Published in final edited form as:

Paediatr Drugs. 2016 February ; 18(1): 45–53. doi:10.1007/s40272-015-0153-1.

Pharmacotherapy for Pediatric Generalized Anxiety Disorder: A Systematic Evaluation of Efficacy, Safety and Tolerability

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Abstract

Background—Randomized controlled trials consistently support the efficacy of antidepressants in treating youth with generalized anxiety disorder (GAD), although integrated examinations of efficacy, safety, and tolerability of psychotropic medications in GAD specifically are rare. With this in mind, we sought to describe the efficacy, safety and tolerability of psychopharmacologic interventions in youth with GAD.

Methods—Randomized, double-blind, placebo-controlled, prospective trials of psychopharmacologic interventions in youth with GAD were identified through a PubMed/Medline (1966–2015) search. Both authors manually reviewed trials and, to evaluate comparative efficacy and tolerability across medications, numbers needed to treat (NNT) (based on Pediatric Anxiety Rating Scale (PARS) remission criteria (PARS ≤ 8 [1]), and number needed to harm (NNH) for selected treatment-emergent adverse events (TEAEs) were calculated. Finally, treatment-emergent suicidality and taper-emergent/post-study adverse events are reported descriptively.

Results—Five trials that involved 1,186 patients and evaluated four medications were reviewed and efficacy data were extracted with regard to dimensional measures of anxiety. SSRI/SNRI demonstrated efficacy in the reduction of anxiety symptoms with NNTs ranging from 2.8 to 9.3. TEAEs varied considerably between studies but tended to be mild and generally did not lead to discontinuation.

Conclusions—Data from five trials of SSRI/SNRI in youth with GAD, many of whom had co-occurring separation and social anxiety disorders, suggest superiority to placebo and favorable tolerability profiles.

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Compliance with Ethical Standards: Mr. Dobson has received support from the American Academy of Child & Adolescent Psychiatry (Campaign for America's Kids) and Dr. Strawn has received support from the National Institute of Mental Health (K23 MH106037). Additionally, Dr. Strawn has received research support from Edgemont, Eli Lilly, Shire, Forest Research Institute, Lundbeck and receives royalties from Springer Publishing for two texts, has produced a rating scale training video for Neurontin and has received material support from Assurx.

1. Introduction

Anxiety disorders are among the most prevalent and persistent psychiatric disorders in pediatric populations [2, 3]. Moreover, children and adolescents with anxiety disorders are more likely to experience suicidal ideation [4] and to attempt suicide [5] than unaffected youth. Additionally, when present in youth, anxiety disorders impair social functioning, result in social withdrawal, cause academic problems [3, 6–8] and increase the likelihood of somatic symptoms such as headaches, stomachaches, muscular tension, and sweating, which in turn are associated with deteriorations in functioning [9, 10]. Also, untreated youth with anxiety disorders are at higher risk for developing other anxiety disorders, depressive disorders, alcohol dependence, and substance use disorders later in life [11–13]. Despite the significant burden associated with anxiety disorders, less than one fifth of affected youth ever receive treatment [14]. Youth who respond favorably to acute treatment are significantly more likely to be in remission six years later than those who do not. However, of all those treated, less than half achieve long-term remission after acute treatment, emphasizing the importance of long-term care [15].

Generalized anxiety disorder (GAD) is one of the most common anxiety disorders in children and adolescents, and affects between 2 and 6% [2, 16]. Youth with GAD experience insomnia, cognitive symptoms (*e.g.*, attentional difficulties), somatic symptoms and these symptoms are accompanied by the *sine quo non* of GAD, excessive, diffuse uncontrollable worry and anxiety [17]. These symptoms, which often begin in early childhood, fluctuate in adolescence and frequently worsen again in middle and late adolescence [18]. GAD follows an onset pattern more similar to depressive disorders than other anxiety disorders, with a core incidence period of adolescence to early adulthood, rather than in childhood [19]. Furthermore, in childhood, GAD is significantly associated with depression [20] and this relationship is buttressed not only by their common co-occurrence and similar neurocircuitries [21, 22] but also by “factor” commonality between GAD and depressive disorders in a number of factor analyses [23–25].

Understanding of the neurobiology of pediatric anxiety disorders, including GAD, has advanced significantly over the first decade and a half of the new millennium. Taken together, the extant neuroimaging data implicate dysfunction in prefrontal-amygdala based circuits, although a myriad of both functional and structural neuroimaging studies also reveal abnormalities (or abnormalities) in the default mode network [26–31]. Specifically, intrinsic functional connectivity data reveal altered connectivity among medial prefrontal cortex, anterior cingulate cortex, insula, and cerebellum while increased activation in the amygdala, ventrolateral prefrontal cortex (VLPFC), and anterior cingulate cortex has been examined in numerous neuroimaging studies of youth with GAD. Among these structures, the VLPFC is of particular interest in that it is not only hyperactivated in youth with GAD, but the degree of activation is inversely proportional to the severity of anxiety symptoms [31, 32]. The anxiety-related alteration in activity within this structure in youth with GAD is of particular interest in that treatment—both psychopharmacologic and psychotherapeutic—appears to alter VLPFC activity [30]. Finally, the cingulate cortex a structure which subtends motivation and cognitive control functions is functionally and structurally abnormal in youth

with GAD and other anxiety disorders [33, 34] glutamatergic tone within this region correlates with the severity of anxiety in adolescents with GAD [31].

Accumulating data from double-blind, placebo-controlled treatment studies support the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) in pediatric patients with GAD [26, 35–38]; however, these medications are associated with a number of treatment-emergent adverse events (TEAEs), including dry mouth, dizziness, and abdominal pain, as well as neuropsychiatric adverse events [39]. Importantly, the relationship between these adverse events and psychopharmacologic interventions in pediatric patients with major depressive disorder compared to youth with primary anxiety disorders has largely been unexplored, despite evidence suggesting that the prevalence patterns of certain adverse events and tolerability differ as a function of disease state [40, 41]. Moreover, several neuropsychiatric adverse effects including an “activation syndrome” which is characterized by irritability/affective instability, agitation, restlessness, insomnia, disinhibition is hypothesized to underlie the suicidality signal detected in the meta-analysis conducted by the US FDA [42] which gave rise to the black box warning for antidepressants in children, adolescents and young adults [43]. Recently, this effect has been hypothesized to relate to a number of receptor-based and medication-specific factors, including the 5-HT_{1A} presynaptic receptors during the acute administration of SSRIs, which potentially inhibit the release of serotonin resulting in an acute hyposerotonergic state [44]. To this end, co-administration of a 5-HT_{1A} antagonist in lower animal models of pediatric mood disorders, who were treated with fluoxetine prevents the negative effects of acute SSRIs [45]. However, while these translational studies shed light on the mechanism of acute neuropsychiatric effects of SSRIs in youth, the immediate clinical impact is unknown.

SSRIs and SNRIs—the current mainstay pharmacotherapy for GAD in youth—may further be associated with withdrawal symptoms upon discontinuation, with the severity of withdrawal symptoms being related to treatment duration, titration schedule, dosing, and medication used [46, 47]. Importantly, given the high prevalence of anxiety-related somatic symptoms in untreated youth with GAD, it is critical to systematically describe the tolerability of these medications based on data from placebo-controlled studies.

With these considerations in mind, we sought to systematically review all available randomized, placebo-controlled trials of psychopharmacological interventions for treatment of GAD in children and adolescents, with a focus on efficacy and tolerability. Additionally, we sought to compare studies reporting similar efficacy measures and adverse events across psychopharmacologic interventions.

3 Methods

3.1 Identification and Selection of Studies

A literature review of the national library of medicine (PubMed) from 1966 to September 2015 was completed using the search terms: “pediatric or child or adolescent or youth AND (“generalized anxiety disorder” or “overanxious disorder”) AND (selective serotonin reuptake inhibitor OR SSRI or selective serotonin norepinephrine reuptake inhibitor OR

SNRI or fluoxetine or venlafaxine or desvenlafaxine or duloxetine or vortioxetine or vilazodone or sertraline or citalopram or escitalopram or fluvoxamine or levomilnacipran or clorazepate or chlordiazepoxide or diazepam or flurazepam or prazepam or halazepam or lorazepam or lormetazepam or oxazepam or temazepam or clonazepam or pregabalin or alprazolam or triazolam or clonazepam or midazolam).” Studies were not excluded based on language of publication and only double-blind, placebo-controlled trials (DBPCTs) involving an exclusively pediatric population (<18 years of age) were included. Articles meeting these requirements were reviewed by the authors and studies in which fewer than 60% of the participants had a diagnosis of GAD were excluded (Figure 1). Moreover, when an article did not specify the proportion of patients with GAD ($n=1$), the authors were contacted to obtain this information.

3.2 Analysis of Efficacy and Side Effects

Efficacy for each individual psychopharmacologic intervention is descriptively reported in terms of primary outcomes. Additionally, to facilitate comparison across studies, numbers needed to treat (NNT) were calculated for remission for each study in which the Pediatric Anxiety Rating Scale (PARS) scores were reported, using the recent definition of PARS 8 as the cutoff for remission [1]. NNT is an epidemiological measure of the effectiveness of an intervention. NNT is defined as the inverse of absolute risk reduction, or the number of patients that need to be treated in order for one to receive a benefit (*e.g.*, remission of an anxiety disorder) relative to placebo. Therefore, a NNT of 1 represents an ideal intervention, large values indicate an intervention with little efficacy and a negative NNT indicates that the intervention is less beneficial than placebo. In the present study, NNT was calculated for each study by generating a normal distribution of 10,000 endpoint PARS scores, based on the mean and variance reported in each study. From these hypothetical patient data, absolute risk reductions were determined based on remission rates (*i.e.*, PARS score 8) and NNTs were determined. Similarly, number needed to harm (NNH) was calculated for selected side effects which were reported in >50% of studies. NNH is an epidemiological measure that indicates, on average, the number of patients that need to be exposed to a risk factor (*e.g.*, a medication) for one patient to receive harm (*e.g.*, an adverse event) relative to placebo. Therefore, a NNH close to 1 indicates a risk factor that frequently results in harm, larger NNH values indicate risk factors that rarely result in harm, and negative NNH values indicate that the “risk factor” is actually protective against harm.

4 Results

Five randomized, double-blind, placebo-controlled trials have assessed the effects of SSRIs [sertraline ($n=2$) and fluoxetine ($n=2$)] and SNRIs [venlafaxine ER ($n=1$) and duloxetine ($n=1$)], in pediatric patients with GAD (Table 1).

4.1 SSRIs in Pediatric Patients with GAD

In a randomized, double-blind, placebo-controlled trial involving youth with a primary diagnosis of GAD ($N=22$) [37], children and adolescents aged 5–17 years with a Hamilton Anxiety Rating Scale (HAM-A) score 16 and a primary diagnosis of GAD were randomized to placebo or to sertraline for 9 weeks of treatment. HAM-A scores, Clinical

Global Impression-Severity (CGI-S) scores, and Clinical Global Impression-Improvement (CGI-I) scores demonstrated statistically significant improvements for sertraline-treated patients relative to placebo-treated patients, beginning at week 4 of treatment. From an adverse event standpoint, sertraline-treated patients experienced more dizziness (18% versus 64%, $p<0.08$), nausea (5% versus 55%, $p<0.06$), and stomach pain (18% versus 64%, $p<0.08$) than youth receiving placebo, but these side effects did not reach the level of statistical significance. No suicidal ideation or suicide attempts were reported in either group.[37] Subsequently, a larger study ($N=488$, age: 7–17 years) examining the efficacy of sertraline in pediatric patients with GAD, social phobia (SoP)/social anxiety disorder and separation anxiety disorder (78% GAD) was completed—Child-Adolescent Anxiety Multimodal Study (CAMS). In this randomized, double-blind, placebo-controlled trial, children and adolescents received sertraline, cognitive-behavioral therapy (CBT), a combination, or placebo for 12 weeks, although there was no CBT + placebo arm. At week 12, CGI-I scores of 1 or 2 (*very much* or *much improved*) were 80.7% for combination therapy, 59.7% for CBT, 54.9% for sertraline, and 23.7% for placebo ($p<0.001$). Significant reductions in PARS scores were observed for the combination arm compared to PARS scores for patients receiving sertraline or CBT monotherapy, and all active treatments were superior placebo. Recently, a systematic evaluation of TEAEs encountered during the acute treatment phase of the CAMS [40] trial revealed no significant difference between sertraline and placebo in terms of total physical, total psychiatric, or any individual TEAE. However, sertraline-treated patients reported more total physical TEAE and higher rates of several specific TEAEs (*e.g.*, insomnia, fatigue, and sedation) relative to patients receiving CBT or CBT+sertraline. Importantly, higher rates of total psychiatric TEAEs (*e.g.*, disinhibition, agitation, anxiety/nervousness) for children relative to adolescents were observed for all treatment groups and the total number of TEAEs in each arm of the study decreased over time. No suicide attempts or completed suicides occurred in either group; although, suicidal ideation was reported by one subject receiving placebo compared to zero sertraline-treated patients.

Birmaher and colleagues assessed the efficacy of fluoxetine in a 12-week double-blind, placebo-controlled trial of youth (7–17 years) with GAD, separation anxiety disorder and/or social anxiety disorder ($N=84$, 64% GAD) [36]. At week 12, significantly more ($p=0.008$) subjects were found to be *very much* or *much improved* on the CGI-I in the fluoxetine group (61%) compared to those receiving placebo (35%). Drowsiness and headaches (reported together as neurological complaints) occurred more frequently in fluoxetine treated patients compared to those receiving placebo (44% versus 14%, $p=0.004$), as did nausea and abdominal pain, reported together as gastrointestinal complaints (46% versus 22%, $p=0.04$). Although, in this trial patients could be removed if there was suicidality, the number of subjects withdrawing for this reason was not reported.

4.3 SNRIs in Pediatric Patients with GAD

Venlafaxine ER was evaluated in an 8-week double-blind, placebo-controlled trial of youth (6–17 years) with GAD ($N=320$) [35]. Venlafaxine-treated patients improved significantly more than patients receiving placebo in terms of PARS, HAM-A, CGI-S, CGI-I, and SCARED (Screen for Child Anxiety Related Disorders) scores. Anorexia was the most

significant TEAE experienced more in the venlafaxine group than the placebo group (13% versus 3%). A ten-year old boy who was treated with venlafaxine withdrew from the study due to suicidal ideation (day 19) and a 17-year-old girl withdrew from the placebo group due to a suicide attempt (day 15). Venlafaxine-treated patients exhibited significantly more taper/post-study-emergent adverse events compared to those who had received placebo (32% versus 16.5%, $p=0.0014$).

Strawn and colleagues (2015) evaluated the safety and efficacy of flexibly-dosed duloxetine in children and adolescents with GAD in a 10-week randomized, double-blind, placebo-controlled trial ($N=272$), aged 7–17 years [50]. Statistically significant differences in remission rates (PARS severity score ≥ 8) were observed (duloxetine: 50% and placebo 34%) at endpoint (week 10). TEAEs occurring at a greater rate in the duloxetine-treated youth compared to those randomized to placebo included: nausea (20% versus 5.8%), vomiting (16% versus 7.3%), anorexia (15% versus 5.1%), oropharyngeal pain, dizziness, cough, and palpitations. Although 8 of the duloxetine-treated patients (5.9%) experienced treatment-emergent suicidal ideation, this rate did not differ statistically from the rate of treatment-emergent suicidality in the placebo group (5.2%). The most common taper-emergent AEs reported in the duloxetine group were headache and upper abdominal pain, although given that this study involved an open-label extension, only a minority of patients entered the taper phase.

4.4 Comparative Efficacy and Tolerability of Antidepressants in Pediatric Patients with GAD

NNT for GAD remission (PARS ≥ 8) and NNH for various TEAEs were calculated when possible and are included in Table 2, along with percent of individuals who discontinued due to AE in each study. NNT values ranged from 2.8 to 9.3, while NNH values varied greatly with respect to TEAE, drug, and study. Comparisons of NNT and NNH values are displayed graphically in Figure 2.

5 Discussion

GAD is among the most prevalent anxiety disorders in youth and is associated with debilitating psychosocial sequelae and increases risk of suicide attempts and self-injurious behavior in pediatric patients. However, the disorder appears to be amenable to both psychotherapeutic and psychopharmacologic interventions [51]. In this regard, all randomized, placebo-controlled, double-blinded trials of pharmacological treatments in pediatric patients with GAD suggest efficacy and good tolerability. Specifically, NNTs for these medications range from 2.7 to 9.3. TEAEs tended to be mild or infrequent.

Herein, we have compared TEAEs across these DBPCTs, although the heterogeneity of TEAE reporting complicates these comparisons. Among the 5 trials reviewed, data related to 50 distinct TEAEs or categories of TEAEs were captured. However, the number reported in a single trial varied considerably (range: 5–36) and only 4 TEAEs were reported in 3 or more of the 5 studies (*e.g.*, nausea, headache, sedation/drowsiness, and adverse event leading to discontinuation). Moreover, reporting of TEAEs and the associated variance is likely attributable to the heterogeneity of reporting as well as trial-specific factors. For example,

one study reported sedation and drowsiness together as “neurological complaints” [36], another reported headache, but not drowsiness [35], a third reported drowsiness, but not headache [37], and two others reported both headache and drowsiness individually [38, 50]. Furthermore, some studies reported only statistically significant TEAEs, while others reported rates of all TEAEs regardless of statistical significance.

The tapering of antidepressants has received little attention, despite being an issue of high clinical relevance, given that, for many, an eventual goal of GAD treatment is long-term remission with successful discontinuation [52]. In this regard, current recommendations for the psychopharmacologic treatment of GAD suggest that treatment should occur for approximately one year following remission, after which discontinuation should be attempted during a stress-free time of the year [53]. However, there are limited data regarding discontinuation of antidepressants in pediatric patients with anxiety disorders. Of the five trials reviewed here, only two trials describe taper-emergent adverse events [46, 47]. Discontinuation syndrome is an important consideration given the lack of evidence for long-term usage of SSRIs/SNRIs in the treatment of pediatric GAD. Additionally, studies suggest that 23% of adults treated with SSRIs discontinue usage by 4 weeks and 36.5% discontinue within 3 months [54]. These numbers may be even greater in children and adolescents, who may discontinue without the knowledge of either doctor or parents. The venlafaxine trial reported that nearly one third (32%) of participants experienced post-treatment AEs compared with 16.5% of the placebo group ($p=0.0014$). Only the most common taper-emergent AE, headache, was explicitly reported (5% venlafaxine versus 1% placebo). The high rates of reporting any post-treatment AE and the low rate of even the most common post-treatment AE suggest that the manifestation of post-treatment symptoms varies significantly. In the registration trial for duloxetine in youth with GAD [50], only taper-emergent symptoms experienced by two or more patients in the duloxetine arm were reported (3 headache, 2 upper abdominal pain). Additionally, the total percentage of patients with any taper-emergent AEs was not reported and there was no explicit comparison between the placebo and the duloxetine arm in terms of taper-emergent AEs. All other trials did not consider taper-emergent AEs.

Suicidality has received significant attention in pediatric antidepressant trials in the era of the black box [55]. In the decade following the US FDA meta-analysis that led to the pediatric antidepressant black box warning [42], several meta-analyses and studies have raised concerns regarding the conclusions of this initial analysis [41, 56, 57]. In this regard, while none of the trials in this review reported a statistically significant increase in suicidal ideation or suicide attempts in the treatment group relative to placebo, consistent with other post-black box meta-analyses using random effects models which found no link between pediatric antidepressant use and treatment-emergent suicidality [41, 56], clinicians would do well to continuously evaluate for suicidality (either treatment-related or disease state-related) in anxious youth. From a generalizability standpoint, it is noteworthy that many of the clinical trials including anxious youth, excluded actively suicidal patients as well as patients with comorbid major depressive disorder (MDD), thus decreasing the likelihood of a “suicidality signal” and potentially increasing the possibility of type II error.

6. Conclusions

Taken together, the extant data suggest that the SSRIs and SNRIs are generally efficacious and well tolerated, with their benefits well outweighing their risks in youth with GAD. However, comparative evaluations of tolerability are difficult which highlights the need for greater uniformity in their reporting of TEAEs, suicidality, and taper-emergent AEs. Similarly, the potential association between treatment with an SSRI/SNRI and suicidality in youth with GAD remains unclear. In this regard, several comparative analyses of antidepressants in youth with anxiety disorders [41, 56] have failed to detect differences between drug and placebo for treatment emergent suicidality underscoring both the importance of the model chosen for this rare event and pointing to differences in treatment related suicidality as a function of diagnosis (e.g., mood disorder vs. anxiety disorder).

References

1. Caporino NE, Brodman DM, Kendall PC, Albano AM, Sherrill J, Piacentini J, et al. Defining treatment response and remission in child anxiety: signal detection analysis using the pediatric anxiety rating scale. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013; 52(1):57–67. [PubMed: 23265634]
2. Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Archives of General Psychiatry*. 2012; 69(4):372–80. [PubMed: 22147808]
3. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49(10):980–9. [PubMed: 20855043]
4. O'Neil KA, Puleo CM, Benjamin CL, Podell JL, Kendall PC. Suicidal ideation in anxiety-disordered youth. *Suicide & Life-Threatening Behavior*. 2012; 42(3):305–17. [PubMed: 22509976]
5. Mars B, Heron J, Crane C, Hawton K, Kidger J, Lewis G, et al. Differences in risk factors for self-harm with and without suicidal intent: findings from the ALSPAC cohort. *Journal of Affective Disorders*. 2014; 168:407–14. [PubMed: 25108277]
6. Verduin TL, Kendall PC. Peer perceptions and liking of children with anxiety disorders. *Journal of Abnormal Child Psychology*. 2008; 36(4):459–69. [PubMed: 18027084]
7. Hansen C, Sanders SL, Massaro S, Last CG. Predictors of severity of absenteeism in children with anxiety-based school refusal. *Journal of Clinical Child Psychology*. 1998; 27(3):246–54. [PubMed: 9789185]
8. Ialongo N, Edelsohn G, Werthamer-Larsson L, Crockett L, Kellam S. The significance of self-reported anxious symptoms in first grade children: prediction to anxious symptoms and adaptive functioning in fifth grade. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 1995; 36(3):427–37.
9. Hughes AA, Lourea-Waddell B, Kendall PC. Somatic complaints in children with anxiety disorders and their unique prediction of poorer academic performance. *Child Psychiatry and Human Development*. 2008; 39(2):211–20. [PubMed: 17786552]
10. Bernstein GA, Massie ED, Thuras PD, Perwien AR, Borchardt CM, Crosby RD. Somatic symptoms in anxious-depressed school refusers. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36(5):661–8. [PubMed: 9136501]
11. Benjamin CL, Harrison JP, Settipani CA, Brodman DM, Kendall PC. Anxiety and Related Outcomes in Young Adults 7 to 19 Years after Receiving Treatment for Child Anxiety. *Journal of Consulting and Clinical Psychology*. 2013; 81(5)doi: 10.1037/a0033048

12. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry*. 1998; 55(1):56–64. [PubMed: 9435761]
13. Costello EJ, Angold A, Keeler GP. Adolescent outcomes of childhood disorders: the consequences of severity and impairment. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1999; 38(2):121–8. [PubMed: 9951210]
14. Merikangas KR, He J-p, Burstein M, Swendsen J, Avenevoli S, Case B, et al. Service Utilization for Lifetime Mental Disorders in U.S. Adolescents: Results of the National Comorbidity Survey–Adolescent Supplement (NCS-A). *Journal of the American Academy of Child & Adolescent Psychiatry*. 2011; 50(1):32–45. [PubMed: 21156268]
15. Ginsburg GS, Becker EM, Keeton CP, Sakolsky D, Piacentini J, Albano AM, et al. Naturalistic follow-up of youths treated for pediatric anxiety disorders. *JAMA Psychiatry*. 2014; 71(3):310–8. [PubMed: 24477837]
16. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *The Psychiatric Clinics of North America*. 2009; 32(3):483–524. [PubMed: 19716988]
17. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5. Washington, DC: American Psychiatric Press; 2013.
18. Van Oort FV, Greaves-Lord K, Verhulst FC, Ormel J, Huizink AC. The developmental course of anxiety symptoms during adolescence: the TRAILS study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2009; 50(10):1209–17.
19. Beesdo K, Pine DS, Lieb R, Wittchen HU. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Archives of General Psychiatry*. 2010; 67(1):47–57. [PubMed: 20048222]
20. Waszczuk MA, Zavos HM, Gregory AM, Eley TC. The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry*. 2014; 71(8):905–16. [PubMed: 24920372]
21. Wehry AM, McNamara RK, Adler CM, Eliassen JC, Croarkin P, Cerullo MA, et al. Neurostructural impact of co-occurring anxiety in pediatric patients with major depressive disorder: a voxel-based morphometry study. *Journal of Affective Disorders*. 2015; 171:54–9. [PubMed: 25285899]
22. Beesdo K, Lau JY, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, et al. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry*. 2009; 66(3):275–85. [PubMed: 19255377]
23. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS study. *Archives of General Psychiatry*. 2001; 58(6):597–603. [PubMed: 11386990]
24. Krueger RF. The structure of common mental disorders. *Archives of General Psychiatry*. 1999; 56(10):921–6. [PubMed: 10530634]
25. Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (DSM-III-R): a longitudinal-epidemiological study. *Journal of Abnormal Psychology*. 1998; 107(2):216–27. [PubMed: 9604551]
26. Strawn JR, Dominick KC, Patino LR, Doyle CD, Picard LS, Phan KL. *Neurobiology of Pediatric Anxiety Disorders*. *Current Behavioral Neuroscience Reports*. 2014; 1(3):154–60. [PubMed: 25745592]
27. Strawn JR, John Wegman C, Dominick KC, Swartz MS, Wehry AM, Patino LR, et al. Cortical surface anatomy in pediatric patients with generalized anxiety disorder. *Journal of Anxiety Disorders*. 2014; 28(7):717–23. [PubMed: 25155256]
28. Strawn JR, Chu WJ, Whitsel RM, Weber WA, Norris MM, Adler CM, et al. A pilot study of anterior cingulate cortex neurochemistry in adolescents with generalized anxiety disorder. *Neuropsychobiology*. 2013; 67(4):224–9. [PubMed: 23635944]
29. Roy AK, Fudge JL, Kelly C, Perry JS, Daniele T, Carlisi C, et al. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013; 52(3):290–9. e2. [PubMed: 23452685]

30. Maslowsky J, Mogg K, Bradley BP, McClure-Tone E, Ernst M, Pine DS, et al. A preliminary investigation of neural correlates of treatment in adolescents with generalized anxiety disorder. *Journal of Child and Adolescent Psychopharmacology*. 2010; 20(2):105–11. [PubMed: 20415605]
31. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry*. 2008; 65(5):568–76. [PubMed: 18458208]
32. Strawn JR, Wehry AM, DelBello MP, Rynn MA, Strakowski S. Establishing the neurobiologic basis of treatment in children and adolescents with generalized anxiety disorder. *Depression and Anxiety*. 2012; 29(4):328–39. [PubMed: 22511364]
33. Strawn JR, Hamm L, Fitzgerald DA, Fitzgerald KD, Monk CS, Phan KL. Neurostructural abnormalities in pediatric anxiety disorders. *Journal of Anxiety Disorders*. 2015; 32:81–8. [PubMed: 25890287]
34. Mueller SC, Aouidad A, Gorodetsky E, Goldman D, Pine DS, Ernst M. Gray matter volume in adolescent anxiety: an impact of the brain-derived neurotrophic factor Val(66)Met polymorphism? *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013; 52(2):184–95. [PubMed: 23357445]
35. Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *The American Journal of Psychiatry*. 2007; 164(2):290–300. [PubMed: 17267793]
36. Birmaher B, Axelson DA, Monk K, Kalas C, Clark DB, Ehmann M, et al. Fluoxetine for the treatment of childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003; 42(4):415–23. [PubMed: 12649628]
37. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *The American Journal of Psychiatry*. 2001; 158(12):2008–14. [PubMed: 11729017]
38. Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *The New England Journal of Medicine*. 2008; 359(26):2753–66. [PubMed: 18974308]
39. Ipser JC, Stein DJ, Hawkrigge S, Hoppe L. Cochrane Review: Pharmacotherapy for anxiety disorders in children and adolescents. *Evidence-Based Child Health: A Cochrane Review Journal*. 2010; 5(2):555–628.
40. Rynn MA, Walkup JT, Compton SN, Sakolsky DJ, Sherrill JT, Shen S, et al. Child/Adolescent anxiety multimodal study: evaluating safety. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015; 54(3):180–90. [PubMed: 25721183]
41. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007; 297(15):1683–96. [PubMed: 17440145]
42. US Food and Drug Administration. Relationship between psychotropic drugs and pediatric suicidality: review and evaluation of clinical data. Available at: <http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf>
43. Goodman WK, Murphy TK, Storch EA. Risk of adverse behavioral effects with pediatric use of antidepressants. *Psychopharmacology*. 2007; 191(1):87–96. [PubMed: 17180618]
44. Barnes NM, Sharp T. A review of central 5-HT receptors and their function. *Neuropharmacology*. 1999; 38(8):1083–152. [PubMed: 10462127]
45. Rahn KA, Cao YJ, Hendrix CW, Kaplin AI. The role of 5-HT1A receptors in mediating acute negative effects of antidepressants: implications in pediatric depression. *Translational Psychiatry*. 2015; 5:e563. [PubMed: 25942044]
46. Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. *Psychotherapy and Psychosomatics*. 2015; 84(2):72–81. [PubMed: 25721705]
47. Hosenbocus S, Chahal R. SSRIs and SNRIs: A review of the Discontinuation Syndrome in Children and Adolescents. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*. 2011; 20(1):60–7. [PubMed: 21286371]

48. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *The New England Journal of Medicine*. 2001; 344(17):1279–85. [PubMed: 11323729]
49. da Costa CZ, de Moraes RM, Zanetta DM, Turkiewicz G, Lotufo Neto F, Morikawa M, et al. Comparison among clomipramine, fluoxetine, and placebo for the treatment of anxiety disorders in children and adolescents. *Journal of Child and Adolescent Psychopharmacology*. 2013; 23(10): 687–92. [PubMed: 24350814]
50. Strawn JR, Prakash A, Zhang Q, Pangallo BA, Stroud CE, Cai N, et al. A randomized, placebo-controlled study of duloxetine for the treatment of children and adolescents with generalized anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015; 54(4):283–93. [PubMed: 25791145]
51. Connolly SD, Bernstein GA. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007; 46(2):267–83. [PubMed: 17242630]
52. Pine DS. Treating children and adolescents with selective serotonin reuptake inhibitors: how long is appropriate? *Journal of Child and Adolescent Psychopharmacology*. 2002; 12(3):189–203. [PubMed: 12427293]
53. Keeton CP, Kolos AC, Walkup JT. Pediatric generalized anxiety disorder: epidemiology, diagnosis, and management. *Paediatric Drugs*. 2009; 11(3):171–83. [PubMed: 19445546]
54. Tanno S, Ohhira M, Tsuchiya Y, Takeuchi T, Tanno S, Okumura T. Frequent early discontinuation of SSRI prescribed by primary care physicians in young males in Japan. *Internal Medicine (Tokyo, Japan)*. 2009; 48(15):1263–6.
55. Sparks JA, Duncan BL. Outside the Black Box: Re-assessing Pediatric Antidepressant Prescription. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*. 2013; 22(3):240–6. [PubMed: 23970915]
56. Strawn JR, Welge JA, Wehry AM, Keeshin B, Rynn MA. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. *Depression and Anxiety*. 2015; 32(3):149–57. [PubMed: 25449861]
57. Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Archives of General Psychiatry*. 2012; 69(6):580–7. [PubMed: 22309973]

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

Figure 2. Efficacy and Tolerability of Antidepressant Medications in Pediatric Patients with Generalized Anxiety Disorder (GAD). Number Needed to Treat (NNT) values calculated from simulated patient population remission rates based on the Pediatric Anxiety Rating Scale (PARS). Number Needed to Harm (NNH) are calculated based on the reported frequency of treatment emergent adverse events in patients with GAD.

Study Design and Efficacy of Antidepressant Trials in Pediatric Patients with Generalized Anxiety Disorder

Table 1

Study	Medication	Age (years)	Study Duration (weeks)	Proportion GAD (%)	Outcome Measurement	Endpoint Dose (mg/day)	Sample Size* (N)	NNT
Rynn et al. (2001) [37]	Sertraline	5–17	9	100	HAM-A	50	22	N/A
Birmaher et al. (2003) [36]	Fluoxetine	7–17	12	64	PARS	20	84	5.77
Rynn et al. (2007) [35]	Venlafaxine ER	6–17	8	100	PARS	NR	320	9.29
Walkup et al. (2008) [38]	Sertraline	7–17	12	78	PARS	133	209	6.37
Strawn et al. (2015) [50]	Duloxetine	7–17	10	100	PARS	53.6	272	2.76

* Sample size indicates the number of patients randomized to either pharmacotherapy or placebo groups only, with CBT or combination arms excluded.

ER, Extended Release; GAD, Generalized Anxiety Disorder; HAM-A, Hamilton Anxiety Rating Scale; NNT, Number Needed to Treat; NR, Not Reported; N/A, Not Applicable; PARS, Pediatric Anxiety Rating Scale

Efficacy, Tolerability, and Discontinuation of Antidepressants in Pediatric Patients with Generalized Anxiety Disorder (GAD).

Table 2

Study	Medication	NNT	NNH GI Cause	NNH Nausea	Headache	NNH Sedation/Drowsiness	NNH Activation ^c	AE Leading to D/C (medication) (%)	AE Leading to D/C (Placebo) (%)
Rynn et al. (2001)	Sertraline	N/A	-2.0	-2.0	NR	3.6	3.6	NR	NR
Birmaher et al. (2003)	Fluoxetine	5.77	4.17	4.17 ^a	3.27 ^b	3.27 ^b	12.5	16.2	0
Rynn et al. (2007)	Venlafaxine	9.29	11.0	66.1	3.33	NR	NR	3.2	5.6
Walkup et al. (2008)	Sertraline	6.37	29.4	-111	24.4	31.3	24.4	1.5	2.6
Strawn et al. (2015)	Duloxetine	2.76	7.04	7.04	31.3	18.9	-71.4	5.2	4.4

N/A, Not Applicable; NNH, Number Needed to Harm; NNT, Number Needed to Treat; NR, Not Reported; AE, adverse event; D/C, discontinuation

^aIncludes nausea and abdominal pain, grouped as “gastrointestinal complaints”^bIncludes headache and drowsiness, grouped as “neurological complaints”^cIncludes activation, irritability, restlessness/fidgetiness, agitation, impulsivity, increased motor activity, emotional outbursts/tantrums, disobedience/defiance