Fluoxetine 🥑

Section: 24. Medicines for mental and behavioural disorders > 24.4. Medicines for obsessive compulsive disorders

		ATC codes: N06AB03
Indication	Obsessive-compulsive disorder ICD11 code: 6B50	
INN	Fluoxetine	
Medicine type	Chemical agent	
List type	Core	
Formulations	Oral > Solid: 20 mg (as hydrochloride)	
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	Fluoxetine	
DrugBank	Fluoxetine	

Expert Committee recommendation

The Expert Committee acknowledged the public health relevance of effective treatments for obsessive-compulsive disorder, from patient, societal and health system perspectives. In particular, the Committee noted the substantial disability associated with the condition, especially in the context of the COVID-19 pandemic. The Committee noted from the evidence presented in the application that SSRIs were superior to placebo and had similar efficacy and a more favourable safety profile than clomipramine in the treatment of obsessive-compulsive disorder. While some differences in efficacy and safety may exist between SSRIs, in general the evidence does not indicate that any medicine significantly outperforms the others; therefore, the choice of medicine within the class should be based on patients' clinical characteristics and preferences. The Committee noted that SSRI therapy was recommended for use in the treatment of obsessive-compulsive disorder in many clinical guidelines, although WHO guidelines for treatment of obsessive-compulsive disorder are not currently available. The Committee noted that the medicines proposed for inclusion were already included on the EML for use in the treatment of depression, and were widely available and generally affordable, with generic brands available. The Expert Committee therefore recommended extending the listing of fluoxetine on the EML to include the new indication of obsessive-compulsive disorder. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline as therapeutic alternatives.

Background

Fluoxetine has not been previously considered for inclusion on the EML for use in the treatment of obsessive-compulsive disorders. The EML currently includes only clomipramine for this indication. Fluoxetine has been included on the EML for treatment of depressive disorders since 2007. A square box was added in 2019 to indicate citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Public health relevance

Obsessive-compulsive disorder is a common mental disorder and is responsible for substantial disability worldwide (1,2). Estimates of the prevalence of obsessive-compulsive disorder in the literature vary, but generally suggest that between 1% and 4% of the population are affected in their lifetime (3-5). In two thirds of cases, the age at onset is younger than 25 years, while in 15% of cases, onset occurs after the age of 35 years. In about one third of cases, age at onset is in childhood or early adolescence. Males tend to have an earlier onset and worse prognosis (6). The COVID-19 pandemic has had a significant impact on obsessivecompulsive disorder, leading to an increase in its prevalence (7,8). A systematic review found that individuals, both with and without a prior diagnosis of obsessive-compulsive disorder, experienced a worsening of symptoms during the pandemic (9). People with obsessive-compulsive disorder experience recurrent and intrusive thoughts (obsessions) that cause anxiety or distress. They often engage in repetitive behaviours or mental acts (compulsions) to cope with these obsessions (10). Obsessive-compulsive disorder greatly affects the quality of life for patients, caregivers and relatives, and is associated with increased mortality (11,12). The condition tends to be chronic, with intermittent episodes (13). Individuals with obsessive-compulsive disorder often have other psychiatric disorders as well, leading to impaired health and functioning (14-16). Obsessive-compulsive disorder is associated with significant impairment in overall functioning and quality of life. Compared with healthy controls or community cohorts, individuals with obsessive-compulsive disorder report significantly worse quality of life in many areas, including overall sense of well-being, social and family relationships, ability to enjoy leisure activities, and general ability to function in daily and working life (17, 18).

Benefits

The applicants conducted a systematic review and network meta-analysis of 48 randomized controlled trials (5840 participants) comparing the efficacy (reduction of obsessive-compulsive symptoms) and acceptability (all-cause discontinuation) of different antidepressants. For the outcome of efficacy, clomipramine (standardized mean difference (SMD) -0.67, 95% confidence interval (CI) -0.89 to -0.45; very low-certainty evidence), sertraline (SMD -0.64, 95% CI -0.92 to -0.36; low-certainty evidence), fluvoxamine (SMD -0.57, 95% CI -0.82 to -0.32; very low-certainty evidence), paroxetine (SMD -0.44, 95% CI -0.70 to -0.17; low-certainty evidence), citalopram (SMD -0.47; 95% CI -1.02 to 0.07; low-certainty evidence), escitalopram (SMD -0.45, 95% CI -0.92 to 0.02; low-certainty evidence) and fluoxetine (SMD -0.39, 95% CI -0.78 to 0.00; low-certainty evidence) were significantly more effective than placebo. In head-to-head comparisons with clomipramine, the only medicine currently included on the EML for obsessive-compulsive disorder, each SSRI demonstrated similar efficacy. Head-to-head comparisons also showed no significant differences between individual SSRIs. For the outcome of acceptability, escitalopram (odds ratio (OR) 0.68, 95% CI 0.46 to 1.02; moderate-certainty evidence), sertraline (OR 0.79, 95% CI 0.58 to 1.08; low-certainty evidence), fluvoxamine (OR 0.83, 95% CI 0.59 to 1.15; moderate-certainty evidence), paroxetine (OR 0.87, 95% CI 0.65 to 1.16; moderate-certainty evidence), citalopram (OR 0.89, 95% CI 0.49 to 1.64; moderate-certainty evidence) and fluoxetine (OR 0.92, 95% CI 0.57 to 1.48; very low-certainty evidence) were comparable to placebo. In contrast, clomipramine was significantly less acceptable than placebo (OR 1.41, 95% CI 10.7 to 1.85; moderate-certainty evidence). Head-to-head comparisons showed escitalopram, sertraline, fluvoxamine and paroxetine were more acceptable than clomipramine. The results from the network meta-analysis conducted by the applicants complement the findings of a 2016 network meta-analysis of 54 trials (6652 participants), which compared the efficacy of pharmacological and psychotherapeutic interventions for the management of obsessive-compulsive disorder in adults (19). The primary outcome was symptom severity as measured by the Yale-Brown Obsessive Compulsive Scale. The SSRIs included were citalopram, escitalopram fluoxetine, fluvoxamine, paroxetine and sertraline. In this analysis SSRIs as a class were more effective than placebo (mean difference (MD) -3.49, 95% credible interval (CrI) -5.12 to -1.81) and equally efficacious in head-to-head comparisons with each other. No significant difference was found between clomipramine and SSRIs as a class (MD -1.23, 95% CrI -3.41 to 0.94).

Harms

The systematic review and network meta-analysis conducted by the applicants evaluated tolerability (drop-outs due to adverse events) using data from 43 randomized controlled trials. Among SSRIs, escitalopram (OR 1.26, 95% CI 0.69 to 2.32), fluoxetine (OR 1.28, 95% CI 0.56 to 2.96), sertraline (OR 1.77, 95% CI 1.05 to 2.98), paroxetine (OR 1.82, 95% CI 1.19 to 2.78) and citalopram (OR 2.42, 95% CI 0.54 to 10.85) did not show a statistically significant difference in tolerability compared with placebo. Fluvoxamine (OR 2.98, 95% CI 1.80 to 4.92) and clomipramine (OR 4.82, 95% CI 3.0 to 7.73) were less tolerable than placebo. In head-to-head comparisons, escitalopram (OR 0.21, 95% CI 0.13 to 0.33), fluoxetine (OR 0.27, 95% CI 0.11 to 0.63), sertraline (OR

0.37, 95% CI 0.21 to 0.63) and paroxetine (OR 0.38, 95% CI 0.22 to 0.64) were better tolerated than clomipramine. Citalopram (OR 0.5, 95% CI 0.10 to 2.42) and fluvoxamine (OR 0.62, 95% CI 0.37 to 1.02) did not show a significant difference in tolerability compared with clomipramine. Data on specific side-effects and tolerability issues were limited, primarily due to reporting bias in the original studies. Risk of suicidality A meta-analysis was done of individual level data of almost 100 000 patients from published and unpublished clinical trials submitted to the United States Food and Drug Administration in 2005–2006 (20). Industry sponsors of 12 antidepressant medicines, including SSRIs, were requested to submit datasets from double-blind randomized placebocontrolled trials of antidepressants in adults for any indication, to evaluate the risk of suicidality in clinical trials of antidepressants. The analysis found that the risk of suicidality associated with antidepressant use was age dependent. Compared with placebo, an increased risk of suicidality and suicidal behaviour was observed in depressed children and adolescents. The net effect was neutral on suicidal behaviour, possibly protective for suicidal ideation in adults aged 25-64 years and reduced the risk of both suicidality and suicidal behaviour in patients aged 65 years and older. No information was specifically reported for anxiety disorders. Risk of QT-prolongation SSRIs can cause delayed repolarization of cardiac myocytes, leading to a prolonged QT interval and risk of life-threatening arrhythmias. A 2014 meta-analysis found that different SSRIs had varying effects on QTc prolongation. Fluoxetine (MD 4.50, 95% CI -4.32 to 13.32) and paroxetine (MD -1.04, 95% CI -5.76 to 3.68) had no significant association with QTc prolongation. Fluvoxamine was associated with shortened QTc (MD -5.00, 95% CI -6.05 to -3.95). Citalopram (MD 10.58, 95% CI 3.93 to 17.23), escitalopram (MD 7.27, 95% CI 3.78 to 10.83) and sertraline (MD 3.00, 95% CI 2.95 to 3.05) were significantly associated with QTc prolongation (21). Risk of sexual side-effects SSRIs are known to cause sexual dysfunction. A 2014 network meta-analysis compared the risk of sexual side-effects of 13 second-generation antidepressants including SSRIs. Most comparisons did not demonstrate significant differences between the SSRIs. Escitalopram (OR 0.37, 95% CI 0.13 to 0.85) and paroxetine (OR 3.86, 95% CI 1.44 to 8.40) had a statistically significant higher risk of sexual dysfunction than fluoxetine (22).

Cost / cost effectiveness

The availability and affordability of SSRIs vary across countries and settings. At the same time, the cost of anxiety disorders is high for individuals, health care systems and society due to productivity loss. Evidence on the cost-effectiveness of SSRIs compared with clomipramine and other pharmacological classes for obsessive-compulsive disorder is lacking. Studies focusing on costeffectiveness compare SSRIs with cognitive behavioural therapy and indicate that monotherapy with SSRIs or a combination of cognitive behavioural therapy and an SSRIs is the most cost-effective approach. A 2016 systematic review of 86 randomized controlled trials evaluated the clinical and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children, adolescents and adults in the United Kingdom (27). The review reported the net monetary benefit to estimate cost-effectiveness if the National Health Service was willing to pay £20 000 for each qualityadjusted life year gained. Fluvoxamine in combination with cognitive behavioural therapy had the lowest net monetary benefit of £57 174 (i.e. least cost-effective), while strategies involving cognitive or behavioural therapies had the highest net monetary benefit of £59 668 and £59 695, respectively (i.e. most cost-effective). Pharmacological monotherapies had net monetary benefit of £58 373 for SSRIs, £58 549 for clomipramine and £58 664 for venlafaxine. A 2018 randomized feasibility study evaluated the cost-effectiveness of combining cognitive behavioural therapy with sertraline versus either treatment given as monotherapy over 52 weeks in 49 adults with obsessive-compulsive disorder in the United Kingdom (28). Resource use and quality of life data were available (at baseline, 16 and 52 weeks) for 23/49 (46.9%) participants. Compared with sertraline monotherapy, mean costs were higher for both cognitive behavioural therapy as monotherapy and combination treatment (£1329 and £2176, respectively. Mean quality-adjusted life year scores for sertraline monotherapy were 0.18 greater than that of cognitive behavioural therapy monotherapy, and 0.11 greater than that of combination treatment. Sertraline monotherapy was considered dominant and costeffective, as it was estimated to be both less costly and more effective than both other options.

WHO guidelines

WHO guidelines for treatment of obsessive-compulsive disorders are not currently available. Many other current clinical guidelines include recommendations for the use of SSRIs as the first-choice pharmacological treatment for obsessive-compulsive disorder (23–26). Clinical guidelines do not provide indications on which individual medicine to choose, generally agreeing on the importance of tailoring the choice to individual characteristics of the patient and actively involving individuals and caregivers in a shared decision-making process.

The proposed SSRIs are available globally, off-patent and with multiple branded and generic versions.

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