The 5-Year Course of Medication Treatment in Childhood Anxiety Disorders

Stephen P. Whiteside, PhD, LP[a,*]; Leslie A. Sim, PhD, LP[a]; Mark W. Olsen, MD[a]; and Melissa K. Hord, PhD[a]

ABSTRACT

Objective: For pediatric psychiatric disorders, given the marked increase in use of medications without an understanding of the typical treatment course, the primary goal of the current study was to examine the course of pharmacotherapy over 5 years in children with newly diagnosed anxiety disorders.

Methods: We reviewed provider billing and prescription ordering records of a tertiary medical center from 2008 through 2015 to identify children (aged 7–17 years) newly diagnosed with an anxiety disorder and to determine the psychopharmacologic treatment that they received from 2010 through 2015. The frequency at which patients received prescriptions from 9 classes of psychotropic medications at any point during the study period was determined. We used χ^2 analyses and independent sample *t* tests to examine the relationship between receiving a psychotropic prescription and various patient characteristics.

Results: The study cohort included 108 patients (mean [SD] age = 12.8 [3.3] years). In this group, 73.1% received pharmacotherapy on at least 1 occasion over the 5-year period, and 41.7% received medications from more than 1 class. Of those who received a prescription, 50% (27/54) of patients remained on medication for 5 years. This estimate rose to 71% (5/7) within the subset of patients who were medication-naive at the beginning of the observation period and were still in high school during year 5.

Conclusions: Guidelines implying discontinuation of medication after symptom remission and a limited period of stability do not accurately reflect clinical practice.

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[a]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota

**Corresponding author:* Stephen P. Whiteside, PhD, LP, Department of Psychiatry and Psychology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (whiteside.stephen@mayo.edu).

Childhood anxiety disorders, the most common mental health diagnoses, are associated with clinically significant short- and long-term impairment.[1,2] Multiple treatment options have been developed and evaluated; the most comprehensive meta-analysis to date on the treatment of pediatric anxiety disorders supports using cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs).[3] In spite of some advantages for cognitive behavioral therapy,[3] as well as parent preference for this treatment approach,[4] pharmacologic interventions are common for childhood anxiety disorders in clinical practice, particularly in primary care settings.[5,6] Moreover, the frequency at which children are prescribed psychotropic medications has increased considerably (ie, 160%) in the past 25 years, with current estimates suggesting that 3.4% of adolescents have taken an antidepressant in the past month.[6,7]

The dramatic increase in antidepressant use in youth has occurred despite the lack of basic information regarding the necessary or expected duration of treatment with these medications.[8,9] Most treatment studies assess initial symptom reduction and remission data after a 12-week period,[10] with follow-up data reported less frequently.[11] Current treatment guidelines for childhood anxiety recommend continuing SSRI use for 1 year after complete remission of symptoms and then discontinuing it during a time of low stress.[12–17] Taken together, outcome studies and treatment guidelines suggest that psychopharmacology for childhood anxiety disorders should be time limited.

In spite of the brief nature of efficacy studies and treatment guidelines recommending episodic treatment, data from real-world settings indicate that psychotropic medication use may be more prolonged. Survey data suggest that nearly 70% of individuals older than 12 years who are taking an antidepressant have been taking it for more than 2 years, with a quarter of patients having been on a medication for 10 years or longer.[7] Moreover, data from clinical trials raise questions about whether medications can be discontinued successfully after symptom improvement.[18–21] Unfortunately, because of the short-term nature of treatment trials, little is known about the risks and benefits associated with longer pharmacotherapy,[8,9,22,23] although persistent adverse effects,[24] steep weight gain,[25] and diabetes mellitus[26] may be associated with longer-term use.

Given the marked discrepancy between the short-term nature of psychopharmacology efficacy studies and treatment guidelines versus emerging data from general psychotropic use suggesting that long-term treatment is the norm, the current study aimed to examine the course of medication use over 5 years (as determined by prescription records) in children newly diagnosed with an anxiety disorder at a large medical center. Although the study was mostly exploratory, we hypothesized that most of these children would be prescribed a medication within a 5-year period and that SSRIs would be the medication most commonly prescribed. We also predicted

Clinical Points

- Medications are frequently used to treat childhood anxiety disorders despite little knowledge about how long children will typically continue to take those medications.
- When deciding whether to prescribe medication (or any intervention) for childhood anxiety disorders, clinicians should consider the likely duration of treatment.

that most patients who were prescribed a medication would remain on the medication throughout the follow-up period.

METHODS

This study was conducted after receiving approval from the Mayo Clinic Institutional Review Board. Minnesota law requires patients to have the opportunity to withhold permission for their medical records to be used for research purposes, and records lacking research authorization were not included.

Study Design and Participant Selection

Records of a regional medical center in the Midwest were searched to identify (1) children aged 7 to 17 years who were newly diagnosed with a psychiatric disorder and (2) the psychopharmacologic treatment that they received. We first searched billing records to identify children and adolescents (hereafter termed *children*) empaneled with a primary care provider who had a new diagnosis of an anxiety disorder in 2010 (using the contemporaneous diagnostic systems; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, and *International Classification of Diseases* (Ninth Revision [*ICD-9*]).[27] We selected all patients billed for an appointment from January through December 2010 that was linked to *ICD-9* diagnostic codes 290.0 through 319. To identify newly diagnosed cases, we then excluded patients who had an appointment linked to any of these codes in 2008 or 2009. Pharmacotherapy was determined by examining prescription orders from 2010 through 2015. After applying inclusion and exclusion criteria, the final study cohort comprised 108 patients.

Medications

Medications were grouped into 9 categories: (1) SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline; (2) other new-generation antidepressants and anxiety medications: bupropion, duloxetine, mirtazapine, venlafaxine, buspirone; (3) benzodiazepines: clonazepam, diazepam, lorazepam; (4) tricyclic antidepressants: amitriptyline, clomipramine, imipramine, nortriptyline; (5) atypical antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone; (6) mood stabilizers: divalproex, valproic acid, valproate sodium, gabapentin, lamotrigine, lithium, oxcarbazepine, topiramate; (7) sleep aids: trazodone, eszopiclone, melatonin, ramelteon, zaleplon, zolpidem; (8) first-generation antipsychotics: haloperidol, prochlorperazine, chlorpromazine; and (9) other medications: disulfiram, prazosin, propranolol, acamprosate, acetylcysteine, benztropine. Medications for attention-deficit/hyperactivity disorder were not examined.

Analytic Plan

The frequency of psychotropic prescriptions from each class was examined first. The association between prescriptions and demographic characteristics was then examined through a series of χ^2 tests and independent sample *t* tests. To examine the persistence of medication use over time, the first year a child received a prescription was designated as year 1 (regardless of the calendar year of the prescription), and each subsequent year was designated as years 2, 3, and so on. Accordingly, the sample size varied each year, depending on the patients with contributing data (eg, patients who received their first prescription in 2014 could contribute data for only 1 year because the study period ended in 2015).

First, data for the entire sample were examined to maximize power and representativeness. Second, to reduce false-negative results (eg, patients not receiving prescriptions because they moved away), patients were removed from the analyses starting with the year they were assumed to have graduated from high school; only data from the last full year before June of the patient's senior year in high school were included. In addition, patients who were already taking psychotropic medication were excluded. Third, persistence of SSRI prescriptions (as opposed to psychiatric medications in general) was then examined. We used χ^2 analyses to examine prescriptions over the course of the observation period, with patients stratified by treatment status at year 1. Similar to the examination of broader psychotropic medication use, the SSRI analyses were repeated after removing patients who had aged out or had a mood disorder diagnosed at some point during the observation period.

RESULTS

Participants

The mean (SD) patient age was 12.8 (3.3) years. More than half the patients were female (n = 65 [60.2%]) and the majority were white (n = 94 [87.0%]). Demographic information and the frequency of *ICD-9* diagnoses abstracted from the billing records are presented in Table 1. The mean (SD) number of anxiety diagnoses was 1.32 (0.6) per patient, with 30 patients (27.8%) receiving 2 or more anxiety diagnoses. In the first year, 43 patients (39.8%) also received a diagnosis of a mood disorder. Most of the cohort was medication naive (n = 81 [75.0%]). Of the 27 already taking medication (presumably for a nonanxiety disorder), SSRIs were most commonly prescribed (n = 17 [63.0%]).

Rates of Pharmacotherapy

The majority of the cohort received pharmacotherapy on at least 1 occasion over the 5-year period (n = 79 [73.1%]). The most commonly prescribed medications were SSRIs

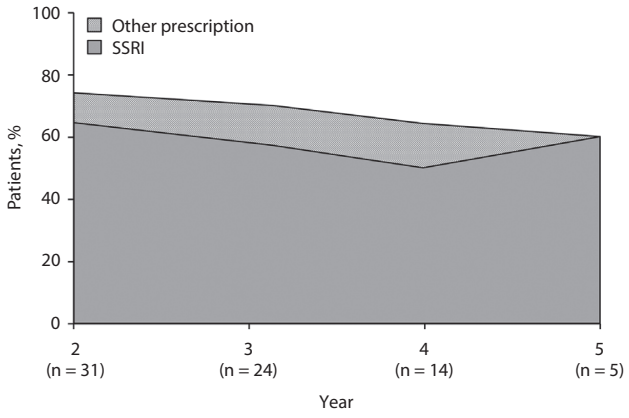
(n = 72 [66.7%]), followed by sleep aids (n = 34 [31.5%]), other new-generation antidepressants and anxiety medications (n = 22 [20.4%]), atypical antipsychotics (n = 21 [19.4%]), benzodiazepines (n = 20 [18.5%]), mood stabilizers (n = 18 [16.7%]), other medications (n = 12 [11.1%]), first-generation antipsychotics (n = 7 [6.5%]), and tricyclic antidepressants (n = 2 [1.9%]). During the 5-year period, 34 patients (31.5%) received prescriptions for only 1 group of medication; 11 (10.2%) received prescriptions for 2 medication groups, 11 (10.2%) from 3 groups, and 23 (21.3%) from 4 or more groups. Boys (67.4%) and girls (76.9%) received prescriptions in similar rates ($\chi^2 = 1.18$; $P = .27$). Patients who received a prescription did not differ significantly in age at the time of first diagnoses from those who did not (2010 data: mean [SD] age, 13.1 [3.2] vs 11.8 [3.5] years); $t_{106} = 1.84$; $P = .07$). Patients were less likely to receive a prescription if they had a diagnosis of obsessive-compulsive disorder (OCD) (44.4% of those with OCD vs 75.8% of those without OCD; $\chi^2 = 4.12$; $P = .04$) or a specific phobia (42.9% vs 77.7%; $\chi^2 = 7.51$; $P = .006$), but they were more likely to receive one if they had a diagnosis of a mood disorder (95.3% vs 58.5%; $\chi^2 = 17.93$; $P = .001$) or posttraumatic stress disorder (PTSD) (94.7% vs 68.5%; $\chi^2 = 5.47$, $P = .02$).

Table 1. Patient Characteristics (N = 108)

Characteristic	Value
Female, n (%)	65 (60.2)
Age, mean (SD), y	12.8 (3.3)
Race/ethnicity, n (%)	
White	94 (87.0)
Hispanic	5 (4.6)
Black or African American	4 (3.7)
Asian	1 (0.9)
Other or unknown	4 (3.7)
Diagnoses, n (%)[a]	
Generalized anxiety disorder	51 (47.2)
Social anxiety disorder	24 (22.2)
Posttraumatic stress disorder	19 (17.6)
Separation anxiety disorder	17 (15.7)
Specific phobia	14 (13.0)
Obsessive-compulsive disorder	9 (8.3)
Panic disorder	9 (8.3)
Mood disorder	43 (39.8)

[a]Total exceeds 100% because of comorbidities. Diagnoses (*International Classification of Diseases*, Ninth Revision) were abstracted from billing records.

Figure 1. Percentage of Medication-Naive Patients at the Beginning of the Observation Period Who Continued to Receive Psychotropic Prescriptions for up to 5 Years After the First SSRI Prescription[a]



[a]Decreasing sample size over time reflects patients being removed from the analyses after the expected date of high school graduation.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Course of Pharmacotherapy

Of the patients who received a prescription for psychotropic medication (n = 75, excluding the 4 who received only sleep aids), most received their first prescription during year 1 (n = 54 [72.0%]); others received their first prescription in year 2 (n = 9 [12.0%]), year 3 (n = 6 [8.0%]), year 4 (n = 2 [2.7%]), and year 5 (n = 4 [5.3%]). Of the 71 patients for whom data were available the year after beginning medication (ie, 4 from year 5 were not analyzed), 48 (67.6%) received a prescription in year 2. For the following years, 40/69 (58%) received a prescription in year 3, 33/63 (52.4%) received a prescription in year 4, and 27/54 (50%) received a prescription in year 5. When the sample was restricted to patients who were medication-naive and still school-aged during the years in question, the number of patients receiving prescriptions in subsequent years was 22/32 (68.8%) in year 2, 18/25 (72.0%) in year 3, 13/22 (59.1%) in year 4, and 5/7 (71.4%) in year 5.

Course of SSRI Treatment

Of the patients who received a prescription for an SSRI (n = 72), the majority received the first one during year 1 (n = 46 [63.9%]); others received the first prescription in year 2 (n = 9 [12.5%]), year 3 (n = 9 [12.5%]), year 4 (n = 2 [2.8%]), and year 5 (n = 6 [8.3%]). Of the 66 for whom data were available the year after beginning medication (ie, data were unavailable for 6 patients from year 5), 46 (69.7%) received a prescription the following year (39 [59.1%] for an SSRI and 7 [10.6%] for another non–sleep aid psychotropic). In the third year after the initial SSRI prescription, 38/64 (59.4%) received a prescription (28 [43.8%] for an SSRI and 10 [15.6%] for another non–sleep aid psychotropic). In the fourth year, 27/55 (49.1%) received a prescription (19 [34.5%] for an SSRI and 8 [14.5%] for another non–sleep aid psychotropic). In the fifth year, 22/46 (47.8%) received a prescription (15 [32.6%] for an SSRI and 7 [15.2%] for another non–sleep aid psychotropic). When the sample was limited to patients who were medication-naive at the beginning of the study period and were still school-aged during each time point, the percentage remaining on medication increased to between 60% and 70% each year (Figure 1).

Comparative Course

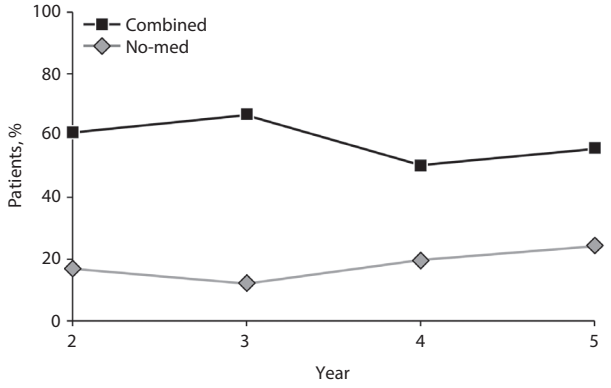
We evaluated 3 subgroups of patients, based on their year-1 status: (1) patients who were medication-naive through the first year (termed *No-med*; n = 47), (2) patients who were initially

Table 2. Psychotropic Prescriptions Over Time, Categorized by First-Year Treatment Status

Patient Group[a]	Year 2	Year 3	Year 4	Year 5
All patients, n (%)				
No-med	9/47 (19.1)	9/47 (19.1)	10/47 (21.3)	13/47 (27.7)
SSRI	16/25 (64.0)	13/25 (52.0)	11/25 (44.0)	12/25 (48.0)
Preexist	20/27 (74.1)	19/27 (70.4)	14/27 (51.9)	13/27 (48.1)
Not aged out, n (%)[b]				
No-med	7/42 (16.7)	7/34 (20.6)	9/32 (28.1)	9/28 (32.1)
SSRI	12/17 (70.6)	9/13 (69.2)	6/8 (75.0)	3/5 (60.0)
Preexist	17/22 (77.3)	9/13 (69.2)	6/11 (54.5)	2/7 (28.6)
No mood disorder diagnosis, n (%)				
No-med	7/41 (17.1)	5/41 (12.2)	8/41 (19.5)	10/41 (24.4)
Combined	11/18 (61.1)	12/18 (66.7)	9/18 (50.0)	10/18 (55.6)

[a]Combined = data from SSRI and preexist categories were combined, No-med = initially medication-naive and remained so through year 1, Preexist = received prescriptions before year 1, SSRI = initially medication naive and then prescribed an SSRI during year 1.
[b]The analysis considered only data from the last full year before June of the patient's senior year in high school.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 2. Patients Without a Mood Disorder Who Received Prescriptions Based on the First Year of Treatment (N = 59)[a]



[a]No-med = medication-naive through year 1; combined = medication-naive and prescribed a selective serotonin reuptake inhibitor during year 1 *or* received prescriptions before year 1.

medication-naive and received an SSRI prescription during year 1 (termed *SSRI*; n = 25), and (3) patients with preexisting medications (termed *Preexist*; n = 27). We excluded patients who were medication-naive and received non-SSRI medications during year 1 (n = 9). The subgroups differed by age (shown as mean [SD] years: No-med, 11.5 [3.3]; SSRI, 14.1 [3.0]; Preexist, 13.9 [2.7]; $F_{2,96} = 8.48$; $P < .001$), the presence of a mood disorder (No med, 12.8%; SSRI, 56.0%; Preexist, 74.1%; $\chi^2 = 30.15$; $P < .001$), the presence of specific phobia (No-med, 23.4%; SSRI, 8.0%; Preexisting, 3.7%; $\chi^2 = 6.52$; $P = .04$), and the presence of PTSD (No-med, 8.5%; SSRI, 16.0%; Preexisting, 37.0%; $\chi^2 = 9.49$; $P = .009$). The groups did not differ in terms of sex or race/ethnicity.

Table 2 presents the percentage of patients who were prescribed any medication in years 2 through 5, stratified by year-1 treatment categories. The differences were significant for years 2 through 4 (all χ^2 values > 8.11, all $P < .05$) but not year 5. When the sample was limited to the patients who were still school-aged during each year, the general pattern remained the same, with significant differences in years 2 through 4 (all χ^2 values > 6.84, all $P < .05$). To control for group differences in mood disorders, all patients with a mood disorder diagnosed during the first-year period were excluded. Because the SSRI (n = 11) and Preexist (n = 7) groups were small compared with the No-med group (n = 41), they were combined. The differences in the number of participants prescribed medications between the medication-naive group and the combined medication group were significant at all 4 time points (all χ^2 values > 5.42, all $P < .05$). Figure 2 shows patients without a mood disorder who received prescriptions.

DISCUSSION

The findings of this study suggest that most children and adolescents with a new-onset anxiety disorder treated at a medical center received medication, frequently multiple medications from more than 1 class. Consistent with treatment guidelines,[14,28,29] the most commonly prescribed medications for this sample were SSRIs. However, almost a fifth of the sample received benzodiazepines and atypical antipsychotics, classes of medications with notable adverse effect profiles and limited evidence of effectiveness when used to treat childhood anxiety disorders.[3] After medication was prescribed, 50%–70% of children remained on it throughout the 5-year evaluation period, suggesting that the persistence of medication use often exceeded the 3 months examined in controlled trials of children with anxiety disorders.[3,14]

Within the overall trend of frequent and persistent medication use, a number of factors were associated with the frequency of prescriptions. SSRIs were more often prescribed for older youth with a mood disorder or PTSD. The age trend was consistent with that of previous research[6] and likely reflects more caution by clinicians when considering medication for younger children. The increased frequency of children with comorbid depression may be associated with a tendency for clinicians to use medications for depression, elevated complexity, or higher treatment recalcitrance. The finding that an SSRI prescription was associated with a PTSD diagnosis was inconsistent with the evidence suggesting minimal benefit of SSRIs for PTSD.[30] Conversely, medication was less likely to be used in the presence of OCD or a specific phobia. The relation between diagnosis and medication use may reflect the presence of therapy resources (eg, specialty OCD program) idiosyncratic to the medical center or the provider preference (eg, treatment of a specific phobia).

The decision to initiate pharmacotherapy with an SSRI had lasting implications on subsequent use. For children and adolescents who were not prescribed medication in year 1, most remained medication free. In contrast, most of the children prescribed an SSRI

in year 1 remained on a medication throughout the period examined. As such, those prescribed an SSRI in year 1 more commonly continued with the medication during each year for up to 5 years (Table 2).

Given the lack of patient-level data, the association of factors (eg, severity or complexity of symptoms) with pharmacotherapy is unclear. However, a previous analysis of data from the initial treatment year suggested that patients seen in an anxiety specialty clinic were less likely to receive medication; thus, illness severity does not necessarily dictate treatment decision.[5] Although treatment-level data are unavailable, such as whether the patients were receiving other treatment for their anxiety disorder, the frequency of use of medications from multiple classes and the relatively high number of children initially treated with SSRIs who then began treatment with a different class of medication suggest that medication treatment was not completely effective.

Limitations of the study include the relatively small sample size and the retrospective nature of data collection. The small sample size necessitated combining multiple anxiety disorders for the analysis (including OCD and PTSD, which are no longer classified with the other anxiety disorders) and prohibited examining the longitudinal treatment course of each disorder individually. Future research is needed to examine the effect of comorbidities on treatment and the courses of different medication classes. In addition, the data were derived from the clinical practice of a single health system with common resources and a fairly homogenous patient population (mostly white); thus, the findings need to be replicated prospectively in a larger and more diverse sample and in other settings. Moreover, the focus on the mental health diagnostic codes did not identify the presence of medical conditions, such as migraines or insomnia unspecified, that might be treated by the same medication classes, eg, tricyclic antidepressants. Nevertheless, the ability to capture all local patients with an anxiety diagnosis from a large medical center is a considerable strength of this naturalistic study of clinical practice, especially in the absence of other data examining the course of pharmacotherapy for childhood anxiety disorders.

The current data have significant implications. In particular, clinicians should be aware, when considering pharmacotherapy, that the duration of treatment is uncertain, but research suggests that the treatment course may extend for 5 years or longer. Future research should examine whether viewing pharmacotherapy as prolonged vs episodic influences the decision-making process of clinicians or families. Additionally, treatment guidelines should be updated to reflect the available data and continued uncertainty regarding duration. Studies are needed to examine the persistence of medication treatment in a larger sample with better documented diagnoses, comorbidity, adjunct treatments, and symptom response. Finally, if extended treatment is indeed common for childhood anxiety disorders, it is imperative to examine the effectiveness, safety, and adverse effects of prolonged exposure to medications during childhood.

In summary, if future research confirms the current findings, it suggests that for a large proportion of children with anxiety disorders, the decision to take medication is a long-term commitment rather than a time-limited intervention. If that turns out to be the case, families should be informed that patients may continue receiving medication for an extended time.

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REFERENCES

1. Ezpeleta L, Keeler G, Erkanli A, et al. Epidemiology of psychiatric disability in childhood and adolescence. *J Child Psychol Psychiatry*. 2001;42(7):901–914.
2. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for *DSM-V*. *Psychiatr Clin North Am*. 2009;32(3):483–524.
3. Wang Z, Whiteside SPH, Sim L, et al. Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders: a systematic review and meta-analysis. *JAMA Pediatr*. 2017;171(11):1049–1056.
4. Brown AM, Deacon BJ, Abramowitz JS, et al. Parents' perceptions of pharmacological and cognitive-behavioral treatments for childhood anxiety disorders. *Behav Res Ther*. 2007;45(4):819–828.
5. Whiteside SP, Ale CM, Young B, et al. The length of child anxiety treatment in a regional health system. *Child Psychiatry Hum Dev*. 2016;47(6):985–992.
6. Meng X, D'Arcy C, Tempier R. Long-term trend in pediatric antidepressant use, 1983–2007: a population-based study. *Can J Psychiatry*. 2014;59(2):89–97.
7. Pratt LA, Brody DJ, Gu Q. Antidepressant use among persons aged 12 and over: United States, 2011–2014. *NCHS Data Brief*. 2017;(283):1–8.
8. Wehry AM, Beesdo-Baum K, Hennelly MM, et al. Assessment and treatment of anxiety disorders in children and adolescents. *Curr Psychiatry Rep*. 2015;17(7):52.
9. Skarphedinsson G, Weidle B, Thomsen PH, et al. Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial. *Eur Child Adolesc Psychiatry*. 2015;24(5):591–602.
10. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008;359(26):2753–2766.
11. Ginsburg GS, Becker-Haimes EM, Keeton C, et al. Results from the Child/Adolescent Anxiety Multimodal Extended Long-Term Study (CAMELS): primary anxiety outcomes. *J Am Acad Child Adolesc Psychiatry*. 2018;57(7):471–480.
12. Keeton CP, Kolos AC, Walkup JT. Pediatric generalized anxiety disorder: epidemiology, diagnosis, and management. *Paediatr Drugs*. 2009;11(3):171–183.
13. Pine DS. Treating children and adolescents with selective serotonin reuptake inhibitors: how long is appropriate? *J Child Adolesc Psychopharmacol*. 2002;12(3):189–203.
14. Connolly SD, Bernstein GA; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(2):267–283.
15. Dobson ET, Strawn JR. Pharmacotherapy for pediatric generalized anxiety disorder: a systematic evaluation of efficacy, safety and tolerability. *Paediatr Drugs*. 2016;18(1):45–53.

16. Southammakosane C, Schmitz K. Pediatric psychopharmacology for treatment of ADHD, depression, and anxiety. *Pediatrics*. 2015;136(2):351–359.
17. Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. *J Am Acad Child Adolesc Psychiatry*. 2015;54(4):251–262.
18. Berwian IM, Walter H, Seifritz E, et al. Predicting relapse after antidepressant withdrawal: a systematic review. *Psychol Med*. 2017;47(3):426–437.
19. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry*. 2003;64(2):123–133.
20. Vittengl JR. Poorer long-term outcomes among persons with major depressive disorder treated with medication. *Psychother Psychosom*. 2017;86(5):302–304.
21. Batelaan NM, Bosman RC, Muntingh A, et al. Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. *BMJ*. 2017;358:j3927.
22. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299–309.
23. Cook EH, Wagner KD, March JS, et al. Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2001;40(10):1175–1181.
24. Bet PM, Hugtenburg JG, Penninx BW, et al. Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol*. 2013;23(11):1443–1451.
25. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry*. 2014;71(8):889–896.
26. Andersohn F, Schade R, Suissa S, et al. Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. *Am J Psychiatry*. 2009;166(5):591–598.
27. Slee VN. *The International Classification of Diseases*, Ninth Revision (ICD-9). *Ann Intern Med*. 1978;88(3):424–426.
28. Birmaher B, Brent D, Bernet W, et al; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(11):1503–1526.
29. Sakolsky D, Birmaher B. Pediatric anxiety disorders: management in primary care. *Curr Opin Pediatr*. 2008;20(5):538–543.
30. Keeshin BR, Strawn JR. Psychological and pharmacologic treatment of youth with posttraumatic stress disorder: an evidence-based review. *Child Adolesc Psychiatr Clin N Am*. 2014;23(2):399–411, x.