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A Review of the Efficacy and Adverse Effects of Fluoxetine in the Treatment of Generalized Anxiety Disorder

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ABSTRACT

Background: Generalized anxiety disorder (GAD) is a persistent mental illness that causes significant distress and impairment in functioning. Selective serotonin reuptake inhibitors (SSRIs) are often used in the treatment of GAD, but evidence for fluoxetine in particular is not as well established as for some other pharmacological options.

Purpose: This review examined the efficacy and adverse effects of fluoxetine in the treatment of GAD while also considering treatment tolerability, pharmacokinetic variability, and emerging personalized medicine approaches.

Methods: A structured narrative review was conducted using PubMed/MEDLINE, PsycINFO, Embase, the Cochrane Library, and Scopus, with database searches conducted between January and April 30, 2026. Nineteen publications were included in the final synthesis, comprising direct adult GAD–fluoxetine studies, pediatric and mixed-anxiety fluoxetine studies, systematic reviews and network meta-analyses, and supportive safety, pharmacokinetic, pharmacogenetic, and biomarker research. Direct adult GAD evidence was distinguished from indirect or supportive evidence throughout the review.

Results: Several studies reported decreases in anxiety symptoms with fluoxetine, but direct adult GAD evidence was limited and did not establish superiority over other pharmacological treatments. However, systematic reviews and network meta-analyses yielded inconsistent results, and the evidence specific to fluoxetine was limited by small sample sizes, open-label designs, and limited data from placebo-controlled trials. Common adverse effects included nausea, insomnia, agitation, dry mouth, and sexual dysfunction. Differences in fluoxetine and norfluoxetine concentrations were associated with CYP2D6 genotype, but present evidence does not support routine genotype-guided dosing of fluoxetine. Biomarker- and patient-specific approaches remain preliminary and are not established for clinical decision-making in GAD.

Conclusions: Fluoxetine may be a treatment option for some patients with GAD, but current evidence does not establish superiority over SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) with stronger GAD-specific evidence. Larger, adequately powered, longer-term placebo-controlled trials are needed to clarify fluoxetine's efficacy and tolerability in GAD and to evaluate the possible role of individualized treatment strategies.

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1. Introduction

1.1. Importance of Evaluating Psychiatric Treatments

Psychiatric disorders create a major burden on individuals because they are highly prevalent and can interfere with quality of life, daily functioning, and overall well-being (Edinoff *et al.*, 2021). Among the most common psychiatric conditions are anxiety disorders, including generalized anxiety disorder (GAD), which has often been linked to significant personal distress, psychosocial impairment, and overall reduced functioning in people's lives (Baldwin *et al.*, 2011; Costa *et al.*, 2021). GAD also imposes a considerable economic burden and can result in levels of disability comparable to other psychiatric and chronic physical illnesses (Baldwin *et al.*, 2011). Thus, it is important to explore treatments for GAD so current

and future pharmaceutical and psychiatric approaches can focus not only on symptom relief but also on broader, sustained clinical improvement (Baldwin *et al.*, 2011; Costa *et al.*, 2021).

Efficacy in the treatment of psychiatric disorders refers to the extent to which treatment reduces symptom severity and produces clinically meaningful improvement (Baldwin *et al.*, 2011). Researchers commonly measure efficacy by analyzing outcomes such as response and remission; for example, Baldwin *et al.* (2011) define response as having at least a 50% reduction from baseline on the Hamilton Anxiety Scale (HAM-A) and remission as having a final HAM-A score of 7 or lower. Improvements in quality of life and overall functioning can also broadly reflect treatment efficacy, as pharmacotherapy for GAD aims to reduce anxiety, improve individuals' living conditions, and prevent relapse (Zou *et al.*, 2013).

Adverse effects are important because treatment-related harms may compromise a patient's safety, comfort, or willingness to continue medication (Edinoff *et al.*, 2021; Sohel *et al.*, 2024). In antidepressant and anxiety research, tolerability refers to the extent to which a medication can be continued without problematic adverse effects. In this review, "adverse effects" refers to unwanted effects attributed to treatment, whereas "adverse events" is used when causality is not established, particularly for pharmacovigilance reports; treatment discontinuation is considered separately as a tolerability outcome. Other common adverse effects associated with selective serotonin reuptake inhibitors (SSRIs) like fluoxetine include nausea, insomnia, somnolence, agitation, sexual dysfunction, and headaches, while withdrawal symptoms may occur following discontinuation (Baldwin *et al.*, 2011; Edinoff *et al.*, 2021; Sohel *et al.*, 2024; Zou *et al.*, 2013). These adverse effects are clinically important because they may contribute to treatment discontinuation. The use of psychiatric drugs needs to be assessed by weighing therapeutic benefits against potential adverse effects (Baldwin *et al.*, 2011; Costa *et al.*, 2021; Edinoff *et al.*, 2021).

1.2. Generalized Anxiety Disorder

Generalized anxiety disorder, a chronic and relapsing anxiety disorder, is characterized by a form of worrying that is excessive, persistent, and difficult to control for individuals (Baldwin *et al.*, 2011; Zou *et al.*, 2013). Although DSM criteria describe GAD as excessive anxiety and worry about various types of events/activities occurring on most days for at least six months, it is important to recognize that GAD is not simply a pattern of everyday stress. Rather, it is a long-term psychiatric condition in which significant distress and impairment can interfere with normal day-to-day functioning of diagnosed individuals (Baldwin *et al.*, 2011; Zou *et al.*, 2013). Individuals may also experience physiological and cognitive symptoms, including muscle tension, restlessness, sleep disturbance, irritability, fatigue, and difficulty concentrating (Zou *et al.*, 2013).

GAD is one of the most common anxiety disorders described in primary care. One review estimated a point prevalence of 5.3% in primary care, 12-month prevalence of 2.1%, and lifetime prevalence of 4.1% in the United States (Zou *et al.*, 2013). The authors also reported that similar trends were found in European studies cited in the same review, with 12-month prevalence rates ranging from 1.7% to 3.4% and lifetime prevalence rates ranging from 4.3% to 5.9%, showing that GAD is a common disorder worldwide (Zou *et al.*, 2013). Comorbidity with other psychiatric disorders may exacerbate the adverse effects of GAD and contribute to an even greater negative impact on individuals' quality of life (Zou *et al.*, 2013).

1.3. Fluoxetine: Uses and Mechanism of Action

Fluoxetine belongs to a class of medications known as selective serotonin reuptake inhibitors and is widely used in psychiatric treatment (Edinoff *et al.*, 2021; Sohel *et al.*, 2024; Zou *et al.*, 2013). Fluoxetine has established uses in conditions such as major depressive disorder (MDD), obsessive-compulsive disorder (OCD), panic disorder, bulimia nervosa, and bipolar depression when used in conjunction with olanzapine (Sohel *et al.*, 2024). Fluoxetine's widespread use is due to its effectiveness across several mental health conditions and its favorable safety and tolerability profile compared with older antidepressants (Edinoff *et al.*, 2021; Sohel *et al.*, 2024). Zou *et al.* (2013) reported that fluoxetine is also used in the clinical management of GAD, despite mixed supporting evidence compared to other pharmacological agents.

Fluoxetine increases serotonin availability in the synapse, which promotes serotonergic signalling, by blocking serotonin reuptake at the presynaptic neuron. Because serotonin is involved in processes related to mood and anxiety, increasing its availability and signalling in the synapse provides a theoretical basis for why fluoxetine may be beneficial in treating psychiatric and anxiety disorders (Edinoff *et al.*, 2021; Sohel *et al.*, 2024). Fluoxetine's relevant clinical uses and mechanism of action are presented visually in Figure 1.

Fluoxetine inhibits the serotonin transporter (SERT), reducing serotonin reuptake and increasing serotonin (5-HT) availability in the synaptic cleft. Fluoxetine has established uses across several psychiatric disorders and has also been studied in GAD (Edinoff *et al.*, 2021; Sohel *et al.*, 2024; Zou *et al.*, 2013).

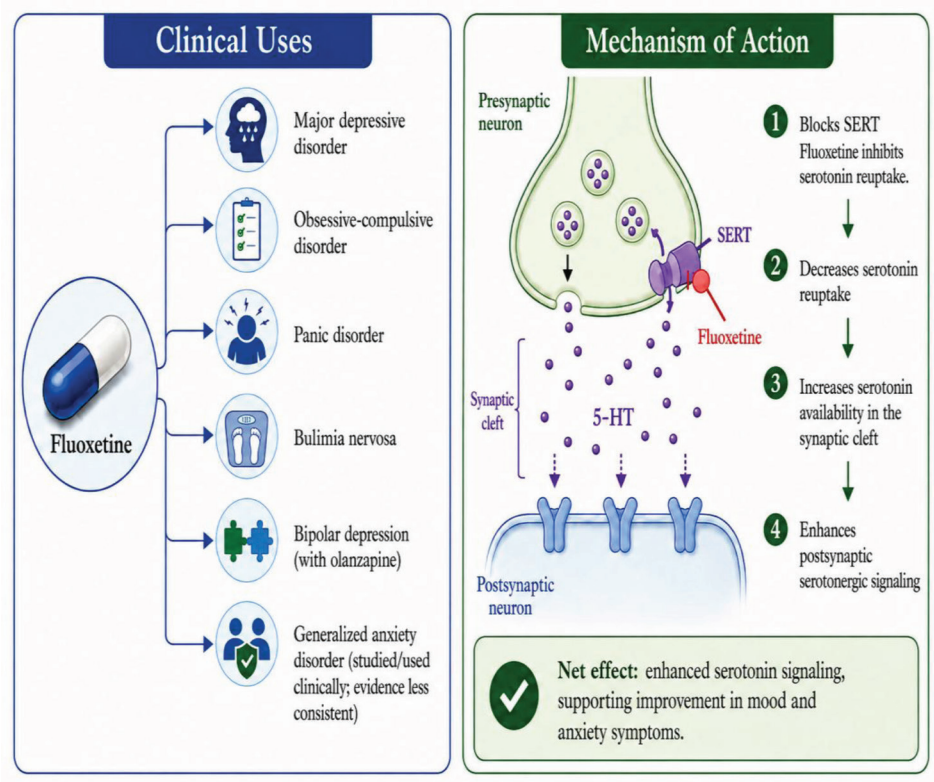

Figure 1: Clinical Uses and Mechanism of Action of Fluoxetine

Selective serotonin reuptake inhibitors (SSRIs) are often recommended as the first-line pharmacological treatment of GAD, and fluoxetine is therefore a particularly relevant drug to study, as it belongs to a drug class that is central to the treatment of anxiety (Baldwin *et al.*, 2011; Zou *et al.*, 2013). SSRIs are also recommended for GAD in more recent guidelines. The World Health Organization recommends SSRIs for adults with GAD, but the SSRIs evaluated (fluoxetine, paroxetine, escitalopram, and sertraline) did not show distinct differences in efficacy and adverse effects (Gray *et al.*, 2024). This supports the use of SSRIs as a class of medication for GAD, while fluoxetine itself is not established as a preferred treatment approach for GAD.

Baldwin *et al.* (2011) found that fluoxetine had the highest estimated probabilities for response and remission in their probabilistic analysis, while evidence reviewed by Zou *et al.* (2013) suggested short-term efficacy, an onset of action of approximately one to two weeks, and possible effectiveness in maintenance treatment. Because the available evidence was limited, the authors did not recommend fluoxetine as a reliable first-line treatment for GAD, highlighting the need for further research on fluoxetine, especially to understand its possible therapeutic benefits alongside its adverse effects (Baldwin *et al.*, 2011; Zou *et al.*, 2013).

1.4. Purpose and Clinical Importance of the Review

This review examines the efficacy and adverse effects of fluoxetine in the treatment of generalized anxiety disorder. Specifically, it aims to determine whether fluoxetine alleviates symptoms of GAD and whether its tolerability and adverse-effect profile are suitable for its use in clinical practice (Zou *et al.*, 2013). This is an important topic because GAD management should be guided by evidence-based prescribing, as available medications differ in the strength of supporting evidence, efficacy, tolerability, and clinical recommendations (Zou *et al.*, 2013).

Baldwin *et al.* (2011) concluded that fluoxetine performed well for response and remission, but the evidence for use in GAD was limited by the small number of randomized trials available.

Adverse effects must also be considered, as psychiatric medications should not only be judged by symptom improvements but also by the ability of patients to safely tolerate and continue the treatment (Edinoff *et al.*, 2021; Zou *et al.*, 2013). The goals of GAD pharmacotherapy are to reduce anxiety, improve quality of life with minimum adverse effects, and prevent relapse (Zou *et al.*, 2013).

In this study, the suitability of fluoxetine for GAD is assessed by comparing efficacy and tolerability with other existing treatments (Baldwin *et al*., 2011; Zou *et al*., 2013). However, data specific to fluoxetine in GAD are scarce, and positive findings should thus be regarded with caution (Baldwin *et al*., 2011; Zou *et al*., 2013).

1.5. Pharmacokinetic Variability

A challenge when evaluating fluoxetine is its interindividual pharmacokinetic variability, which may contribute to differences in treatment response. Moreover, fluoxetine is metabolized to its active metabolite, norfluoxetine, through multiple cytochrome P450 pathways, with CYP2D6 playing an important role (Nordby *et al*., 2025; Bousman *et al*., 2023).

1.6. Safety and Tolerability Considerations

Newer SSRIs, such as fluoxetine, have more favorable adverse-effect profiles than earlier antidepressants but are nevertheless associated with adverse effects that may affect adherence and treatment continuation.

1.7. Personalized Medicine and Future Directions

Differences in responsiveness to treatment, pharmacokinetics, and adverse effects underscore the importance of customized medication as a future avenue in anxiety treatment. However, personalized healthcare is still an emerging method rather than an established therapeutic strategy (Nordby *et al*., 2025; Roseberry *et al*., 2023).

2. Methods

2.1. Study Design

This study was conducted as a structured narrative review of the efficacy and adverse effects of fluoxetine in generalized anxiety disorder (GAD). The review integrated direct clinical evidence involving fluoxetine treatment in patients with GAD with supportive evidence from systematic reviews, network meta-analyses, pediatric anxiety studies, pharmacokinetic and pharmacogenetic research, pharmacovigilance studies, and emerging personalized-medicine literature. Direct adult GAD–fluoxetine evidence was given greater weight when drawing conclusions regarding clinical efficacy, whereas indirect evidence was used primarily to provide comparative, safety, pharmacological, or future-treatment context. Because this was a structured narrative review rather than a systematic review, a formal PRISMA flow diagram was not used.

2.2. Evidence Classification

Evidence was classified into four categories: (1) direct adult GAD–fluoxetine evidence; (2) pediatric or mixed-anxiety fluoxetine evidence; (3) broader GAD pharmacotherapy evidence involving SSRIs, SNRIs, or network comparisons; and (4) supportive fluoxetine-specific evidence from pharmacokinetic, pharmacogenetic, pharmacovigilance, or biomarker studies not conducted specifically in GAD. Findings from the latter three categories were not treated as direct evidence of fluoxetine efficacy in adults with GAD.

2.3. Data Collection

A structured search of PubMed/MEDLINE, PsycINFO, Embase, the Cochrane Library, and Scopus was conducted between January and April 30, 2026, with the final search conducted on April 30, 2026. No publication-date restriction was applied. A representative clinical search strategy was ("fluoxetine" OR "Prozac") AND ("generalized anxiety disorder" OR "generalized anxiety disorder" OR "GAD") AND (efficacy OR response OR remission OR tolerability OR safety OR "adverse effects"). Additional searches combined "fluoxetine" with "CYP2D6," "pharmacokinetics," "pharmacogenetics," "pharmacovigilance," "personalized medicine," "precision medicine," and related terms.

Studies that examined fluoxetine efficacy were then evaluated for treatment outcomes such as reductions in anxiety symptoms, treatment response, remission, and maintenance of therapeutic effects. In addition, studies that focused on fluoxetine's adverse effects were examined for medication tolerability, treatment discontinuation, reported adverse effects, and safety considerations. The review also included literature on pharmacokinetic variability and personalized medicine to evaluate emerging factors associated with individual treatment response.

2.4. Inclusion and Exclusion Criteria

Articles were included if they examined fluoxetine, SSRIs, or pharmacological treatments that were relevant to GAD; reported information related to the treatment's efficacy, response, remission, adverse effects, safety, or tolerability; examined pharmacokinetic or pharmacogenetic factors relevant to fluoxetine, including CYP2D6 metabolism, when applicable to understanding variability in treatment outcomes; provided relevant information regarding fluoxetine pharmacology, safety, or emerging treatment approaches that could inform its clinical use; examined personalized or precision medicine approaches relevant

to anxiety disorders and pharmacological treatment; were peer-reviewed and available in English; and provided findings that directly contributed to evaluating the benefits, limitations, or future clinical application of fluoxetine.

Studies were excluded if they provided very limited or no information at all about fluoxetine, GAD, anxiety pharmacotherapy, adverse effects, pharmacokinetic variability, or personalized treatment approaches; focused on unrelated psychiatric conditions without providing any relevant information about fluoxetine or anxiety treatment; or focused on conditions other than GAD without providing relevant evidence regarding fluoxetine's pharmacology, safety, pharmacokinetics, or emerging treatment approaches applicable to treating anxiety. Indirect evidence was included only when it provided relevant comparative, safety, pharmacokinetic, pharmacogenetic, or emerging-treatment context for interpreting fluoxetine use in GAD.

2.5. Data Analysis

Studies judged potentially relevant based on title and abstract screening underwent full-text review, after which articles meeting the inclusion criteria were included and relevant information was extracted and organized in line with the literature review's main objectives. Nineteen publications were included in the final synthesis. More specifically, the findings presented in the literature were organized by recurring themes based on fluoxetine's efficacy for treating GAD, adverse effects and tolerability, and pharmacokinetic variability, as well as personalized medicine.

We compared efficacy evidence across studies using reported outcomes such as symptom reduction, response, and remission. Safety findings were evaluated based on reported adverse effects, tolerability, and treatment discontinuation. In addition, we examined pharmacokinetic studies to identify factors that may contribute to interindividual differences in fluoxetine's metabolism and treatment outcomes. We also reviewed personalized medicine literature to analyze various emerging approaches that may help individualize anxiety treatment. Finally, the review highlights the methodological limitations, inconsistencies between studies, and gaps in the evidence to identify key areas that require further research to understand the efficacy and adverse effects of fluoxetine in treating GAD.

No validated risk-of-bias instrument was applied because this was a structured narrative review rather than a systematic review. Instead, methodological limitations were evaluated narratively according to randomization, blinding, presence of a placebo or active comparator, sample size, treatment duration, population heterogeneity, and directness of evidence.

3. Results and Discussion

3.1. Efficacy of Fluoxetine in Generalized Anxiety Disorder

3.1.1. Comparative and Network Meta-Analytic Evidence

The literature reviewed suggests that fluoxetine may reduce symptoms of GAD; however, the strength of the evidence remains limited. Baldwin *et al.* (2011), in a systematic review and meta-analysis, compared nine pharmacological treatments for GAD and reported that fluoxetine had the highest estimated probabilities for both response and remission in the probabilistic analysis, with probabilities of 62.9% and 60.6%, respectively. However, the fluoxetine-specific evidence underlying these rankings was limited, and the authors' frequentist analysis was inconclusive because of the uncertainty present in the effect estimates and the small number of comparative trials. Therefore, these probabilistic rankings should not be interpreted as evidence that fluoxetine is superior to other established treatments for GAD.

Evidence for fluoxetine was less consistent across broader meta-analyses of GAD pharmacotherapies. In a systematic review (Slee *et al.*, 2019) of 89 trials with 25,441 participants, a network meta-analysis was performed. They concluded that fluoxetine seemed to be effective and well tolerated. However, the authors noted that the findings were limited by the small sample sizes of available fluoxetine trials. By contrast, He *et al.* (2019) conducted a network meta-analysis of 41 randomized controlled trials and did not find a significant difference in the estimated effect of fluoxetine on HAM-A symptom reduction in comparison with placebo. Several other first-line drugs showed significantly greater reductions. Because these findings were derived largely from network comparisons rather than a large body of direct fluoxetine-versus-placebo trials, they should be interpreted as indirect comparative evidence rather than definitive evidence of fluoxetine-specific efficacy. Overall, these results further suggest the uncertainty in fluoxetine's comparative efficacy for GAD (He *et al.*, 2019; Slee *et al.*, 2019).

3.1.2. Direct Evidence in Adults With GAD

Short-term evidence suggests that fluoxetine may reduce symptoms in adults with GAD. In Chinese patients with GAD, Zou *et al.* (2013) reviewed 15 non-placebo-controlled, open-label studies and found that fluoxetine was generally as effective as several other anxiolytic medications. One study in particular reported a HAM-A score of 25.03 decreasing to 8.28 in patients on fluoxetine, with a response rate of 73.3% and a remission rate of 43%. These results were comparable to those of escitalopram, with a response rate of 76.7% and a recovery rate of 50%. Another comparative study showed no significant difference between fluoxetine and

escitalopram in response and remission rates after 4 weeks. A six-week trial demonstrated fluoxetine and duloxetine had similar efficacy (Zou *et al*., 2013). However, because these studies were generally small, open-label, and lacked placebo controls, they provide direct but methodologically limited evidence for fluoxetine in adults with GAD.

More recent evidence comes from an eight-week randomized clinical trial in which participants receiving fluoxetine showed improvement on measures of anxiety and worry (Costa *et al*., 2021). In addition, fluoxetine was superior to the active Quality of Life and Psychoeducation (QoL) comparison group on several clinical outcomes and was superior to the Body in Mind Training intervention on measures of worry and anxiety (Costa *et al*., 2021). The response rate was 50% in the fluoxetine group, and the remission rate was 21.7% without any significant difference between the other treatment groups. Therefore, the study adds to evidence that fluoxetine can reduce symptoms of GAD. However, because the trial did not include a pharmacological placebo group and response and remission rates did not differ significantly between treatment groups, the findings do not establish fluoxetine's superiority across all measures of treatment success.

3.1.3. Pediatric and Mixed-Anxiety Evidence

Evidence in pediatric populations also suggests that fluoxetine may have short-term efficacy, but these findings should be distinguished from evidence in adults with GAD. Birmaher *et al*. (2003) randomized 74 youths aged 7 to 17 years with GAD, social anxiety disorder, and/or separation anxiety disorder to 12 weeks of fluoxetine or placebo. Overall, 61% of participants on fluoxetine improved much or very much compared with 35% on placebo. Castagna *et al*. (2023) reported that in participants with GAD, approximately 67% treated with fluoxetine achieved the desired clinical outcome on the CGI-I compared with 36% treated with placebo. However, a large percentage of participants were still symptomatic post-treatment, and there was significant overlap of different anxiety disorders in the study. As such, Birmaher *et al*. (2003) provide placebo-controlled evidence for fluoxetine in anxious youth. Castagna *et al*. (2023) point out that pediatric pharmacotherapy studies typically include heterogeneous and comorbid anxiety samples, limiting GAD-specific conclusions. Therefore, these findings should be considered supportive pediatric evidence and should not be interpreted as direct evidence of fluoxetine efficacy in adults with GAD.

3.1.4. Dose and Treatment Duration

The available fluoxetine trials had different dosages and treatment durations, and the populations and study designs were diverse. In the adult GAD studies examined by Zou *et al*. (2013), fluoxetine was frequently provided at doses of 20–60 mg/day throughout the acute therapy phase of around 4 to 8 weeks. Costa *et al*. (2021) likewise tested fluoxetine over 8 weeks, dosages ranging from 20 to 60 mg/day, starting at 20 mg/day and titrating up depending on clinical response and tolerability. In the pediatric placebo-controlled trial of Birmaher *et al*. (2003), fluoxetine 20 mg/day was administered for 12 weeks. These studies provide information regarding the doses utilized in clinical research, yet the various study designs, populations, comparators, and durations of therapy do not permit a reliable conclusion regarding a dose-response relationship for fluoxetine in GAD.

These results suggest fluoxetine may produce clinically meaningful reductions in anxiety symptoms and may have clinical benefits for some patients with GAD. However, the evidence is not strong enough to support fluoxetine as a preferred first-line treatment for GAD. The evidence specific to fluoxetine reviewed by Zou *et al*. (2013) consisted of relatively small, open-label studies without placebo controls, and evidence on long-term relapse prevention, functional improvement, and long-term adverse effects remains limited. Thus, the current literature suggests that fluoxetine may be effective in GAD; however, it does not provide strong evidence that it is superior to better-established SSRIs or SNRIs. A summary of the key evidence regarding the efficacy of fluoxetine for GAD is presented in Table 1.

Table 1: Summary of Evidence on the Efficacy and Tolerability of Fluoxetine for Generalized Anxiety Disorder

Study	**Design / Population**	**Sample Size**	**Fluoxetine Dose**	**Treatment Duration**	**Comparator / Placebo**	**Main Efficacy Outcome**	**Adverse Effects / Tolerability**	**Important Limitation**
Baldwin *et al*. (2011)	Systematic review and meta-analysis of GAD pharmacotherapies	27 trials included in the meta-analysis; fluoxetine evidence came from one included trial	Varied across included studies	Varied across included studies	Multiple pharmacological treatments	Highest estimated probabilities for response (62.9%) and remission (60.6%) in probabilistic analysis	Fluoxetine-specific tolerability data were not separately quantified in this review	Fluoxetine evidence was based on very limited comparative data; frequentist findings were inconclusive

Zou *et al.* (2013)	Review of 15 Chinese studies in patients with GAD	370 fluoxetine-treated patients in the reported safety analysis	20–60 mg/day	Approximately 4–8 weeks for acute treatment	Various active comparators, including escitalopram and duloxetine; generally no placebo control	Generally showed symptom reduction and efficacy comparable to several other anxiolytic medications; reported outcomes included HAM-A reduction, response, and remission	Dry mouth 11.3%, nausea 11.0%, insomnia 6.2%, drowsiness 5.4%, constipation 5.1%, and agitation 4.3%; most adverse effects were mild or moderate	Mostly small, open-label, non-placebo-controlled studies with methodological limitations that increase the potential for bias
Slee *et al.* (2019)	Systematic review and network meta-analysis; 89 trials, 25,441 participants	25,441 participants across 89 trials	Varied across included trials	Varied across included trials	Multiple pharmacological treatments and placebo through network comparisons	Fluoxetine appeared efficacious	Fluoxetine appeared well tolerated	Fluoxetine findings were based on small sample sizes and limited direct fluoxetine evidence
He *et al.* (2019)	Network meta-analysis; 41 RCTs	15,739 participants across 41 RCTs; fluoxetine-specific sample size was not reported separately	Varied across included trials	Varied across included trials	Placebo and other first-line pharmacological treatments	Estimated HAM-A symptom reduction for fluoxetine did not significantly differ from placebo	Fluoxetine-specific adverse-effect data were not separately reported	Network estimates relied on limited direct fluoxetine evidence
Costa *et al.* (2021)	8-week randomized clinical trial in adults with GAD	249 participants randomized; 223 analyzed, including 79 in the fluoxetine group	20–60 mg/day, beginning at 20 mg/day	8 weeks	Quality of Life and Psychoeducation and Body in Mind Training; no pharmacological placebo	Fluoxetine reduced anxiety and worry; response 50% and remission 21.7%	Fluoxetine-specific adverse-effect frequencies were not reported separately	Response and remission did not significantly differ across treatment groups; no pharmacological placebo
Birmaher *et al.* (2003)	12-week placebo-controlled RCT; 74 youths with anxiety disorders	74 youths	20 mg/day	12 weeks	Fluoxetine vs placebo	61% improved with fluoxetine vs 35% with placebo; approximately 67% of participants with GAD achieved target CGI-I outcome vs 36% with placebo	Mild, transient headaches and gastrointestinal symptoms; 5 of 37 participants receiving fluoxetine (13.5%) discontinued because of significant agitation	Pediatric sample included multiple and comorbid anxiety disorders

Castagna *et al.* (2023)	Review of pediatric GAD pharmacotherapy	Not applicable; review of pediatric GAD pharma-cotherapy studies	Varied across reviewed studies	Varied across reviewed studies	Varied across reviewed studies	Supports possible short-term efficacy of fluoxetine in youth	Reported adverse effects included drowsiness, difficulty sleeping, decreased appetite, nausea, abdominal pain, and excitability	Pediatric studies were heterogeneous and frequently included multiple anxiety disorders

3.2. Adverse Effects, Safety, and Tolerability

3.2.1. Clinical Adverse Effects and Treatment Discontinuation

GAD-specific studies suggest that fluoxetine is generally tolerated during short-term treatment, although several adverse effects have been reported. In the studies reviewed by Zou *et al.* (2013), the most commonly reported adverse effects among the 370 patients included in the pooled adverse-event analysis were dry mouth at 11.3%, nausea at 11.0%, insomnia at 6.2%, drowsiness at 5.4%, constipation at 5.1%, and agitation at 4.3%. Less commonly reported effects included headache, somnolence, tremor, sweating, and sexual problems. Most adverse effects in these studies were described as mild or moderate in severity. Across 436 participants receiving fluoxetine, two discontinued treatments because of gastrointestinal adverse events (approximately 0.5%) (Zou *et al.*, 2013). Taken together, the most frequently reported adverse effects involved gastrointestinal symptoms, sleep-related effects, and CNS/activation-related symptoms, while sexual adverse effects were reported less frequently (Zou *et al.*, 2013).

Pediatric data also provide further information on fluoxetine tolerability. Birmaher *et al.* (2003) found that fluoxetine was well tolerated, with adverse effects limited to mild, transient headaches and gastrointestinal symptoms. Five of 37 participants receiving fluoxetine (13.5%) discontinued treatment because of significant agitation, but the incidence of mild to moderate agitation or disinhibition was not significantly different from the placebo group.

Castagna *et al.* (2023) also reported on pediatric fluoxetine studies where adverse effects included drowsiness, difficulty sleeping, decreased appetite, nausea, abdominal pain, and excitability.

3.2.2. Comparative Tolerability

The comparative evidence also suggests that tolerability may differ depending on the medications with which fluoxetine is compared. Zou *et al.* (2013) reported that fluoxetine was better tolerated than diazepam, doxepin, and amitriptyline, whereas escitalopram demonstrated better tolerability than fluoxetine. Fluoxetine showed similar tolerability to duloxetine and alprazolam. For example, one comparison with doxepin reported 24 adverse events in the doxepin group compared with five in the fluoxetine group. Another comparison found substantially higher rates of anticholinergic effects, such as dry mouth, constipation, and tachycardia, among patients receiving amitriptyline than those receiving fluoxetine (Zou *et al.*, 2013). These findings suggest that fluoxetine may have tolerability advantages over older medications, but that does not mean that it is the best-tolerated option among newer antidepressants used to treat GAD.

3.2.3. Indirect Evidence on Early Activation

Early research on SSRIs generally suggests that some people might experience worsening anxiety symptoms in the early stages of treatment. Gollan *et al.* (2012) treated 201 adults with major depressive disorder (MDD) with different SSRIs, including fluoxetine (31 patients). At 2 weeks of SSRI treatment, 48.8% of participants reported improvement in anxiety symptoms, 36.3% reported minimal change, and 14.9% reported worsening of anxiety. However, these results were not specific to either fluoxetine or GAD, as participants had MDD and were on different SSRIs. Therefore, the study cannot establish the frequency of early anxiety exacerbation in patients treated with fluoxetine for GAD, but it provides relevant evidence regarding the variability of individual responses to SSRIs in the early stages of treatment (Gollan *et al.*, 2012).

3.2.4. Pharmacovigilance Safety Signals

Real-world pharmacovigilance evidence provides complementary safety-signal information but should be interpreted separately from controlled clinical safety data because it cannot establish adverse-event incidence or causality. Gao *et al.* (2025) analyzed FAERS reports from 2004 to 2023 and identified 22,884 reports in which

fluoxetine was the primary suspected medication, resulting in 862 adverse-event signals across 27 system organ classes. The study identified signals involving psychiatric and nervous-system outcomes, along with pregnancy- and neonatal-related signals. Similarly, Zhao *et al.* (2024) examined 427,655 reports involving six SSRIs, including 64,232 involving fluoxetine, and found safety signals involving psychiatric, nervous, cardiac, reproductive, and other physiological systems.

However, these pharmacovigilance findings do not establish a causal relationship between fluoxetine and each reported event. FAERS is a spontaneous reporting system and is prone to reporting bias, incomplete information on patients, differences in exposure to medications, comorbidities, and concomitant medications. Therefore, pharmacovigilance data are valuable for identifying potential safety issues that require further investigation, but controlled clinical evidence is needed to determine the incidence and causality of adverse effects (Gao *et al.*, 2025).

3.3. Balancing Efficacy and Adverse Effects

The efficacy of fluoxetine in GAD should be balanced against its adverse effects. Fluoxetine was associated with reductions in anxiety symptoms in several studies and appears to have a favorable tolerability profile relative to older anxiolytic and antidepressant medications. However, response and remission are not universal, and adverse effects such as nausea, insomnia, agitation, and sexual dysfunction may reduce a patient's willingness or ability to continue treatment.

Recent evidence further supports the importance of balancing treatment efficacy and tolerability. High-certainty evidence from a Cochrane review of 37 studies involving 12,226 patients with GAD found that antidepressants were more effective than placebo to produce a treatment response (Kopcalic *et al.*, 2025). However, participants who were given antidepressants were also more likely to stop treatment due to adverse effects compared to placebo (Kopcalic *et al.*, 2025). Most importantly, however, the review found no eligible trials comparing fluoxetine with placebo. Therefore, these results are supportive of the use of antidepressants to treat GAD more generally, rather than demonstrating the efficacy of fluoxetine specifically. This further emphasizes the need to consider the evidence for antidepressants as a class, as distinct from the more limited direct evidence for fluoxetine.

The benefit of antidepressant treatment may also differ according to the initial severity of GAD symptoms. In an individual patient data meta-analysis of 3,430 participants with GAD across eight trials, de Vries *et al.* (2018) found that the antidepressant-placebo difference increased as baseline symptom severity increased. The difference was 1.4 HAM-A points among participants with a baseline HAM-A score of 10 but increased to 4.0 points among participants with a baseline score of 30. The authors concluded that the benefits of antidepressants were relatively small at lower levels of GAD severity and that the benefit-risk balance may become less favorable as initial severity decreases (de Vries *et al.*, 2018). However, these findings reflect antidepressant treatment more broadly and should not be interpreted as demonstrating a fluoxetine-specific severity effect.

The therapeutic goal in GAD also extends beyond reducing HAM-A scores to improving quality of life, supporting long-term functioning, minimizing adverse effects, and reducing relapse risk (Zou *et al.*, 2013). Evidence from these studies does not support the conclusion that fluoxetine is either universally beneficial or unsuitable for GAD. Instead, its clinical value appears to depend on the balance between symptom improvement and tolerability for an individual patient.

Although fluoxetine remains clinically relevant, there is more direct evidence for treating GAD with some of the other SSRIs and SNRIs. Compared with the broader evidence supporting SSRIs and SNRIs, fluoxetine-specific evidence is limited by fewer placebo-controlled adult GAD trials and limited long-term data, and current evidence does not establish superior efficacy or tolerability. The literature supports fluoxetine as a possible rather than preferred treatment option given the limited fluoxetine-specific evidence, especially when considering individual patient characteristics, severity of symptoms, previous response to medications, comorbidities, and susceptibility to adverse effects.

3.4. Pharmacokinetic Variability as a Treatment Challenge

Interindividual pharmacokinetic variability may complicate the balance between efficacy and adverse effects even further. Fluoxetine metabolism to the active metabolite, norfluoxetine, may be affected by the CYP2D6 genotype (Nordby *et al.*, 2025). The combined active moiety of fluoxetine and norfluoxetine did not differ significantly between CYP2D6 phenotype groups, but the relative concentrations of parent drug and metabolite did differ significantly. Adult poor and ultrarapid metabolizers had approximately two to three times the odds of switching to another antidepressant compared with normal metabolizers (Nordby *et al.*, 2025).

These results suggest that total active drug exposure may not account for differences in treatment outcomes. Nordby *et al.* (2025) proposed that differences in the relative proportions of fluoxetine and norfluoxetine may

contribute to variability in tolerability or efficacy because the two compounds have different pharmacokinetic and pharmacodynamic properties. However, the clinical significance of this finding remains uncertain. Nordby *et al*. (2025) were unable to identify the reason for switching medications, which could be due to lack of efficacy, adverse effects, or other clinical reasons.

Pharmacokinetic variability may therefore contribute to inconsistent treatment outcomes but is not an established determinant of clinical decision-making. Available data do not support routine individualization of dose based on CYP2D6 genotype for fluoxetine. Consistent with this, the Clinical Pharmacogenetics Implementation Consortium does not give a CYP2D6-based dosing recommendation for fluoxetine because there is insufficient evidence that differences in fluoxetine and norfluoxetine concentrations across CYP2D6 phenotypes affect clinical outcomes or safety (Bousman *et al*., 2023). This is also consistent with Nordby *et al*. (2025), who found that the CYP2D6 phenotype influenced the relative concentrations of fluoxetine and norfluoxetine but did not substantially change their combined active moiety. Nonetheless, these findings support the need for further research to determine whether pharmacokinetic differences may help explain variability in efficacy and adverse effects. At present, CYP2D6 variability is pharmacokinetically relevant but does not provide an established basis for genotype-guided fluoxetine dosing.

3.5. Emerging Personalized Treatment Approaches

Variability in treatment response, tolerability, and pharmacokinetics has prompted interest in personalized approaches to GAD pharmacotherapy. Roseberry *et al*. (2023) investigated blood gene-expression biomarkers as potential objective measures for anxiety, predictors of clinical deterioration, and tools for treatment selection. The predictive performance of certain biomarkers improved when analyses accounted for factors such as sex and psychiatric diagnosis; however, these findings remain preliminary.

Patient-specific clinical characteristics may also contribute to variability in fluoxetine response. Simon *et al*. (2006) studied 23 men and 22 women with a primary diagnosis of GAD during six weeks of open-label fluoxetine treatment. Women showed poorer responses on both HAM-A and CGI-S measures compared with men, even with similar baseline symptom severity. Treatment response also varied according to the interaction between gender and age at GAD onset.

Specifically, the findings suggested poorer response among women with a later age of GAD onset. However, these results were preliminary because of the small sample size, absence of a placebo control, and post hoc analyses (Simon *et al*., 2006). The results do not support the selection of fluoxetine on the basis of gender or age of onset but suggest that these clinical characteristics warrant further study as potential moderators of treatment response.

Additionally, Roseberry *et al*. (2023) investigated the possibility of using existing medications such as fluoxetine to align with anxiety-related biomarker profiles. The authors hypothesized that biomarkers could play a role in pharmacogenomic approaches to treatment selection and monitoring. In the future, combining clinical characteristics, pharmacokinetic factors, genetic information, and biological markers may help identify individuals who are more likely to respond favorably to treatment or experience poor tolerability; however, this approach has not been validated for fluoxetine in GAD.

However, personalized treatment of fluoxetine in GAD is still emerging. Roseberry *et al*. (2023) did not demonstrate improved treatment response with biomarker-guided fluoxetine selection in patients with GAD, and the findings regarding gender and age of onset from Simon *et al*. (2006) require replication in larger placebo-controlled studies. Therefore, these findings should be interpreted as preliminary insights into treatment variability rather than validated approaches to clinical decision-making. Future studies should determine whether biomarker-, pharmacogenetic-, or patient-characteristic-guided prescribing improves response, remission, adherence, or tolerability compared with conventional treatment selection.

3.6. Challenges in the Current Evidence

In the literature reviewed, the evidence for fluoxetine as a treatment for GAD is still much weaker than the evidence for SSRIs as a class of medication. This difference is also reflected in the recent Cochrane review by Kopcalic *et al*. (2025) that found high-certainty evidence for antidepressants for GAD but found no eligible trials of fluoxetine versus placebo. Although Baldwin *et al*. (2011) reported high estimated probabilities for fluoxetine response and remission, those estimates were affected by the relatively small number of fluoxetine-specific comparative trials. Similarly, the 15 studies reviewed by Zou *et al*. (2013) were mostly small, open-label, non-placebo-controlled trials conducted in Chinese populations, with methodological limitations that increase the potential for bias and limit the assessment of clinically important outcomes.

Furthermore, much of the additional evidence is indirect, restricting the extent to which these findings can be directly applied to fluoxetine treatment for GAD. Many pediatric studies did not include GAD alone but participants with multiple anxiety disorders, making it difficult to differentiate the effects of fluoxetine on GAD

specifically (Birmaher *et al.*, 2003; Castagna *et al.*, 2023). In addition, de Vries *et al.* (2018) investigated the effectiveness of antidepressants in general and not only fluoxetine, and Gollan *et al.* (2012) investigated adults with major depressive disorder on different SSRIs. Fluoxetine was examined directly in participants with GAD by Simon *et al.* (2006), but the study was limited by a small sample size, lack of a placebo control, and post hoc exploratory analyses. Thus, these studies do provide useful information regarding possible moderators of response and tolerability, but their findings should not be considered definitive evidence for individualized fluoxetine prescribing for GAD. Differences in study populations, comparators, treatment durations, and outcome measures further limit comparability across studies and the generalizability of the findings. Because no validated risk-of-bias tool was applied, this review does not provide a formal quantitative or tool-based assessment of study quality.

3.7. Future Scope

Further studies should include adequately powered, randomized, double-blind, placebo-controlled trials specifically evaluating the effects of fluoxetine in patients with GAD. Longer-term follow-up is needed to determine whether initial short-term reductions in symptoms are sustained, whether fluoxetine prevents relapse, and whether adverse effects vary with long-term treatment. Outcomes should extend beyond symptom scores to include quality of life, functional improvement, treatment adherence, patient perspectives, and discontinuation.

Future studies could also investigate sources of variability among patients. Differences in exposure of fluoxetine and norfluoxetine could influence efficacy or tolerability, and pharmacokinetic and pharmacogenetic studies could clarify this. Clinical factors such as baseline symptom severity, age, gender, and age of GAD onset may also warrant further study (de Vries *et al.*, 2018; Simon *et al.*, 2006). Biomarker research may further help explain why some patients respond to treatment while others do not. At present, neither CYP2D6-guided dosing nor biomarker-guided fluoxetine selection is established for clinical use. However, integrating these areas into future GAD trials may help identify which patients are most likely to experience meaningful benefit with the fewest adverse effects rather than simply determining whether fluoxetine works on average.

4. Conclusion

This literature review discussed the efficacy and adverse effects of fluoxetine in generalized anxiety disorder treatment. The available literature generally suggests that fluoxetine can reduce symptoms of anxiety and can provide meaningful clinical benefit to a subset of individuals with GAD. Comparative evidence suggests that fluoxetine may have efficacy similar to some other pharmacological treatments, although fluoxetine-specific evidence remains limited. Pediatric data from placebo-controlled trials have also indicated that it may be effective in younger patients with GAD and related anxiety disorders (Birmaher *et al.*, 2003; Castagna *et al.*, 2023).

However, the evidence for fluoxetine in GAD remains limited because much of the available data are based on small sample sizes, open-label designs, limited placebo-controlled data, and limited long-term outcome data. The available evidence does not support considering fluoxetine superior or preferable to SSRIs or SNRIs with stronger GAD-specific evidence.

Safety, tolerability, and variability in treatment responses are also important clinical considerations. The adverse effects most commonly reported are nausea, insomnia, agitation, and sexual dysfunction, and these may affect adherence and continuation of treatment. Further evidence is needed to determine whether baseline symptom severity, and possibly gender and age at GAD onset, influence treatment outcomes (de Vries *et al.*, 2018; Simon *et al.*, 2006). Recent studies on pharmacokinetic variability and individualized medicine indicate that biological differences between patients could affect fluoxetine metabolism and response. However, CYP2D6-guided dosing and biomarker-guided medication selection have not been established for clinical use in GAD.

Further studies should be directed at large, high-quality, long-term clinical trials evaluating therapeutic outcomes, adverse effects, and patient-specific factors that could influence treatment response. A more personalized approach requires further validation before it can be used to identify patients most likely to benefit from fluoxetine while minimizing adverse effects.

Abbreviations

5-HT: 5-Hydroxytryptamine; CGI-I: Clinical Global Impression–Improvement; CGI-S: Clinical Global Impression–Severity; CYP2D6: Cytochrome P450 2D6; DSM: Diagnostic and Statistical Manual of Mental Disorders; FAERS: FDA Adverse Event Reporting System; GAD: Generalized Anxiety Disorder; HAM-A: Hamilton Anxiety Rating Scale; MDD: Major Depressive Disorder; OCD: Obsessive-Compulsive Disorder; QoL: Quality of Life; RCT: Randomized Controlled Trial; SERT: Serotonin Transporter; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding this manuscript.

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