Fluoxetine

ATC codes: N06AB03

Indication	Palliative care ICD11 code: QB9B
INN	Fluoxetine
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 20 mg (as hydrochloride)
EML status history	First added in 2011 (TRS 965) Changed in 2013 (TRS 985) Changed 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	Fluoxetine
DrugBank	Fluoxetine

Expert Committee recommendation

The Expert Committee noted that fluoxetine had been included on the EMLc for the treatment of children with depression aged 8 years and older since 2007, before the publication of the first WHO mhGAP guidelines in 2010. The mhGAP guidelines were updated in 2023 and include a recommendation not to use antidepressants for the treatment of depression in children younger than 12 years. The Committee acknowledged that depression has been reported to affect only a small proportion of children younger than 12 years – the population covered by the EMLc. Most studies report a prevalence lower than 1% in this age group and that prevalence substantially rises throughout adolescence and into adulthood. The Committee acknowledged the comprehensive approach taken by the applicants to evaluate the available evidence on the efficacy, acceptability and tolerability of fluoxetine and other antidepressants for the treatment of children with depression. Notably, most systematic reviews identified did not focus specifically on children aged 12 years and younger, but instead included a mixed population of children and adolescents. From six randomized clinical trials that investigated the efficacy of fluoxetine versus placebo to treat depression in children younger than 12 years, there was very low-certainty evidence suggesting no statistically significant differences between fluoxetine and placebo. The point estimate favoured fluoxetine, however the difference was not considered to be clinically meaningful. The Committee agreed that the evidence presented in the application for use of fluoxetine in children younger than 12 years was inconclusive and insufficient to support the ongoing inclusion of this medicine in the EMLc for the treatment of depression in children. However, some Committee members reported that fluoxetine was considered a relevant treatment option and is currently used in clinical practice in children aged between 8 and 12 years in some settings where access to mental health services and non-pharmacological management is limited. Based on the evidence presented in the application, and in alignment with recommendations in the WHO mhGAP guidelines, the Expert

Committee recommended the deletion of fluoxetine from the EMLc. This recommendation also applies to the listing of fluoxetine on the EMLc in Section 2.3 Medicines for other common symptoms in palliative care. Fluoxetine is still included on the EML for use in the treatment of depression in adolescents and adults.

Background

Fluoxetine has been included on the EMLc since the first list was published in 2007 for the treatment of children aged > 8 years with depression (1). In 2013, the Expert Committee considered a request to revise the age restriction from > 8 years to > 12 years (i.e. effective deletion from the EMLc) made by the WHO Department of Mental Health and Substance Abuse. The Committee recognized that depression was rare in children, and that WHO's Mental Health Gap Action Programme (mhGAP) guideline made a strong recommendation to set the age limit at 12 years for the pharmacological treatment with antidepressants of children with a depressive episode/disorder in non-specialist settings. However, the Committee decided to retain the minimum age for fluoxetine at 8 years as the evidence on alternative antidepressants in children was not reviewed. At the same time, the Committee highlighted the need for a thorough review of the section of medicines used in depressive disorders on the EMLc (2).

Public health relevance

For the purpose of the application, children are defined as individuals up to and including 12 years of age, in line with the population for which the EMLc is intended. Depression in children has been increasingly treated with antidepressant medicines over the past several years (3). This trend occurred despite the onset of depressive disorder being rare in children of prepubertal age (4). Longitudinal studies of community samples of children and adolescents suggest an average age at onset between 11 and 14 years for major depressive disorder and depressive disorder (5). Evidence from prospective epidemiological studies reveals a large increase in the prevalence of major depressive episodes after age 11 years (6). Prospective data from the Oregon Adolescent Depression Project showed that the rates of new onset of depression increase from 1% to 2% at age 13 years and from 3% to 7% at age 15 years (7). The incidence of depression continues to increase throughout early adulthood (8).

Benefits

The application presented the results of a comprehensive literature search for systematic reviews on the topic of antidepressant efficacy, acceptability and tolerability in children with depression. No systematic reviews were found on the efficacy of fluoxetine specifically focused on children aged 12 years or younger. Existing reviews included a mixed population of children and adolescents, largely composed of individuals between 13 and 18 years of age. Twenty-one systematic reviews were included, from which data from 22 randomized controlled trials were extracted and reanalysed using standard Cochrane methodology. Fluoxetine Six randomized controlled trials (795 participants) were identified on the use of fluoxetine for the treatment of children (mean age < 12 years) with depression (9–14). Only short-term efficacy (up to 10 weeks) was evaluated. No data were available on medium-term (13–26 weeks) or long-term (more than 26 weeks) follow-up. All trials were industry-sponsored. Five studies (587 participants) compared fluoxetine with placebo and evaluated depressive symptomology at study endpoint using the Children's Depression Rating Scale-Revised (CDRS-R) (9–13). Pooled results did not show any significant difference between fluoxetine and placebo (mean difference (MD) –2.43, 95% confidence interval (CI) –5.37 to 0.50). Based on Grading of Recommendations, Assessment, Development, and Evaluations (GRADE), the quality of evidence was judged to be very low. The only two positive studies were published in 1997 and 2002 (9,10). These two studies were the subject of a statistical review by the Center for Drug Evaluation and Research of the United States Food and Drug Administration (15). The review showed that the prespecified primary outcome measure in the first study (9) (proportion of completing patients who achieved recovery, defined as a score of ≤ 28 on the CDRS-R and a clinical global impression-improvement (CGI-I) score of 1 or 2) was changed in the published manuscript, probably because this measure did not reach statistical significance. For the second study (10) the authors identified a reduction from baseline of ≥ 30% on the CDRS-R as the single primary endpoint.

However, as they found no difference between fluoxetine and placebo, the focus was on secondary endpoints (symptom reduction) that favoured fluoxetine. The Food and Drug Administration independent statistical review concluded that “The sponsor did not win on these two paediatric depression studies based on the protocol specified endpoint. The evidence for efficacy based on the pre-specified endpoint is not convincing” (15). One study (23 participants) compared fluoxetine with placebo and evaluated response using depression rating scales (Birleson Depression Self-Rating Scale, CGI scale and Children's Global Assessment Scale) (14). No significant differences between treatment groups were found in any of the rating scales. Other antidepressants Eighteen trials were identified that compared other antidepressants with placebo, of which nine were suitable for quantitative synthesis. Only short-term efficacy (up to 12 weeks) was evaluated. No data were available on medium-term (13–26 weeks) or long-term (more than 26 weeks) follow-up. • One randomized controlled trial (96 participants) suggested that paroxetine was less effective than placebo in ameliorating depressive symptomology (MD 2.49, 95% CI 1.45 to 3.03) (16). • One randomized controlled trial (171 participants) suggested no difference in efficacy between sertraline and placebo (MD –0.17, 95% CI –0.47 to 0.13) (17). • Two randomized controlled trials (255 participants) suggested no difference in efficacy between duloxetine and placebo (MD –0.16, 95% CI –0.43 to 0.11) (11,12). • One randomized controlled trial (170 participants) suggested no difference in efficacy between venlafaxine and placebo (MD 0.10, 95% CI –0.23 to 0.44 (18). Another trial (40 participants), not be included in the analysis due to lack of detailed data, reported lack of efficacy of venlafaxine versus placebo (19). • Two randomized controlled trials (194 participants) suggested no difference in efficacy between desvenlafaxine and placebo (MD –0.17, 95% CI –0.46 to 0.12) (13,20). • One randomized controlled trial (38 participants) suggested no difference in efficacy between imipramine and placebo (MD 0.00, 95% CI –0.64 to 0.64) (21). • One randomized controlled trial (50 participants) suggested no difference in efficacy between nortriptyline and placebo (MD 0.08, 95% CI –0.47 to 0.64) (22). One randomized controlled trial (174 participants) suggested a greater reduction in depressive symptoms in participants taking citalopram compared with placebo at 8 weeks follow-up (23). One randomized controlled trial (104 participants) found no statistically significant improvement in any efficacy measure in the subgroup of patients aged 6–11 years for escitalopram compared with placebo (24). Two randomized controlled trials failed to show superiority of mirtazapine over placebo (25). One randomized controlled trial (nine participants) comparing amitriptyline with placebo showed no statistical differences in reduction of depressive symptoms between treatment groups at 4 weeks follow-up (26).

Harms

The adverse effect profile of fluoxetine in the adult population is well established. However, it is not possible to ascertain whether the frequency of adverse events is the same in adults and children. In general, knowledge of unwanted effects associated with antidepressant treatments for depression in children is inadequate. Systematic reviews have only evaluated unwanted effects of treatments for depression in mixed populations of children and adolescents. Aside from effects on suicidality, the negative effects of selective serotonin reuptake inhibitors (SSRIs) are under-reported or not reported (27). The safety of fluoxetine for paediatric patients has not been systematically assessed for chronic treatment longer than several months. No studies have directly evaluated the longer-term effects of fluoxetine on growth, development and maturation of children and adolescents. The safety of prescribing antidepressants to children has been the subject of increasing concern, particularly regarding the risk of suicidality, which has led to precautions and recommendations against their use in children and adolescents (28). Meta-analyses of randomized controlled trials have produced inconsistent findings. For example, one meta-analysis found that the overall risk ratio for suicidal ideation and behaviour in paediatric patients with depression taking SSRIs was 1.66 (95% CI 1.02–2.68) (29), and another that severe adverse events were significantly more common with SSRIs and serotonin and norepinephrine reuptake inhibitors than placebo (30). However, another recent meta-analysis of randomized controlled trials concluded that only venlafaxine was associated with an increased risk of suicidal behaviour or ideation in the young population (31,32). A systematic review evaluated observational studies reporting completed or attempted suicide in depressed individuals who were exposed to SSRIs compared with those who were not exposed to antidepressant medicines, and measured the overall risk of completed or attempted suicide (33). The use of SSRIs was associated with a reduced risk of suicide in adults with depression, while in children and adolescents, the use of SSRIs was associated with an increased suicidality

behaviours. The aforementioned association was the only so-called convincing evidence included in a recent umbrella review of meta-analyses of observational studies that evaluated the adverse outcomes of antidepressants (34). A recent and updated systematic review of observational studies confirmed that SSRI exposure might have an increased suicidal risk in children and young adults (35). Across 15 studies that examined the association between SSRIs and completed or attempted suicide, SSRI exposure significantly increased the risk of completed and attempted suicide compared with no or any other antidepressant use, with a pooled risk ratio for incidence of suicide or suicide attempt of 1.28 (95% CI 1.09–1.51).

Cost / cost effectiveness

No cost–effectiveness data on the use of antidepressant medications in children are available. Available data in adults are not considered generalizable to children.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that antidepressant medicines are not recommended for the treatment of children 12 years of age and below with depressive episode/disorder (low certainty evidence) (36).

Availability

Fluoxetine is available globally, however specific data on availability was not considered relevant for its proposed deletion from the EMLc.

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