Fluoxetine

Section: 24. Medicines for mental and behavioural disorders > 24.3. Medicines for anxiety disorders

ATC codes: N06AB03

Indication	Social anxiety disorder ICD11 code: 6B04
INN	Fluoxetine
Medicine type	Chemical agent
List type	Core (EML) Complementary (EMLc)
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 anxiety disorders, from patient, societal and health system perspectives. In particular, the Committee noted the substantial disability and lost-productivity costs associated with anxiety disorders. The Committee noted from the evidence presented in the application that SSRIs were more effective in reducing anxiety symptoms than placebo and had a well known and acceptable safety profile. 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 anxiety disorders in many clinical guidelines and would also be included in the updated the WHO mhGAP guidelines. The Committee noted that the medicines proposed for inclusion were already in 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 indications of generalized anxiety disorder, panic disorder and social anxiety 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 anxiety disorders. The EML currently includes only diazepam 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

Anxiety disorders are prevalent and disabling, creating a large global burden of disease. People affected by these disorders suffer from excessive fear and nervousness, avoidance of perceived threats and autonomic dysfunction (e.g. palpitations, dizziness and insomnia) (1–3). Early onset and persistent relapses further add to the severity (4). Anxiety disorders are responsible for more than 28.6 million years lived with disability (YLD), accounting for 3.34% of the total global YLD, and 26.7 million disability-adjusted life years (DALYs) per year, or 1.13% of total DALYs due to any disease (5). Overall, anxiety disorders have been among the top 10 causes of YLDs for the past 20 years (6). The COVID-19 pandemic has had a serious effect on global mental health, including a 26% rise in anxiety disorders cases (7). Women and younger people are more affected, with the highest increases in countries with high COVID-19 infection rates and severe restrictions on movement (lockdowns and school closures). Anxiety affects overall health as it is associated with a heightened risk of coronary artery disease, unstable angina and heart attacks, and increased mortality rates. Furthermore, anxiety can lead to insulin resistance and may contribute to noncommunicable illnesses such as diabetes, heart disease and cancer (8–10). Anxiety disorders also have large financial costs. Globally, an estimated 12 billion work days are lost every year to depression and anxiety at an annual cost of US$ 1 trillion in lost productivity (11).

Benefits

A 2022 systematic review and network meta-analysis of 87 randomized controlled trials (12 800 participants) evaluated medicines for treatment of adults with panic disorder (with or without agoraphobia) (12). A total of 21 comparisons were considered for analysis. Most studies compared benzodiazepines or SSRIs with placebo. Other comparisons included tricyclic antidepressants versus placebo and comparisons between different drug classes. The most common duration of treatment was 8 weeks (35%), followed by 12 weeks (19%). Compared with placebo, the risk ratios (RR) for symptom remission significantly favoured serotonin-noradrenaline reuptake inhibitors (RR 1.27, 95% confidence interval (CI) 1.12 to 1.42), SSRIs (RR 1.38, 95% CI 1.26 to 1.5), monoamine oxidase inhibitors (RR 1.30, 95% CI 1.00 to 1.69), benzodiazepines (RR 1.47, 95% CI 1.36 to 1.6) and tricyclic antidepressants (RR 1.39, 95% CI 1.26 to 1.54). SSRIs were found to be the most effective (66.4%) with the fewest adverse events (58.5%) for treating panic disorder, according to the surface under cumulative ranking curves (SUCRA) clustered ranking plot. Certainty of evidence against placebo was rated as moderate. A 2019 systematic review and meta-analysis of 89 randomized controlled trials (25 441 participants) evaluated pharmacotherapy for the treatment of adults with generalized anxiety disorder (13). Most studies used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for diagnosis. Duration of follow-up ranged from 4 to 26 weeks, and measured change in the Hamilton Anxiety Scale (HAM-A) score as the efficacy outcome. Most medicines (16/22, 73%) performed better than placebo. SSRIs were superior to placebo in reducing symptoms of anxiety. Standardized mean differences of treatment efficacy were: –2.22 (95% CI –4.28 to –0.19) for citalopram; –2.45 (95% CI –3.27 to –1.63) for escitalopram; –2.43 (95% CI –3.74 to –1.16) for fluoxetine; –2.29 (95% CI –3.11 to –1.47) for paroxetine; and –2.88 (95% CI –4.17 to –1.59) for sertraline. The certainty of evidence was rated as moderate for sertraline, low for citalopram, escitalopram and fluoxetine, and very low for paroxetine. A 2020 systematic review and network meta-analysis of 67 randomized controlled trials (12 122 participants) evaluated pharmacotherapy for the treatment of adults with social anxiety disorder (14). The primary efficacy outcome was change in symptom severity measured using the Leibowitz Social Anxiety Scale. Paroxetine was significantly more effective than placebo in reducing symptom severity (mean difference (MD) –15.89, 95% CI –29.94 to –1.84), based on low to very low-certainty evidence. Other SSRIs investigated were also superior to placebo, however the differences were not statistically significant: MD –17.45, 95% CI –43.76 to 8.86 for sertraline; MD –8.05, 95% CI –41.81 to 25.71 for escitalopram; and MD –2.132, 95% CI –21.88 to 17.64 for fluvoxamine.

Harms

The 2022 systematic review and network meta-analysis of medicines for treatment of adults with panic disorder (with or without agoraphobia) provided data on the acceptability of treatments (i.e. all-cause treatment discontinuation) and tolerability (i.e. adverse events) (12). SSRIs were more acceptable than tricyclic

antidepressants (RR 0.78, 95% CI 0.61 to 0.99) and benzodiazepines (RR 0.51, 95% CI 0.38 to 0.67), and equally acceptable as placebo (RR 0.92, 95% CI 0.77 to 1.1). In terms of tolerability, SSRIs had a higher risk of adverse events than placebo (RR 1.19, 95% CI –1.01 to 1.41). However, benzodiazepines (RR 1.47, 95% CI 1.18 to 1.84) and tricyclic antidepressants (RR 1.50, 95% CI 1.20 to 1.88) had a higher risk of adverse events than SSRIs. The 2019 systematic review and meta-analysis of pharmacotherapy for the treatment of adults with generalized anxiety disorder provided data on acceptability (i.e. all cause discontinuation) (13). The risk of discontinuation for SSRIs did not differ significantly from placebo, except for paroxetine (odds ratio (OR) 1.24, 95% CI 1.03 to 1.50), which had a higher discontinuation rate. The 2020 systematic review and network meta-analysis of pharmacotherapy for the treatment of adults with social anxiety disorder also provided data on acceptability (i.e. all cause discontinuation) (14). Discontinuation rates for SSRIs were not significantly different from placebo, with the exception of fluvoxamine (OR 1.51, 95% CI 1.06 to 2.14). Risk of suicidality A meta-analysis of individual-level data from almost 100 000 patients from published and unpublished clinical trials was undertaken using data collected by the United States Food and Drug Administration in 2005–2006 (15). Industry sponsors of 12 antidepressant medicines, including SSRIs, were requested to submit datasets from double-blind randomized placebo-controlled trials on the use of antidepressants in adults for any indication to evaluate the risk of suicidality in clinical trials of antidepressants. The risk of suicidality associated with antidepressant use was found to be age dependent. Compared with placebo, an increased risk of suicidality and suicidal behaviour was seen in depressed children and adolescents. The net effect was: neutral for suicidal behaviour; possibly protective for suicidal ideation in adults aged 25–64 years; reduced for 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 have 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 (16). 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 show significant differences in the risk of sexual side-effects 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 (17).

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. Comparative cost–effectiveness studies suggest that cognitive behavioural therapy with or without SSRIs is the most cost-effective intervention for anxiety disorders (25,26). However, implementing widespread access to cognitive behavioural therapy poses equity and feasibility challenges due to the need for policy changes and resources. Evidence on the cost–effectiveness of SSRIs specifically for anxiety disorders is lacking, but indirect evidence of the cost–effectiveness of these medicines for depression is available. A 2015 network meta-analysis in Singapore estimated the cost–effectiveness of different antidepressants and found that agomelatine was the most cost-effective antidepressant, followed by venlafaxine and mirtazapine (27). Escitalopram was the most cost-effective SSRI for depression, followed by fluvoxamine. The effectiveness-based model used in the study had limitations, effectiveness was based on efficacy (rather than recorded costs) and the estimated costs were specific to Singapore's health system, limiting generalizability. Another meta-analysis compared the efficacy of 10 antidepressants for treating moderate to severe depression in primary care (28). Escitalopram was the most effective in achieving remission at the 8- to 12-week follow-up. Despite its higher acquisition cost, escitalopram was both more effective and had lower total costs than other antidepressants from a societal perspective. From a health care perspective, the cost per quality-adjusted life year of escitalopram was €3732 compared with venlafaxine.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders include a conditional recommendation that SSRIs be considered for adults with panic disorder and adults with generalized anxiety disorder (low certainty of evidence) (18). Many other current clinical guidelines include recommendations for the use of SSRIs as first-choice pharmacological treatment for generalized anxiety disorder, panic disorder and social anxiety disorder (19–24). 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.

Availability

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

1. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? Depress Anxiety. 2009;26(12):1066–85.
2. Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, et al. Anxiety disorders. Nat Rev Dis Primers. 2017;3:17024.
3. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204–22.
4. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17(3):327–35.
5. Global Burden of Disease database [internet]. Seattle, WA: Institute for Health Metrics and Evaluation; 2019 (https://vizhub.healthdata.org/gbd-results/, accessed 6 October 2023).
6. World mental health report: transforming mental health for all. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/356119, accessed 6 October 2023).
7. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398(10312):1700–12.
8. Wen Y, Yang Y, Shen J, Luo S. Anxiety and prognosis of patients with myocardial infarction: a meta-analysis. Clin Cardiol. 2021;44(6):761–70.
9. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. Psychosom Med. 2010;72(6):563–9.
10. Smith KJ, Béland M, Clyde M, Gariépy G, Pagé V, Badawi G, et al. Association of diabetes with anxiety: a systematic review and meta-analysis. J Psychosom Res. 2013;74(2):89–99.
11. Mental health at work [internet]. Geneva: World Health Organization; 2022 (https://www.who.int/news-room/fact-sheets/detail/mental-health-at-work, accessed 6 October 2023).
12. Chawla N, Anothaisintawee T, Charoenrungrueangchai K, Thaipisuttikul P, McKay GJ, Attia J, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2022;376:e066084.
13. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393(10173):768–77.
14. Williams T, McCaul M, Schwarzer G, Cipriani A, Stein DJ, Ipser J. Pharmacological treatments for social anxiety disorder in adults: a systematic review and network meta-analysis. Acta Neuropsychiatr. 2020;32(4):169–76.
15. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ. 2009;339:b2880.
16. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014;75(5):e441–9.
17. Reichenpfader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. Drug Saf. 2014;37(1):19–31.
18. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Third edition. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/374250, accessed 21 November 2023).
19. Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113]. London: National Institute for Health and Care Excellence; 2020 (https://www.nice.org.uk/guidance/cg113, accessed 6 October 2023).
20. Social anxiety disorder: recognition, assessment and treatment. Clinical guideline [CG159]. London: National Institute for Health and Care Excellence; 2013 (https://www.nice.org.uk/guidance/cg159, accessed 6 October 2023).
21. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28(5):403–39.
22. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018;52(12):1109–72.
23. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guideli

nes for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(1):S1.
24. Practice guideline for treatment of patients with panic disorder. Second edition. Washington, DC: American Psychiatric Association; 2009 (https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf, accessed 6 October 2023).
25. Heuzenroeder L, Donnelly M, Haby MM, Mihalopoulos C, Rossell R, Carter R, et al. Cost-effectiveness of psychological and pharmacological interventions for generalized anxiety disorder and panic disorder. Aust N Z J Psychiatry. 2004;38(8):602–12.
26. van Apeldoorn FJ, Stant AD, van Hout WJ, Mersch PP, den Boer JA. Cost-effectiveness of CBT, SSRI, and CBT+SSRI in the treatment for panic disorder. Acta Psychiatr Scand. 2014;129(4):286–95.
27. Khoo AL, Zhou HJ, Teng M, Lin L, Zhao YJ, Soh LB, et al. Network meta-analysis and cost-effectiveness analysis of new generation antidepressants. CNS Drugs. 2015;29(8):695–712.
28. Ramsberg J, Asseburg C, Henriksson M. Effectiveness and cost-effectiveness of antidepressants in primary care: a multiple treatment comparison meta-analysis and cost-effectiveness model. PLoS One. 2012;7(8):e42003.

