Risperidone

Essential medicine status ✓

ATC codes: N05AX08

Indication	Schizophrenia or other primary psychotic disorders ICD11 code: 6A4Z
INN	Risperidone
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 0.25 mg ; 0.5 mg ; 1 mg ; 2 mg ; 3 mg ; 4 mg ; 6 mg
EML status history	First added in 2013 (TRS 985) Changed in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	aripiprazole (ATC codes: N05AX12) olanzapine (ATC codes: N05AH03) paliperidone (ATC codes: N05AX13) quetiapine (ATC codes: N05AH04)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Risperidone
DrugBank	Risperidone

Expert Committee recommendation

The Expert Committee noted that evidence from several high-quality meta-analyses on acute and maintenance treatment of schizophrenia and other chronic psychoses found most oral second-generation antipsychotics were similarly effective and tolerable. The Expert Committee accepted the criteria applied by the applicants in identifying the proposed therapeutic alternatives and recommended the addition of a square box to the listing of risperidone on the EML for treatment of schizophrenia and related chronic psychotic disorders, specifying oral aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives.

Background

Oral risperidone was added to the EML in 2013 as a treatment for schizophrenia. In making this recommendation, the Expert Committee considered that except for clozapine, the efficacy and safety of the second-generation antipsychotics were comparable but noted that the availability of generics varied considerably. The Expert Committee recommended that risperidone be added to the EML without the square box symbol. However, the Committee indicated that it would welcome further applications for additional second-generation antipsychotics, based on careful consideration of suitable alternatives or additions to risperidone (1).

Public health relevance

In 2019, about 24 million people in the world were estimated to have schizophrenia (2). The prevalence of schizophrenia ranged from 0.2% to 0.4% across countries, while its incidence was 16.7 per 100 000 person-years (3). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which are attributable to schizophrenia spectrum disorders. Schizophrenia is also associated with direct and indirect health care costs, and it is considered the costliest mental health condition per person globally (2,4). The relationship between schizophrenia and stress-related noncommunicable diseases is well known (5). People with schizophrenia have a 15–20 year shorter life expectancy than the general population

(6,7). While suicide explains some of this reduced life expectancy, physical diseases probably account for most of the premature mortality (7,8). According to current evidence, regular pharmacological treatment from the early phases of the disease may preserve neurocognitive abilities, prevent structural brain changes and delay progression to chronic functional deterioration, thus resulting in better life conditions and increased survival (9). However, treatment adherence is an important problem, with up to half of all individuals with schizophrenia not taking medications as prescribed and only one third fully adhering to antipsychotic treatment. Such non-adherence increases the risk of relapse (10–13). Not all antipsychotics are equally effective and tolerable, and not all are supported by high-quality evidence (14–19). Both clinical response and individual vulnerability to adverse events vary widely between individuals, therefore health practitioners treating patients with schizophrenia should tailor the choice of antipsychotic medicine based on individual characteristics, weighing expected benefits and harms (12). The median value for treatment coverage in low- and middle-income countries has been estimated at about 30% (20), suggesting that 70% of people with schizophrenia spectrum disorders in these countries do not receive adequate treatment. The treatment gap for schizophrenia disorders was larger in low-income countries (89%) than in lower middle-income (69%) and upper middle-income countries (63%). The size of the treatment gap is negatively associated with the prevalence of schizophrenia disorders in the general population, gross national income, availability of psychiatric hospital beds, number of psychiatrists per 100 000 population and number of nurses in mental health facilities per 100 000 population (20). Furthermore, few countries are aligned with the general principle of providing full access to essential psychotropic medicines, with limited availability and high prices being major barriers (21).

Benefits

The application presented the results of a comprehensive literature search for systematic reviews on the efficacy, acceptability, tolerability and safety of antipsychotic medicines in adults with schizophrenia spectrum disorders. Two key systematic reviews and network meta-analyses were identified (15,16). A 2019 network meta-analysis including both placebo-controlled and head-to-head randomized controlled trials compared 32 oral antipsychotics for the acute treatment of adults with multiepisode schizophrenia (15). The primary outcome analysis of change in overall symptoms at the end of the study was based on 218 studies (40 815 participants). Most antipsychotics (81%) outperformed placebo, with standardized mean differences (SMD) ranging between –0.89 (clozapine) and –0.26 (brexpiprazole). Effect sizes and 95% credible intervals (95% CrI) were largely overlapping. Certainty of evidence according to the confidence in network meta-analysis (CINeMA) approach was high only for risperidone and paliperidone, and moderate for amisulpride, zotepine, olanzapine, perphenazine, haloperidol and quetiapine. In the head-to-head comparisons, clozapine, amisulpride, zotepine, olanzapine and risperidone were among the best-performing medications. Amisulpride outperformed risperidone (SMD –0.18, 95% CrI –0.33 to –0.02), which in turn outperformed quetiapine (SMD –0.13, 95% CrI –0.23 to –0.04), aripiprazole (SMD –0.14, 95% CrI –0.25 to –0.03), ziprasidone (SMD –0.14, 95% CrI –0.25 to –0.03), sertindole (SMD –0.15, 95% CrI –0.30 to –0.01), asenapine (SMD –0.16, 95% CrI –0.30 to –0.02), lurasidone (SMD –0.19, 95% CrI –0.32 to –0.05), cariprazine (SMD –0.21, 95% CrI –0.36 to –0.05), iloperidone (SMD –0.22, 95% CrI –0.34 to –0.10) and brexpiprazole (SMD –0.29, 95% CrI –0.45 to –0.14). Most of these comparisons barely reached statistical significance and the differences were clinically negligible (Cohen d < 0.2) (22), with the exception of cariprazine, iloperidone and brexpiprazole, for which the differences were small (0.2 < Cohen d < 0.5). A 2022 network meta-analysis including both placebo-controlled and head-to-head randomized controlled trials compared 32 oral and long-acting antipsychotics for the prevention of relapse in adults with schizophrenia or schizoaffective disorder with stable symptoms who were already treated with antipsychotics (16). The primary outcome analysis of risk of relapse was based on 100 studies (16 812 participants). All antipsychotics had risk ratios (RR) less than 1 compared with placebo, and all except for oral cariprazine, oral lurasidone and long-acting injectable clopenthixol had 95% CrI excluding no effect. Certainty of evidence according to the CINeMA approach was moderate for most of the best-performing medications, with the exception of oral fluphenazine, oral tiotixene and oral iloperidone oral which were rated as low-certainty of evidence. From the head-to-head comparisons, clozapine, amisulpride, zotepine, olanzapine and risperidone were among the best-performing medications, while in most cases the differences were small or non-significant. No statistically significant differences emerged in head-to-head comparison of risperidone and other oral second-generation antipsychotics. Two additional network meta-analyses were described which confirmed and expanded the efficacy findings described above (17,19).

Harms

The network meta-analysis on the acute treatment of adults with multiepisode schizophrenia provided data on the acceptability of treatments (all-cause discontinuation) (15). The analysis included 226 randomized controlled trials (42 672 participants) and showed that most of the included medications were significantly more acceptable than placebo and none was less acceptable than placebo. Certainty of evidence according to the CINeMA approach was high for olanzapine, paliperidone, risperidone, iloperidone, aripiprazole, quetiapine and asenapine, and moderate for amisulpride, clotiapine, zuclopenthixol, zotepine and

levomepromazine. In head-to-head comparisons between risperidone and other second-generation antipsychotics, risperidone was outperformed by olanzapine (RR 0.93, 95% confidence interval (CI) 0.87 to 0.98). However, risperidone outperformed lurasidone (RR 0.90, 95% CI 0.84 to 0.98), ziprasidone (RR 0.88, 95% CI 0.80 to 0.96), brexpiprazole (RR 0.89, 95% CI 0.83 to 0.97), cariprazine (RR 0.87, 95% CI 0.81 to 0.94) and sertindole (RR 0.81, 95% CI 0.70 to 0.90). In all cases, the differences between risperidone and other second-generation antipsychotics were clinically and statistically very small. The network meta-analysis on the prevention of relapse in adults with schizophrenia or schizoaffective disorder showed that the risk of discontinuation for any reason was significantly lower for most of the included antipsychotics compared with placebo. None of the included antipsychotic medicines was associated with a significantly higher risk of discontinuation for any reason compared with placebo (16). Certainty of evidence according to the CINeMA approach was moderate for most of the medications, with the exception of oral sertindole oral, for which the certainty of evidence was rated as high, and zotepine and cariprazine for which it was rated as low. In head-to-head comparisons between risperidone and other second-generation antipsychotics, risperidone outperformed lurasidone (RR 2.28, 95% CI 1.29 to 3.84) and cariprazine (RR 3.26, 95% CI 1.13 to 7.43), with no significant differences with the remaining second-generation antipsychotics. Results reported in another network meta-analysis (87 randomized controlled trials, 21 772 participants) were generally consistent with these findings for clinically stable adults with schizophrenia spectrum disorder (19). A 2017 network meta-analysis of 19 randomized controlled trials (2669 participants) on acute treatment of first-episode schizophrenia showed a significantly lower risk of all cause discontinuation for oral aripiprazole, quetiapine, risperidone and olanzapine compared with haloperidol (17). The certainty of evidence according to CINeMA was low due to the relatively small number of participants included. A 2018 meta-analysis of 352 randomized controlled trials (84 988 participants) compared the risk of short-term mortality between second-generation antipsychotics and placebo for multiple diagnoses (23). No significant differences were found between antipsychotics and placebo for mortality by any cause in the subgroup of people with schizophrenia (odds ratio (OR) 0.69, 95% CI 0.35 to 1.35). A 2019 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 multiple diagnoses (24). Subgroup analyses of the individual antipsychotics showed a significantly higher risk of serious adverse events for 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) compared with placebo, while for the other medications no significant differences emerged.

Cost / cost effectiveness

Second-generation antipsychotics are generally more expensive than first-generation antipsychotics. In resource-constrained countries, the use of first-generation agents is prevalent and second-generation agents are usually reserved in case of serious adverse effects or inefficacy (26,27). There is debate about whether routine use of second-generation antipsychotics in these countries could be favourable in terms of medical-economic resources as compared with first-generation antipsychotics, despite their higher procurement cost. Current evidence on the matter is scant and controversial. Among second-generation antipsychotics, olanzapine and risperidone often appear to have the most favourable cost–effectiveness profile. In a multicentre randomized controlled trial in the United Kingdom, the relative costs and efficacy of first-generation versus second-generation antipsychotics were compared in more than 200 patients diagnosed with of chronic psychosis (schizophrenia, schizoaffective disorder and delusional disorder) for whom a medication change was needed. The results suggested that switching to first-generation agents was generally associated with lower costs and higher quality-adjusted life years (QALYs) compared with second-generation agents (28). A pharmacoeconomic analysis modelling clinical and economic outcomes of various antipsychotics in both oral (amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone) and long-acting formulation (haloperidol and risperidone) over a 1-year horizon found that the most cost-effective treatments were haloperidol, haloperidol decanoate and olanzapine. Of the second-generation agents, olanzapine and risperidone were the most favourable treatments for outpatients with chronic schizophrenia (29). In a study in Singapore modelling the cost–effectiveness of 11 oral antipsychotics (amisulpride, aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, trifluoperazine and ziprasidone) for prevention of psychotic relapse over a life time, olanzapine was the most favourable treatment with the highest QALYs gained and the lowest lifetime costs, while ziprasidone, aripiprazole and paliperidone were the least favourable (30). A cohort study in Germany using data from a statutory sickness fund, including more than 3000 patients diagnosed with schizophrenia, found no differences between atypical versus typical antipsychotics for rehospitalization rates (31). A large-scale study including more than 3000 patients recruited from 1999 to 2004 and treated for first-episode psychosis indicated that haloperidol was more expensive than olanzapine, zotepine or quetiapine based on total hospitalization expenses and overall treatment costs (32). In another cost–effectiveness analysis based on the Ugandan health care system, risperidone was potentially cost-saving compared with haloperidol and quetiapine (33). In a 2005 systematic review of the cost and effectiveness of risperidone and olanzapine for schizophrenia found that the evidence was insufficient to distinguish the relative total cost of care associated with risperidone versus olanzapine, although available evidence suggested that the difference was small (34). A 2019 cost–utility analysis in the United Kingdom from the National Health Service

perspective between 2016 and 2017 evaluated paliperidone and amisulpride for treatment of schizophrenia. The results indicated that paliperidone was associated with an incremental cost–effectiveness ratio of £10 941 per additional QALY gained, which was lower than the suggested National Health Service threshold of £20 000–30 000. The study concluded that paliperidone should be preferred to amisulpride (35). Newer antipsychotics on the market, such as asenapine, ziprasidone and lurasidone have also been the subject of pharmacoeconomic studies using Markov models. They have shown promising results for cost–effectiveness, mostly attributable to the lower incidence of cardiometabolic side-effects (36–38). Different medicine formulations might also have an effect on cost–effectiveness. Studies have shown that olanzapine orodispersible treatment (ODT) is generally preferred by patients to the standard oral treatment (SOT) and therefore ODT tends to be associated with better treatment adherence and lower relapse risk (39). In a 12-week multinational, randomized, crossover, open-label study, 175 patients with schizophrenia were randomly assigned to olanzapine ODT or SOT for 6 weeks and then switched to the other formulation. The results showed that 61% of the sample preferred the ODT formulation, whereas only 27% favoured SOT and 12% expressed no preference (40). In addition, olanzapine ODT has proven particularly useful when treatment needs to be administered under difficult circumstances, such as in the case of acutely ill non-compliant or agitated patients, thus reducing the burden on nursing staff (41,42). According to some cost–effectiveness analyses, olanzapine ODT also has a favourable pharmacoeconomic profile compared with the corresponding SOT and with other antipsychotics. A cost–effectiveness comparison of olanzapine, aripiprazole and risperidone ODT and SOT using a 1-year Monte Carlo microsimulation economic model found that, although olanzapine ODT was more expensive than olanzapine SOT and risperidone SOT, it was cost-effective (with incremental cost-effectiveness ratios of US$ 19 643 and US$ 39 966, respectively) due to lower relapse and hospitalization rates. Moreover, if compared with risperidone and aripiprazole ODT, olanzapine ODT was not only less expensive but also more effective (43). A similar cost–effectiveness analysis in China gave similar results with olanzapine ODT being more cost-effective than olanzapine SOT (US$ 16 798 per QALY gained), and more cost saving than aripiprazole SOT over a 1-year horizon (44). The application included a summary of costs for second-generation antipsychotics from Australia, India, Italy, South Africa, the United Kingdom and the United States, showing wide variability across markets.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that adults with a psychotic disorder (including schizophrenia) should be offered oral antipsychotic medicines (namely aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone), carefully balancing effectiveness, side-effects and individual preference (moderate certainty of evidence) (25).

Availability

Risperidone, and all the proposed alternative second-generation antipsychotics are available in innovator and generic brands worldwide.

Other considerations

The applicants identified the second-generation antipsychotics proposed as therapeutic alternatives to risperidone according to the following criteria. • Performs better than placebo in terms of efficacy for both acute and maintenance treatment. • Performs better or no worse than placebo in terms of acceptability (overall drop-out rate) for both acute and maintenance treatment. • Has a moderate or high certainty of evidence according to CINeMA appraisal for most (≥ 3/4) of these outcomes.

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