ltd reviewed the document and provided additional technical information.

Declarations of interest

The expert adviser has a non-personal pecuniary interest in the form of ongoing studies related to unipolar depression with AstraZeneca.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- [NICE Evidence Services](#)
- [NICE](#)
- [Euroscan](#)

- Broad internet search: Google, for example, quetiapine AND (~guideline OR ~algorithm) filetype:pdf
- Scirus

MEDLINE & Embase (via Ovid)

1. Antipsychotic Agents/ (38374)
2. (seroquel or quetiapine).ti,ab. (2698)
3. Anxiety Disorders/ (20729)
4. (general* adj3 anxiety).ti,ab. (5724)
5. 1 or 2 (38878)
6. 3 or 4 (23443)
7. 5 and 6 (325)
8. exp review/ (1740175)
9. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (69739)
10. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (6092)
11. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (13557)
12. (pooling or pooled or mantel haenszel).ti,ab,sh. (45264)
13. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2605)
14. or/9-13 (119852)
15. 8 and 14 (53177)
16. Meta Analysis/ (36776)
17. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (65234)
18. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (52315)

19. (integrative research review\$ or research integration).ti,ab,sh. (82)
20. or/16-19 (101586)
21. 15 or 20 (129141)
22. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (234208)
23. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (864659)
24. 22 or 23 (959230)
25. (animal\$ not human\$).sh. (3662859)
26. 24 not 25 (855606)
27. (cost\$ or economic\$).tw. (419234)
28. 21 or 26 or 27 (1310236)
29. 7 and 28 (97)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Antipsychotic Agents] this term only

#2 seroquel:ti,ab,kw

#3 quetiapine:ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Anxiety Disorders] this term only

#6 general* adj3 anxiety:ti,ab,kw

#7 #5 or #6

#8 #4 and #7

CRD HTA, DARE and EED database

1. MeSH DESCRIPTOR Antipsychotic Agents EXPLODE ALL TREES

2. (quetiapine) OR (seroquel)

3. #1 OR #2

4. MeSH DESCRIPTOR Anxiety Disorders EXPLODE ALL TREES

5. (general*) AND (anxiety)

6. #4 OR #5

7. #3 AND #6

Grey literature and ongoing trials

- [FDA](#)
- [EMA](#)
- [MHRA](#)
- [Scottish Medicines Consortium](#)
- [All Wales Medicine Strategy Group](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

Manufacturers' websites

[Accord Healthcare Limited](#)

[Actavis UK Ltd](#)

[AstraZeneca UK Limited](#)

[Pfizer Limited](#)

Sandoz Limited

Zentiva

Evidence selection

This evidence summary included only randomised controlled trials that have investigated the efficacy of quetiapine for people with a primary diagnosis of GAD; non-comparative studies were not included.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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