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COMMENTARY

The loss of efficacy of fluoxetine in pediatric depression: explanations, lack of acknowledgment, and implications for other treatments

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Abstract

Objectives: Fluoxetine is among the most used antidepressants for children and adolescents and frequently recommended as first-line pharmacological treatment for pediatric depression. However, in contrast to earlier studies and reviews, a Cochrane network meta-analysis from 2021 concluded that the estimated efficacy of fluoxetine was no longer clinically meaningful. We aimed to explain the discrepant findings between the recent Cochrane review and earlier reviews, and to explore if this was acknowledged in guidelines and treatment recommendations appearing since then.

Study Design and Setting: Meta-analytical aggregation of trial results over time, exploring potential biases, and a nonsystematic search for recent treatment guidelines/recommendations from major medical organizations.

Results: The estimated efficacy of fluoxetine in clinical trials declined over time into the range of clinical equivalence with placebo when more recent studies were included in analyses and when considering common thresholds of clinical significance. This remains unacknowledged in treatment guidelines and related publications, including some that continue to recommend fluoxetine as first-line pharmacological treatment. Finally, we find that the loss of efficacy over time is likely explained by biases such as the novelty bias or by variations of expectancy effects.

Conclusion: The seeming lack of clinically meaningful efficacy of fluoxetine for the treatment of pediatric depression needs to be considered by those who develop treatment recommendations as well as by patients and clinicians. The biases we observed are not only relevant in the evaluation of fluoxetine and other antidepressants for pediatric depression, but also for any new treatment.

Keywords: Antidepressants; Fluoxetine; Efficacy; Pediatric; Meta-analysis; Biases; Guidelines

1. Two meta-analyses supporting the use of fluoxetine for pediatric depression

Antidepressant prescription rates in children and adolescents are ever increasing and fluoxetine is among the most frequently prescribed antidepressants [1–4]. Fluoxetine was a blockbuster drug and in 2003 the first second-generation antidepressant approved by the Food and Drug Administration for pediatric use. One reason why fluoxetine continued to be so popular for use in this population is that it was the only drug showing a statistically significant superiority to placebo in a high-impact meta-analysis by Cipriani et al (2016) in ''The Lancet'' [5] that has been cited 828 times, according to Google Scholar on 2025-02-05. Cipriani et al came to a sobering conclusion for antidepressants as a class but less so for fluoxetine specifically: ''When considering the risk-benefit profile of antidepressants in the acute treatment of major depressive disorder, these drugs do not seem to offer a clear advantage for children and adolescents. Fluoxetine is probably the best option

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What is new?

Key findings

- The efficacy of fluoxetine for pediatric depression has lost clinical significance.

What this adds to what is known?

- This has not been adequately addressed in guidelines of major medical organizations.
- The novelty bias and expectancy effects may explain the loss of estimated efficacy.

What is the implication and what should change now?

- Recommending fluoxetine as a first-line treatment is at odds with the evidence.
- This may create challenges for clinical practice that deserve further elaboration.

to consider when a pharmacological treatment is indicated.'' Furthermore, it was the only drug for which the drug-placebo difference did not overlap with a null-effect and the point estimate was clinically significant according to common thresholds of clinical significance [6], standardized mean difference (SMD) = −0.51, (95% credible interval −0.99 to −0.03). A more recent network meta-analysis by Zhou et al (2020) reported very similar findings [6]. Of note, the confidence in the efficacy findings for fluoxetine was rated as ''very low'' in both meta-analyses due to imprecision, heterogeneity, and inconsistency. However, this important contextual information was not included in recent major clinical guidelines that rely on these two meta-analyses to support recommendations for the use of fluoxetine in this population (eTable 1). On the contrary, the American Psychological Association interpreted the results of Cipriani et al as ''clear evidence'' in favor of fluoxetine [7].

2. A subsequent Cochrane review with less favorable results for fluoxetine

In May 2021, Hetrick et al published a Cochrane review about pediatric antidepressant treatment [8]. The efficacy of fluoxetine now was only three points (95% confidence interval (CI), −4.12 to −1.56) on the Children's Depression Rating Scale-Revised (CDRS-R; score range 17−113), with a ''moderate'' confidence rating. This corresponds to an effect size of SMD = −0.2 (CI −0.28 to −0.11), based on Hetrick et al's suggestion to use a standard deviation of 14.47. Compared with the preceding meta-analyses by Cipriani et al and Zhou et al., the point estimate and the lower end of the CI were now about 50% smaller. Hetrick et al defined the area of clinical unimportance as anything smaller than five points on the CDRS-R (SMD = 0.35), a rather conservative boundary [9]. The efficacy of fluoxetine is clearly below this threshold even when considering uncertainty. Consequently, Hetrick et al concluded that any difference between drug and placebo was ''small and unimportant,'' adding that this ''raises the question of whether [antidepressants] should be used at all.'' Other antidepressants either were not statistically significantly superior to placebo (escitalopram, mirtazapine, citalopram, venlafaxine, paroxetine, vilazodone, desvenlafaxine, and vortioxetine), or were significant but with a wide CI, thus leaving much uncertainty as to whether efficacy is in the clinically meaningful range or not (sertraline and duloxetine). None of the point estimates of any antidepressant exceeded the threshold of clinical significance.

3. Response of guidelines

Consequently, fluoxetine can no longer be considered a first-line antidepressant for the treatment of pediatric depression. Unfortunately, based on a nonsystematic review of treatment recommendations from major medical organizations which appeared or were updated at least 6 months after the Hetrick et al review, these implications have not been acknowledged. For example, the guideline from the American Academy of Child and Adolescent Psychiatry, which was published in May 2023, included Hetrick's 2021 review; but instead of acknowledging the findings it used Hetrick's review to support a recommendation to use fluoxetine for pediatric depression [10]. Other major health organizations also continue to recommend fluoxetine in their guidance as first-line treatment and/or failed to include the important finding by Hetrick et al (eTable 1).

4. Potential explanations for the loss of efficacy—novelty bias and reduced expectancy effects

Understanding the reason for the loss of fluoxetine's estimated efficacy has wider implications which should be understood and considered by those who develop treatment recommendations and also by clinicians and patients. Initial evidence for fluoxetine was most likely affected by the so-called ''novelty bias,'' a bias observed in different medical treatments [11]. One mechanism involved in the novelty bias is that, initially, the novel drug is investigated by the manufacturer of the drug, often just by comparing it with placebo in clinical trials. Later, when the drug is approved and established in guidelines and clinical practice, the drug will be used as comparator-drug in clinical trials of newer drugs, typically conducted by competitor companies. It is known that efficacy is larger when the drug is investigated by the manufacturer of the drug and not by a

competing drug company. This effect was demonstrated for antidepressants in general and for fluoxetine in particular in adult patient samples [12,13]. A Restoring Invisible and Abandoned Trials (RIAT) reanalysis of two pediatric trials on fluoxetine provides insight into the mechanisms generating these differences, such as the use of different outcomes, time-points, or methods to deal with missing data and drop-out [14].

Another bias that may be involved in fluoxetine's loss of efficacy is reduced expectancy effects [15]. Initially, as there is no competitor drug, the novel drug will be just compared with placebo and clinicians and patients know that the probability of receiving placebo is 50% (given a 1:1 randomization). Later, trials of competing drugs often use both the established drug for comparison in addition to a placebo group, meaning that the probability of receiving placebo is less than 50%. For example, one study used two different doses of vortioxetine (the new drug) and compared these with fluoxetine (the comparator drug) and placebo, thus the probability of receiving placebo was only 25% [16]. It was found that, in pediatric antidepressant trials, the drug-placebo difference was larger for trials with a 50% chance of receiving placebo (SMD = 0.22) than compared to the overall trial database (SMD = 0.12) where the chance of receiving placebo was <50% in about two-thirds of trials [17]. These findings support the assumption that varying expectancy-effects in relation to the probability of receiving placebo impact efficacy estimates.

Here, we show that similar findings can be seen in the results of fluoxetine for pediatric depression. In the Figure we depict the fluoxetine-placebo differences from clinical trials across time, together with their meta-analytic aggregation over time. We used studies from Hetrick et al which reported results from the CDRS-R and we also searched newer trials in two registers of clinical trials (clinicaltrials.gov, EudraCT) and from a recent systematic review [18]. It can be seen that the early trials produced effects in the range of clinical importance. With the appearance of new evidence, the efficacy declined and since 2022 the effect is clearly in the area of clinically unimportant effects, since the 95% CIs no longer extend outside this area. Whereas a meta-regression model with time as predictor failed to achieve statistical significance (P = .13), a subgroup meta-analysis showed that fluoxetine was significantly more efficacious (P = .003) in trials where it was the experimental (novel) drug (mean difference in CDRS-R points = −5.72, CI −7.93 to 3.50), compared to when it was the comparator drug (−1.85, CI −3.02 to −0.67) (see supplement for details).

5. Implications for research and clinical practice

Fluoxetine has been on the market long enough to be used as a comparator drug in pediatric antidepressant trials of other drugs. No other drugs were used as a comparator in the studies included in the Hetrick 2021 review, and it is plausible to assume that when these drugs have been studied only by the drug company and solely against placebo they will also have been affected by the novelty bias. Unfortunately, this was not discussed in the review by Hetrick et al and there was also no discussion about the smaller efficacy for fluoxetine compared to previous meta-analyses and potential explanations. Moreover, there should be an examination of how variation in other characteristics of trial methods or patient selection impacted efficacy estimates of fluoxetine over time. Furthermore, antidepressant trials are affected by other biases likely leading to an overestimation of the true efficacy, such as biases from using placebo wash-out phases, withdrawal effects from previous

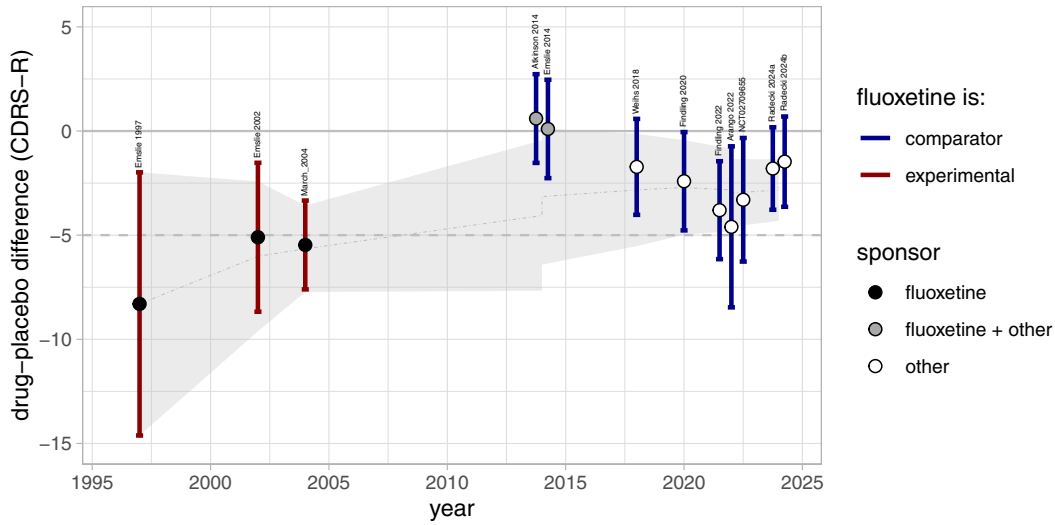

Figure. Efficacy of fluoxetine over time. Error-bars correspond to the 95% confidence interval (CI). The dot-dashed gray line is the result of the meta-analytic aggregation of the studies over time, together with the 95% CI-Band shaded in gray. The horizontal dashed gray line is the threshold of clinical significance.

antidepressant use, or breaking the blind [19]. Another cause for concern is the adverse events that tend to occur more frequently with antidepressants than with placebo [20]. Thus, based on the evidence from clinical trials, there is likely a problematic harm/benefit ratio for fluoxetine in children and adolescents because its average efficacy in clinical trials is not clinically meaningful. It is worth adding that most treatment recommendations are predominantly based on short-term trials (6-12 weeks) but that antidepressants are often used much longer and potential harms from long-term use and after ending treatment are not fully understood and should be taken into account in research and practice [21,22]. Suggestions to improve future clinical research include the use of outcomes less prone to bias and which are important to patients, longer follow-up time frames, larger sample sizes, which are adequately powered, and systematic assessment of adverse events [23].

We think it is important to assume a novelty bias in treatment recommendations and early trial results should be met with skepticism until they are used as comparator drugs and in multiarm trials. Consequently, drugs with clinically meaningful efficacy demonstrated even in comparator trials should be drugs of choice because the evidence is more robust. In addition, safety issues are better known as time passes.

In conclusion, the efficacy of fluoxetine for pediatric depression cannot be considered as being clinically meaningful anymore when considering the available evidence. This has so far not been acknowledged in treatment guidelines where fluoxetine continues to be recommended as first-line pharmacological treatment for young people. As reviewers of this commentary pointed out, hesitancy to acknowledge the recent evidence for fluoxetine may relate to the fact that fluoxetine is the only licensed pediatric drug for this indication. Another reason could simply be that it takes time until new evidence is included in guidelines. The small effects for antidepressants in general create challenges for treatment recommendations and clinical practice where alternatives to medications can be difficult to access—although this implementation issue should not be the only variable to influence guideline construction. However, some alternatives are cheaply available, such as basic behavioral measures [24] or watchful waiting, as remission without treatment occurs in up to half of people with depression and is more likely in children and adolescents [25]. Clinicians should be aware that in light of small or doubtful efficacy, side-effects create an unfavorable harm-benefit ratio. A common assumption is that some patients may benefit especially well from antidepressants thus clearly outweighing side effects. However, robust predictors of subgroups of patients with substantially larger drug-placebo-differences have not yet been identified despite substantial research efforts and there are good reasons to remain skeptical about such a project [26]. Recognition that antidepressants lack clinical meaningful average efficacy in this age group does not mean leaving depressed patients without support, and we should also avoid the situation that patients abruptly stop medication as this can create problematic withdrawal symptoms. Patients who decide they wish to stop an antidepressant should be advised to consult a clinician expert in deprescribing. Overall, resolving these challenges goes beyond the scope of our commentary and we hope that it will stir necessary discussions, reevaluations of guidelines, and treatment recommendations.

CRediT authorship contribution statement

Martin Plöderl: Writing − review & editing, Writing − original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Richard Lyus:** Writing − review & editing, Writing − original draft, Validation, Data curation, Conceptualization. **Mark A. Horowitz:** Writing − review & editing, Writing − original draft, Validation, Conceptualization. **Joanna Moncrieff:** Writing − review & editing, Supervision.

Declaration of competing interest

MAH and JM are co-applicants on the RELEASE and RELEASE + trials in Australia, funded by the Medical Research Future Fund (MRFF) and the National Health and Medical Research Council (NHMRC), evaluating hyperbolic tapering of antidepressants against care as usual. MAH reports being a co-founder of and consultant to Outro Health, a digital clinic which provides support for patients in the US to help stop no longer needed antidepressant treatment using gradual, hyperbolic tapering; and receives royalties for the Maudsley Deprescribing Guidelines. JM receives royalties for books about psychiatric drugs, and was a co-applicant on the REDUCE trial, funded by the National Institute of Health Research, evaluating digital support for patients stopping long-term antidepressant treatment. MP and RL have no conflicts of interest to declare.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2025.112016.

Data availability

Data will be shared on the OSF https://osf.io/wux24/

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