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Antidepressant Treatment Duration in Pediatric Depressive and Anxiety Disorders: How Long is Long Enough?

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Abstract

Anxiety and depressive disorders are common in the pediatric primary care setting, and respond to both psychotherapeutic and antidepressant pharmacotherapy treatment. However, there are limited data regarding the optimal treatment duration. This paper systematically reviews guidelines and clinical trial data related to antidepressant treatment duration in pediatric depressive and anxiety disorders. The extant literature suggests 9–12 months of SSRI treatment for youth with major depressive disorder. For generalized, separation and social anxiety disorders, 6–9 months of SSRI treatment may be sufficient, though many clinicians extend treatment to 12 months based on extrapolation of data from adults with anxiety disorders. Such extended treatment periods may decrease the risk of long-term morbidity and recurrence; however, the goal of treatment is ultimately remission, rather than duration of antidepressant pharmacotherapy. Evidence-based guidelines represent a starting point; however, appropriate treatment duration varies and patient-specific response, psychological factors, and timing of discontinuation must be considered for individual pediatric patients.

Keywords

Selective Serotonin Reuptake Inhibitor (SSRI); Selective Norepinephrine Reuptake Inhibitor (SNRI); antidepressants; psychopharmacology; relapse; recurrence; treatment duration

INTRODUCTION

Anxiety and depressive disorders are common in the pediatric primary care setting and affect 10% of children and adolescents.¹ Successful treatment of depressive and anxiety disorders

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in youth—whether psychotherapeutic or psychopharmacologic—should restore function, establish remission and decrease the likelihood of relapse and recurrence. With successful treatment, however, the following questions frequently arise in clinical care: *How long should this patient be treated with an antidepressant? When can the antidepressant that I've started be discontinued? Will the treatment gains be sustained upon discontinuation of the patient's antidepressant medication? If the patient cannot come off medication what is the next best solution?*

To inform best practices for determining duration of antidepressant treatment, we systematically reviewed: (1) current practice guidelines for antidepressant treatment duration; (2) evidence for optimal duration of antidepressant treatment and (3) specific psychotherapeutic and psychopharmacologic strategies for preventing relapse.

BACKGROUND

Anxiety and depression are associated with substantial morbidity, including impaired social and academic functioning and increase the risk of suicide and suicide attempts². Anxiety and depression both respond to psychotherapeutic and psychopharmacologic interventions. However, in some pediatric primary care settings these disorders may be under-recognized and untreated.³ Data have accumulated during the last several decades that support symptomatic and functional improvement with the use of psychotherapy^{4,5} and selective serotonin reuptake inhibitors (SSRIs),^{6–8} particularly fluoxetine^{9–11} for the treatment of depressive and anxiety disorders in youth.^{4,12–14} Despite the efficacy of these interventions in short-term treatment studies, the risk of relapse and recurrence remains high, with five-year recurrence rates of up to 70% and 50% in children and adolescents with major depressive disorder or anxiety disorders, respectively.^{15,16}

In adults with affective and anxiety disorders, common strategies to prevent recurrence include: (1) continuation of acute treatment; (2) utilization of psychotherapy booster sessions to prolong response; and (3) implementation of uniquely tailored recurrence prevention interventions.¹⁷ However, the evidence for these interventions is limited in the pediatric population and these limitations are compounded by the short duration of many acute psychopharmacologic treatment studies, that often describe acute response over 12 weeks.^{4,9,13,14,18,19} These studies were primarily aimed at establishing the efficacy and determining the safety profile of antidepressants in the short-term; but, data regarding the impact on longer-term outcomes associated with these interventions are limited.

Major Depressive Disorder (MDD): Current Guidelines

Acute Treatment Guidelines for Pediatric MDD—Current treatment guidelines focus on the acute treatment of MDD in pediatric patients. Generally, for moderate to severe illness, these guidelines recommend treatment with a combination of an evidence-based psychotherapy and an SSRI.^{20–22} SSRIs have the most favorable risk-benefit profile as a first-line medication, with assessment of response every four weeks and dose titration when partial response is encountered. While symptom remission should occur in many studies by twelve weeks of psychopharmacologic treatment, there are conflicting recommendations for the duration of treatment following depression in pediatric patients. The GLAD-PC

guidelines²³ recommend “medications should be maintained for 6–12 months after the full resolution of depressive symptoms.” Similarly, the American Academy of Child & Adolescent Psychiatry (AACAP) Practice Parameters recommend continuation of treatment for 6–12 months “for all patients who have responded to the acute treatment.”²⁴ Further, these parameters suggest that summer may be a preferred period for antidepressant discontinuation and suggest that longer treatment may be recommended for some individuals, particularly for those with risk factors such as multiple past episodes, comorbid disorders, or socio-environmental concerns.²⁴

The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Guidelines for MDD recommend that maintenance treatment for 6–12 months in youth without a history of MDD prior to the index episode and recommend >1 year of treatment for youth with a prior history of >2 depressive episodes or 1 “severe or chronic episode.”²⁵ These guidelines note that the evidence for these recommendations is limited. Additionally, multiple studies have evaluated longer-term treatment since the publication of GLAD-PC²³ and AACAP Practice Parameters.

Relapse and Remission in Youth with MDD—While the medical vernacular is replete with references to “relapse” and “remission,” there is considerable variability in its application to depression. *Relapse* is defined as a *Diagnostic and Statistical Manual of Mental Disorders*-defined depressive episode during a remission period, with remission being a period of no or few depressive symptoms for 2 weeks but <2 months.²⁶ Recurrence represents the onset of a new depressive episode during a recovery period, with recovery being the absence of significant depressive symptoms for at least two months²⁶ (Figure 1). Defining relapse and recurrence in adolescents is complicated by fluctuations in affective symptoms whether related to developmental factors or the underlying internalizing disorder.^{17,27}

Controlled Medication Trials in Youth with MDD: Duration of Treatment Effects

Long-term Outcomes in the Treatment for Adolescents with Depression Study (TADS)—The *Treatment for Adolescents with Depression Study* (TADS) evaluated the acute efficacy of: (1) fluoxetine (monotherapy), (2) CBT (monotherapy), (3) fluoxetine + CBT, and (4) placebo in adolescents with MDD.¹¹ During the initial 12-week treatment phase both fluoxetine monotherapy and fluoxetine+CBT resulted in higher response rates compared to CBT alone.²⁸ During the extension phase, by week 18, response rates to CBT (65%) were comparable to fluoxetine (69%), but fluoxetine+CBT resulted in a response rate of 85%.¹¹ In addition, combined treatment resulted in a more rapid effect, but by week 36 comparable response rates (81–86%) were observed.²⁹ Taken together, the results of this study suggest a benefit to longer treatment duration, with remission rates for treated patients increasing from 23% at week 12 to 60% at week 36.²⁹ The proportion of patients who experienced a sustained response (not necessarily remission) improved similarly, across treatment conditions but *sustained* response was more likely to be maintained through week 36 if the acute treatment included CBT.²⁹

TADS¹¹ included 1-year of naturalistic follow up, after the 36 week treatment period, with assessments at 3, 6, 9, and 12 months³⁰. Response rates and suicidality did not differ among the treatments at 12 months, although patients treated with CBT + fluoxetine “generally maintained numerical superiority relative to CBT and fluoxetine [monotherapies].”³⁰ Symptomatic recurrence varied by acute treatment type but generally occurred in fewer than one third of participants during the 12 months following acute treatment.³⁰ This is a lower rate than reported in many other relapse studies.¹⁶

Finally, the *Survey of Outcomes Following Treatment for Adolescent Depression* (SOFTAD) study³¹ evaluated nearly half (45%) of TADS participants at six-month intervals for the 3½ years following the initial 12 month acute/naturalistic treatment. During this period, 96% of patients recovered from their index major depressive episode. Recovery, by two years, was significantly more likely for those who responded to acute treatment. However, 47% of patients who recovered experienced a recurrence during the SOFTAD study period, with recurrence significantly more common in females (57% [females], versus 32.9% [males]). Last, recurrence rates did not differ among acute treatments in TADS.³¹

Long-Term Outcomes in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Study—The *Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Study* evaluated (1) switching to another SSRI, (2) switching to another SSRI and adding CBT, (3) switching to venlafaxine, or (4) switching to venlafaxine and adding CBT in adolescents ($N=334$) who failed to respond to an adequate initial SSRI treatment. Greater improvement was observed with the addition to CBT to either a new SSRI or SNRI.³² Following acute treatment (12 weeks), responders continued to receive their previously assigned treatment for an additional 12 weeks, while those who failed to respond to the medication switch or addition of CBT, were followed while receiving naturalistic (non-protocol directed) care (re-assessment at weeks 48 and 72). The cumulative remission rate at 24 weeks was 39% (62% of responders to acute 12-week treatment and 18.3% of non-responders). Nearly 20% of week 12 responders experienced a relapse by week 24. Moreover, approximately one quarter of week 24 responders experienced a relapse within 48 weeks. Remission rate improved to 61.1% by week 72, though many participants had residual symptoms. Continuation of antidepressant treatment for >48 weeks was associated with higher remission rates than for patients who discontinued treatment <48 weeks, although this difference was no longer statistically significant by approximately 18 months. Unlike in TADS, CBT was not associated with a longer term impact on remission or non-relapse³³ but the “dose” of CBT treatment was relatively low and those not initially assigned to CBT were able to pursue this during the open treatment phase. This complicates interpretation, particularly given that subsequent studies have suggested a role of CBT for relapse prevention in depressed youth.^{34,35}

Adolescent Depression and Psychotherapy Trial (ADAPT)—The *Adolescent Depression and Psychotherapy Trial* (ADAPT), pragmatic randomized controlled trial of combination therapy randomized adolescents ($N=208$) with moderate to severe MDD who failed to respond to a brief initial intervention (>2 sessions focused on an explanation of MDD and exploration of recent family and/or peer group conflict) to SSRI monotherapy

(primarily fluoxetine) or SSRI+CBT.³⁶ The proportion of participants who reported significant improvement increased from 43% at week 12 to 57% at week 28 and SSRI + CBT was not superior to SSRI monotherapy at 12 or 28 weeks of treatment. However, patients in the ADAPT trial may have had higher depressive symptom burdens than those in TADS which may subtend the differences in outcome. Interestingly, in a subgroup analysis of the most severely ill participants in TADS, superiority of combined treatment versus fluoxetine alone was not observed.³⁶

Other Depression Randomized Controlled Trials with Long-Term Response

Data—One study of adolescents with MDD who responded to fluoxetine (open-label, 12 weeks) randomized patients to continue fluoxetine or placebo for 6 months. Relapse was significantly more common in patients randomized to placebo than those randomized to fluoxetine (69% vs. 42%, $N=102$, $p=0.009$) and earlier relapse was observed in those patients treated with placebo (8–14 weeks vs. >24 weeks, $p<0.006$).³⁷ An additional longer-term study of youth who had responded to acute treatment with sertraline (12 weeks) observed that during 24-weeks following the acute treatment phase, sertraline-treated patients had higher rates of sustained response compared to placebo (38% vs. 0%, $p<0.05$) during a 52-week double-blinded maintenance treatment period. This study, although well-designed, was limited by sample size and *eo ipso* power limitations (*e.g.*, maintenance phase included only 22 participants).³⁸ Finally, a 2012 Cochrane review of nine RCTs, evaluated relapse and recurrence in pediatric patients with MDD and noted that “antidepressant medication reduces the chance of relapse-recurrence in the future” and “limited evidence that continued medication is more effective than placebo in preventing the next episode of depression once a child or adolescent has initially responded to medication during acute phase treatment.” However, the optimal continuation therapy was not determined.

Major Depressive Disorder: Predictors of Recurrence

Recovery from an initial major depressive episode occurs within 1–2 years for most youth; however, recurrence is common and frequently occurs 6–12 months following the discontinuation of the acute treatment.³⁹ Randomized controlled trials have recently suggested predictors of treatment response (*e.g.*, low family conflict, higher socioeconomic status, lack of co-occurring anxiety) (Table 1). The evidence for longer-term predictors of relapse and recurrence are limited or, in some cases, conflicting (Table 1).

Anxiety Disorders: Current Acute and Long-Term Treatment Recommendations

Although more than a decade old, the AACAP Practice Parameters for the treatment of anxiety disorders²⁰ suggest evidence-based psychotherapy (*e.g.*, CBT) as the initial treatment for mild anxiety disorders in youth, while SSRIs are recommended for patients with (1) moderate to severe anxiety disorders; (2) impairments that limit their ability to engage in psychotherapy; and (3) partial response to psychotherapy.²⁰ Following acute antidepressant treatment for anxious youth, only one recommendation has addressed the duration of treatment. This recommendation consists of an expert opinion paper, more than 15 years old,⁴⁰ that recommends antidepressant discontinuation during a low-stress period, >1 year following reduction in anxiety or depressive symptoms. However, descriptions of relapse and remission, that have been operationalized in MDD, have—at times—been

difficult to operationalize with pediatric anxiety disorders. Definitions for such terminology in anxiety disorders have adopted terminology specifically for MDD.²⁶ Differences in assessment scales and definitions of treatment response and remission are frequently cited as a source of variation in findings across studies.^{15,41}

Anxiety Disorders: Evidence for Antidepressant Treatment Duration

Child/Adolescent Anxiety Multimodal Study (CAMS)—The *Child/Adolescent Anxiety Multimodal Study* (CAMS) randomized youth with separation, generalized and/or social anxiety disorder ($N=488$) to: (1) sertraline monotherapy, (2) CBT monotherapy, (3) combined sertraline and CBT, and (4) pill placebo.⁴² After 12 weeks of acute treatment, all three treatments were superior to placebo, and combined therapy was associated with a response rate of approximately 80% and was superior to either monotherapy (CBT 60% vs. sertraline 55%, $t=-1.32$, $p=0.19$).⁴ Participants who had responded to any of the three treatment arms during the initial 12 week acute treatment period were followed for a 6-month maintenance period.⁴³ Similar to TADS, the two monotherapy treatments continued to improve. Statistically significant differences for the monotherapies (*i.e.*, sertraline or CBT) compared to combined therapy were no longer present by weeks 24 (combined treatment vs sertraline $p=0.092$; combined treatment vs CBT $p=0.16$; sertraline vs. CBT $p=0.859$) and 36 (combined treatment vs. sertraline $p=0.176$; combined treatment vs CBT $p=0.144$; sertraline vs. CBT $p=0.931$). However, when remission was defined as “no longer meeting diagnostic criteria for the anxiety disorders under study,” combined therapy maintained superiority at week 36 (combined treatment vs. sertraline $p<0.005$; combined treatment vs. CBT $p<0.006$).⁴³

Child/Adolescent Anxiety Multimodal Extended Long-Term Study (CAMELS)—The Child/Adolescent Anxiety Multimodal Extended Long-term Study (CAMELS) followed a sub-set of CAMS participants for an average of 6.2 years (range: 3.7–9.9 years) following CAMS randomization ($N=288$).⁴¹ Nearly half (47%) of CAMELS participants were in remission, including 52% of those who responded to acute CAMS treatment and 37.6% of those who did not. However, the context of these remission rates is important. Participants left university-based care and were treated with community-based care. They were monitored at lower frequency, may have had shorter appointment times and may have had more conservative dosing and less aggressive management of co-morbid conditions.

Other Longer-Term Trials in Pediatric Anxiety Disorders—One follow up study of the Research Units on Pediatric Psychopharmacology Anxiety Study found that 94% of those who had previously responded to fluvoxamine during an acute 8-week treatment course ($N=35$) maintained remission status during a 6-month open treatment period.⁴⁴ Another extension study of duloxetine showed continued treatment effects at 18 weeks, following acute treatment. In this study, improvement in anxiety severity was observed for both treatment groups (*i.e.*, patients randomized to placebo followed by open-label duloxetine [PBO/DLX] as well as those randomized to duloxetine and then beginning open-label duloxetine [DLX/DLX]). The probability of achieving remission at Week 28 was identical (83%) for the DLX/DLX and PBO/DLX treatment groups.¹⁴

Anxiety Disorders: Predictors of Recurrence

As with MDD in youth, evidence for predictors of relapse and recurrence in pediatric anxiety disorders is limited⁴⁵ and inconclusive. Longer-term studies suggest that children and adolescents who develop anxiety disorders are more likely to have persistent symptoms if the initial pathology is more severe or more functionally disabling, and even if the initial disorder remits, are more likely to develop new anxiety disorders or comorbidities. One study examined long-term (>2 years) outcomes (e.g., remission status, anxiety severity, global functioning) in anxious children and adolescents following treatment.⁴¹ This study involved 59% of CAMS participants; patients were followed for 6.2±1.4 years post-randomization). At follow-up, nearly half of the sample (47%) had achieved remission, which was defined as no longer meeting diagnostic criteria for social anxiety disorder, separation anxiety disorder or generalized anxiety disorder (GAD). Responders to acute treatment during the 12-week period CAMS were significantly more likely to be in remission than non-responders (OR=1.83, 95% CI: 1.08–3.09), and they had less severe anxiety ($p=0.02$) and improved global functioning scores ($p=0.02$). Other predictors of remission status included male sex (OR=1.69, 95% CI: 1.01–2.84), better family functioning, and lower baseline anxiety severity. Other variables, which were associated with positive outcomes, included higher socioeconomic status (lower anxiety severity, better functioning) and the absence of a comorbid externalizing disorder. The absence of attention-deficit/hyperactivity disorder (ADHD) predicted better functioning at follow-up. Predictors of long-term remission/response in pediatric anxiety disorders and depressive disorders are shown in Table 1.

DISCUSSION

While the evidence base that informs the optimal duration of treatment for pediatric patients with depressive and anxiety disorders significantly lags the data from adult studies, several studies that examine relapse as well as open-label continuation and some follow-up studies may enable clinicians to make informed recommendations regarding the duration of treatment. However, in discussing these studies the goal of treatment—remission—should be emphasized. For depressive disorders, current data suggest high and sustained remission rates associated with longer treatment durations (e.g., approximately 9–12 months).^{29,33,37} One study reported a lower recurrence rate with a 52-week maintenance phase³⁸ compared to discontinuation prior to 12 months, the current data support acute antidepressant treatment for 6–12 months as an initial strategy for pediatric patients with MDD. By contrast, the anxiety literature suggests that the salutary effects of SSRI treatment—regardless of whether administered with CBT—are robust at 9 months while other open-label extension studies of antidepressants in anxious youth generally suggest similar findings at 6–7 months.^{14,44} However, based on a double-blinded antidepressant discontinuation study in adults with GAD that suggests that 12 months of treatment (relative to 6 months of treatment) halved the relapse rate,⁴⁶ many clinicians treating anxious youth treat for 12 months rather than 6 months. Regardless of whether optimal treatment should be for 6–12 months, it is important for clinicians to bear in mind that there is no evidence suggesting harm from long-term SSRI treatment in the absence of problematic side effects. Though these approaches have not been

systematically evaluated in the context of an adaptive design trial, clinicians would do well to tailor antidepressant treatment duration based on risk factors for poor prognosis (Table 1).

When antidepressants are to be discontinued, some data⁴⁷ and expert opinion⁴⁰ suggest that the timing of antidepressant discontinuation should be considered with regard to the adolescent's psychosocial milieu. Shamseddeen and colleagues demonstrated that adolescents who end treatment during summer vacation were nearly twice as likely to demonstrate adequate treatment response.⁴⁷ Thus, clinicians should consider planning discontinuation of antidepressant treatment during lower stress periods, recognizing the importance of incorporating non-disease state dependent factors (*e.g.*, school, separation-related events) into the antidepressant discontinuation approach. However, clinicians should be reminded that for the anxious or depressed child some "low stress periods" for healthy youth (*e.g.*, family vacations, summer camp) may be suffused with stress and anxiety that could be mistakenly attributed to medication discontinuation.

An important clinical consideration with regard to the duration of psychopharmacologic treatment in youth with both MDD and anxiety disorders is the type, frequency and duration of concurrent psychotherapeutic treatment. Long-term data in youth with MDD and anxiety disorders suggest more rapid improvement associated with combined therapy (*i.e.*, SSRI + psychotherapy) relative to antidepressant treatment or psychotherapy alone.^{15,48} A patient who has successfully engaged in psychotherapy during the course of pharmacologic treatment or a patient with a more rapid response to acute treatment (more likely with combined treatment) might require a briefer psychopharmacologic intervention. However, no prospective, randomized controlled trials have evaluated this possibility.

While debate remains regarding the optimal duration of antidepressant treatment for youth with MDD or anxiety disorders, the overarching goal of treatment is obvious: remission. Any discussion regarding treatment discontinuation is predicated on the patient having achieved remission of depressive or anxiety symptoms; remission status indicates clinical relief is linked to functional recovery.³³ If remission is not achieved with acute treatment with either antidepressant monotherapy or antidepressant treatment paired with psychotherapy, clinicians should consider changing antidepressants. Such a change should not be delayed excessively in hopes of a late response to the initial SSRI (unlikely after an initial 8 week treatment period.⁴⁹ Moreover a switch in SSRI among non-responders has been associated with benefit.^{32,44} In fact, the results of the TORDIA study remind clinicians that, following a switch in antidepressant, "eventual remission is evident within the first 6 weeks in many, suggesting that earlier intervention among non-responders could be important."³⁹

In sum, 9–12 months of SSRI treatment is recommended for pediatric patients with MDD. For children and adolescents with generalized, separation and social anxiety disorders, 6–9 months of SSRI treatment may be sufficient. Many clinicians extend treatment to 12 months based on extrapolation of data from adults with anxiety disorders. Such extended treatment periods may decrease the risk of long-term morbidity and recurrence; however, the goal of treatment is ultimately remission, rather than duration of antidepressant pharmacotherapy.

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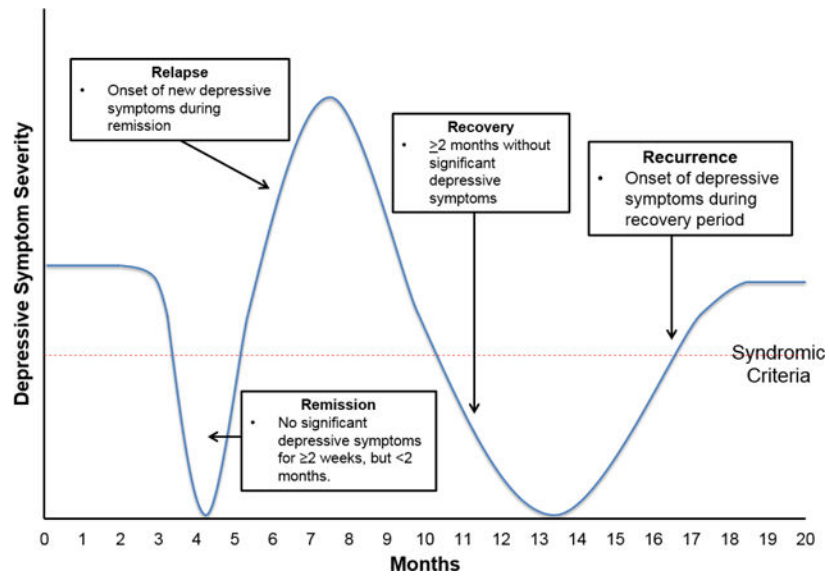


Figure 1. Definitions of disease course in children and adolescents with major depressive disorder

Definitions are operationalized from studies of the course of MDD in adults (Frank et al. 1991).

Table 1

Factors associated with a lower likelihood of response and/or remission in the long-term treatment of MDD and anxiety disorders in children and adolescents.

Major Depressive Disorder	Anxiety Disorders
More prior depressive episodes (Kovacs et al. 1984)	Older age (Ginsburg et al. 2011)
Residual symptoms after treatment (in adults) Greater family levels of expressed emotion (Asarnow 1993)	Female sex (Ginsburg, et al. 2014)
Perceived family conflict (Birmaher et al. 2000, Goodyer et al. 2002)	Minority status (Ginsburg et al. 2011)
Non-response to acute therapy (Survey of Outcomes Following Treatment for Adolescent Depression Study, unpublished)	Baseline symptom severity Ginsburg et al. 2011 and 2014
Female sex (Survey of Outcomes Following Treatment for Adolescent Depression Study, unpublished)	Lower socioeconomic status (Ginsburg et al. 2014)
	Co-occurring internalizing disorder (Ginsburg et al. 2011)
	Social anxiety disorder(Ginsburg et al. 2011)
	Greater negative life events (Gibby et al. 2017)

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