Olanzapine

Essential medicine status

Section: 24. Medicines for mental and behavioural disorders > 24.1. Medicines for psychotic disorders

ATC codes: N05AH03

Indication	Schizophrenia or other primary psychotic disorders ICD11 code: 6A4Z
INN	Olanzapine
Medicine type	Chemical agent
List type	Core
Formulations	Parenteral > General injections > IM: 10 mg in vial powder for injection
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Olanzapine
DrugBank	Olanzapine

Expert Committee recommendation

The Expert Committee noted that injectable, intramuscular immediate-release formulations of antipsychotic medicines were relevant for the management of people with schizophrenia and related psychotic disorders, especially for short-term treatment of acute psychomotor agitation when treatment cannot be administered orally. The Committee noted that the most updated and high-quality scientific literature showed that evidence supporting chlorpromazine injection was quantitatively and qualitatively poor (no evidence against placebo, and low/very low-certainty evidence against haloperidol injection). The Committee also noted that chlorpromazine injection may be associated with an increased risk of adverse effects and was not included in current WHO guidelines. The Committee noted that the evidence presented in the application showed injectable haloperidol, olanzapine and aripiprazole had similar efficacy profiles, but that olanzapine and aripiprazole generally had a more tolerable safety profile in terms of motor symptoms (including acute dystonia and other extrapyramidal symptoms) than injectable haloperidol. The Committee noted that olanzapine was available in generic forms in many countries, while generic forms of aripiprazole were currently not available. Based on these considerations, the Expert Committee recommended the removal of chlorpromazine immediate-release injection from the core list of the EML. The Committee also recommended the addition of olanzapine immediate-release injection on the core list of the EML for treatment of adults with schizophrenia and related psychotic disorders.

Background

Chlorpromazine, with a square box, has been included on the EML since the first list was published in 1977. Listed formulations include the injection being proposed for removal, as well as oral liquid and tablets. Haloperidol is the only other immediate-release injectable antipsychotic currently included on the EML. In 2021, as part of a comprehensive review of square box listings on the EML and EMLc, the Expert Committee requested that the therapeutic alternatives for chlorpromazine under the square box listing be reviewed. In addition to the current application, a separate application considered at the 2023 Expert Committee meeting provided a review of therapeutic alternatives among first-generation antipsychotics.

Public health relevance

About 24 million people in the world are estimated have schizophrenia (1). The prevalence of schizophrenia ranges from 0.2% to 0.4% across countries, while its incidence is reported to be 18.7 per 100 000 person-years (2). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which are attributable specifically 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 (1,3). Acute psychomotor agitation is a multifactorial clinical manifestation that can occur in a broad spectrum of psychiatric and neurological syndromes. Although data on the epidemiology of acute agitation are lacking, up to 20% of psychiatric emergency visits in the United States might involve agitated individuals with schizophrenia (4). Other studies report an overall prevalence of between 4% and 10% in emergency settings (5). In psychiatric inpatient settings, a literature review estimated an overall incidence of episodes of violence of about 32% (6). Acute agitation might include heterogeneous manifestations, including highly disorganized behaviours, verbal or physical hostility and overt aggressiveness towards oneself, objects or other individuals. Paranoid delusional thoughts, hallucinations and substance abuse or withdrawal, along with social and environmental triggers, are among the most common underlying cause of acute agitation in people with chronic psychoses (5). Although non-pharmacological management can be effective in many cases, more invasive or coercive measures are sometimes required, particularly when: the insight of disease is poor; there is immediate risk to personal safety; and effective environmental measures cannot be promptly applied.

Benefits

Chlorpromazine A 2017 Cochrane systematic review and pairwise meta-analysis included four randomized controlled trials that compared injectable chlorpromazine and injectable haloperidol for rapid tranquilization in adults with psychosis-induced aggression or agitation (7). These trials provided heterogeneous measures of efficacy and could not be all pooled for any efficacy outcomes. Although a number of outcomes were reported in the meta-analysis, the applicants selected only those pooling at least two randomized controlled trials. For the outcome “not marked improvement”, no significant differences were found between injectable haloperidol and chlorpromazine, although the point estimate favoured haloperidol (risk ratio (RR) 0.79, 95% confidence interval (CI) 0.61 to 1.02; two randomized controlled trials, 89 participants, very low-certainty evidence). Results for the outcome “not any improvement” significantly favoured haloperidol (RR 0.15, 95% CI 0.05 to 0.49; two randomized controlled trials, 89 participants, very low-certainty evidence). Olanzapine A systematic review and network meta-analysis of 10 randomized controlled trials (1964 participants) compared short-acting intramuscular second-generation antipsychotics (aripiprazole, olanzapine and ziprasidone), haloperidol and placebo in acutely agitated individuals with schizophrenia spectrum disorders (8). For the primary outcome of response 2 hours after the injection, all included second-generation antipsychotics were found to significantly outperform placebo, while no significant differences emerged in comparison with intramuscular haloperidol. Olanzapine was significantly more effective than aripiprazole for reducing agitation at 2 hours (RR 1.24, 95% CI 1.05 to 1.45; low-certainty evidence), but not haloperidol (RR 1.13, 95% CI 0.99 to 1.28; low-certainty evidence) or ziprasidone (RR 1.26, 95% CI 0.76 to 2.09; very low-certainty evidence). For the outcome of treatment response at 24 hours, no significant differences were found between olanzapine and haloperidol or olanzapine and aripiprazole.

Harms

Chlorpromazine A meta-analysis of four randomized controlled trials (153 participants) compared injectable haloperidol and injectable chlorpromazine for acceptability outcome “leaving the study early”. The analysis found very low-quality evidence of significant benefit in favour of haloperidol (RR 0.21, 95% CI 0.07 to 0.71). Analysis of adverse events generally found no difference between treatments (7). A revision of psychotropic medicines included in the interagency emergency health kit was conducted in 2011 (9). Injectable chlorpromazine was removed from the kit and was replaced by injectable haloperidol based on concerns of the risk of cardiovascular side-effects with chlorpromazine and its local irritation when administered intramuscularly (10). Olanzapine A systematic review and pairwise meta-analysis of randomized controlled trials compared side-effects of intramuscular olanzapine with those of any other antipsychotic or placebo for treatment of acute agitation in people with schizophrenia spectrum disorders (11). Compared with placebo, there was very low-certainty evidence of no significant difference for intramuscular olanzapine in terms of serious adverse events (RR 0.48, 95% CI 0.05 to 5.18) or other specified adverse events with the exception of QT prolongation, which significantly favoured placebo (RR 0.34, 95% CI 0.16 to 0.70). Compared with haloperidol, no significant

differences were found with olanzapine for study discontinuation for any reason (RR 1.02, 95% CI 0.47 to 2.23) or other specified undesirable outcomes with the exception of the use of anticholinergic medicines, extrapyramidal effects and dystonia, for which results favoured olanzapine.

Cost / cost effectiveness

A 2022 cost–effectiveness analysis using data from a randomized clinical trial in Hong Kong between December 2014 and September 2019 compared the costs associated with intramuscular midazolam, haloperidol and olanzapine for the management of acute agitation in an emergency department (13). The main cost driver was labour costs for agitation management; the cost of the medicine was a minor contributor to total expenditure. Midazolam was the most cost–effective intervention, while no difference was found between haloperidol and olanzapine. A 2009 retrospective study compared the medical records of 27 patients who received intramuscular haloperidol for the treatment of acute agitation episodes with those of 26 patients who received intramuscular olanzapine (14). No differences were found between the two treatments for mean number of repeated medication doses per episode of agitation and the proportion of patients requiring the use of seclusion and restraints. The authors concluded that, with equal effectiveness, haloperidol was the less expensive option. In a 2011 retrospective cohort study based on a review of electronic medical records, 136 patients with a diagnosis of schizophrenia or schizoaffective disorder treated with different short-acting intramuscular antipsychotics (haloperidol, aripiprazole, olanzapine and ziprasidone) were compared for duration of hospital stay, number of injections received and associated costs (15). No difference in the length of hospitalization was found between the group of patients treated with haloperidol and those treated with second-generation antipsychotics. Treatment with haloperidol was associated with a significant reduction in the number of required injections and with lower costs compared to second-generation antipsychotics. Among the second-generation antipsychotics, ziprasidone was associated with a shorter duration of hospital stay compared with olanzapine. The costs of chlorpromazine, haloperidol, olanzapine and aripiprazole intramuscular injections in different countries presented in the application are shown in Table 29 (refer TRS 1049).

WHO guidelines

The proposed deletion of chlorpromazine intramuscular injection and inclusion of olanzapine intramuscular injection are aligned with recommendations in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guidelines (12).

Availability

Olanzapine intramuscular injection is available globally in branded and generic forms.

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