Quetiapine

Section: 24. Medicines for mental and behavioural disorders > 24.2. Medicines for mood disorders > 24.2.2. Medicines for bipolar disorders

ATC codes: N05AH04

Indication	Bipolar or related disorders ICD11 code: 6A6Z
INN	Quetiapine
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 25 mg (immediate-release) ; 100 mg (immediate-release) ; 150 mg (immediate-release) ; 200 mg (immediate-release) ; 300 mg (immediate-release) ; 50 mg (modified-release) ; 150 mg (modified-release) ; 200 mg (modified-release) ; 300 mg (modified-release) ; 400 mg (modified-release)
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Quetiapine
DrugBank	Quetiapine

Expert Committee recommendation

The Expert Committee noted the increasing prevalence of bipolar disorders worldwide, the significant disability associated with it, and recognized the importance of its treatment to reduce the associated morbidity and mortality. The Committee noted that the EML currently includes only carbamazepine, lithium carbonate and valproic acid for use in bipolar disorders. The Committee agreed that second-generation antipsychotics have an important role in treatment of bipolar disorders in patients who do not adequately respond to or experience adverse events from mood stabilizers. Moreover, the Committee noted that the two classes of medicines may be used in combination in selected patients in clinical practice. The Committee noted that the detailed analysis of oral antipsychotics included in the application was aligned with the work carried out for the update of the WHO mhGAP guidelines for psychosis. The Committee also noted that the proposed inclusion of quetiapine and the specified therapeutic alternatives on the EML for treatment of bipolar disorders was aligned with recommendations in the forthcoming update of the guidelines. According to the most recent and high-quality meta-analytical evidence on the acute and maintenance treatment of bipolar disorders, second-generation antipsychotics have been found to be either superior or non-inferior to placebo, and at least as effective as the classic mood stabilizers currently included on the EML for both treatment of acute affective episodes (mania, hypomania and depression) and maintenance treatment in clinically stable patients. Among the medicines proposed for inclusion, head-to-head comparisons generally showed no significant differences in efficacy or acceptability between them, with moderate-to-high certainty of evidence. The Committee noted that second-generation antipsychotics can help to manage

the symptoms of bipolar disorder and improve the overall quality of life of patients by reducing the frequency and severity of manic and depressive episodes and preventing hospitalizations. They therefore reduce the burden of the disease for both individuals and healthcare systems. The Committee noted that quetiapine, and the proposed therapeutic alternative antipsychotics, were available as generics in most countries, at varying prices and affordability. The Expert Committee accepted the criteria applied by the applicants in identifying the second-generation antipsychotics proposed and recommended the inclusion of quetiapine, with a square box indicating aripiprazole, olanzapine and paliperidone as specified therapeutic alternatives, on the core list of the EML for treatment of bipolar disorders.

Background

Neither quetiapine nor the proposed therapeutic alternatives has previously been evaluated for inclusion on the EML for the treatment of bipolar disorders. Medicines for the treatment of bipolar disorders currently included on the EML are lithium carbonate (since 1977), carbamazepine (since 1997) and valproic acid (since 1997).

Public health relevance

Bipolar disorders affect about 40 million people globally, accounting for about 4% of all mental disorders in 2019. These disorders affect about 1 in 150 adults worldwide and their prevalence is relatively consistent across different regions and in males and females (1,2). Bipolar disorder type I has a lifetime prevalence of around 1.0%, while bipolar disorder type II has a lifetime prevalence of about 1.6% (3). The disease burden of bipolar disorders has been increasing over the years, with about 9.29 million disability-adjusted life years (DALYs) reported globally in 2017, a 54.4% increase from 1990 (4). People with bipolar disorders have a lower life expectancy than the general population. A recent meta-analysis of 11 observational studies, including 96 601 individuals, found that the pooled life expectancy of those with bipolar disorders was 67 years (95% confidence interval (CI) 64 to 69 years). Women with bipolar disorders tended to have a slightly higher life expectancy than men. The weighted average of years of potential life lost (YPLLs) was 12.9 years (95% CI 12.7 to 13.1 years), with the highest YPLLs reported in Africa (5). Suicide is the most common cause of unnatural deaths in people with bipolar disorders; they have a 20- to 30-fold greater risk compared with the general population (6). However, excess mortality from natural causes can also be attributed to various factors, such as unhealthy lifestyle choices (including sedentary habits, smoking and substance use), metabolic side-effects of antipsychotic medications and inequitable medical care. Moreover, bipolar disorders are associated with a high prevalence of comorbid mental health conditions that develop over their course. These comorbidities add to the overall burden and challenges faced by individuals with bipolar disorders (7). Bipolar disorders are associated with significant costs for individuals, health care systems and society due to factors such as reduced work productivity and unemployment. A meta-analysis of 56 United States studies estimated an annual national economic burden of more than US$ 195 billion, with 25% attributed to direct medical costs (8). Prompt pharmacological treatment is crucial for managing acute manic/hypomanic and depressive episodes in bipolar disorders, along with continuous maintenance treatment from the early stages of the disease. This approach helps prevent chronic functional deterioration, reduce subthreshold symptoms and lower the risk of suicide (9,10). However, treatment non-adherence is an important challenge, affecting up to 40% of individuals with bipolar disorders (11). In recent years, scientific evidence has increased substantially on the comparative efficacy and tolerability of pharmacological treatments for bipolar disorders, which include lithium, antiseizure medicines and antipsychotics. Not all treatments are equally effective or well tolerated, and the choice of treatment should be personalized through a shared-decision making process based on individual needs. It is important to note that treatment effectiveness may vary across different phases of the disease, such as acute manic/hypomanic/depressive episodes or long-term prevention of recurrences. Additionally, the certainty of evidence supporting various treatments may differ (12–16). As well as pharmacological interventions, psychosocial approaches such as psychoeducation, cognitive behavioural therapy and family therapy have been effective in treating bipolar disorders. A comprehensive approach that combines pharmacological and psychosocial interventions is essential for effectively managing the condition (17). In low and middle-income countries, treatment coverage for mental disorders, including bipolar disorders, is inadequate. Up to 50% of individuals with bipolar disorders do not receive sufficient treatment (18). Additionally, only a few countries can be

considered fully aligned with the principle of providing complete access to essential psychotropic medications such as antipsychotics and mood stabilizers. Low availability and high costs of these medicines are significant barriers to access in these regions (19).

Benefits

A 2022 systematic review and network meta-analysis of 56 randomized controlled trials (14 503 participants) evaluated pharmacological treatments (oral antipsychotics and mood stabilizers) as monotherapy for acute treatment of bipolar mania (16). Overall, all the included antipsychotics (risperidone, haloperidol, olanzapine, cariprazine, quetiapine, aripiprazole, paliperidone, ziprasidone and asenapine) showed better response to treatment compared to placebo: risk ratio (RR) 1.69 (95% CI 1.41 to 2.02) for risperidone, RR 1.55 (95% CI 1.32 to 1.83) for quetiapine and RR 1.28 (95% CI 1.05 to 1.56) for asenapine. In head-to-head comparisons, few differences were seen between treatments. Olanzapine outperformed haloperidol (RR 1.37, 95% CI 1.11 to 1.69), cariprazine (RR 1.56, 95% CI 1.13 to 2.13), brexpiprazole (RR 1.73, 95% CI 1.14 to 2.63), asenapine (RR 1.54, 95% CI 1.18 to 2.01) and aripiprazole (RR 1.30, 95% CI 1.05 to 1.61). When comparing oral second-generation antipsychotics with mood stabilizers included in the EML, there were relatively few and small differences. Carbamazepine showed no statistically significant differences when compared to any second-generation antipsychotic. However, olanzapine (RR 1.59, 95% CI 1.28 to 1.98) and quetiapine (RR 1.36, 95% CI 1.02 to 1.81) outperformed lithium, and olanzapine outperformed valproic acid (RR 0.76, 95% CI 0.63 to 0.93). The certainty of evidence was generally low or very low for most comparisons, except for quetiapine, for which the certainty of evidence against placebo was moderate. A 2021 network meta-analysis of 18 randomized controlled trials (7969 participants) evaluated the efficacy and tolerability of atypical antipsychotics in the treatment of acute bipolar depression (14). As measured by the mean change in Montgomery Åsberg Depression Rating Scale (MADRS) score from baseline to the end of the study, cariprazine, olanzapine, quetiapine, and lurasidone were more effective than placebo, with mean differences (MD) ranging from −4.80 (95% CI −5.93 to −3.72) for quetiapine to −2.29 (95% CI −3.47 to −1.09) for cariprazine. Aripiprazole and ziprasidone did not show significant differences compared with placebo. In head-to-head comparisons, olanzapine outperformed aripiprazole (MD –3.49, 95% CI –6.07 to –0.92), cariprazine (MD –2.29, 95% CI –4.09 to –0.46) and ziprasidone (MD –3.23, 95% CI –5.66 to –0.83). Quetiapine outperformed aripiprazole (MD –4.80, 95% CI –5.93 to –3.72), cariprazine (MD –2.52, 95% CI –4.11 to –0.92) and ziprasidone (MD –3.46, 95% CI –5.76 to –1.24). Lurasidone outperformed aripiprazole (MD –3.63, 95% CI –6.78 to –0.50) and ziprasidone (MD –3.36, 95% CI –6.38 to –0.39). The certainty of evidence based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach for network meta-analyses was high for cariprazine, lurasidone, olanzapine and quetiapine compared with placebo. It was moderate for: aripiprazole and ziprasidone compared with lurasidone; and cariprazine and aripiprazole compared with quetiapine and olanzapine. It was low for: aripiprazole and ziprasidone compared with placebo; cariprazine, olanzapine, and quetiapine compared with lurasidone; ziprasidone, and olanzapine compared with quetiapine; and cariprazine compared with aripiprazole. It was very low for all other comparisons. A 2021 systematic review and network meta-analysis of 41 randomized controlled trials (9821 participants) evaluated antipsychotics and mood stabilizers, alone or in combination, for long-term prevention of any mood episode in clinically stable adults with bipolar disorders (15). Most oral antipsychotics (aripiprazole, asenapine, olanzapine, quetiapine and paliperidone) and the combination aripiprazole + lamotrigine were more effective than placebo in decreasing recurrence/relapse rate of manic/hypomanic/mixed episodes: with RRs ranging from 0.21 (95% CI 0.08 to 0.53) for asenapine to 0.55 (95% CI 0.43 to 0.71) for quetiapine. In head-to-head comparisons of oral antipsychotic monotherapies, asenapine outperformed paliperidone (RR 0.35, 95% CI 0.13 to 0.96) and quetiapine (RR 0.37, 95% CI 0.14 to 0.98), and olanzapine outperformed paliperidone (RR 0.59, 95% CI 0.37 to 0.94) and quetiapine (RR 0.62, 95% CI 0.44 to 0.89). Compared with mood stabilizers currently included in the EML: lithium was outperformed by olanzapine (RR 1.56, 95% CI 1.17 to 2.06) and asenapine (RR 0.39, 95% CI 0.15 to 0.99); carbamazepine was outperformed by asenapine (RR 0.10, 95% CI 0.01 to 0.99); and valproic acid was outperformed by olanzapine (RR 0.54, 95% CI 0.38 to 0.78) and asenapine (RR 0.33, 95% CI 0.12 to 0.86). Considering only monotherapies, the certainty of evidence was: moderate for aripiprazole, asenapine, olanzapine and paliperidone versus placebo; low for olanzapine versus placebo, and aripiprazole versus asenapine, carbamazepine, olanzapine, paliperidone,

quetiapine and valproic acid; and very low for the remaining comparisons. For the recurrence/relapse rate of depressive episodes in individuals with bipolar disorders, meta-analysis of 25 randomized controlled trials (6438 participants) was performed (15). The results showed that aripiprazole + valproic acid, quetiapine and olanzapine were more effective than placebo, with RRs ranging from 0.27 (95% CI 0.08 to 0.99) for aripiprazole + valproic acid to 0.74 (95% CI 0.56 to 0.98) for olanzapine. Estimates for asenapine, aripiprazole, paliperidone and cariprazine were not significant. In head-to-head comparisons of oral antipsychotic monotherapies, asenapine outperformed paliperidone (RR 0.29, 95% CI 0.09 to 0.91) and quetiapine outperformed olanzapine (RR 1.55, 95% CI 1.05 to 2.28) and paliperidone (RR 2.73, 95% CI 1.55 to 4.8). Compared with mood stabilizers already included in the EML, carbamazepine was outperformed by asenapine (RR 0.14, 95% CI 0.02 to 0.84) and quetiapine (RR 5.69, 95% CI 1.29 to 25.01), valproic acid was outperformed by quetiapine (RR 0.57, 95% CI 0.37 to 0.87), and lithium was outperformed by quetiapine (RR 1.65, 95% CI 1.21 to 2.25). The remaining head-to-head comparisons were not significant. The certainty of evidence for antipsychotic monotherapies compared with placebo and mood stabilizers was generally low, except for the comparison of paliperidone with quetiapine, which had moderate certainty according to the confidence in network meta-analysis (CINeMA) approach (15).

Harms

In the 2022 network meta-analysis on the acute treatment of adults with bipolar mania (16), all-cause discontinuation (acceptability) was used as a pragmatic measure of the balance between desirable and undesirable effects of medications. The acceptability analysis included 70 randomized controlled trials with 16 324 participants. Olanzapine, quetiapine, risperidone and aripiprazole were significantly more acceptable than placebo. Paliperidone, ziprasidone, haloperidol, asenapine, cariprazine, brexpiprazole and chlorpromazine did not show significant differences from placebo in terms of acceptability. Head-to-head comparisons between second-generation antipsychotics showed that olanzapine was more acceptable than aripiprazole (RR 1.30, 95% CI 1.05 to 1.61), asenapine (RR 1.54, 95% CI 1.18 to 2.01), brexpiprazole (RR 1.73, 95% CI 1.14 to 2.63), cariprazine (RR 1.56, 95% CI 1.13 to 2.13), haloperidol (RR 1.37, 95% CI 1.11 to 1.69) and ziprasidone (RR 0.75, 95% 0.56 to 0.99). When comparing second-generation antipsychotics to mood stabilizers already included on the EML, both olanzapine (RR 1.59, 95% CI 1.28 to 1.98) and quetiapine (RR 1.36, 95% CI 1.02 to 1.81) outperformed lithium, and olanzapine outperformed valproic acid (RR 0.76, 95% CI 0.63 to 0.93). No significant differences were seen between second-generation antipsychotics and carbamazepine. The certainty of evidence based on the CINeMA approach was generally low or very low for most of the comparisons, indicating limited confidence in the results (16). In the 2021 network meta-analysis on the acute treatment of adults with bipolar depression (14), the analysis for all-cause discontinuation included 18 randomized controlled trials with 7969 participants. Aripiprazole had a significantly higher risk of all-cause discontinuation compared with placebo (odds ratio (OR) 1.68, 95% CI 1.09 to 2.48). For cariprazine, lurasidone, olanzapine, ziprasidone and quetiapine, no significant differences in all-cause discontinuation rates were observed. In head-to-head comparisons, aripiprazole was more effective than olanzapine (OR 0.44, 95% CI 0.24 to 0.73) and quetiapine (OR 0.62, 95% CI 0.37 to 0.96), while ziprasidone outperformed olanzapine (OR 2.03, 95% CI 1.15 to 3.30). The certainty of evidence based on the CINeMA approach was rated as very low for ziprasidone, moderate for aripiprazole, cariprazine, olanzapine and quetiapine, and high for lurasidone (14). In the 2021 network meta-analysis on long-term prevention of any mood episode in clinical stable adults with bipolar disorder (15), the analysis for all-cause discontinuation included 29 randomized controlled trials with 6899 participants. Most antipsychotics did not show significant differences in all-cause discontinuation rates compared with placebo. However, quetiapine, (RR 0.66, 95% CI 0.52 to 0.83), asenapine (RR 0.45, 95% CI 0.27 to 0.75) and olanzapine (RR 0.68, 95% CI 0.56 to 0.84) had lower discontinuation rates than placebo. In head-to-head comparisons, asenapine outperformed aripiprazole (RR 2.15, 95% CI 1.17 to 3.95) and paliperidone (RR 0.50, 95% CI 0.27 to 0.93). No other statistically significant differences were observed between antipsychotics. When mood stabilizers already included in the EML were considered, carbamazepine was outperformed by asenapine (RR 0.46, 95% CI 0.25 to 0.84) and quetiapine (RR 1.49, 95% CI 1.02 to 2.19). Asenapine outperformed valproic acid (RR 0.56, 95% CI 0.32 to 0.99) and lithium (RR 0.54, 95% CI 0.32 to 0.91). When considering monotherapies only, the certainty of evidence, based on the CINeMA approach, was very low for quetiapine versus placebo, carbamazepine and lithium, moderate for asenapine versus placebo, aripiprazole and

carbamazepine, and low for all the remaining comparisons (15). A 2018 systematic review and meta-analysis of 352 randomized controlled trials (84 988 participants) compared mortality risk between second-generation antipsychotics and placebo for various diagnoses. No significant differences were seen between antipsychotic medicines and placebo for death from any cause (OR 1.19, 95% CI 0.93 to 1.53), death from natural causes (OR 1.29, 95% CI 0.85 to 1.94), suicide (OR 1.15, 95% CI 0.47 to 2.81) or other non-natural causes (OR 1.55, 95% CI 0.66 to 3.63). Furthermore, significant differences in mortality risk between antipsychotics and placebo were not observed in the subgroup analysis that specifically focused on people with bipolar disorders (OR 1.09, 95% CI 0.53 to 2.25) (20). A 2019 systematic review and meta-analysis of 314 randomized controlled trials (67 642 participants) compared the risk of somatic serious adverse events between second-generation antipsychotics and placebo for various diagnoses. In the subgroup analyses for each antipsychotic, haloperidol (OR 1.61, 95% CI 1.07 to 2.43), olanzapine (OR 1.35, 95% CI 1.04 to 1.74) and risperidone (OR 1.33, 95% CI 1.04 to 1.70) showed a significantly higher risk of serious adverse events compared with placebo. No significant differences in the risk of serious adverse events compared with placebo were observed for the other antipsychotic medications studied (21). The most common side-effects of quetiapine include drowsiness, dizziness, weight gain and dry mouth. As with other second-generation antipsychotics, quetiapine can also cause metabolic changes, such as increased cholesterol and blood sugar levels in some people. More serious adverse effects such as tardive dyskinesia and neuroleptic malignant syndrome are rare. Quetiapine should be used with caution during pregnancy and breastfeeding, as the medication may pose risks to the developing fetus or infant.

Cost / cost effectiveness

A pharmacoeconomic study in the Kingdom of the Netherlands compared the cost–effectiveness of mood stabilizers alone (lithium or valproic acid) with combination therapy of lithium plus a second-generation antipsychotic (quetiapine, olanzapine or risperidone) for the treatment of acute mania (23). The study assessed direct treatment costs, including hospitalizations, outpatient visits and medications for adverse effects, over a 100-day period. Monotherapies with lithium or valproic acid were more expensive than combination therapies. Among the combination therapies, lithium plus quetiapine was significantly more expensive (€2555) compared with lithium plus risperidone (€2365) or olanzapine (€2429) due to higher acquisition costs. However, the lithium plus quetiapine combination was associated with fewer side-effects. Additionally, other pharmacoeconomic analyses provided evidence supporting the cost–effectiveness of the quetiapine plus lithium combination therapy over lithium alone for the maintenance treatment of bipolar disorders (24–26). Two retrospective studies analysed the direct costs and health care outcomes associated with different atypical antipsychotics for the treatment of bipolar disorders. The first study, using data from a Medicaid programme, compared the direct health care costs of quetiapine, olanzapine and risperidone monotherapies in the year after the start of treatment. No significant difference in total health care costs was seen between the three antipsychotics (quetiapine US$ 14 417, olanzapine US$ 13 804 and risperidone US$ 16 214) or in costs related to bipolar disorder (quetiapine US$ 4372, olanzapine US$ 4596 and risperidone US$ 4435) (27). The second study used datasets of insurance claims to compare time to hospitalization and health care costs (pharmacy costs, mental health costs and overall health care costs) of different atypical antipsychotics over a year. Aripiprazole had a significantly lower time to hospitalization compared with ziprasidone, olanzapine and quetiapine (hazard ratio (HR) 1.96, 1.55 and 1.56, respectively; $P < 0.05$), but no significant difference was found between aripiprazole and risperidone (HR 1.37, $P = 0.10$). Monthly mental health care costs were significantly lower for aripiprazole compared with ziprasidone (US$ 487 versus US$ 631) and quetiapine (US$ 430 versus US$ 519), but not significantly different when compared with olanzapine (US$ 447 versus US$ 484) or risperidone (US$ 449 versus US$ 442). Total monthly health care costs were significantly lower for aripiprazole compared with quetiapine (US$ 875 versus US$ $1060), with no significant differences with the other comparators (28). A Canadian cost–utility analysis compared the economic impact of asenapine versus olanzapine in treating bipolar disorder over a 5-year horizon. The study focused on weight gain and long-term metabolic complications, including diabetes, hypertension, coronary heart diseases and stroke. The use of asenapine was cost-effective, resulting in a gain of 84.8 quality-adjusted life years (QALYs) per 1000 patients and lower costs from both the Ministry of Health and societal perspectives by about Can$ 3.8 million less in each case (29). In a Swedish study, the cost–effectiveness of aripiprazole versus olanzapine was

investigated over a lifetime horizon using a Markov health-state transition model. Assuming equivalent efficacy, the study used the annual incidence rate of metabolic syndrome to estimate the long-term cardiovascular consequences. The lower incidence of type II diabetes and coronary artery disease in patients treated with aripiprazole led to a gain of 0.09 QALYs and cost savings of US$ 3720 compared with olanzapine (30).

WHO guidelines

The proposed inclusion of quetiapine and the specified therapeutic alternatives on the EML for treatment of bipolar disorder is aligned with recommendations in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use (22).

Availability

A recent analysis of 112 national essential medicine lists found that second-generation antipsychotics are not commonly included in these lists. First-generation antipsychotics such as haloperidol and chlorpromazine are more frequently listed. Inclusion of second-generation antipsychotics appears to be associated with the socioeconomic status of the country; these antipsychotics are more often included in the essential medicine lists of high-income countries but are only found in a minority of lower middle-income countries (19). Quetiapine and the proposed therapeutic alternatives are variably available worldwide, in innovator and generic brands.

Other considerations

The applicants identified the second-generation antipsychotics proposed for EML listing by applying the following criteria: • being superior to placebo in terms of efficacy for both acute treatment and long-term prevention of mania/hypomania and/or depression; • having moderate-to-high certainty of evidence according to GRADE/CINeMA assessment for efficacy for at least one of the subpopulations considered, that is, acute mania, acute depression and clinically stable bipolar disorders; • being superior/non-inferior to placebo in terms acceptability (all-cause discontinuation) for most of the subpopulations considered, that is, at least two among acute mania, acute depression and clinically stable bipolar disorders.

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