



FIRST OF 2 PARTS

Generalized anxiety disorder: 8 studies of biological interventions

Evidence suggests several medications and rTMS may offer benefit

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Generalized anxiety disorder (GAD) typically begins in early adulthood and persists throughout life. Many individuals with GAD report they have felt anxious their entire lives. The essential symptom of GAD is excessive anxiety and worry about numerous events or activities. The intensity, duration, and/or frequency of the anxiety and worry are out of proportion to the actual likelihood or impact of the anticipated event. The individual finds it difficult to control their worry and prevent worrisome thoughts from interfering with attention to everyday tasks.¹

Treatment of GAD typically consists of psychotherapy and pharmacotherapy. Several studies have suggested that concurrent psychotherapy amplifies the benefits of pharmacotherapy.²⁻⁵ Additionally, combined treatment may differentially target specific symptoms (eg, cognitive vs somatic). The addition of psychotherapy may also increase treatment adherence and decrease potential adverse effects of pharmacotherapy.

Multiple classes of medications are available for treating GAD. Current guidelines and evidence suggest that selective serotonin reuptake inhibitors (SSRIs) should be considered a first-line intervention, followed by serotonin-norepinephrine reuptake inhibitors.⁶⁻¹¹ While the evidence supporting pharmacotherapy for GAD continues to expand, many patients with GAD do not respond to first-line treatment. There is limited data regarding second-line or augmentation strategies for treating these patients. Because current treatment



Generalized anxiety disorder

Clinical Point

Understanding a patient's CYP2C19 phenotype may help guide dosing of escitalopram for generalized anxiety disorder



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options for GAD are commonly associated with suboptimal treatment outcomes, researchers are investigating the use of nonpharmacologic biological interventions, such as repetitive transcranial magnetic stimulation (rTMS), which was first cleared by the FDA to treat major depressive disorder (MDD) in 2008.

In Part 1 of this 2-part article, we review 8 randomized controlled trials (RCTs) of biological interventions for GAD that have been published within the last 5 years (Table,¹²⁻¹⁹ page 22).

1. Strawn JR, Mills JA, Schroeder H, et al. Escitalopram in adolescents with generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychiatry.* 2020;81(5):20m13396. doi:10.4088/JCP.20m13396

GAD is highly prevalent in adolescents, and SSRIs are often used as first-line agents. However, treatment response is often variable, and clinicians often use trial-and-error to identify an appropriate medication and dose that will result in meaningful improvement. Understanding an individual's pharmacokinetic response may help predict response and guide therapy. Adult studies have shown cytochrome P450 (CYP) 2C19 metabolizes several SSRIs, including escitalopram, with faster CYP2C19 metabolism leading to decreased plasma concentrations. Strawn et al¹² studied the effects of escitalopram in adolescents with GAD as well as the effects of CYP2C19 metabolism.

Study design

- A double-blind, placebo-controlled trial evaluated 51 adolescents (age 12 to 17) who met DSM-IV-TR criteria for GAD. They had a baseline Pediatric Anxiety Rating Scale (PARS) score ≥ 15 and a Clinical Global Impressions–Severity (CGI-S) Scale score ≥ 4 .

- Participants were randomized to escitalopram ($n = 26$; scheduled titration to 15 mg/d, then flexible to 20 mg/d), or placebo ($n = 25$) and monitored for 8 weeks.

- Patients with panic disorder, agoraphobia, or social anxiety disorder were

also enrolled, but GAD was the primary diagnosis.

- The primary outcome was change in PARS score and change from baseline in CGI-S and Clinical Global Impressions–Improvement (CGI-I) scale scores, with assessments completed at Week 1, Week 2, Week 4, Week 6, and Week 8, or at early termination.

- Genomic DNA was obtained via buccal swab to assess 9 alleles of CYP2C19. Plasma concentrations of escitalopram and its major metabolite, desmethylescitalopram, were collected to assess plasma escitalopram and desmethylescitalopram area under the curve for 24 hours (AUC_{0-24}) and maximum plasma concentration (C_{MAX}).

Outcomes

- Escitalopram was superior to placebo, evident by statistically significantly greater changes in PARS and CGI scores.

- Greater improvement over time on PARS was correlated with intermediate CYP2C19 metabolizers, and greater response as measured by CGI-I was associated with having at least 1 long allele of *SLC6A4* and being an intermediate CYP2C19 metabolizer.

- While plasma escitalopram exposure (AUC_{0-24}) significantly decreased and desmethylescitalopram-to-escitalopram ratios increased with faster CYP2C19 metabolism at 15 mg/d, escitalopram exposure at the 15 mg/d dose and escitalopram-to-desmethylescitalopram ratios did not differ at Week 8 between responders and nonresponders. Patients with activation symptoms had higher C_{MAX} and AUC_{0-24} .

- Changes in vital signs, corrected QT interval, and adverse events were similar in both groups.

Conclusions/limitations

- For adolescents with GAD, escitalopram showed a benefit compared to placebo.

- Allelic differences in CYP2C19 metabolism may lead to variations in pharmacokinetics, and understanding a patient's CYP2C19 phenotype may help guide dosing escitalopram and predicting adverse effects.



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Vortioxetine was associated with benefits in anxiety symptoms, functioning, and quality of life in patients with GAD

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- This study enrolled a small, predominantly female, White, treatment-naïve sample, which may limit conclusions on allelic differences. Additionally, the sample included adolescents with severe anxiety and comorbid anxiety conditions, which may limit generalizability.

2. Christensen MC, Loft H, Florea I, et al. Efficacy of vortioxetine in working patients with generalized anxiety disorder. *CNS Spectr.* 2019;24(2):249-257. doi:10.1017/S1092852917000761

Vortioxetine, an FDA-approved antidepressant, has been shown to improve anxiety symptoms in patients with GAD. Additionally, vortioxetine has shown positive effects in patients with MDD, with greater improvement seen in the working and professional population. Due to the overlap between MDD and GAD, Christensen et al¹³ assessed the effectiveness of vortioxetine on anxiety symptoms in individuals who were working.

Study design

- Researchers conducted a post-hoc analysis of a previously completed randomized, placebo-controlled trial of 301 patients as well as a previously completed randomized, placebo-controlled relapse prevention study of 687 patients. Patients in both groups met DSM-IV-TR criteria for GAD.

- Inclusion criteria included a Hamilton Anxiety Rating Scale (HAM-A) score ≥ 20 with HAM-A scores ≥ 2 on items 1 (anxious mood), and 2 (tension), and a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≤ 16 at screening and baseline.

- Researchers compared participants who were working or pursuing an education vs the full study sample.

Outcomes

- Vortioxetine was significantly associated with benefits in anxiety symptoms, functioning, and quality of life in both working participants and the total population, with the greatest effects seen in profes-

sional (ie, managers, administrators) and associate professional (ie, technical, nursing, clerical workers, or secretarial) positions. Working participants who received placebo were more likely to relapse compared to those receiving vortioxetine.

- There did not appear to be a statistically significant benefit or increase in relapse among the skilled labor group (ie, building, electrical/factory worker, or services/sales) while receiving vortioxetine.

Conclusions/limitations

- Vortioxetine may have a more pronounced effect in patients who are working or pursuing an education vs the full GAD population, which suggests that targeting this medication at particular patient demographics may be beneficial.

- Working patients with GAD may also differ from nonworking patients by factors other than work, such as education, support system, motivation, and other personal factors.

- This study was a post-hoc analysis, which limits definitive conclusions but may help guide future studies.

3. Xie ZJ, Han N, Law S, et al. The efficacy of group cognitive-behavioural therapy plus duloxetine for generalised anxiety disorder versus duloxetine alone. *Acta Neuropsychiatr.* 2019;31(6):316-324. doi:10.1017/neu.2019.32

Treatment of GAD should include non-medication options such as psychotherapy to help enhance efficacy. Few studies have evaluated whether combined cognitive-behavioral therapy (CBT) plus medication has more benefit than medication monotherapy, specifically in patients with GAD. In this randomized trial, Xie et al¹⁴ examined how a study population undergoing CBT and receiving duloxetine differed from those receiving duloxetine monotherapy for GAD.

Study design

- In this randomized, open-label trial, adults who met DSM-IV criteria for GAD and had a HAM-A score > 14 were random-



Generalized anxiety disorder

Clinical Point

Compared to duloxetine monotherapy, group CBT plus duloxetine resulted in faster improvement of GAD symptoms

Table

Biological interventions for generalized anxiety disorder: 8 studies

Study	Design
Strawn et al ¹²	Adolescents who met DSM-IV-TR criteria for GAD and had a baseline PARS score ≥ 15 and CGI-S score ≥ 4 were randomized to escitalopram (n = 26) or placebo (n = 25)
Christensen et al ¹³	Post-hoc analysis of 2 randomized, placebo-controlled trials of vortioxetine that included a total of 988 patients who met DSM-IV-TR criteria for GAD
Xie et al ¹⁴	Patients who met DSM-IV criteria for GAD and scored >14 on HAM-A were randomized to group CBT plus duloxetine (n = 89) or duloxetine alone (n = 81)
Huang et al ¹⁵	Patients who met DSM-IV criteria for GAD and insomnia and scored ≥ 14 on HAM-A, >7 on PSQI, and <20 on HAM-D were randomized to low-intensity rTMS (n = 18) or a sham procedure (n = 18)
Amsterdam et al ¹⁶	A total of 179 adults who met DSM-IV-TR criteria for GAD (79 with comorbid depression and 100 without comorbid depression) received open-label <i>Matricaria chamomilla</i> L. (chamomile) extract for 8 weeks
Dilkov et al ¹⁷	Forty adults who met DSM-IV criteria for GAD were randomized to excitatory rTMS (n = 15) or a sham procedure (n = 25)
Keefe et al ¹⁸	Forty-five adults who met DSM-IV criteria for GAD collected saliva samples so their cortisol levels could be assessed 4 times daily while receiving 8 weeks of open-label treatment with chamomile extract capsules
Stein et al ¹⁹	In a 12-week, double-blind study, 523 adults who met DSM-IV-TR criteria for GAD were randomized to receive agomelatine (n = 261) or escitalopram (n = 262)

BDI: Beck Depression Inventory; CBT: cognitive-behavioral therapy; CGI-S: Clinical Global Impressions–Severity Scale; GAD: generalized anxiety disorder; GAF: Global Assessment of Functioning Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-PA: Hamilton Anxiety Rating Scale, psychic subscale; HAM-SA: Hamilton Anxiety Rating Scale, somatic anxiety subscale; PARS: Pediatric Anxiety Rating Scale; PSQI: Pittsburgh Sleep Quality Index; rTMS: repetitive transcranial magnetic stimulation; SF-12: 12-item Short-Form Health Survey

ized to group CBT plus duloxetine (n = 89) or duloxetine only (n = 81), with follow-up at Week 4, Week 8, and Month 3.

- The primary outcomes included response and remission rates based on HAM-A score. Secondary outcomes included HAM-A total score reductions, psychic anxiety (HAMA-PA) and somatic anxiety (HAMA-SA) subscale score reductions, Hamilton Depression Rating Scale score reductions, and reductions in overall illness severity as measured by CGI-S, the Global Assessment of Functioning Scale, and the 12-item Short-Form Health Survey.

Outcomes

- At Week 4, combined therapy was superior to duloxetine alone as evident by the primary and most secondary outcomes, with continued benefits but smaller effect size at Week 8.

- At Month 3, combined therapy was significantly better only in HAM-A total score and HAMA-PA score reductions.

Conclusions/limitations

- Patients who received group CBT plus duloxetine treatment experienced faster improvement of GAD symptoms compared to patients who received duloxetine monotherapy, though the difference reduced over time.

- The most benefit appeared to be for psychic anxiety symptoms, which suggests that group CBT can help change cognition style.

- This study had a short follow-up period, high dropout rates, and recruited patients from only 1 institution.

4. Huang Z, Li Y, Bianchi MT, et al. Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: a randomized, double-blind, sham-controlled pilot study. *Brain Stimul.* 2018;11(5):1103-1109. doi:10.1016/j.brs.2018.05.016

Insomnia and anxiety often present together. rTMS has demonstrated efficacy

Outcomes

Escitalopram was superior to placebo, evident by statistically significantly greater changes in PARS and CGI scores. Changes in vital signs, corrected QT interval, and adverse events were similar in both groups
Participants who received vortioxetine experienced significant benefits in anxiety symptoms, functioning, and quality of life, with the greatest effects seen in individuals who worked in professional and associate professional positions
Group CBT plus duloxetine provided improvements over duloxetine alone based on reductions in HAM-A total scores, HAM-PA and HAM-SA subscale scores, HAM-D scores, CGI-S scores, GAF scores, and SF-12 scores
Significantly more patients in the rTMS group had a meaningful response as measured by change in HAM-A score at posttreatment and 2-week and 1-month follow-up. Those who received rTMS also experienced significant improvements in insomnia symptoms
Participants with comorbid depression experienced a greater, statistically significant reduction in HAM-D symptom scores and a nonsignificant reduction in total HAM-D and BDI scores
rTMS of the right dorsolateral prefrontal cortex provided a statistically significant reduction in GAD symptoms as measured by HAM-A. In the rTMS group, scores on the CGI and HAM-D also improved compared to the sham group
Participants who experienced improvements in GAD symptoms had relative increases in morning cortisol levels and a greater decrease in cortisol levels throughout the day. This suggests treatment of GAD may help improve dysregulated stress biology
At Week 12, both groups reported similar, clinically significant mean reductions in HAM-A scores. There were no significant differences between the groups in secondary measures

Clinical Point

Low-frequency rTMS over the right parietal cortex was effective for patients with comorbid GAD and insomnia

in various psychiatric illnesses, but there is limited research regarding its effectiveness in GAD. Additionally, little is known regarding the benefits of rTMS for patients with comorbid insomnia and GAD. Huang et al¹⁵ examined the therapeutic effects of rTMS in patients with comorbid insomnia and GAD.

Study design

- Adults who met DSM-IV criteria for GAD and insomnia were randomized to receive 10 days of low-intensity rTMS on the right parietal lobe (n = 18) or a sham procedure (n = 18). Inclusion criteria also included a score ≥ 14 on HAM-A, ≥ 7 on the Pittsburgh Sleep Quality Index (PSQI), and < 20 on the 24-item Hamilton Depression Rating Scale (HAM-D).

- rTMS settings included a frequency of 1 Hz, 90% intensity of the resting motor threshold, 3 trains of 500 pulses, and an intertrain interval of 10 minutes.

- Study measurements included HAM-A, PSQI, and HAM-D at baseline, posttreatment at Day 10, Week 2 follow-up, and Month 1 follow-up.

Outcomes

- Significantly more patients in the rTMS group had a meaningful response as measured by change in HAM-A score at posttreatment and both follow-up sessions.

- The rTMS group had significant remission compared to the sham group at posttreatment and Week 2 follow-up, but showed no significant difference at Month 1.

- There were significant improvements in insomnia symptoms in the rTMS group at the posttreatment and follow-up time points.

Conclusions/limitations

- Low-frequency rTMS over the right parietal cortex is an effective treatment option for patients with comorbid GAD and insomnia.

continued



Generalized anxiety disorder

Clinical Point

Chamomile extract may help reduce depressive symptoms in patients with GAD who also have depression

- This study had a small sample size consisting of participants from only 1 institution.

5. Amsterdam JD, Li QS, Xie SX, et al. Putative antidepressant effect of chamomile (*Matricaria chamomilla* L.) oral extract in subjects with comorbid generalized anxiety disorder and depression. *J Altern Complement Med.* 2020;26(9):813-819. doi:10.1089/acm.2019.0252

GAD often presents with comorbid depression. While antidepressants are the standard approach to treatment of both conditions, patients may seek alternative therapies. In previous studies,²⁰ *Matricaria chamomilla* L. (chamomile) has been shown to reduce GAD symptoms, and post-hoc analyses²¹ have shown its benefits in treating depression. Amsterdam et al¹⁶ assessed the effects of chamomile on patients with GAD with and without comorbid depression.

Study design

- As part of an RCT, 179 adults who met DSM-IV-TR criteria for GAD underwent an 8-week open-label phase of chamomile extract therapy (1,500 mg/d). Participants who responded were enrolled in a randomized, double-blind, placebo-control trial. Amsterdam et al¹⁶ specifically analyzed the 8-week open label portion of the study.

- Participants were divided into 2 groups: GAD without comorbid depression (n=100), and GAD with comorbid depression (n=79).

- Outcome measures included the 7-item generalized anxiety disorder scale (GAD-7), HAM-A, Beck Anxiety Inventory, 17-item HAM-D, 6-item HAM-D, and the Beck Depression Inventory (BDI).

Outcomes

- Patients with comorbid depression experienced a greater, statistically significant reduction in HAM-D core symptom scores (depressed mood, guilt, suicide ideation, work and interest, retardation, and somatic symptoms general).

- The comorbid depression group experienced a trend (but not significant) reduction in total HAM-D and BDI scores.

Conclusions/limitations

- Chamomile extract may help reduce depressive symptoms in patients with GAD who also have depression.

- This study was not powered to detect significant differences in depression outcome ratings between groups, was exploratory, and was not a controlled trial.

6. Dilkov D, Hawken ER, Kaludiev E, et al. Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: a randomized, double-blind sham controlled clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry.* 2017;78:61-65. doi:10.1016/j.pnpbp.2017.05.018

Nonpharmacologic modalities, including rTMS, may be effective alternatives for treating GAD. Dilkov et al¹⁷ examined whether excitatory rTMS is an effective treatment option for GAD.

Study design

- In this double-blind, sham-controlled trial, adults who met DSM-IV criteria for GAD were randomized to excitatory rTMS of the right dorsolateral prefrontal cortex therapy (n = 15) or a sham procedure (n = 25).

- rTMS settings included a frequency of 20 Hz, 110% intensity of resting motor threshold, 20 trains, 9 seconds/train, and 51-second intertrain intervals.

- Outcomes were measured by HAM-A, CGI, and 21-item HAM-D.

Outcomes

- At the conclusion of 25 treatments, the rTMS group experienced a statistically significant reduction in GAD symptoms as measured by HAM-A.

- Improvements were also noted in the CGI and HAM-D scores in the rTMS group compared to the sham group.

- The benefits continued at the Week 4 follow-up visit.

Conclusions/limitations

- Participants in the rTMS group experienced a significant decrease in anxiety symptoms, which suggests that rTMS may be an effective treatment for GAD.

- The benefits appear sustainable even after the conclusion of the rTMS sessions.

- This study had a small sample size and excluded patients with comorbid psychiatric conditions.

7. Keefe JR, Guo W, Li QS, et al. An exploratory study of salivary cortisol changes during chamomile extract therapy of moderate to severe generalized anxiety disorder. *J Psychiatr Res.* 2018;96:189-195. doi:10.1016/j.jpsychires.2017.10.011

Dysregulated stress response has been proposed as a mechanism for anxiety.^{22,23} Patients with GAD have been reported to have alterations in cortisol levels, specifically lower morning cortisol levels and a less steep diurnal cortisol slope; however, it is not clear how treatment affects these levels. Keefe et al¹⁸ examined whether chamomile therapy in patients with GAD affects cortisol levels.

Study design

- In an 8-week, open-label study, 45 adults who met DSM-IV criteria for GAD received chamomile extract capsules 1,500 mg/d.

- Participants used at-home kits to collect their saliva so cortisol levels could be assessed at 8 AM, 12 PM, 4 PM, and 8 PM.

- The GAD-7 was used to assess anxiety symptoms.

Outcomes

- Participants who experienced greater improvements in GAD symptoms had relative increases in morning cortisol levels compared to their baseline levels.

- Participants who experienced greater improvements in GAD symptoms had a greater decrease in cortisol levels throughout the day (ie, greater diurnal slope).

Conclusions/limitations

- Greater improvement in GAD symptoms after treatment with chamomile extract appeared to be correlated with increased morning cortisol levels and a steeper diurnal cortisol slope after awakening, which suggests that treatment of GAD may help improve dysregulated stress biology.

- This study had a small sample size and was not placebo-controlled.

8. Stein DJ, Khoo JP, Ahokas A, et al. 12-week double-blind randomized multicenter study of efficacy and safety of agomelatine (25-50 mg/day) versus escitalopram (10-20 mg/day) in out-patients with severe generalized anxiety disorder. *Eur Neuropsychopharmacol.* 2018;28(8):970-979. doi:10.1016/j.euroneuro.2018.05.006

Compared to the medications that are FDA-approved for GAD, agomelatine has a different mechanism of action, and has shown to be efficacious and tolerable in previous studies.²⁴⁻²⁶ In this study, Stein et al¹⁹ compared agomelatine vs escitalopram for patients with severe GAD.

Study design

- In a 12-week, double-blind study, adults who met DSM-IV-TR criteria for GAD were randomized to agomelatine 25 to 50 mg/d (n = 261) or escitalopram 10 to 20 mg/d (n = 262).

- Participants had to meet specific criteria for severe anxiety, including a HAM-A total score ≥ 25 .

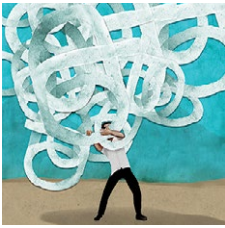
- The primary outcome measure was the change in HAM-A score from baseline to Week 12. Secondary outcome measures included the rate of response as determined by change in scores on the HAM-PA, HAM-SA, CGI, Toronto Hospital Alertness Test, Snaith-Hamilton Pleasure Scale, and Leeds Sleep Evaluation Questionnaire.

Outcomes

- Participants in both the agomelatine and escitalopram groups reported similar,

Clinical Point

Participants who received rTMS experienced a significant reduction in anxiety symptoms as measured by HAM-A



Generalized anxiety disorder

Clinical Point

Greater improvements in GAD symptoms in patients treated with chamomile may be related to changes in cortisol levels

Related Resources

- Abell SR, El-Mallakh RS. Serotonin-mediated anxiety: how to recognize and treat it. *Current Psychiatry*. 2021;20(11):37-40. doi:10.12788/cp.0168

Drug Brand Names

Duloxetine • Cymbalta Vortioxetine • Trintellix
Escitalopram • Lexapro

clinically significant mean reductions in HAM-A scores at Week 12.

- There were no significant differences in secondary measures between the 2 groups, and both groups experienced improvement in psychic and somatic symptoms, alertness, and sleep.

- Overall, the agomelatine group experienced fewer adverse events compared to the escitalopram group.

Conclusions/limitations

- Agomelatine may be an efficacious and well-tolerated treatment option for severe GAD.

- This study excluded individuals with comorbid conditions.

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Bottom Line

Recent research suggests that escitalopram; vortioxetine; agomelatine; duloxetine plus group cognitive-behavioral therapy; repetitive transcranial magnetic stimulation; and chamomile extract can improve symptoms in patients with generalized anxiety disorder.

19. Stein DJ, Khoo J, Ahokas A, et al. 12-week double-blind randomized multicenter study of efficacy and safety of agomelatine (25-50 mg/day) versus escitalopram (10-20 mg/day) in out-patients with severe generalized anxiety disorder. *Eur Neuropsychopharmacol.* 2018;28(8):970-979. doi:10.1016/j.euroneuro.2018.05.006
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